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VITAMIN B12 DEFICIENCY

Science

Rossen Mihaylov Medical Laboratory Ramus, MU Sofia, MK "J. Filaretova"

Blagovesta Pencheva Medical Laboratory Ramus

Stanislava Zlateva Medical Laboratory Ramus

KEYWORDS

The term vitamin B12 includes several chemical compounds similar in chemical structure (1,2,3,4). There are 4 known kinds of vitameres of vitamine B12: (a) cyanocobalamin, which is metabolized in the body to an active coenzyme; (b) hydroxocobalamin which is not normally present in the human body; (c) adenosylcobalamin (adoB12), an active cofactor; and (d) methylcobalamin (MeB12), an enzymatically active cofactor (1,3). In the body, vitamin B12 is mostly stored as adoB12 in the liver. Vitamin B12 is very stable at high temperature, while in strongly acidic and strongly alkaline conditions it loses its activity. Its levels are negatively affected by alcohol and estrogens. Serum vitamin B12 binds to proteins known as transcobalamins. 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 (1,4,5). Holo-transcobalamin (holo-TC) is TCII with attached cobalamin, which delivers vitamin B12 to the cells. The low serum vitamin B12 concentration can be associated with a deficiency of TCI. Methylmalonic acid and homocysteine are indicators of the status of vitamin B12 in the body cells. Methylmalonic acid is considered to be a specific indicator of cobalamin metabolism (5,6,7). Homocysteine is a derivative of methionine which is supplied through the proteins in the food. The body converts the greater part of homocysteine back to methionine with the help of vitamin B12 (7,8). In case of B12 deficiency, homocysteine levels increase, because this reaction cannot take place. Normal serum levels of homocysteine are from 2.2 to 13.2 μmol / l. Vitamin B12 is not synthesized by multicellular or unicellular eukaryotes (1,5,8). All of the substrate cobalt-corrin molecules, from which B12 is made, are synthesized by bacteria. The human body has the ability to convert any form of B12 to an active form, by means of enzyme action. Animals store vitamin B12 in the liver and muscles. Meat (lamb, veal, beef and turkey), liver, eggs, cheese and milk are sources of vitamin B12. As vegetarian diets generally include high content of folic acid, elevated levels of homocysteine in vegetarians are typically due to the low intake of B12 (1,4,6).

2. Physiological Relevance

The total amount of vitamin B12 stored in the body is about 2-5 mg in adults. Around 50% of it is stored in the liver (1,2,4,9). Approximately 0.1% of it is lost per day by secretions in the intestines. The bile is the main form of B12 excretion; however, considerable part is recycled be means of enterohepatic circulation. Vitamin B12 is involved in the metabolism of every cell in the human body. It is essential for the nervous system, DNA and RNA, erythrocytes synthesis, immune and cardiovascular system, and for the maintenance of the general energy levels. It protects nerve and brain cells against damage by free radicals. It participates in the methylation synthesis of nucleic acid and neurotransmitters, the metabolism of fatty acids and amino acids. Vitamin B12 functions as a coenzyme in three basic enzyme reactions – of isomerases, methyltransferases and dehalogenases. Lately, the seven most important functions of B12 have been discussed (2,7,8,9): (a) maintains body energy; (b) protects the cardiovascular system by eliminating homocysteine; (c) it is associated with osteoporosis, which is manifested with higher levels of homocysteine and low levels of B12; (d) protects the myelin sheaths against toxins and free radicals in the blood; (e) improves the mood with the help of serotonin; (f) it is necessary for the cortical functions and its levels are decreased in Alzheimer's disease and other dementias; (g) slows down aging. B12 is absorbed in the body by means of two processes: an intestinal mechanism using intrinsic factor and a diffusion process (1,3,7).

