Fullscript

REFERENCE SHEET:

Vitamin B12

Pronunciation

Cobalamin (koh-bal-ah-min)

Summary

Vitamin B12 is an essential water-soluble nutrient found primarily in food derived from animal sources, such as meat, eggs, dairy, and seafood. It can also be found in shiitake mushrooms, green and purple lavers (nori), and fortified cereals. Vitamin B12 contains cobalt compounds that can be converted to the active coenzymes, methylcobalamin, and adenosylcobalamin. It is also a cofactor for methionine synthase and l-methylmalonyl-CoA mutase, which synthesize methionine from homocysteine, and convert methylmalonyl coenzyme A to succinyl coenzyme A, respectively. B12 is crucial for the formation of DNA and red blood cells, and proper neurological function. Vegans and vegetarians have an increased risk of B12 deficiency due to the dietary restriction of animal-derived foods. Elderly individuals and other populations with conditions of malabsorption are also at risk of deficiency.

Main Medical Uses

Vitamin B12 supplementation is used to prevent and treat B12 deficiency, as deficiencies in B12 can lead to a wide variety of related health conditions. Treatment with B12 is effective in deficiency-related conditions such as pernicious anemia, megaloblastic anemia, and recurrent aphthous stomatitis. B12 deficiencies also can lead to hyperhomocysteinemia. Elevated homocysteine levels can occur via methylenetetrahydrofolate reductase (MTHFR) genetic polymorphisms, which are associated with B12 deficiency. Some evidence supports the use of B12 to reduce homocysteine levels in individuals with MTHFR polymorphisms, though it may only play a secondary role to folate.

Low B12 levels may be associated with an increased risk of developing age-related macular degeneration and depression, particularly with older women. Vitamin B12 supplementation has been shown to reduce the risk of depressive relapse and symptom onset. B12 may also be effective in treating autism spectrum disorder.

B12 may decrease pain in subacute herpetic neuralgia and compressive neuralgia, as well as treat diabetic neuropathy. B12 may also improve the quality of life and decrease the use of analgesics in patients with postherpetic neuralgia. Research has shown that supplementation may also play a role in cognition, fatigue, and growth. Furthermore, B12 may treat multiple sclerosis and have some benefit in celiac's disease, migraines, and chronic obstructive pulmonary disease. Hydroxocobalamin injections are used to treat suspected cyanide poisoning and may assist in treating Bell's Palsy when combined with acupuncture.

Dosing and Administration

Recommended Dietary Allowance (RDA) for vitamin B12:

- Ages 0-6 months 0.4 µg (adequate intake)
- Ages 7-12 months 0.5 µg (adequate intake)
- Ages 1-3: 0.9 µg
- Ages 4-8: 1.2 µg
- Ages 9-13: 1.8 µg
- Ages 14+: 2.4 µg
- Pregnancy: 2.6 µg
- Lactation: 2.8 µg

B12 is found in high concentrations in cow's liver (26-58 µg/100g), beef and lamb (1-3 µg/100g), eggs (1-2.5 µg/100g), dairy (0.3-2.4 µg/100g) and chicken (up to 1 µg/100g).

