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Medical Science

HOW FREQUENCY IS VITAMIN B12 DEFICIENCY?

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KEYWORDS :

1.Vitamin B12

Much attention has been given to B-vitamins, in particular to folate and vitamin B12, because of their potential influence on cardiovascular diseases (CVD). The rates of deficiency vary depending on the country, as local laws, the economic situation, cultural trends and the environment can affect supply of vitamins and minerals. Vitamin B-12 deficiency and depletion are common in some countries, particularly among the elderly, and are most prevalent in poorer populations around the world(1,2,3). Pernicious anemia is a common cause of megaloblastic anemia throughout the world and especially in persons of European . Dietary deficiency of vitamin B12 due to vegetarianism is increasing and causes hyperhomocysteinemia. In large surveys in the United States and the United Kingdom, ≈6% of those aged ≥60 y are vitamin B-12 deficient (plasma vitamin B-12 < 148 pmol/L), with the prevalence of deficiency increasing with age. The deficiency affected ≤3% of those aged 20–39 y, ≈4% of those aged 40–59 y, and ≈6% of persons aged ≥70 y. Deficiency was present in <1% of children and adolescents but was ≤3% in children aged <4 y. Marginal depletion (serum vitamin B-12 148–221 pmol/L) was more common and occurred in ≈14–16% of those aged 20–59 y and >20% of those >60 y. Plasma methylmalonic acid (MMA) concentrations were markedly higher after age 60 y. The term vitamin B12 includes several chemical compounds similar in chemical structure (4,5,6,7). 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) About 60% of the total amount of B12 in the body is stored in the liver and 30% is stored in the muscles . The body has a special circuit between the digestive tract and the liver. It is then reabsorbed at the end of the small intestine (the ileum) and taken back to the liver where it is used again(figure 1). The body can store vitamin B12 for years 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). Haptocorrin is a glycoprotein produced by the salivary glands of the mouth. It primarily serves to protect Vitamin B12 from acid degradation in the stomach by producing a Haptocorrin-Vitamin B12 complex. Once the complex has traveled to the more neutral duodenum, pancreatic proteases degrade haptocorrin, releasing free cobalamin, which now binds to intrinsic factor for absorption by ileal enterocytes(figure 1). The active transport protein for vitamin B12 is transcobalamin II (TCII), which carries about 20% of the vitamin in the circulation (2,7,8). 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. High levels of Methymalonic Acid (MMA) and Homocysteine (HC) have been identified as better indicators of B-12 deficiency than the actual serum B-12 level itself. Methylmalonic acid is considered to be a specific indicator of cobalamin metabolism (8,9,10). 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 (11,12). 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 (4,8,12). 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 (4,6,9).

2. Physiological significance

Vitamin B12 deficiency was first described in 1849, and was considered to have a fatal outcome until 1926 when a diet of liver, high in vitamin B12, was shown to slow the disease process. Surprisingly, given its pivotal physiological significance, our understanding of the role vitamin B12) in health and brain function is limited. The folate and vitamin B12 t play the most obvious roles in homocysteine metabolism. The total amount of vitamin B12 stored in the body is about 2-5 mg in adults. About 60% of the total amount of B12 in the body is stored in the liver and 30% is stored in the muscles (4,5,7,13). 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. There are also urine excretion strongly correlated with urine volume. 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 (5,11,12,13): (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 (4,6,11).

