IJPSR (2012), Vol. 3, Issue 10 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 16 June, 2012; received in revised form 14 September, 2012; accepted 25 September, 2012

CAUSES AND CONDITIONS ASSOCIATED WITH REDUCED LEVEL OF VITAMIN B_{12}: A REVIEW

Chandrakant Belwal

Sterling Biotech Research Center, Vadodara, Gujarat, India

Keywords:
Vitamin B_{12},
Cyanocobalamin,
Pernicious anaemia,
Neurological disorder,
Animal products

Correspondence to Author:

Chandrakant Belwal

Sr. Manager R&D, Sterling Biotech Research Center, Vadodara, Gujarat, India

E-mail: belwalck@yahoo.co.in

ABSTRACT

Vitamin B_{12} plays an important role in building of genetic material, in development of normal red blood cells and in maintenance of nervous system. Major deficiency symptoms of Vitamin B_{12} include anemia and neurological disorders. The daily recommended intake of vitamin B_{12} for an adult is 1.5µg a day. Eating a diet containing required amount of vitamin B_{12} is the best way to treat the conditions associated with its low level. Vitamin B_{12} found only in animal based foods such as meats, liver, kidney, fish, eggs, milk and milk products, oysters and shellfish. Hence, vegetarians are more likely to have low level of Vitamin B_{12}.

INTRODUCTION: Vitamins were discovered in the early part of the twentieth century, In 1912, Polish scientist Cashmir Funk named the special nutritional parts of food as a "vitamine" after "vita" meaning life and "amine" from compounds found in the thiamine he isolated from rice husks. Vitamine was later shortened to vitamin. Funk isolated vitamin B_1 (thiamine) from rice [1].

There are two types of vitamins, fat-soluble (A, D, E, and K) and water-soluble (B and C). Water-soluble vitamins dissolve easily in water and, in general, are readily excreted from the body, to the degree that urinary output is a strong predictor of vitamin consumption [2]. Because they are not readily stored, consistent daily intake is important. Many types of water-soluble vitamins are synthesized by bacteria [3]. Fat-soluble vitamins are absorbed through the intestinal tract with the help of lipids.

Eight of the water-soluble vitamins are known as the B-complex group: thiamin (vitamin B_1), riboflavin (vitamin B_2), niacin, vitamin B_6, folate, vitamin B_{12}, biotin and pantothenic acid. These vitamins are widely distributed in foods. Their influence is felt in many parts of the body. They function as coenzymes that help the body obtain energy from food. They also are important for normal appetite, good vision, healthy skin, healthy nervous system and red blood cell formation. Beriberi, pellagra and pernicious anemia are three well-known B-vitamin deficiencies.

Vitamin B_{12} aids in building of genetic material, aids in development of normal red blood cells and aids in maintenance of nervous system. Major deficiency symptoms of Vitamin B_{12} include anemia and neurological disorders. Vitamin B_{12} found only in animal based foods such as meats, liver, kidney, fish, eggs, milk and milk products, oysters and shellfish. Hence vegetarians are more likely to have low level of Vitamin B_{12}.

QUICK RESPONSE CODE

IJPSR: ICV- 4.57

Website: www.ijpsr.com

Vitamin B_{12} works with the B vitamin folate to make DNA, our body's genetic material. B_{12} is needed to protect nerve cells from damage. It also helps keep blood levels of the amino acid homocysteine low. This may help to decrease heart disease risk in some people [4].

Vitamin B_{12} is essential for two types of enzymatic reactions in humans; methyl group transfer and transfer of a hydrogen atom from one carbon to an adjacent carbon atom.

Vitamin B_{12} participates in three essential enzymatic reactions in the human body. Methionine synthetase requires methylcobalamin for conversion of homocysteine to methionine. Methylmalonyl CoA mutase requires 5'-deoxyadenosylcobalamin to convert L-methylmalonyl CoA to succinyl CoA. Leucine aminomutase requires 5'-deoxyadenosylcobalamin to isomerize L-leucine and beta-leucine

Structure and chemical composition of Vitamin B_{12}: Vitamin B_{12} is the largest and most complex of all the vitamins. The name vitamin B_{12} is generic for a specific group of cobalt-containing corrinoids with biological activity in humans. Interestingly it is the only known metabolite to contain cobalt, which gives this water-soluble vitamin its red colour. This group of corrinoids is also known as cobalamins.