Condition	Dosing & Administration	Outcome	Class of Evidence	MOA
B12 Deficiency	> 1000 µg per day	↑ serum and total B12, ↓ methylmalonic acid (MMA) and total homocysteine	A	↑ B12 levels via active absorption as most cases are due to inadequate intake
Pediatric B12 Deficiency	1000 µg per day, 4 months	↑ B12 levels in children, but decreases with increased body weight	A	↑ B12 levels via passive diffusion after oral admin
B12 Deficiencies caused by GI Disorders	1000 µg per day for 1 month, then 125-1000 µg ongoing to normalization	↑ serum B12 in deficiencies from food malabsorption (atrophic gastritis, chronic carriage of H. pylori, bacterial overgrowth, long-term antacid use, chronic alcoholism, gastric surgeries, chronic pancreatitis, or Crohn's disease), vegan/vegetarianism deficiencies	A	↑ serum and total B12, ↓ MMA & homocysteine ↑ synthesis of co-factor MeCbl to reduce homocysteine to methionine and SAMe, of which methyl groups used for DNA, neurotransmitter & hormone synthesis ↑ synthesis of co-factor AdCbl to convert methylmalonyl CoA to succinyl CoA for energy production in Krebs cycle
Gastric Bypass/ Bariatric Surgery	1000 µg per day after Roux-en-Y Gastric Bypass	↑ B12 levels	A	
	350 µg perioperatively in bariatric surgery	↑ B12 levels	A	
Pernicious Anemia	1000 µg per day, ongoing	↑ B12 levels	A	↑ B12 levels via passive diffusion after oral administration ↑ leukocytes, lymphocytes, CD8+, CD3, CD19, serum IgG, IgA, IgM & natural killer cell activity
Recurrent aphthous stomatitis (RAS)	1000 µg per day, 6 months	↓ duration, number, and pain of canker sores	B	Function of B12 in RAS improvement remains speculative

Condition	Dosing & Administration	Outcome	Class of Evidence	MOA
Multiple Sclerosis	1000 µg per week (intramuscular) for 24 weeks	↓ Guy's Neurological Disability Scale	B	Improved visual & brainstem auditory evoked potentials IFN-β + B12: ↑ motor function, oligodendrocyte maturation, sonic hedgehog & its receptor expression; ↓ astrocytosis, demyelination, Notch-1 expression in mice
Hyper-homocysteinemia	2-10 µg per day (cyanocobalamin) for 4-12 months 1000 µg every other day (methylcobalamin) for 16 weeks, vegetarians	↓ total homocysteine ↓ total plasma homocysteine	B C	↓ total homocysteine ↓ hemoglobin, and hematocrit ↓ homocysteine from MTHFR polymorphism ↑ synthesis of co-factor MeCbl to reduce homocysteine to methionine and SAMe
Growth	1.8 µg per day for infants aged 6-11 months; 3.6 µg for older than 12 months for 6 months	↑ weight for age; ↑ weight for age & height for age in wasted, underweight, stunted children	B	↑ hemoglobin, hematocrit, erythrocyte, & thrombocyte levels possibly through increased succinyl CoA synthesis; ↓ mean corpuscular volume & hemoglobin, red cell volume distribution width
Diabetic Neuropathy	500 mg three times per day (methylcobalamin) for 4 months 1500 µg per day (methylcobalamin) for 3 months	↓ somatic symptoms, autonomic symptoms, & peripheral neuropathy signs score ↑ 2-point discrimination ability, median nerve max motor conduction velocity & scalp somatosensory response; ↓ pain & cramps	B C	↑ median nerve & ulnar nerve conduction velocity, & nerve reflection ↑ scalp- somatosensory response ↑ neurite outgrowth, neuronal survival, nerve regeneration & recovery, erk1/2 & Akt activity in rats

Condition	Dosing & Administration	Outcome	Class of Evidence	MOA
Celiac's Disease	0.5 mg (cyanocobalamin) with 0.8 mg folic acid and 3 mg pyridoxine per day for 6 months	↑ well being, anxiety, mood; ↓ total homocysteine	B	↓ total plasma homocysteine
Cognition	15 µg per day for 5 weeks	↑ memory performance	B	↑ hematocrit; ↓ red blood cell volume & abnormalities in blood hypersegmented neutrophils with or without macroovalocytes, MMA & total homocysteine
Autism Spectrum Disorder in children	75 µg/kg subcutaneous injection every 3 days (methylcobalamin) for 8 weeks 64.5 µg/kg subcutaneous injection every 3 days (methylcobalamin) for 6 weeks	↓ Clinical Global Impressions-Improvement score and was positively correlated with ↑ plasma methionine, SAM:SAH ratio, & ↓ SAH ↓ Clinical Global Impression score in 30% of Px; ↑ plasma GSH & GSH:GSSG ratio only in responsive subgroup	B C	↓ homocysteine with B12, B6 & folic acid ↓ SAH; ↑ plasma methionine, SAM:SAH ratio) ↑ plasma GSH & GSH:GSSG ratio only in responsive subgroup
Fatigue	5 mg (hydroxocobalamin injections) twice weekly for 2 weeks	↑ appetite, mood, energy, sleep & well-being	C	↓ fatty acid oxidation and energy metabolism via dysregulated acetylation/ methylation related to SAM synthesis from B12 + folate deficiency
Chronic Obstructive Pulmonary Disease	500 mg per day, 8 weeks	↑ serum B12 and exercise tolerance alone and with exercise compared with exercise and placebo groups	C	Theoretical improvement in VO2 kinetics via decreased homocysteine may lead to decreased endothelial dysfunction, mitochondrial toxicity, and harm to cardiac muscle