3. B12 Deficiency.

The first description of vitamin B12 deficit was made by British physician Thomas Addison in 1855, who called it pernicious anemia and it was described as a disease that manifested itself with macrocytic anemia, glossitis, and neurological symptoms(1,5,8) .Vitamin B12 deficiency is a multifactorial condition caused by insufficient intake (nutritional deficiency) as well as acquired or inherited defects that disrupt B12 absorption, processing and trafficking pathways (functional deficiency). Much is now known about the biochemistry and metabolism of vitamin B12, however, the diagnosis of its deficiency has become more complicated with the classification of a "sub-clinical" deficiency category, characterized by serum vitamin B12 concentrations that were once considered to be adequate. Insufficient supply of B12 and genetic defects impairing its cellular processing and trafficking lead to the accumulation of homocysteine (Hcy) and methylmalonic acid (MMA), which enter circulation and give rise to hyperhomocystinemia and methylmalonic acidemia. Vitamin B12 was discovered while clarifying the etiology of megaloblastic anemia (9,11,14,15,16). 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.Vitamin B12 is transferred to the intrinsic factor in the intestinal lumen by means of a pH dependent process. In the terminal ileum, the intrinsic-B12 complex binds to receptors on the membrane surface of enterocytes and is then transferred through the ileal membrane. It is subsequently released in the enterocytes and transferred to transcobalamin II. 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 (17). 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. Vitamin B12 deficiency is frequently under-diagnosed in pregnancy and in infants from mothers having insufficient levels of the micronutrient 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 (6,8,11,18). Loikas et al. (19) 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). Total serum vitamin B12 is a late, relatively insensitive and unspecific biomarker of deficiency. Holotranscobalamin (holoTC), also known as active B12, is the earliest laboratory parameter for B12 deficiency, while methyl malonic acid (MMA) is a functional B12 marker that will increase when the B12 stores are depleted. Isolated lowering of holoTC shows B12 depletion (negative B12 balance), while lowered holoTC plus elevated MMA and homocysteine indicates a metabolically manifest B12 deficiency, although there still may be no clinical symptom The most direct assessment and perhaps preferred first-assay to determine vitamin B12 status is the measurement of total serum vitamin B12. Ranges for normal (>250 pmol/L), low (150–249 pmol/L), and acute deficiency (<149 pmol/L) vitamin B12 have been defined and are used in most clinical chemistry laboratories worldwide One limitation of this biomarker is that it assesses total circulating vitamin B12, of which ~80% is bound to haptocorrin, and therefore, not bioavailable for cellular uptake. Another limitation of this assay lies in its unreliability to reflect cellular vitamin B12 status. Results from studies assessing serum and cellular vitamin B12 have shown that the levels of serum B12 do not always represent cellular(16,17,18). In particular, patients with inborn errors of vitamin B12 metabolism can present with normal or low serum values of the vitamin, while being deficient at the cellular level. Intracellular levels of vitamin B12 may correspond to the total plasma concentration of homocysteine. Homocysteine is a metabolite of the methionine cycle. It degraded by cystathionine β-synthase. The normal range of total plasma Hcy in human plasma is 5–15 µmol/L and values >13 µmol/L may be considered elevated in adults. Homocysteine levels are always higher in serum compared to plasma due to the release of Hcy bound to cellular components. This biomarker is of limited value to assess vitamin B12..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 (11,13,14). MMA is considered a more specific marker of vitamin B12 deficiency . Serum values of MMA, ranging from >260 to 350 nmol/L indicate elevation of this metabolite. Vitamin B12 concentrations in serum with elevated MMA concentrations may reflect renal dysfunction. B12 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. People at risk of a B12 deficiency include :the elderly; those whit removes the part of the bowel that absorbs B12; people on the drug metformin for diabetes; people following a strict vegan diet; those taking long-term antacid drugs for heartburn. Low levels of B12 cause your folate levels to drop. However, if you have a B12 deficiency, correcting low folate levels may simply mask the deficiency and fail to fix the underlying problem A slight deficiency may have no clinical manifestation, but if it is not treated, it can lead to following symptoms: pale or jaundiced skin; weakness and fatigue; nerve damage with sensations of pins and needles; changes to mobility; glossitis and mouth ulcers; breathlessness and dizziness caused by unable to transport enough oxygen to all its cells; disturbed vision; depressed mood; high temperature. Vitamin B12 deficiency may potentially cause severe and irreversible damage, especially to the brain, nervous and cardiovascular system (4,8,9,14,15). 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%. Schick, 2017 (16) 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, as other authors (14,15,`16,17). New data demonstrated that metformin treatment of type 2 diabetes affects the serum concentrations of vitamin B-12, folic acid and homocysteine (16,18,19). 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 (11,20,21,). 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 2)(22,23,24). The main serum indicators are concentration of vitamin B12, methylmalonic acid, homocysteine, holotranscobalamin and intrinsic factor antibodies(23). 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 (22,23,24,25). 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.

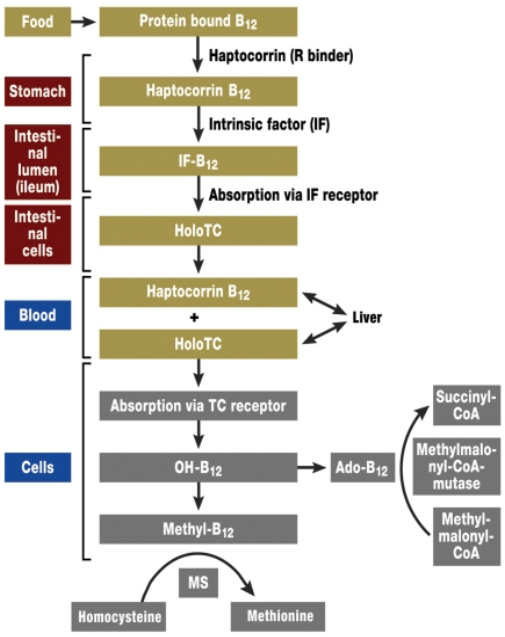

Fig. Transport and cellular absorption of vitamin B12 (Herrmann W, 2008, N 25). Review Article

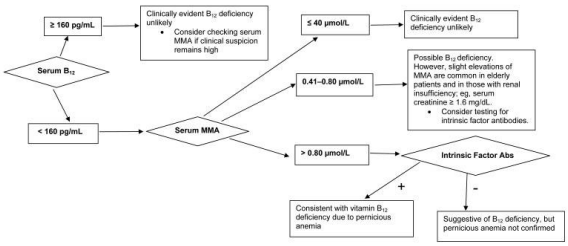

Figure 2. Cascade of tests for laboratory evaluation of vitamin B12 deficiency (Berg, 2013, N 22).

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