

Vitamin B12 - Do You Know Everything?

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ABSTRACT

BACKGROUND

The term Vitamin B12 is used as a generic descriptor for the cobalamins; cobalt containing compound possessing the corrin ring having the biological activity of vitamin. The active coenzyme forms of vitamin B12 are methylcobalamin and deoxyadenosylcobalamin. Dietary sources of vitamin B12 are of animal origin and include meat, eggs, milk, dairy products, fish and poultry. Vitamin B12 is absent in plant foods and humans obtain small amount of vitamin B12 from their intestinal flora. Vitamin B12 plays a crucial role in DNA synthesis, nucleoprotein, erythropoiesis, myelin synthesis, normal growth and cell reproduction and one carbon metabolism. Vitamin B12 deficiency may arise due to decreased dietary intake. Vitamin B12 helps in isomerization of methylmalonyl-CoA to succinyl-CoA by methylmalonyl-CoA mutase and also helps in conversion of homocysteine to methionine by methionine synthase. Dietary deficiency is seen in strict vegetarians, since vitamin found only in foods of animal origin or in microorganism. Deficiency of Vitamin B12 causes pernicious anaemia, megaloblastic anaemia, methylmalonic aciduria, Neuropathy and folate trap. The present review concludes that vitamin B12 deficiency affects a person's mental and physical health and it can cause severe, irreversible neurologic damage, disorientation, nerve damage, insomnia and many other diseases as mentioned in article. Adults should take 2.4 mcg of vitamin B12, deficiency is mainly seen commonly in Vegetarian they have to add vegan sources of vitamin B12 to their diet which include fortified cereals, bread, nutritional yeast and plant milks. Early identification of vitamin B12 status should be preliminary screening step to reverse the damage caused by vitamin B12 deficiency which will helps in prevention of diseases.

KEY WORDS

Vitamin B12, Cardiovascular Diseases, Dementia, Metformin, Pregnancy, Diabetes Mellitus, Neuropathy, Osteoporosis, Ageing, Neural Tube Defects, Depression.

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BACKGROUND

A Brief History of B12

The inceptive discovery of Vitamin B12 arose from the need to find the cause and cure for pernicious anaemia, first reported in 1849 by Thomas Addison.¹ Treatment was discovered in 1926 when the consumption of lightly cooked liver led to the correction of anaemia and reduced the death rate, even though at that time proteins and iron in the liver were considered to be the curative factors.² In late 1940s two groups announced the discovery of a new vitamin, which induced and sustained pernicious remission of anaemia.³ In 1956 Dorothy Hodgkin an X-ray crystallographer, discovered the structure of vitamin B12 and in 1973 Robert Woodward synthesized vitamin B12.^{4,5} William Castle summed up his work by showing the underlying cause of pernicious anaemia, which was due to lack of gastric intrinsic factor.⁶ B12 depletion characterized subclinical cobalamin deficiency has emerged as a major public health issue. Over the past 20 – 30 years, the prevalence of subclinical cobalamin deficiency has created interest in testing of B12 status.⁷⁻⁹ The highest prevalence of irregular B12 status biomarkers is observed in people and populations with a low intake of food from animal sources and the elderly.

