White Paper:
Vitamin B12

B12 – THE BASICS

Vitamin B12, otherwise known as cobalamin, is a water-soluble vitamin found predominantly in animal protein. It is the largest of the B vitamins and has a complex structure featuring a central cobalt atom.[1]

Vitamin B12 was first discovered in 1948, when it was isolated from liver and identified as being responsible for relieving the pernicious anemia. Some 20 years prior, Minot and Murphy were awarded a Nobel prize for showing that eating large amounts of liver could help correct pernicious, now we know it was, in fact, the B12 content of liver that helped to correct pernicious anemia.[2]

B12 FORMS

There are five known forms of B12:

Cyancobalamin – a synthetic form of B12 that has a cyanide molecule attached to the cobalt.

Hydroxycobalamin – a hydroxyl group is attached to the cobalt, this form is mostly used for parental administration.

Aquacobalamin – a water group bound to the cobalt.

The final 2 forms of B12 are known to be the most enzymatically active forms of B12 in mammals.

5-deoxyadenosylcobalamin - commonly referred to as adenosylcobalamin - where a 5-deoxyadenosyl group is bound to the cobalt atom.

Methylcobalamin – a methyl group is bound to the cobalt atom.

SOURCES

The only dietary sources of vitamin B12 for humans are from animal products such as liver, sardines, egg yolk, cheese, milk, fish and beef. Most organisms such as bacteria and algae, synthesize B12 which then make their way into the food chain. Human intestinal microbes also synthesize a small amount of vitamin B12.[1]

DIGESTION, ABSORPTION, TRANSPORT AND STORAGE

Once ingested, cobalamins must be released from the proteins/polypeptides to which they are bound. This release usually occurs through the actions of the gastric proteolytic enzyme pepsin and hydrochloric acid in the stomach. Once released, B12 binds to R proteins, known collectively as cobalophilins or haptocorrins(HCs). The R protein typically binds to the vitamin as it is emptied from the stomach into the duodenum, the proximal or upper region of the small intestine.[4]

Within the duodenum, the R protein is hydrolysed by pancreatic proteases and free cobalamin is released. After release from the R protein, Vitamin B12 binds to intrinsic factor (IF), a glycoprotein that is synthesized by gastric parietal cells.[4]

The cobalamin-IF complex travels from the duodenum to the ileum, where receptors (called cubilins) for vitamin B12 are present and allow for absorption. The vitamin is absorbed throughout the ileum, especially the distal third.[4]

Absorption of the cobalamin-IF-vitamin B12 complex into the enterocyte is thought to occur by receptor-mediated endocytosis. A protein, megalin, is also thought to bind to the complex and to play a role in its transport into the cell. Within the enterocyte, B12 is released from the IF complex. B12 can then be bound to transcobalamin II in readiness for transport across the basolateral membrane of the ileal cells and into the bloodstream.[4]

There is some passive diffusion of vitamin B12, approximately 1-3%, that generally occurs when pharmacological doses of vitamin B12 are ingested.[4]

Following absorption, vitamin B12 appears in circulation about 3 to 4 hours later, peak levels in the blood are not typically reached for another 4-8 hours. In the blood, Methylcobalamin comprises about 60-80% and adenosylcobalamin up to 20% of the total plasma cobalamin.

FUNCTIONS AND MECHANISMS OF ACTION

Important Cofactor

B12 is in high demand by cells with a high turnover rate, such as epithelial cells in the GI and oral mucosa and the skin. B12 is also instrumental to the DNA synthesis required for optimal cell replication and differentiation.[3]

B12 is also involved in the metabolism of carbohydrates, proteins and lipids alongside fatty acid and nucleic acid production, making it important in energy production. B12 also plays a role in red blood cell formation.[1]

Homocysteine Reduction

Methylcobalamin (B12) is required for the conversion of homocysteine to methionine via 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR). Methionine then goes on to make S-adenosylmethionine (SAM), which is necessary for the methylation of numerous biochemical reactions, including myelin sheath production and the synthesis of certain neurotransmitters, for maintaining brain and nervous system function.[3]