The main cobalamins in humans and animals are hydroxocobalamin, adenosylcobalamin and methyl-cobalamin, the last two being the active coenzyme forms. Cyanocobalamin is a form of vitamin B_{12} that is widely used clinically due to its availability and stability. It is transformed into active factors in the body.

In 1934, three researchers won the Nobel prize in medicine for discovering the lifesaving properties of vitamin B_{12}. They found that eating large amounts of raw liver, which contains high amounts of vitamin B_{12}, could save the life of previously incurable patients with pernicious anaemia. Vitamin B_{12} was isolated from liver extract in 1948 and its structure was elucidated 7 years later by A. R. Todd in 1955.

The structure of vitamin B_{12} (**Figure 1)** is based on a corrin ring, which has two of the pyrrole rings directly bonded. The central metal ion is Co (cobalt). Four of the six coordinations are provided by the corrin ring nitrogens, and a fifth by a dimethylbenzimidazole group. The sixth coordination partner varies, being a cyano group (-CN) (cyanocobalamin), a hydroxyl group (-OH) (hydroxocobalamin), a methyl group (-CH3) (methylcobalamin) or a 5'-deoxyadenosyl group (5-deoxyadenosylcobalamin) [5, 6, 7, 8, 9, 10, 11, 12, 13].

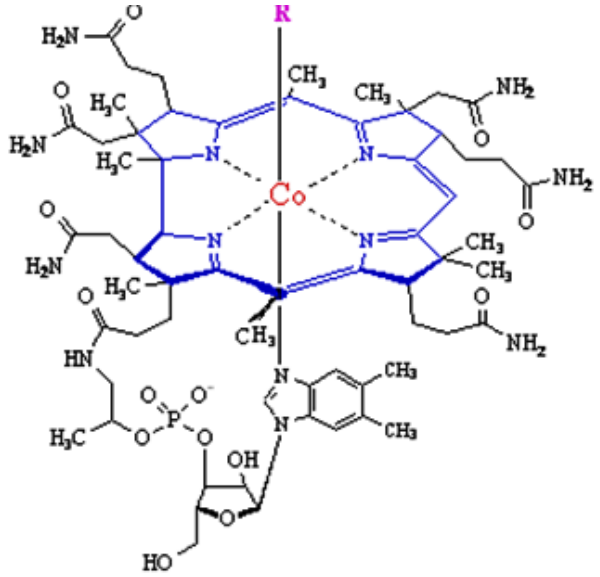

FIGURE 1: GENERAL STRUCTURE OF VITAMIN B_{12}

R represent to either a cyano group (-CN) (cyanocobalamin), a hydroxyl group (-OH) (hydroxocobalamin), a methyl group (-CH3) (methylcobalamin) or a 5'-deoxyadenosyl group (5-deoxyadenosylcobalamin)

Vitamin B_{12} is the only known essential biomolecule with a stable metal-carbon bond, it is an organometallic compound. The cobalt can link to:

1. A methyl group - as in methylcobalamin
2. A 5'-deoxyadenosine at the the 5' positon - as in adenosylcobalamin (coenzyme b_{12})
3. A cyanide group - as in vitamin b_{12} - as synthesized and supplied from drug companies

Sources and Daily requirement of Vitamin B_{12}: Most microorganisms, including bacteria and algae, synthesize vitamin B_{12}, and they constitute the only source of the vitamin [14]. The vitamin B_{12} synthesized in microorganisms enters the human food chain through incorporation into food of animal origin. In many animals, gastrointestinal fermentation supports the growth of these vitamin B_{12} synthesizing microorganisms, and subsequently the vitamin is absorbed and incorporated into the animal tissues.