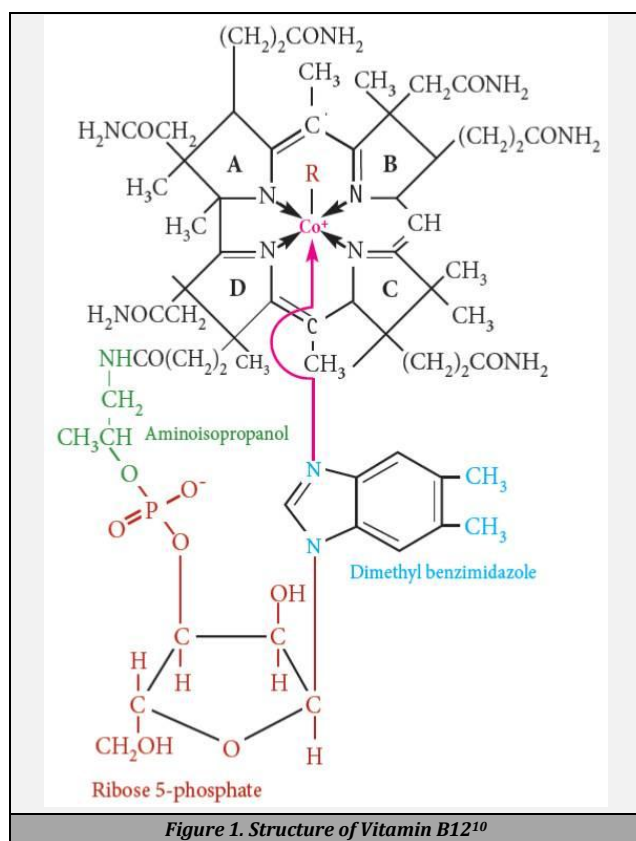


Figure 1. Structure of Vitamin B12¹⁰

Vitamin B12 plays a key role in the synthesis of DNA,¹¹ normal erythropoiesis, nucleoprotein, and myelin synthesis, cell replication, normal growth¹² and one-carbon metabolism.¹³ Vitamin B12 exist in number of forms: cyano, methyl, deoxyadenosyl, aqua, nitro and hydroxy cobalamin. Vitamin B12 is synthesized in gastrointestinal tract by bacteria *Lactobacillus reuteri*, in animals and found in foods of animal origin,^{9,14,15} therefore vegetarians are at increased risk for B12 deficiency. Liver, meat, fish, eggs, milk, curd and cheese are good sources of vitamin B12.^{10,16}

Food Sources and Bioavailability of Vitamin B12

Vitamin B12 is ultimately the product of microbial synthesis, because plants do not use vitamin, vitamin B12 is abundant in animal tissues and thus vitamin B12 can only be found in animal-derived foods, the main dietary sources are meat and meat products, dairy products, fish and shellfish and fortified ready to eat cereals.¹⁷

Animal Derived Food Rich in Vitamin B12 ($\mu\text{g} / 100 \text{ g}$)	
Liver	26 - 58 $\mu\text{g} / 100 \text{ g}$
Beef and lamb	1 - 3 $\mu\text{g} / 100 \text{ g}$
Chicken	Trace - 1 $\mu\text{g} / 100 \text{ g}$
Eggs	1 - 2.5 $\mu\text{g} / 100 \text{ g}$
Dairy Products	0.3 - 2.4 $\mu\text{g} / 100 \text{ g}$

Table 1. Vitamin B12 Derived Food

There are no bioactive forms of vitamin B12 from plant sources, naturally. Some plant foods contain added vitamin B12, while some contain vitamin B12 analogs, e.g. seaweed and mushrooms.¹⁸

Age Group	RDA (mcg)
Adults	2.0
Children	1.4
Infants	0.5
Pregnant and Lactating Women	2.6

Table 2. Recommended Dietary Allowance in Different Age Groups¹⁹

Absorption of Vitamin B12

Cobalamin absorption occurs through 2 mechanisms, one occurs passively through buccal, duodenal and ileal mucosa, and the other occurs through ileum by physiological mechanism and seems to be successful for small oral doses of cobalamin, mediated by gastric intrinsic factor. Two types of Vitamin B12 binders are found in human gastric juice, one with slow and one with rapid mobility in zone electrophoresis. The rapid component is R protein and slow component is IF. R proteins are mainly found in plasma, amniotic fluid, saliva, ascitic fluid, milk and granulocytes. Dietary cobalamin released by enzymes in the stomach, duodenum, and jejunum from protein complexes²⁰ and binds to a glycoprotein-R protein secreted by salivary gland belonging to the family of cobalamin-binding protein known as haptocorrins.^{11,20}