3. B12 Deficiency.

Vitamin B12 was discovered while clarifying the etiology of megaloblastic anemia (10,11,12). This autoimmune disease destroys the parietal cells of the stomach, which are responsible for the secretion of intrinsic factor, as well as the secretion of gastric acid in the stomach. The intrinsic factor is crucial for the normal absorption of B12 and its lack causes a deficiency. Whipple, Minot and Murphy won the Nobel Prize in 1934 for discovering the role of the vitamin with regard to pernicious anemia. The human body needs a certain amount of vitamin B12, depending on age, sex, physical and social conditions. The daily allowance is difficult to determine and this explains the slight fluctuations in the international recommended dietary allowances. According to German, European, US and WHO recommendations, the daily allowance for adults should be 3.0, 2.5 or 2.4 μg, but recently higher levels have also been recommended (13). In extensive studies in the US and UK, approximately 6% of the people aged ≥ 60 years old had vitamin B-12 deficiency (B-12 < 148 pmol / L), and the distribution of this deficiency increases with age, mainly due to gastric atrophy. About 20% of the study subjects demonstrated vitamin B-12 levels between 148 and 221 pmol/L. In developing countries, this deficiency is much more prevalent due to the low consumption of foods of animal origin. Vitamin B12 deficiency can be found in 4-40% of the general population (3,5,14). Loikas et al. (15) 2007 studied 1048 elderly patients (65-100 years old) and found a deficiency in 12%, where in 6.1% vitamin B12 was < 50 pmol/l and in 32% it was 150-250 pmol/l. In the past, vitamin B12 deficiency was more common than nowadays. Around 40% of the US population suffers from some form of B12 deficiency. In the US, vitamin B12 in food supplements is expressed as a percentage of the daily value (% DV) (4,8,15). Intracellular levels of vitamin B12 may correspond to the total plasma concentration of homocysteine (3,9). Cobalamin deficiency is most often caused by low intake, but may also be the result of malabsorption, lack of binding proteins, use of certain drugs, alcoholism, smoking, increased consumption by the body during pregnancy and neoplasia (9,10). Vitamin B12 deficiency can occur in 40% to 80% of vegetarians. The deficiency is much more common in atrophic gastritis, malignant anemia, Crohn's disease, disorders of the immune system in Graves' disease, lupus, etc.

A slight deficiency may have no clinical manifestation, but if it is not treated, it can lead to symptoms such as weakness, fatigue, dizziness, palpitations, shortness of breath, pale skin, smooth tongue, constipation, diarrhea and loss of appetite. Vitamin B12 deficiency may potentially cause severe and irreversible damage, especially to the brain, nervous and cardiovascular system (1,5,6,10,11). The damage to the central or peripheral nervous system in case of vitamin B12 deficiency ranges between 30-72%. It is characterized by myeloneuropathy, encephalopathy, myeloencephalopathy, cognitive dysfunction and behavioral changes. Paresthesias are present in 33% and psychiatric or cognitive symptoms in 3% of the patients. Involvement of the autonomic nervous system occurs in 26%. Van der Wal, 2015 (17) monitored 610 patients (68 ± 12 years old) with chronic heart failure. He registered a deficiency in the serum of vitamin B12 (< 200 pg/mL) and folic acid (< 4.0 ng/mL), respectively at 4% and 5%. Schick, 2017 (12) discussed the role of vitamin B12 for the

development of megaloblastic anemia, as well as the role of abnormal copper and zinc levels for the same disease (10,11,12). Jager et al., (18) 2010 explores how metformin treatment of type 2 diabetes affects the serum concentrations of vitamin B-12, folic acid and homocysteine. The decrease in cobalamin is not a transient phenomenon; it continues and increases with time, along with minor changes in the folic acid level and increases in homocysteine concentration. It is still controversial which cut off value for vitamin B12 deficiency should be adopted, regardless of the clinic (7,19,20,21). Here is where age, diet, social status and other factors come into play. The most frequently reported levels are: normal > 300 pg/ml; moderate deficiency between 201 and 300, and severe deficiency < 201 pg/ml. Currently, there is no "gold standard" for vitamin B12 deficiency. Recently, a cascade of serum biomarkers was proposed (Figure 1). The main serum indicators are concentration of vitamin B12, methylmalonic acid, homocysteine, holotranscobalamin and intrinsic factor antibodies. The elevated plasma level of homocysteine is considered to be a good screening test. A normal homocysteine level, together with the folate, effectively excludes vitamin B12 deficiency in clinically asymptomatic patients. The test, however, is not specific and many situations can lead to an increased level. Conversely, the elevated serum level of methylmalonic acid is considered more specific for B12 deficiency at a cellular level. Homocysteine and methylmalonic acid are better metabolic indicators of a deficiency at tissue level. Determining vitamin B12 in the serum does not detect all cases of deficiency. The laboratory at Mayo Clinic offers a diagnostic algorithm for B12 deficiency: Vitamin B12 > 400 ng/L – there is no deficiency, no need for additional tests; Vitamin B12 is 150 to 400 ng/L – cut-off level, methylmalonic acid test should be performed. If it is > 0.40 nmol/mL, intrinsic factor blocking antibody testing shall be performed; Vitamin B12 < 150 ng/L - vitamin B12 deficiency. If the intrinsic factor blocking antibody is negative, then gastrin is performed; MMA ≤0.40 nmol/mL - a lack of vitamin B12 deficiency at a cellular level.

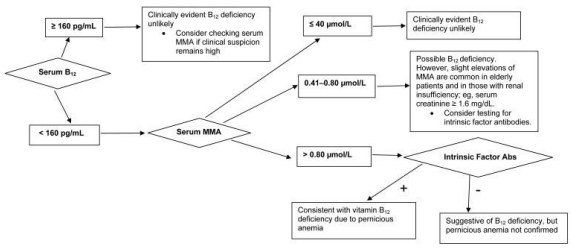


Figure 1. Cascade of tests for laboratory evaluation of vitamin B12 deficiency (Berg, 2013, N 21).

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