

An Overview on Metabolism and Consequences of Deficiency of Vitamin B₁₂

Nupur Chatterji¹, Renu Saraswat² 1&2

Associate Professor, Department Of Chemistry Meerut College, Meerut

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ABSTRACT

Vitamin B₁₂ is a water-soluble vitamin that is naturally present in some foods. vitamin B₁₂ is essential for DNA synthesis and for cellular energy production. This review aims to outline the metabolism of vitamin B₁₂, and to evaluate the causes and consequences of sub-clinical vitamin B₁₂ deficiency. Vitamin B₁₂ deficiency is common, mainly due to limited dietary intake of animal foods or malabsorption of the vitamin. Vegetarians are at risk of vitamin B₁₂ deficiency as are other groups with low intakes of animal foods or those with restrictive dietary patterns. Malabsorption of vitamin B₁₂ is most commonly seen in the elderly, secondary to gastric achlorhydria. The symptoms of sub-clinical deficiency are subtle and often not recognized. The long-term consequences of sub-clinical deficiency are not fully known but may include adverse effects on pregnancy outcomes, vascular, cognitive, bone and eye health. This vitamin contains the mineral cobalt hence the compounds with vitamin B₁₂ activity are collectively called "cobalamins". Methylcobalamin and 5-deoxyadenosylcobalamin are the metabolically active forms of vitamin B₁₂. Two others forms, hydroxycobalamin and cyanocobalamin, become biologically active after they are converted to methylcobalamin or 5-deoxyadenosylcobalamin Vitamin B₁₂ is essential for DNA synthesis and for cellular energy production.

This review aims to outline the metabolism of vitamin B₁₂, and to evaluate the causes and consequences of sub-clinical vitamin B₁₂ deficiency. Vitamin B₁₂ deficiency is common, mainly due to limited dietary intake of animal foods or malabsorption of the vitamin. Vegetarians are at risk of vitamin B₁₂ deficiency as are other groups with low intakes of animal foods or those with restrictive dietary patterns. Malabsorption of vitamin B₁₂ is most commonly seen in the elderly, secondary to gastric achlorhydria. The symptoms of sub-clinical deficiency are subtle and often not

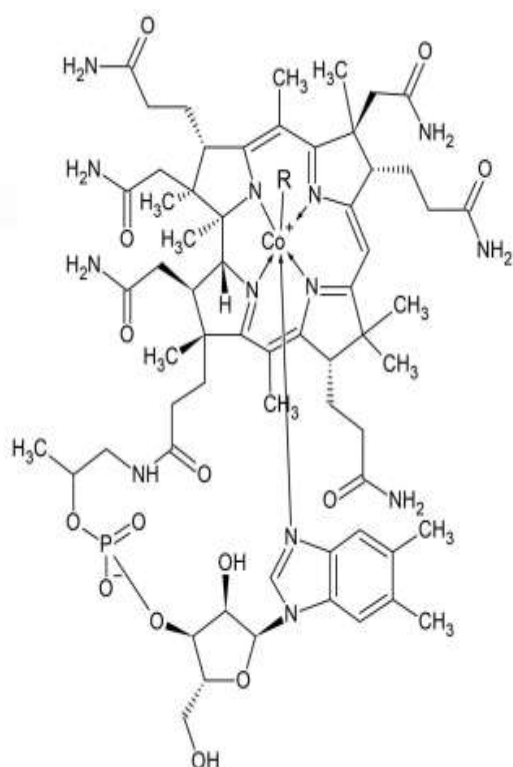
recognized. The long-term consequences of sub-clinical deficiency are not fully known but may include adverse effects on pregnancy outcomes, vascular, cognitive, bone and eye health.

Keywords: vitamin B₁₂, Cobalamin physiology, nutrition, adults, chronic,

Vitamin B₁₂ and its mechanism :

Vitamin B₁₂ is a water-soluble vitamin which is present naturally in some foods and available as a dietary supplement and prescription medications. vitamin B₁₂ contains the mineral cobalt, compounds with vitamin B₁₂ activity are collectively called "cobalamins". Methylcobalamin and 5-deoxyadenosylcobalamin are the metabolically active forms of vitamin B₁₂. - deoxyadenosylcobalamin However, two others forms, hydroxycobalamin and cyanocobalamin, become biologically active after they are converted to methylcobalamin. Vitamin B₁₂ is also known as Cobalamin and comprises of a number of forms including cyano, methyl, deoxyadenosyl – cobalamin and hydroxy-cobalamin.

The cyano form is found in supplements and found in very small amounts in food. The cobalamin can be converted to methyl and 5-deoxyadenosyl forms of cobalamin and are required as co factors for the methionine synthase and L-methyl-mathonyl-CoA mutase.