Methylcobalamin also helps to regenerate tetrahydrofolate (THF), which is involved in DNA Synthesis. In B12 deficiency the conversion of homocysteine to methionine is affected as is the conversion of 5-methyltetrahydrofolate to tetrahydrofolate, this leading to a build-up of homocysteine and 5-methyltetrahydrofolate in the body.[4]

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Studies have shown that vitamin B12 supplementation reduces plasma homocysteine concentration by an average of 28% in as little as 2 weeks.[5]

Nervous System

Vitamin B12 is involved in the formation of the myelin sheath, the protective sheath surrounding many nerves in the periphery, spinal cord and brain. A deficiency of B12 leads to demyelination of nerves leading to a multitude of symptoms such as loss of balance, tingling in the periphery, nerve pain, and cognitive symptoms.

Through its important contribution to myelin formation and remyelination, Vitamin B12 significantly supports the regeneration of nerves after injury.[8] Vitamin B12 has been shown to promote axon growth of neuronal cells after peripheral nerve injury, and is currently being used for the treatment of peripheral nerve damage in clinical trials.[6]

Immune system

Vitamin B12 supports the immune system via its involvement in nucleic acid and protein synthesis alongside vitamin B6 and folate.

In studies with vitamin B12 deficient patients an abnormally high CD4+/CD8+ ratio and suppressed NK cell activity was reported, which could be restored with Vitamin B12 supplementation.[7]

Vitamin B12 has also shown to relieve the severity of aphthous ulcers and various autoimmune conditions such as atopic dermatitis and rheumatoid arthritis. B12 has been shown to have a balancing effect on the immune response by downregulating inflammatory processes mediated by inducible nitric oxide synthase (iNOS).

B12 DEFICIENCIES

There are many causes of B12 deficiency, a fairly common occurrence, one that is most likely far more common than many practitioners may realize. Vitamin B12 is found only in animal foods, in a wide range of meat and dairy products. Thus, vegetarians and vegans should be tested for B12 deficiency and should supplement vitamin B12 daily. Keep in mind that a serum deficiency may not show up for quite some time. Functional markers, such as the methylmalonic acid (MMA) test is a preferred method of determining functional B12 status in individuals.

Common Causes of Functional B12 Deficiency

a. Inadequate dietary intake of B12.

Vitamin B12 is readily available only in animal products, primarily dairy, meat, and eggs,[9] making vegetarians and vegans at highest risk for deficiency. Many vegan sources of B12, such as fermented spirulina or brewer's yeast, may include a high proportion of B12 analogues with no B12 activity in human physiology.[10,11] Also, as much as 33% of vitamin B12 may be lost due to heating, which is commonly used with animal-derived foods.[12]

b. Malabsorption of B12 from food.

This becomes more prevalent with aging, especially after the age of 50.[13]

B12 malabsorption may be caused by any of the following: [14,15]

b.1. Inadequate stomach acidity.
Hydrochloric acid (HCl) releases B12 from food proteins, which is a prerequisite for its binding to haptocorrin and then to intrinsic factor (IF), which carries it during GI absorption.[16] However, the metabolism of B12 found in nutritional supplements does not require optimal HCl levels.

Insufficient stomach acidity may be due to:

- *Suboptimal HCl production*, which may be the result of conditions such as atrophic gastritis or H. Pylori infection. Atrophy of the gastric mucosa is more prevalent in the elderly[17] and those infected with H. Pylori (H. Pylori has a 30%-40% incidence in the US and 70% in developing countries.[18]
- Pharmaceutical drugs that neutralize HCl or reduce HCl production.
- Nutritional supplements containing calcium carbonate.

b.2. Inadequate pancreatic protease production, which cleaves B12 from haptocorrin and transfers it to IF.

b.3. Impaired production of IF.
This may be due to congenital IF deficiency, atrophic gastritis or autoimmune conditions that cause antibodies to gastric parietal cells or IF (also referred to as pernicious anemia). Other potential causes include gastric surgeries (gastric bypass), gastric ulcers or cancer.

b.4. GI disorders:
ulcerative colitis, celiac disease and other gastro-pathologies due to GI inflammation/ infections; treatment with antibiotics or chemotherapy.[19]

b.5. Pharmaceutical drug side-effects.
Metformin interferes with B12 absorption.[20]

b.6. Poor B12 binding to transcobalamin
(a B12 transport protein in the blood), due to genetic polymorphisms.

c. Poor intracellular metabolism of B12.