This is particularly true for the liver, where vitamin B_{12} is stored in large concentrations. Products from herbivorous animals, such as milk, meat, and eggs, thus constitute important dietary sources of the vitamin, unless the animal is subsisting in one of the many regions known to be geochemically deficient in cobalt [15]. Milk from cows and humans contains binders with very high affinity for vitamin B_{12}, though whether they hinder or promote intestinal absorption is not entirely clear. Omnivores and carnivores, including humans, derive dietary vitamin B_{12} almost exclusively from animal tissues or products (i.e. milk, butter, cheese, eggs, meat, and poultry).

It appears that the vitamin B_{12} required by humans is not derived from microflora in any appreciable quantities, although vegetable fermentation preparations have been reported as being possible sources of vitamin B_{12} [16, 17].

Recommended Dietary Intake (RDI) for vitamin B_{12} (**Table 1**) were set in 1998 by the National Academy of Sciences. Recommended Dietary Intake (RDI) for vitamin B_{12} is summarized in table-1 [18, 19].

TABLE 1: RECOMMENDED DIETARY INTAKE (RDI) FOR VITAMIN B_{12}

Category	Age	RDI
Infants	0-6 months	400 nanograms
	6-12 months	500 nanograms
Children	1-3 years	900 nanograms
	4-8 years	1.2 micrograms
Male	9-13 years	1.8 micrograms
	14 years and older	2.4 micrograms
Females	9-13 years	1.8 micrograms
	14 years and older	2.4 micrograms
Pregnant females	any age	2.6 micrograms
Lactating females	any age	2.8 micrograms

Metabolic processes and Vitamin B_{12}: There are only two vitamin B_{12}-dependent enzymes [20]. One of these enzymes, methionine synthase, uses the chemical form of the vitamin which has a methyl group attached to the cobalt and is called methylcobalamin. The other enzyme, methylmalonyl coenzyme (CoA) mutase, uses a form of vitamin B_{12} that has a 5-adeoxyadenosyl moiety attached to the cobalt and is called 5-deoxyadenosylcobalamin, or coenzyme B_{12}.

In nature, there are two other forms of vitamin B_{12}: hydroxycobalamin and aquacobalamin, where hydroxyl and water groups, respectively, are attached to the cobalt. The synthetic form of vitamin B_{12} found in supplements and fortified foods is cyanocobalamin, which has cyanide attached to the cobalt. These three forms of vitamin B_{12} are enzymatically activated to the methyl- or deoxyadenosylcobalamins in all mammalian cells [21].

Measurement techniques of Vitamin B_{12}: There are several methods to assay and calculate vitamin B_{12}. Some of these methods are used in medical field, and some others in pharmacological studies/investigations, these methods are [22, 23]:

1. Electroluminescence (ECL)
2. Inductive-coupled plasma (ICP) - mass spectrometry (MS) (ICP-MS)
3. Atomic absorption spectroscopy
4. Radioimmunoassay (RIA)
5. High-performance liquid chromatography (HPLC)
6. Capillary electrophoresis

Causes of low level of Vitamin B_{12} in humans: Vegetarian diets can be classified as lacto vegetarian (dairy products), ovovegetarian (eggs), lactoovo-vegetarian (both dairy products and eggs), or vegan (no animal products at all). Vegan diets have very low content of vitamin B_{12} [24]. Lack of vitamin B_{12} may be caused by insufficient intake of vitamin or by malabsorption of the vitamin [25].

Pernicious anaemia: Pernicious anaemia is the most common cause of B_{12} deficiency. It is an autoimmune disease. The immune system normally makes antibodies to attack bacteria, viruses and other germs. But if a person is suffering from autoimmune disease, the immune system makes antibodies against certain tissues of body resulting the vitamin cannot be absorbed into the body. Pernicious anaemia usually develops over the age of 50. Women are more commonly affected than men, and it tends to run in families. It occurs more commonly in people who have other autoimmune diseases such as thyroid diseases.