R = 5'- deoxyadenosyl, OH, CN, CH₃
(Chemical Structure Of Vitamin B₁₂)

Vitamin B₁₂ or cobalamin is obtained principally from food of animal origin. Cobalamin becomes bioavailable through a series of steps pertaining to its release from dietary protein, intrinsic factor-mediated absorption, haptocorrin which is transcobalamin-mediated transport, cellular uptake, and two enzymatic conversions into cofactor forms: methylcobalamin and adenosylcobalamin. Vitamin B₁₂ deficiency can lead to a multitude of illnesses, presenting different perspective of human health conditions. Increased patient awareness and physician vigilance often accounts for its early presentation, and testing sometimes occurs during a phase of Vitamin B₁₂ insufficiency before the main onset of the disease. Vitamin B₁₂ is needed to form red blood cells and DNA. It is also a key player in the function and development of brain and nerve cells. Vitamin B₁₂, or cobalamin, is naturally found in animal foods. It can also be added to foods or supplements. Vitamin B₁₂ is needed to form red blood cells and DNA. It is also a key player in the function and development of brain and nerve cells. Vitamin B₁₂ binds to the protein in the foods we eat. In the stomach, hydrochloric acid and enzymes unbind vitamin B₁₂ into its free form. From there, vitamin B₁₂ combines with a protein called intrinsic factor

so that it can be absorbed further down in the small intestines.

Methionine synthase is essential for the synthesis of purines and pyrimidines. The reaction depends on methyl cobalamin as a co-factor and is also dependent on folate, in which the methyl group of methyltetrahydrofolate is transferred to homocysteine to form methionine and tetrahydrofolate. A deficiency of vitamin B₁₂ and the interruption of this reaction leads to the development of megaloblastic anaemia. Folate deficiency independent of vitamin B₁₂ also causes megaloblastic anaemia. Methylmalonyl CoA mutase converts methylmalonyl CoA to succinyl CoA, with 5-deoxy adenosyl cobalamin required as a cofactor. It is a defect in this reaction, and the subsequent accumulation of methylmalonyl CoA that is thought to be responsible for the neurological effects in vitamin B₁₂ deficiency.

Serum vitamin B₁₂ is bound to proteins known as transcobalamins (TC). The majority of the vitamin, approximately 80%, is transported on the inactive TCI (also called haptocorrin). The active transport protein for vitamin B₁₂ is transcobalamin II (TCII), which carries about 20% of the vitamin in the circulation. Holo-transcobalamin (holo-TC) is TCII with attached cobalamin, which delivers vitamin B₁₂ to cells. A low serum vitamin B₁₂ concentration can be associated with a deficiency of TCI, while TCII levels and so vitamin B₁₂ status remain adequate.

Drug Interactions and Vitamin B₁₂:

Some medications are thought to interfere with the absorption or metabolism of this vitamin. These mainly include the proton pump inhibitor (PPI) medications, metformin, nitrous oxide anaesthesia, certain anti-inflammatory drugs like Colchicine used to decrease the build up of uric acid crystals and non-steroidal agent used in the treatment of Asthma and also some epileptic medications. The PPI medications are commonly used in the elderly for the treatment of gastro-oesophageal reflux disease whereby they reduce the amount of stomach acid pepsin made by glands in the lining of human stomach leading to a decrease in the absorption of protein-bound vitamin B₁₂. PPI usage and vitamin B₁₂ status is inconsistent and needs to be investigated further. The monitoring of vitamin B₁₂ concentrations is recommended for patients undergoing prolonged PPI treatment, in recognition with the bioavailability of food-bound vitamin B₁₂. Metformin is a biguanide used for the treatment of non-insulin dependent diabetes and some patients taking this medication develop

megaloblastic anaemia. This may relate to intestinal mobility changes or bacterial overgrowth.

Importance of Vitamin B₁₂ in human health:

Vitamin B₁₂ is required for the development, myelination, and function of the central nervous system; healthy red blood cell formation; and DNA synthesis. The process starts in the mouth when food is mixed with saliva. The freed vitamin B₁₂ then binds with haptocorrin, a cobalamin-binding protein in the saliva. More vitamin B₁₂ is released from its food matrix by the activity of hydrochloric acid and gastric protease in the stomach, where it then binds to haptocorrin. In the duodenum, digestive enzymes free the vitamin B₁₂ from haptocorrin, and this freed vitamin B₁₂ combines with intrinsic factor, a transport and delivery binding protein secreted by the stomach's parietal cells. The resulting complex is absorbed in the distal ileum by receptor-mediated endocytosis. If vitamin B₁₂ is added to fortified foods and dietary supplements, it is already in free form and therefore does not require the separation. Traditionally vitamin B₁₂ status is assessed by its concentrations in serum, however, concerns have been raised about the use of serum vitamin B₁₂ measurements alone. Although low serum vitamin B₁₂ concentrations are a sensitive indicator of vitamin B₁₂ deficiency and high vitamin B₁₂ concentrations generally indicate sufficiency, the interpretation of the intermediate range of vitamin B₁₂ concentrations is unclear. Factors causing vitamin B₁₂ deficiency include the avoidance of animal products since it is only found naturally in animal products. Studies have shown that vegetarians have low vitamin B blood levels. Persons who follow a vegetarian or vegan diet should include B₁₂-fortified foods or a B₁₂ supplement in their diets and is specially necessary for pregnant women adequate vitamin B₁₂ for the neurologic development of the foetus. Another important factor is **Pernicious Anemia**, which is an autoimmune disease that destroys the gut cells causing the lack of the intrinsic factor leading to the malabsorption of this vitamin. There are certain medications that cause decrease in levels of stomach acid. This condition is most prevalent in elderly people and in those who regularly taking medications to suppress stomach acid. This prevents the vitamin from releasing into its free usable form in the stomach. Intestinal surgeries and digestive disorders cause malabsorption of the vitamin.

