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BIOCHEMISTRY OF VITAMIN B_{12} AND ACTIVE VITAMIN B_{12} – AN UPDATE

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ABSTRACT
Vitamin B_{12} is also known as Cobalamin, which is a water-soluble vitamin. It has a complex structure with corrin ring and a central cobalt atom. Deficiencies lead to inefficient erythropoiesis and megaloblastic anemia. General tissue effects of this vitamin and folate deficiencies result in complications of pregnancy – recurrent fetal loss & neural tube defects, cardiovascular disease, malignancy and neurological manifestations. A high rate of deficiency among vegetarians or vegans exists because B_{12} is only naturally present in animal products, so those who do not consume diets high in fortified products are at risk. In serum it is bound to two proteins, namely transcobalamin and haptocorrin. The transcobalamin-vitamin B_{12} complex is called Holotranscobalamin known as Active Vitamin $B_{12,}$ which contains the biologically available cobalamin. This article is focussed on the details of various studies on Vitamin B_{12} and Active Vitamin B_{12} by various researchers.

KEYWORDS: Vitamin $B_{12,}$ Active Vitamin B_{12}, Cobalamin, Megaloblastic anemia.

INTRODUCTION
Vitamin B_{12} or Cobalamin is a water-soluble vitamin, synthesized only by microorganisms. It has a complex structure with corrin ring and central cobalt atom.[1] It is important for DNA synthesis and neurological functions and also for the metabolism of carbohydrate, protein and fat. Deficiencies in B_{12} lead to inefficient erythropoiesis and megaloblastic anemia.[2] Neurological disorders such as neuropathy, myelopathy, memory impairment, dementia, depression and brain atrophy may occur in those with low B_{12} status.[3] Vegetarians and elderly are at higher risk of vitamin B_{12} deficiency. Among elderly, vitamin B_{12} deficiency occurs in about 20% of the population; more than 60% of these deficiencies are due to food-cobalamin malabsorption syndrome caused by gastrointestinal problems. Deficiency related to lack of intrinsic factor results in severe neurologic damage and life-threatening anemia and such individuals require medical treatment including vitamin B_{12} injections. The pernicious anemia and food-bound malabsorption account for less than half of poor B_{12} status among elderly.[4] A high rate of deficiency among vegetarians or vegans exists because B^{12} is only naturally present in animal products, so those who do not consume diets high in fortified products are at risk.[5] This article is focussed on the details of various studies on Vitamin B_{12} by the researchers which will be useful for others.

Sources
Vitamin B_{12} is mainly synthesized by microorganisms. The main dietary sources are animal products including meat, fish, eggs, and dairy products.[3] Other sources include fortified plant products such as cereals, plant-based milk, soy products and B_{12}-fortified yeast extract.[5]

Recommended Dietary Allowance (RDA)
The RDA per day for children is 0.5 – 1.5 µg, for adults is 3 µg, during pregnancy and lactation is 4 µg. The daily loss through urine and feces is 1 to 3µg.

Biochemical Function and Vitamin B_{12} Deficiency
The coenzyme forms of Vitamin B_{12} are (1) Methylcobalamin and (2) 5-Deoxyadenosyl cobalamin. Methylcobalamin is a coenzyme for Homocysteine methyltransferase, which converts homocysteine to methionine. 5-Deoxyadenosyl cobalamin is a coenzyme for Methylmalonyl CoA mutase which converts Methylmalonyl CoA to Succinyl CoA. Vitamin B_{12} involves in red blood cell production and if there is vitamin B_{12} deficiency, DNA synthesis becomes defective and so the red blood cell formation and maturation are affected. The red blood cell morphology changes leading to oversized and poorly shaped cells, ineffective function leading to a condition called pernicious anemia. It also involves in nerve cell development and the vitamin B_{12} deficiency affects myelin sheath formation. The defect in homocysteine to methionine conversion leads to accumulation of S-Adenosyl Methionine in brain, which inhibits transmethylation reactions, resulting in neurological manifestations.

General tissue effects of vitamin B_{12} and Folate Deficiencies result in complications of pregnancy – recurrent fetal loss & neural tube defects, cardiovascular disease, malignancy and neurological manifestations

Vitamin B_{12} and Birth outcomes

Adequate folate and vitamin B_{12} are shown to reduce the incidence of neural tube defects (NTDs). Improving vitamin B_{12} intakes might result in higher functioning of the enzyme methionine synthase that converts homocysteine to methionine.[6,7] Families at risk for NTDs might have genetic variations that impair the metabolism of folate and vitamin B_{12}. A mutation in the methylenetetrahydrofolate reductase (MTHFR) gene or low vitamin B_{12} levels, in combination with a polymorphism in methionine synthase reductase (the enzyme that activates B_{12}-dependent methionine synthase), has recently been shown to increase the risk of NTDs by up to 5 times.[8] Few suggested that the transport of vitamin B_{12} to tissues by transcobalamin II (TC II) might be affected by genetics. Afman and colleagues[9] noted that genetic variation in the TC II gene probably causes a reduced affinity for vitamin B_{12}. Supplementation with B_{12} might raise TC II levels, increasing cellular vitamin B_{12} and decreasing homocysteine, which is higher in mothers of children with NTDs.