The R protein is hydroxylated in the duodenum in the presence of alkaline medium and pancreatic proteases to release vitamin B12, which later binds a 50kDa molecular weight glycoprotein with intrinsic factor.^{9,11} It (chromosome gene 11q13) is produced in fundus and stomach parietal gastric cells. Vitamin B12-IF passes to the ileum, where it attaches to the enterocyte microvillus membrane at a specific receptor (Cubilin). Cubilin is also present in the yolk sac and epithelium of the renal tubules. Cubilin appears to be trafficking via amnion less, an endocytic receptor protein that guides cubilin sub-localization and endocytosis with its ligand vitamin B12-IF complex entering the ileal cell, where it is destroyed. Vitamin B12 enters the circulation about 2 - 3 hours and appears in portal blood attached to transcobalamin 2.^{14,20}

Transport

Transcobalamin 1 (TC-1) and transcobalamin 2 (TC-2) transports vitamin B12. TC-1 is derived from specific granules in neutrophils, also known as haptocorrin and encoded by TCN 1 gene. TC-1 does not facilitate the entry of cobalamin into tissues. The removal of TC-1 from plasma includes the

glycoprotein receptors in liver cells, it also plays role in transport of cobalamin analogues to the liver for excretion in bile and TC-2, gene is present on chromosome 22q11q13.1 with a molecular weight of 43kDa¹ synthesized by liver, macrophage, ileum and vascular endothelium.²¹ 80 % of vitamin is transported in circulation as inactive TC-1 and 20 % vitamin is transported in circulation in active form called

Transcobalamin II (TC II). The TC II complex also alluded to as holo TC II is taken actively by the liver, bone marrow, and other vital cells.^{11,14}

Liver can store about 4 - 5 mg, an amount sufficient to meet the body requirements of B12 for 4 - 5 years, and the clinical features of deficiency become apparent by 5 years.