For an explanation of the classes of evidence, please see the Rating Scales for Evidence-Based Decision Support.

Forms

Vitamin B12 has four main forms, including synthetic cyanocobalamin and naturally-occurring methylcobalamin, hydroxocobalamin, and adenosylcobalamin. There is currently not enough evidence to suggest differences in bioavailability, biological outcomes, or efficacy between forms. However, the use of cyanocobalamin supplementation is popular due to its inexpensive and stable nature. Vitamin B12 can be administered intranasally, intravenously, intramuscularly, or orally in tablet, sublingual lozenge, liquid, or capsule form.

Administration	Formulation	Bioavailability	Class of Evidence
Oral	1000 µg B12	Sufficient to safely reverse B12 deficiencies and related disorders, without cost, discomfort, & possible contraindications of parenteral administration	A
	5000 µg cyanocobalamin	2% bioavailability, 5% bioavailability in formulation with the addition of SNAC carrier compared with I.V	D
	1, 5 & 25 µg of cyanocobalamin, methylcobalamin & hydroxocobalamin	Mean whole body retention of doses after 16 days for: • Cyanocobalamin: 1µg (49.2%), 5µg (20.4%), 25µg (5.6%) • Methylcobalamin: 1µg (44.6%), 5µg (18.8%), 25µg (6.1%) • Hydroxocobalamin: 1µg (55.7%), 5µg (16.3%), 25µg (7.4%)	D
	Oral cyanocobalamin or hydroxocobalamin solution in rats	More hydroxocobalamin accumulated in the liver, more cyanocobalamin accumulated in brain, muscle & plasma	D
Sublingual	130-290 µg cyanocobalamin fortified toothpaste	↑ serum B12, holotranscobalamin, ↓ total homocysteine, MMA after 12 weeks compared to placebo toothpaste (greatest effect observed in patients not using B12 supplements)	B
	1000 µg methylcobalamin sublingual tablet w/ 400 µg folate, & 5 mg B6	Equal decrease total serum homocysteine after 6 weeks compared to matching oral placebo	C
	500 µg sublingual tablet of cyanocobalamin	Equal increase in serum cobalamin to the oral group at 4 and 8 weeks	D

Administration	Formulation	Bioavailability	Class of Evidence
Parenteral	Single 500 or 1000 µg injection of hydroxocobalamin or cyanocobalamin intramuscularly	Hydroxocobalamin increased B12 more than cyanocobalamin between hours 5-72 post-administration and by the end of week 4. • Hydroxocobalamin: 16% of 500 µg and 27% of 1000 µg dose excreted in urine after 72 hours. • Cyanocobalamin: 60% and 69% of respective doses excreted	D
Intranasal	1000 µg cyanocobalamin (500 µg each nostril)	2% bioavailability compared to intramuscular	D
	750-1500 µg hydroxocobalamin	2-5% bioavailability, highly & rapidly absorbed, increased absorption at higher doses	D
	1500 µg hydroxocobalamin	↑ 8-fold serum B12 after 1 hour compared with baseline and sustained increase 1 week after administration	D