Vitamin B_{12} and cardiovascular disease

Increased plasma homocysteine levels have been recognized as an important risk factor for Cardio Vascular Disease (CVD). Supplementation with folic acid and Vitamin B_{12} reduce plasma homocysteine levels and lower CVD risk. Several studies have shown that folic acid in combination with B_{12} lowers homocysteine levels.[10,11]

Vitamin B_{12} and Cancer

Vitamin B_{12} is associated with DNA synthesis & Neurological Functions. Different forms of MTHFR gene carry different risks of colon cancer. The CC genotype with low micronutrient intake carries the highest risk of colon cancer. A Study showed that the high intakes of folate, vitamin B_6 and vitamin B_{12} were associated with a 30% to 40% risk reduction in colon cancer among those with the TT genotype relative to those with the CC genotype and low intakes.[12]

Vitamin B_{12} and mental health

An earlier study shows that the folic acid and vitamin B_{12} lower plasma homocysteine concentration by 30% in those with dementia or mild cognitive impairment, but no effect on cognitive function. Some studies have shown that folic acid might be more important to cognitive function than vitamin B_{12}, but B_{12} supplementation has been shown to improve symptoms indicative of delirium or to improve some functions in patients with cognitive impairment, even when the underlying condition of dementia remains unchanged.[13] A systematic review of vitamin B_{12} and cognition concluded that the evidence is currently insufficient to show that B_{12} improves the cognitive function of people with dementia.[14] Meins and colleagues found that patients with Alzheimer disease who had lower than normal vitamin B_{12} levels showed more frequent behavioural and psychological symptoms of dementia than patients with normal values. Vitamin B_{12} deficiency rises with age, but only about 10% of those with low vitamin B_{12} also have low folate levels.[15] Therefore, given the prevalence of both vitamin B_{12} deficiency and mental disability among the elderly, supplementation with vitamin B_{12} might reduce the risk of age-associated mental disability or improve the quality of life among those with dementia, but more studies are needed to determine how biologically important vitamin B_{12} might be. Hyperhomocysteinemia, vitamin B_{12} deficiency and impaired one carbon metabolism due to genetic polymorphism have also been associated with depression.[16] Hintikka and colleagues found that higher vitamin B_{12} levels were significantly associated with a better outcome for treatment of major depression, suggesting that vitamin B_{12} supplementation could be used to augment antidepressant treatments.[17]

Pernicious anemia

Vitamin B_{12} deficiency results in pernicious anemia, in which not enough red blood cells are produced. The symptoms are feeling tired, shortness of breath, pale skin, chest pain, numbness in the hands and feet, poor balance, a smooth red tongue, poor reflexes, depression and confusion.[18,19] The causes are autoimmune destruction of gastric parietal cells that secrete intrinsic factor, hereditary malabsorption of vitamin B_{12}, gastrectomy and strict vegetarians. Other causes of low vitamin B_{12} include not enough dietary intake (such as in a vegan diet), celiac diseases, or tapeworm infection.[20] Pernicious anemia is suspected when a patient's blood smear shows large, fragile, immature erythrocytes, known as megaloblast. The diagnosis requires demonstration of megaloblastic anemia by conducting a full blood count and blood smear, which evaluates the mean corpuscular volume and mean corpuscular haemoglobin concentration.[21]

Active Vitamin B_{12}

Vitamin B_{12} in serum is bound to two proteins namely transcobalamin (TC) and haptocorrin (HC). The Transcobalamin-Vitamin B_{12} complex is called Holotranscobalamin (HoloTC), which is known as Active Vitamin B_{12}, contains the biologically available cobalamin as only HoloTC promotes the uptake of cobalamin by all cells via specific receptors. In comparison, approximately 80% of the circulating cobalamin that is carried by haptocorrin is considered metabolically inert because no cellular receptors exist, with the exception of receptors found in the liver. Genetic absence of haptocorrin is rare and not considered a serious condition. Genetic absence or abnormalities of TC, however, manifest as typical hematological, neurological and metabolic pathologies of cobalamin

deficiency, which require aggressive treatment even if a serum analysis results in normal cobalamin concentrations. The shorter circulating half-life of HoloTC compared to HoloHC makes a decrease of HoloTC one of the earliest markers of cobalamin deficiency.[22] The measurement of total serum cobalamin suffers from some limitations, particularly, most of the cobalamin that is measured is bound to haptocorrin. A number of studies have been published to support that HoloTC would be a better indicator of vitamin B_{12} status than total serum cobalamin.[23,24] Methods based on specific anti-transcobalamin antibodies have been available and confirm the usefulness of HoloTC for diagnosing B_{12} deficiency. As expected, HoloTC levels are low in patients with biochemical signs of vitamin B_{12} deficiency. Notably, low values have been reported in vegetarians, vegans and in populations with low intake of this vitamin.[25] In addition, low levels of HoloTC (but not total vitamin B_{12}) in serum were reported in patients with Alzheimer's disease compared to levels of HoloTC in a healthy control group.[26] HoloTC levels reflect vitamin B_{12} status, independent of recent absorption of the vitamin.[27]

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