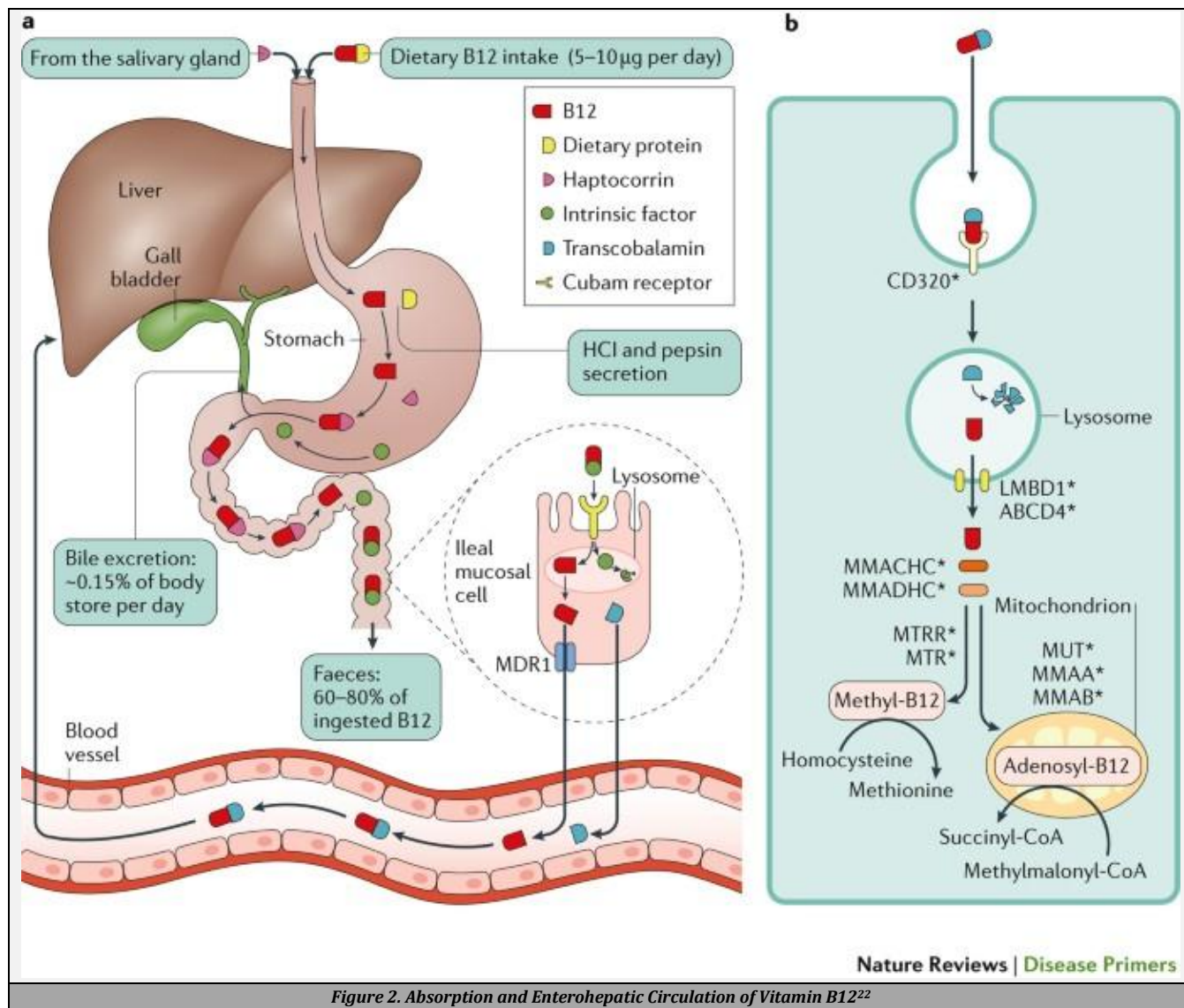


Figure 2. Absorption and Enterohepatic Circulation of Vitamin B12²²

Biochemical Role of Vitamin B12

Vitamin B12 acts as a methyl donor to membrane phospholipids, neurotransmitters, amines, DNA and RNA, and myelin-based proteins.^{10,23} The deficiency of vitamin B12 causes myelin damage by increasing myelinotoxic growth factors and cytokines. It also helps to transform methyl tetrahydrofolate, the circulating form of folate to tetrahydrofolate, the active form of folate that helps in the synthesis of nucleotides and DNA.^{20,24}

Biochemical Assessment of Vitamin B12 Status

Homocysteine and methylmalonic acid known as markers of Vitamin B12, assessment of these biomarkers demonstrated the presence of a subclinical disorder, whose implications are still being elucidated. The main cobalamin metabolic predictor is methylmalonic acid, and homocysteine is increased in

vitamin B12 deficiency along with Vitamin B6 and folate deficiencies. Physiological or environmental factors may confound certain biomarkers, homocysteine levels are elevated in renal dysfunction and MMA levels are elevated in renal insufficiency, typically in older persons.^{25,26}

VITAMIN B12 DEFICIENCY

Causes

- Pernicious anaemia.
- Gastric disease.
- Chronic atrophic gastritis.
- Pancreatic disease or pancreatectomy.
- Ileal resection.