Associated Depletions and Interactions

Class of Drug	Pharmaceutical	Effect	Class of Evidence
Prostaglandins	Alprostadil	↑ efficacy in treating diabetic peripheral neuropathy compared to methylcobalamin alone with no adverse events	A
Dithiolanes	Lipoic Acid	↑ efficacy in treating diabetic peripheral neuropathy (300-600 mg i.v. doses daily) compared to methylcobalamin (500-1000 mg i.v. or im.) alone with no serious adverse events over 2-4 weeks	A
Acid Lowering Agents	Proton Pump Inhibitors (PPI), H2 blockers	↑ risk for B12 deficiency long-term PPI use associated with lowering of serum B12. B12 supplements slowed but did not prevent prolonged diminishment in elderly population. H2 blockers had no effect	A D

Class of Drug	Pharmaceutical	Effect	Class of Evidence
Biguanide	Metformin	↑ association with B12 deficiency incidence, ↓ serum B12	A
		↓ serum B12 in dose dependent manner in treatments both shorter and longer than 3 years	A
		↓ serum B12 corrected with single 1000µg hydroxocobalamin injection or daily sublingual methylcobalamin tablet	D
		B12 malabsorption in 30% of diabetic patients with long term metformin use. ↓ serum HgB, ↑ serum folate	D
	Phenformin	↓ serum and kidney B12, ↑ liver B12 in rats. No difference in absorbed B12 in tissues between metformin and control suggesting metformin does not alter B12 absorption	D
		B12 malabsorption in 46% of diabetic patients, not statistically different than previously reported malabsorption in 30% of patients on metformin	D
Proton Pump Inhibitors	Omeprazole	↓ cyanocobalamin absorption from 3.2% to 0.9% and 3.4% to 0.4% with 20 or 40mg omeprazole respectively over 2 weeks	D
		↓ absorption of protein-bound B12, but not unbound B12 with 20 or 40 mg omeprazole in patients with gastroesophageal reflux disease	D
	Omeprazole, Esomeprazole, Pantoprazole, Lansoprazole, or Rabeprazole	Long term users (>1 year) had an associated 18% lower serum B12 compared with non-users. Significantly more PPI users had low serum B12 (50% participants)	D
Calcium	Calcium	↓ serum B12, serum holoTCII with metformin use. 1.2g calcium per day reversed serum holoTCII decline caused by metformin suggesting decreased B12 malabsorption	D
		↓ B12 uptake in dog epithelial cells with calcium depletion	E

Class of Drug	Pharmaceutical	Effect	Class of Evidence
Aminosalicylic acids	Para-Aminosalicylic Acid	↓ B12 absorption without effect on intrinsic factor	D
Acetylsalicylic acids	Acetylsalicylic Acid	More frequently associated with B12 deficiency in hospitalized patients for CVD	D
Alcohol	Alcohol	↓ mean serum B12 (5%), ↑ mean serum homocysteine (3%) after increasing from 0-30g of alcohol per day	D
		↓ B12 after one month of daily 375 ml of white wine. ↑ B12 concentration in wine + 200 µg B12 after one month	D
		Higher mean concentration of B12, lower mean homocysteine and folic acid concentration in alcoholics compared with controls. Only higher B12 concentration in alcoholic liver disease compared with controls. Suggests alcohol induced hepatic liver damage	D
		↓ B12 absorption with alcohol, but not as B12-intrinsic factor complex in rats	D
Tropones	Colchicine	↓ B12 absorption in healthy patients. Did not increase urinary excretion, but increased fecal excretion	D
Vitamin C	Ascorbic Acid (AA)	Low serum B12 in 22% of patients with traumatic spinal cord injury using 2g AA per day	D
		Sodium ascorbate in absence of potassium cyanide (KCN) reduced B12 suggesting stability of cyanocobalamin	E
		AA decreased B12 levels in food and in serum in vitro, but improved with KCN	E
Urinary Alkalinizing Agents	Potassium Citrate	Slightly lower B12 absorption. Calcium did not improve absorption	D
Biopolymer	Chitosan	Eliminate B12 in vitro	E