Stomach or Gut Problems: Various problems of the stomach or gut can be a cause of vitamin B_{12} deficiency. Such as:

- Surgery to remove the stomach or the end of the small intestine. This will mean absorption of vitamin B_{12} may not be possible.
- Some diseases that affect the end of the small intestine where vitamin B_{12} is absorbed may affect the absorption of the vitamin. i.e. Crohn's disease.

Drugs: Certain drugs used for other conditions may affect the absorption of vitamin B_{12}. The most common example is metformin which is a drug commonly used for diabetes.

Dietary causes: The people who take no animal or dairy produce are more prone for vitamin B_{12} deficiency.

Conditions associated with reduced level of Vitamin B_{12}: Vitamin B_{12} deficiencies manifest primarily as anemia and neurologic changes, although a deficiency of this vitamin inhibits DNA synthesis, which affects growth and repair of all cells.

Pernicious anemia is a form of megaloblastic anemia caused by either inadequate vitamin B_{12} intake or reduced gastric secretion of intrinsic factor, which inhibits absorption. The hematologic effects of vitamin B_{12} deficiency are indistinguishable from those of folate deficiency. These include pallor of skin, tiredness, syncope, headache, shortness of breath, and palpitations. Hematologic complications are completely reversed by treatment with vitamin B_{12}.

Neurologic changes due to vitamin B_{12} deficiency can occur in the absence of any hematologic abnormalities. Depending on the duration of symptoms, neurologic complications of vitamin B_{12} deficiency may or may not be reversible following treatment.

The main Condition associated with reduced level of Vitamin B_{12} is Biermer's disease (pernicious anemia). It is characterized by:

1. Anemia with bone marrow promegaloblastosis (megaloblastic anemia). This is due to the inhibition of DNA synthesis (specifically purines and thymidine)
2. Gastrointestinal symptoms: These are thought to be due to defective DNA synthesis inhibiting replication in a site with a high turnover of cells. This may also be due to the autoimmune attack on the parietal cells of the stomach in pernicious anemia.
3. Neurological symptoms: Sensory or motor deficiencies (absent reflexes, diminished vibration or soft touch sensation), sub acute combined degeneration of spinal cord, or even symptoms of dementia and or other psychiatric symptoms may be present. The presence of peripheral sensorymotor symptoms or subacute combined degeneration of spinal cord strongly suggests the presence of a B_{12} deficiency instead of folate deficiency.

Pernicious anaemia is a condition where vitamin B_{12} cannot be absorbed into the body. It is the most common cause of vitamin B_{12} deficiency. Vitamin B_{12} deficiency is easily treated by regular injections of vitamin B_{12}, by taking oral supplements of vitamin B_{12} and by taking diet rich in vitamin B_{12}.

The other condition associated with reduced level of Vitamin B_{12} is the fact that Vitamin B_{12} deficiency can potentially cause severe and irreversible damage, especially to the brain and nervous system.

CONCLUSION: Vitamin B_{12} play an important role in the formation of blood and in the normal functioning of the brain and nervous system. The daily recommended intake for an adult is 1.5µg a day. Eating a diet containing required amount of vitamin B_{12} is the best way to treat the conditions associated with its low level. Vegetarians should consider taking a regular vitamin B_{12} supplement to prevent the conditions associated with its low level.

REFERENCES:

1. McCollum EV: A History of Nutrition Boston. Houghton Mifflin1957
2. Fukuwatari T and Shibata K: Urinary water-soluble vitamins and their metabolite contents as nutritional markers for evaluating vitamin intakes in young Japanese women. J. Nutr. Sci. Vitaminol 2008; 54 (3): 223–9.
3. Said HM and Mohammed ZM: Intestinal absorption of water-soluble vitamins: an update. Curr. Opin. Gastroenterol 2006**;** 22 (2): 140–6.
4. Linda B: Facts about Vitamin B_{12}, University of Florida 2008
5. Hodgkin DC: The crystal structure of the hexacarboxylic acid derived from B_{12} and the molecular structure of the vitamin. Nature 1955; 176, 325
6. Dodson G, Glusker JP and Sayre D: Structural studies on molecules of biological interest, Clarendon, Oxford 1981
7. Randaccio L, Geremia S and Wuerges J: Crystallography of Vitamin B_{12} Proteins. J. Organometal. Chem. 2007; 692, 1198-1215.
8. Chemistry and Biochemistry of B_{12}: John Wiley & Sons; New York, NY, USA 1999
9. Randaccio L, Bresciani-Pahor N, Zangrando E and Marzilli LG: Structural Properties of Organocobalt Coenzyme B_{12} Models. Chem. Soc. Rev. 1989; 18, 225-250.
10. Sauer K and Thauer RK: The Role of Corrinoids in Methanogenesis. In Chemistry and Biochemistry of $B_{12.}$ John Wiley & Sons. New York, NY, USA 1999
11. Folkers K: History of Vitamin B_{12}: Pernicious Anemia to Crystalline Cyanocobalamin. In Vitamin B_{12}. John Wiley & Sons. New York, NY, USA 1982
12. Weir DG and Scott JM: Cobalamins physiology, dietary sources and requirements, Encyclopedia of human nutrition. Volume 1. San Diego, CA, Academic Press 1998; 394–401.
13. Weir DG and Scott JM: Vitamin B_{12}. Modern nutrition in health and disease. Baltimore, MA, Williams & Wilkins 1999; 447–458.
14. Chanarin I: The megaloblastic anaemias, Oxford, Blackwell Scientific Publications 1979.
15. Smith RM: Trace elements in human and animal nutrition, 5th ed. San Diego, CA, Academic Press 1987;143–184.
16. Van den Berg H, Dagnelie PC and Staveren WA: Vitamin B_{12} and seaweed. Lancet 1988; 1:242–243.
17. Areekul S and Pattanamatum S: The source and content of vitamin B_{12} in the tempehs. J Med Assoc Thai 1990; Mar 73(3):152-156 1990.
18. Herbert I: Recommended dietary intakes (RDI) of vitamin B12 in humans. Am J Clin Nutr 1987; 45:671-8
19. Herbert I: Vitamin B_{12}. In: Brown ML, ed. Present Knowledge in Nutrition, 6th ed. Washington, D.C.: The Nutrition Foundation 1990; 170-8.
20. Scott JM and Weir DG: Folate/vitamin B_{12} interrelationships. Essays in Biochemistry 1994; 28:63–72.
21. Recommended dietary intakes (RDI) of vitamin B-12 in humans: American journal of clinical nutrition. 1987; 45, 671-678
22. Karmi O, Zayed A, Baraghethi S, Qadi M and Ghanem R: Measurement of vitamin B12 concentration: a review on available methods. IIOAB Journal 2011; Vol. 2; Issue 2: 23-32
23. Manisagar A: Measurement of vitamin B12 concentration: a review on available methods. International Journal of Pharmaceutical Sciences and Research (IJPSR) 2012; Vol. 3(6): 1846-1852
24. Herrmann W, Schorr H, Obeid R and Geisel J: Vitamin B_{-12} status, particularly holotranscobalamin II and methylmalonic acid concentrations, and hyperhomocysteinemia in vegetarians. Am J Clin Nutr 2003; 78:131–6.
25. Chanarin I: The Megaloblastic Anaemias. 3rd ed; London: Blackwell Scientific Publications 1990
26. Elmadfa I and Singer I: Vitamin B_{-12} and homocysteine status among vegetarians: a global perspective. Am J Clin Nutr. 2009; 89: 1693S-1698S.
27. Herrmann W and Geisel J: Vegetarian lifestyle and monitoring of vitamin B-12 status. Clin. Chim. Acta, 326(1-2): 47-59, (2002).
28. Stabler SP and Allen RH: Vitamin B12 deficiency as a worldwide problem. Ann. Rev. Nutr, 24: 299-326, (2004).
29. Baik HW and Russell RM: Vitamin B12 deficiency in the elderly. Ann. Rev. Nutr, 19: 357-377, (1999).

How to cite this article:
Belwal C: Causes and Conditions associated with reduced level of Vitamin B_{12}: A Review. *Int J Pharm Sci Res*. 3(10); 3651-3655.