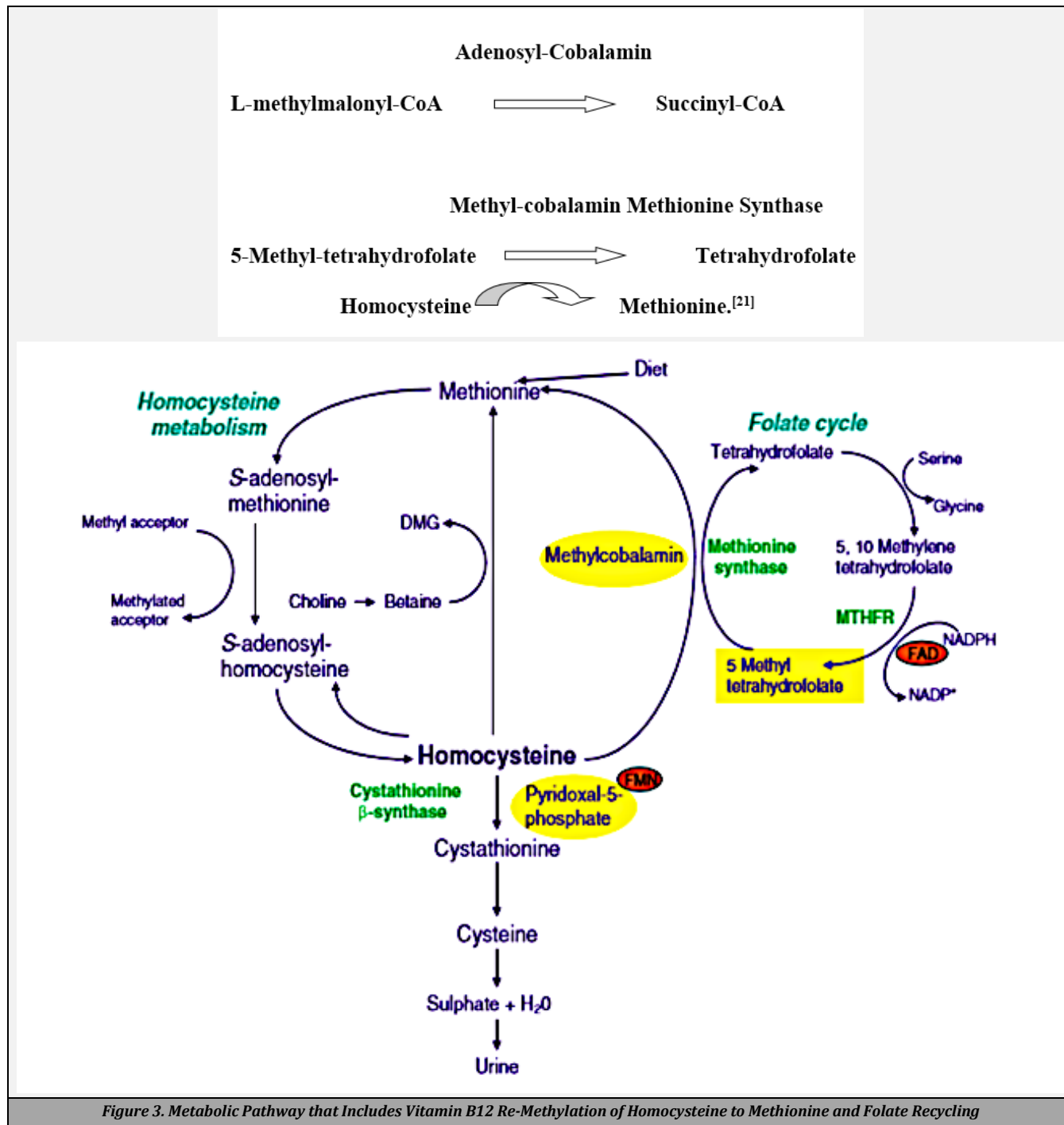


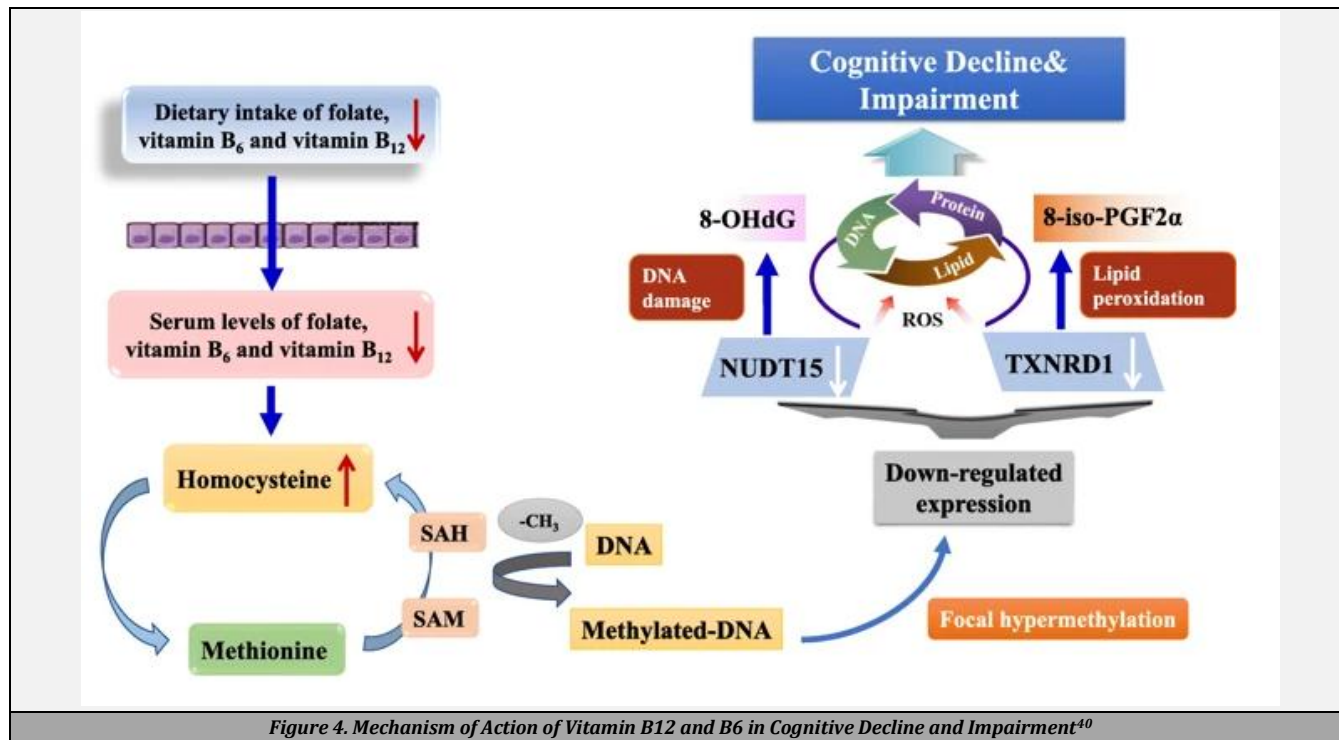
Figure 3. Metabolic Pathway that Includes Vitamin B12 Re-Methylation of Homocysteine to Methionine and Folate Recycling

- Bacterial overgrowth.
- Dietary factors like: General malnutrition, vegetarian or vegan diet, and chronic alcoholism.
- Inherited disorders.
- Miscellaneous: Nitrous oxide anaesthesia and HIV infection.²⁷

Vitamin B12 and Neural Tube Defects

Neural tube defects (NTDs) are central nervous system congenital abnormalities (CAs). Alongside congenital heart abnormalities (CHAs) and urinary system disorders, they are the most common birth defects. The neurulation is a significant phase in brain development, involving the creation

of the first well-defined neural tunnel. The neural tube forms in the third week of gestation (20 - 28 days).^{28,29} Twenty percent of the foetuses die in utero (therapeutic abortions or stillbirths). Many people die in the first week of existence, with only 10 percent of people dying in the first year. Many living after this time would usually have poor healthy lives and frequent interventions in medicine, surgery, and physiotherapy.³⁰ Vitamin B12-dependent synthase of methionine is a checkpoint reaction in which folate molecules are introduced into the cells, since folate exists primarily as circulating methyl folate. Folate cofactors will then assist in the transition of other one-carbon groups to nucleotide molecules intended for DNA synthesis or other molecular products after