Pharmacokinetics

Absorption and Distribution
The oral bioavailability of vitamin B12 is low. The stomach, pancreas, ileum, and intrinsic factor produced by the stomach are involved in the digestion and active absorption of orally-ingested vitamin B12. Even with a dysfunctional GI system, however, small amounts of free-form B12 from supplements can be absorbed by passive diffusion. Supplemental B12 is not bound to proteins as it would be when found in food. While the total absorption increases with higher intake, relative absorption decreases.
For example, 50% of a 1 µg dose may be absorbed, 20% of a 5 µg dose, 5% of a 25 µg dose, and as little as 1% may be absorbed in doses of 500 µg. However, these amounts are often sufficient to meet the RDA for vitamin B12.

After oral ingestion, stomach acid and pepsin uncouple vitamin B12 bound to proteins in food thus allowing B12 to bind to R proteins produced by the salivary glands and gastric mucosa. Supplements containing vitamin B12 are more readily available to bind with R proteins and can be more easily uptaken in the gastrointestinal mucosa as the B12 is not bound to food proteins. As vitamin B12 bound to R proteins enters the small intestine, B12 is released from the R proteins that make contact with pancreatic proteases, allowing free B12 to bind with intrinsic factor or to undergo diffusion in the gastrointestinal mucosa if ingested in concentrations that are higher than typically found from food sources. This allows B12 to bind with receptors in the mucosa of the ileum and move to enterocytes. After a few hours, B12 may circulate through the blood after binding with transcobalamin I, II or III. Most B12 is bound to transcobalamin I but transcobalamin II is primarily responsible for its deposition in most tissues.

Metabolism
After transport into peripheral tissue cells, vitamin B12 is disassociated from transcobalamin II by lysosomes in the cytosol. All forms of vitamin B12 are reduced in the cytosol to its core inactive cobalamin form. Free cytosolic cobalamin can be converted to the active cofactor, methylcobalamin, with the addition of a methyl group derived from 5-MTHF or SAMe. Methionine synthase may then use methylcobalamin as an active cofactor to reduce homocysteine and produce methionine, tetrahydrofolate, and subsequently, purines and pyrimidines used in RNA and DNA synthesis. The use of vitamin B12 in practice is closely tied to folate and vitamin B6, especially in lowering homocysteine levels.

The core cobalamin can also enter the mitochondria to combine with adenosyl derived from ATP molecules to form the active cofactor, adenosylcobalamin. The adenosylcobalamin may then be used by methylmalonyl CoA mutase to convert methylmalonyl CoA to Succinyl CoA, which enters the Krebs cycle.

Excretion
The liver acquires 50% of the circulating vitamin B12 with an estimated storage capacity of 2-3 mg, which decreases the likelihood of deficiency. Vitamin B12 can be used in bile and reabsorbed in the presence of intrinsic factor. Vitamin B12 is primarily excreted in the stool, though if it reaches blood saturation, it may be excreted in the urine. Between 1.4-5.1 µg are lost each day in healthy and elderly individuals.

Adverse Effects

Vitamin B12 does not currently have an assigned upper limit (UL). Adverse effects from B12 intake and supplementation are atypical. Intramuscular, intravenous, and oral supplementation in diabetic peripheral neuropathy is safe and is not associated with adverse effects. Doses of 1000 µg orally and intramuscularly over three months are well tolerated in B12-deficient patients and considered safe for patients with GI disorders. Oral cyanocobalamin has been shown to be safe at doses of 1000µg for 18 months. Intravenous administration of hydroxocobalamin at doses ranging from 2.5 to 10 grams over 30 minutes was reported to produce reddening of the skin (the color of hydroxocobalamin), pustular/papular rash, headaches, erythema at the injection site, decrease in lymphocyte percentage, nausea, pruritus, chest discomfort, dysphagia, and increased blood pressure in some volunteers.