Various genetic polymorphisms may result in the poor release of cobalamin from the lysosome or poor conversion of cobalamin to the active forms of B12. Glutathione-S transferase is involved in this step.

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CLINICAL CONDITIONS THAT MAY BENEFIT FROM B12 SUPPLEMENTATION

Supplementation with B12 may be beneficial for:

- **Nervous system related impairments:** brain and nerve function, conditions where the need for myelin repair is increased, such as during chemotherapy (for cancer, arthritis, lupus) or any condition involving neurological autoimmunity. Many of these conditions may involve poor cognition, dementia, dizziness, postural hypotension, tinnitus, neuropathy, or hyporeflexia.
- **Impaired healing of oral or GI mucosa:** aphthous sores, various inflammatory conditions of the gut, or during treatment with NSAIDs or chemotherapy. Gastric mucosal damage causes B12 malabsorption, thus creating a vicious cycle of worsening B12 status and the health of all mucosal membranes.[21]
- **Low white blood cells:** which impairs immunity.
- **Low platelet count:** which impairs healing.
- **Anemia, and/or macrocytic red blood cells:** (high mean corpuscular volume), impaired circulation and oxygen supply.
- **Elevated homocysteine:** associated with increased risk of birth defects, cardiovascular disease and Alzheimer's. It is also an indicator of systemically impaired capacity for methylation, which is involved in neurotransmitter synthesis and clearance, hormone methylation and genetic expression through DNA methylation. Some of these conditions may involve depression, anxiety, mania, poor appetite, loss of taste, and a higher risk of some cancers.
- **Conditions that involve impairment of energy production and low oxygen supply to cells**, such as generalized fatigue, anemia, heart failure, respiratory disease, and shortness of breath.
- **Poor sleep quality:** B12 may be involved in the normalization of circadian rhythm.[22]
- **Infertility or high risk of miscarriage or birth defects** (5X higher for spina bifida) and poor cognitive and motor development of the fetus or infant, due to mother's B12 deficiency during pregnancy and breastfeeding.

ADVANTAGES OF VITAMIN B12 FROM SUPPLEMENTS VS. FOOD

- **High doses (>1000 mcg) of B12** can be incorporated in supplements at levels approximately 100X higher than even those found in healthy diets at 10-20 mcg B12/day. A survey found an average intake of B12 of 5.3 mcg/day from food alone and 24.4 mcg/day from food + B12 fortified food + B12 supplements.[23]
- **Circumvent the deficiency of IF** and push B12 absorption through the GI border and oral mucosa by diffusion at rates of 1-1.2%. Absorption by IF may be saturated at around 1-2 mcg per meal.
- **Supplemental B12 forms are not protein-bound**, thus they bypass the need for HCl and proteolytic enzymes, which are typically required to separate B12 from food proteins.
- **B12 deficiency may take a long time to be corrected without high dose supplementation.** Body stores of B12 (mostly in the liver) have been estimated at 2500 mcg. Thus, a patient who is very depleted in B12 may need high doses to support a significant repletion (assuming that 10-12 mcg are absorbed from 1mg of B12). The amount of B12 derived from most multivitamins and fortified foods is often inadequate, as they contain much less than 1000 mcg of B12 per dose and are often in the cyanocobalamin form, which may only be 70-80% bioavailable for some individuals, but not bioavailable at all for those with of genetics-related difficulty cleaving the cyano ligand.

References supplied on request.

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