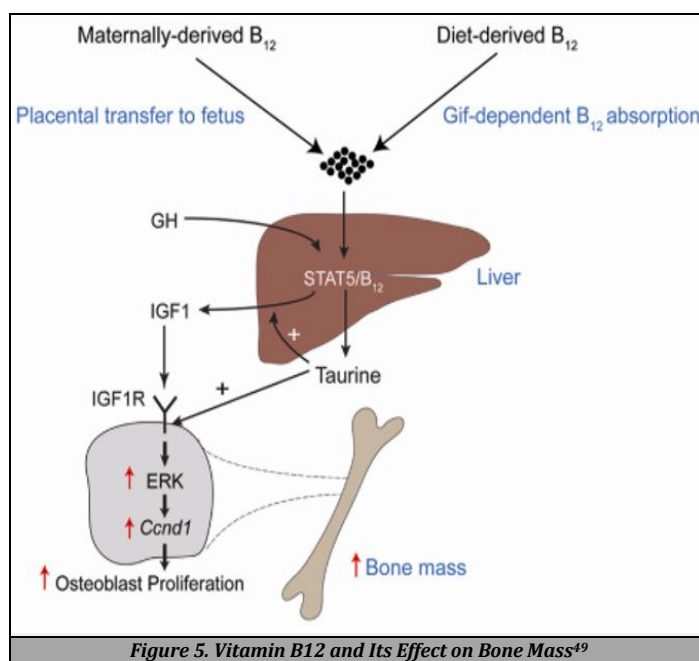
releasing the methyl group into homocysteine through the methionine synthase reaction within the cell.³¹ Impaired methionine synthase contribute to the cellular accumulation of the methyl folate substratum, which has no alternative metabolic outlet. The cell is thus functionally deficient in folates, and the synthesis of folate-dependent DNA is impaired, leading to megaloblastic anaemia. The cell is thus functionally deficient in folates, and the synthesis of folate-dependent DNA is impaired, leading to the classic megaloblastic anaemia that characterizes folate and B12 deficiency. It is significant to mention that folic acid bypass vitamin B12 dependent methionine synthase to enter the cellular folate pool and resume folate functions in relation to DNA synthesis, but it cannot correspond to supplying methyl group for the above-mentioned methylation functions. Lower levels of serum folate and vitamin B12 are linked with an increased incidence of developmental anomalies, such as neural tube defect.³² Folate and Vitamin B12 were considered important in the occurrence and recurrence of NTD and essential factors for range of metabolic pathways in cells involving the transfer of one carbon units and methylation reactions.³³ Vitamin deficiency and elevated levels of homocysteine plays a possible role in early pregnancy.

Vitamin B12 and Cardiovascular Diseases

Coronary artery disease (CAD) was caused primarily by endothelial dysfunctional atherosclerosis^{34,35} and is significantly harmful to the stable condition of people in both developed and developing countries. Folic acid and vitamin B12 are instrumental in controlling the metabolic process of Hcy (Homocysteine). Conversely, HHcy (Hyperhomocysteinaemia) may result in a shortage of folic acid and vitamin B12. Deficiency of vitamin B12 and HHcy are related to risk factors for cardiovascular disease in patients with CAD.

Vitamin B12 and Cognitive Decline

An elevated level of Hcy as a neurotoxin was also shown to affect the redox signalling pathways in neurons through the generation of reactive oxygen species (ROS) and a decrease in endogenous antioxidants.³⁶ If patterns of DNA methylation in redox-related genes can modulate cognitive impairment caused by vitamin B12 deficiency and hyperhomocysteinaemia is therefore of interest, low levels of vitamin B12 can cause serious cognitive dysfunction.³⁷ Increased homocysteine levels are related to cardiovascular disease, stroke and Alzheimer’s disease and a low level of vitamin B12 and increased concentration of homocysteine causes silent injury to brain due to oxidative stress, which results in calcium inflow and apoptosis.^{38,39}



Vitamin B12 and Osteoporosis

Low vitamin B12 levels increase risk of decreased mineral density and fractures in the bones. Low vitamin B12 levels in conjunction with a deficiency in folate and vitamin B6 are closely related to the Hcy metabolism. Contrasting findings have been shown in the combination with hyperhomocysteinaemia with lower bone mineral density (BMD) and risk of osteoporotic fractures.^{41,42} Hyperhomocysteinaemia is associated with increased bone remodelling markers and thus an increased risk of fracture. Thus, hyperhomocysteinaemia caused by vitamin B12 deficiency as well as folate can be considered as potential risk factors for osteoporosis due to these micronutrient deficiencies. Homocysteine reduces bone blood flow, increases metalloproteinase matrix,⁴³ and interferes with cross-linking of collagen.^{44,45} Collagen cross-linking provides strength and stability to the bone matrix collagen network. Cathepsin-K (CathK) is expressed mainly in osteoclasts and is necessary for bone resorption.⁴⁶ High CathK levels are seen in osteoporotic women.^{47,48}