The signs of deficiency include Megaloblastic or Pernicious anemia—a condition of larger than normal sized red blood cells and a smaller than normal amount due to poor absorption

of vitamin B₁₂, fatigue or weakness, nerve damage leading to numbness and tingling in the hands and legs, confusion and memory loss, depression, dementia and seizures.

Food Sources and Bioavailability Of Vitamin B₁₂:

Vitamin B₁₂ is found in food of animal origin like beef and lamb, chicken, eggs and in low amounts in dairy products. Certain bacteria in the gastrointestinal tract of animals synthesise vitamin B₁₂ which is absorbed by the host animal. Vitamin B₁₂ is concentrated in animal tissues, hence found abundantly in foods of animal origin. Japanese seaweed (nori) and mushrooms contain vitamin B₁₂ but are inactive in humans. However this Japanese seaweed (nori) prevents vitamin B₁₂ deficiency in vegans. Some foods which are contaminated or fermented by bacteria e.g., tempeh and Thai fish sauce which is made by the fermentation by bacteria is reported to contain vitamin B₁₂ but its absorbance in the body is low.

The bioavailability of vitamin B₁₂ in humans is dependent on an individual's gastrointestinal absorption capacity. The absorption of vitamin B₁₂ is complex and there are adverse changes with age and the gastrointestinal capacity absorption of an individual. Little data on the bioavailability of dietary vitamin B₁₂ in humans is available.

Vitamin B₁₂ Requirement :

The recommended dietary intake (RDI) of an individual is set to prevent megaloblastic anemia and maintain the vitamin concentration. The assumptions are that 50 percent of dietary vitamin B₁₂ are absorbed. The estimated average requirement and recommended dietary intake values are not variable once adulthood is reached. The elderly adults with atrophic gastritis however require higher intakes of vitamin B₁₂ rich foods, vitamin B₁₂ enriched foods or supplements. Adults over 51 years of age consume most of this vitamin from fortified foods or from supplements suggesting that the malabsorption is due to gastritis that occurs with age. The deficiency is slow as the storage of this vitamin lasts several years. The combination of malabsorption and inadequate dietary intake hastens the deficiency of Vitamin B₁₂.

Vitamin B₁₂ Deficiency :

Malabsorption of the Vitamin B₁₂ usually leads to the deficiency as also the dietary inadequacy commonly seen in elderly, vegans and the ovo-lacto vegetarians with poor diets. Causes can also be due to atrophic gastritis, the uptake of

Vitamin B₁₂ in the ileum due to disease, bacterial overgrowth and drug interactions and some lesser known genetic defects. Vegans who consume no food of animal origin and the ovo-lacto vegetarians with only small intake of dairy foods require supplements of Vitamin B₁₂. Pregnant and lactating women who are following vegetarian or vegan diets are at high risk of Vitamin B₁₂ deficiency due to increased metabolic demand.

The elderly due to reduced intake as a result of illness, due to lack of physical activity and depression are at high risk of Vitamin B₁₂ deficiency. Protein bound malabsorption is the most common cause of clinical vitamin B₁₂ deficiency in the elderly and is associated with atrophic gastritis. The inflammation of the gastric mucosa or gastritis increases with age resulting in reduction or complete loss of the acid that is required to cleave this vitamin from protein however the synthetic vitamin B₁₂ which is not protein bound is available for absorption. Pernicious anemia is the last stage of auto-immune gastritis resulting in the loss of IF that causes the deficiency of the vitamin and if left untreated results in megaloblastic anemia and severe neurological complications.

Reduced ileal uptake of vitamin B₁₂ can be caused in patients with bacterial overgrowth or parasitic infection. Crohn's disease or chronic bowel inflammatory conditions also lead to the malabsorption of vitamin B₁₂. Folic acid or vitamin B₉ helps in masking vitamin B₁₂ by folate fortification whereby vitamins and minerals are added to foods to allow DNA, prevent megaloblastic anemia and potentially mask vitamin B₁₂ deficiency thus allowing homocysteine and methyl malonic acid (MMA) concentrations to rise and progression in neurological damage is observed.

CONCLUSION :

Vitamin B₁₂ is an important vitamin for child bearing age women and elderly people. The maintenance of adequate vitamin B₁₂ status is needed for optimal health throughout life. Renewed interest in vitamin B₁₂ is observed since the reporting of associations between homocysteine and chronic disease. The effects of sub-clinical deficiency are not fully known and many aspects of vitamin B₁₂ absorption, bioavailability and metabolism are yet to be determined. The identification of vitamin B₁₂ status will help elucidate the relationships between vitamin B₁₂ and chronic disease, and help to identify the ones who are at risk of clinical or subclinical deficiency.

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