Vitamin B12 and Ageing

At present, vitamin B12 deficiency is considered to be normal and its prevalence increases with age. Depending on the diagnostic criteria used,⁵⁰ it is estimated to affect 5 - 40 percent of the age group. Vitamin B12 was linked to age related macular degeneration growth and frailty risk, both leading causes of elderly disability. AMD is the leading cause of loss in vision in older people. Host factors include high age, hypertension, family history, obesity, sunlight sensitivity, smoking and hypercholesterolemia. Frailty is characterized by muscle waste, depleted strength, often with weight loss with or without reduced food intake.⁵¹

Vitamin B12 and Diabetes Mellitus

Type 2 diabetes mellitus is a multifactorial disease linked to energy metabolism mainly carbohydrates and fats and has macro vascular and micro vascular complications.⁵² RBC of vitamin B12 deficient patients contains dwindled glutathione or enzymes, which were essential for degradation of glucose to ribose and further leads to elevation of coenzyme A in the liver.⁵³ The increased fatty acid metabolism leads to increased intra-mitochondrial acetyl Coenzyme A; which inhibits pyruvate dehydrogenase resulting in inhibition of phosphofructokinase the key enzyme in glycolysis. Hyperglycaemia develops advanced glycation end products (AGE). AGE contributes to pathogenesis of demyelination by macrophages. Schwann cell abnormalities include both reactive changes (accumulation of lipid droplets, glycogen and Pi granules of Reich) and degenerative changes (effacement of cristae, mitochondrial enlargement, degeneration of axonal and adaxonal cytosol and organelles) leading initially to demyelination with development of neuropathy, axonal degeneration and inducing loss of nerve fibre.⁵⁴ Vitamin B12 is important to monitor in patients with type 2 diabetes mellitus as the declining vitamin B12 levels hampers the maintenance of enzyme system essential for utilization of carbohydrates and fats.⁵⁵

Vitamin B12 and Metformin

Metformin is used for the treatment of diabetes, it affects the calcium dependent ileal cell membrane receptors needed for uptake of B12 intrinsic factor and reduces serum vitamin B12 absorption up to 30 %.⁵⁶ Metformin-induced vitamin B12 deficiency in T2DM patients, which involves alteration in small intestine motility, bacterial flora, competitive inhibition and inactivation of vitamin B12 absorption, alteration in intrinsic factors levels, interactions with endocytic cubilin receptors or the effect of calcium on cell membrane, was suggested to play a role as a biguanide group that is protonated and prevents calcium dependent absorption which was reserved with calcium supplementation.⁵⁷

Depression and Vitamin B12

Vitamin B12 plays a significant role in development of the neurology and DNA synthesis. Its deficiency has to do with hematology, neurology and psychological symptoms, the latter involving irritability, changes in personality, depression, dementia, and rarely psychosis. The linkages between deficiency of vitamin and depression have been established in recent literature. High serum B12 levels are blessed with improved treatment response, high levels of homocysteine typical of folate / B12 deficiency, and poor response to antidepressant therapy are associated with those with depression.⁵⁸ Hyperhomocysteinaemia can have direct effects on depression-implied neurotransmitters.⁵⁹

CONCLUSIONS

The present review concludes that vitamin B12 deficiency affects a person's physical and mental health and it can cause severe, irreversible neurologic damage, disorientation, nerve damage, insomnia and many other diseases as mentioned in the article. Adults should take adequate amount of vitamin B12 and deficiency is mainly seen commonly in vegetarians and they have to add vegetarian and vegan sources of Vitamin B12 to their diet. As vitamin B12 plays a major role in nervous system; its deficiency may cause tingling in the hands or feet; sometimes peripheral nerve damage leads to movement problems; it also causes megaloblastic anaemia, shortness of breath, fast heart rate, cognitive impairment, irritability or depression, and pernicious anaemia. So, people who are having vitamin deficiency should take B12 supplements in the form of oral or sublingual tablets, or injections, add fish and red meat in diet, and add variety of fruits and vegetables in diet. So, early identification of vitamin B12 status should be preliminary screening step to mitigate the damage caused by vitamin B12 deficiency which will help in prevention of diseases and life threatening complications.

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Disclosure forms provided by the authors are available with the full text of this article at jemds.com.

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