

Review Article

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Effects of Vitamin B12 Deficiency on the Central Nervous System

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ABSTRACT

Vitamin B12 is a water-soluble vitamin, not synthesized by the human body, present in foods of animal origin, performing important metabolic and neurotrophic functions. Its deficiency is very common among the elderly, vegetarians and individuals who have a problem with gastrointestinal absorption or adopt a low-protein diet. The present study aims to demonstrate the effects on the nervous system caused by the lack of vitamin B12. The work was carried out through a bibliographical review, through the reading of scientific articles selected in databases, in addition to reference materials in the area. As a result, it was found that the vitamin B12 deficit has consequences such as changes in the Central Nervous System (CNS), responsible for neurological/psychiatric illnesses, such as depression, peripheral neuropathy, behavioral changes, cognitive degeneration, leading to dementia, in addition to disorders hematologic.

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Introduction

Vitamins are organic substances that the body needs and are absorbed through of animal and vegetable origin foods, classified as fat-soluble (Vitamins A, D, E and K) and water-soluble (Vitamins B1, B2, B6, Pantothenic acid, Niacin, Biotin, Folic Acid, Vitamin B12 and Vitamin C) [1]. Vitamin B12 also known as Cobalamin, is part of a family of compounds generically called cobalamin. It is a water-soluble vitamin, synthesized exclusively by microorganisms, absorbed in the distal ileum, and the liver is its main reservoir in the body in the form of adenosylcobalamin, with a storage capacity of 2 to 5mg of B12, found in practically all tissues. The natural source of vitamin B12 in the human diet is restricted to foods of animal origin, especially milk, meat and eggs [2].

The storage of this vitamin is one of the main characteristics of water-soluble vitamins, as well as Vitamin B6 and Vitamin C. Its elimination mechanism is very slow, for this reason its daily intake is not necessary, as it can be stored in large amounts [3]. Vitamin B12 is essential for development in the human body, performing important metabolic and neurotrophic functions in the body, being necessary for the function of several enzymes important for energy metabolism and DNA synthesis [4].

Its deficiency leads to hematological, cardiovascular and neurological disorders that can be serious, mainly because it interferes with the metabolism of homocysteine (Hcy) and in the body's methylation reactions. In many cases, the deficiency can remain asymptomatic for long periods, triggering a chronic deficiency that can lead to irreversible neurological manifestations

[5]. Neurological manifestations caused by lack of vitamin B12 include polyneuropathy, myelopathy, dementia and optic neuropathy [6].

Vitamin B12 deficiency can be easily corrected with its supplementation, as long as its diagnosis is made early to avoid the extension of damage and prevent further injuries. Knowing the seriousness and importance of this vitamin for the human body, and its association with diseases, diagnosis through laboratory tests is essential, especially in risk groups [7]. According to studies about 1% of dementia in the elderly are due to vitamin B12 deficiency. In addition to the elderly, other population groups are at high risk for developing vitamin B12 deficiency, they are: vegetarians, people who have undergone bariatric surgery, patients with atrophic gastritis, pernicious anemia, gastric malabsorption, in addition to some medications that can interfere with the vitamin B12 absorption [4]. Estudos apontam que existe relação entre o aumento dos níveis de vitamina B12 e o sucesso no tratamento transtornos psicológicos e da depressão [8].

Therefore, in order to avoid irreversible damage, the early diagnosis of vitamin B12 deficiency is of paramount importance. However, the laboratory methodology for diagnosing vitamin B12 deficiency still has problems with sensitivity and specificity. Therefore, due to these aspects, this deficiency must be considered an important public health problem, especially among the elderly and restricted vegetarians [9]. The present work aims to present the effects of vitamin deficiency B12 can cause in the human nervous system, taking into account the groups/age groups that suffer most from the lack, namely: elderly, anemic, vegans, pregnant women with low protein replacement, restricted vegetarians and people who underwent bariatric surgery. Vitamin B12 plays important roles mainly in the maturation of red blood cells, in addition to multiple

roles in metabolic pathways necessary for the central nervous system and the peripheral nervous system [10]. The story of vitamin B12 began as a cure for pernicious anemia. Pernicious anemia is when the stomach is lacking a substance called intrinsic factor that makes the body unable to absorb vitamin B12. In 1920 Whipple conducted studies with dogs, letting them bleed to induce anemia, and then feeding them raw beef liver. And in 1926, two American physicians, Dr. Murphy and Dr. Minot, also found that consumption of liver was effective in treating pernicious anemia, then identified that it was due to an intrinsic factor produced by the stomach and an extrinsic dietary factor [9]. In 1945, an active principle, effective as an antianemic, was concentrated from liver tissue. Lester Smith and Folkers, in 1947, crystallized the active principle of the liver extract involved in the regression of anemia and called it vitamin B12, describing it as a cyanide compound containing a cobalt atom. The nutrient was only synthesized in 1948 by Dr. Dorothy Hodgkin [11].

Vitamin B12 Chemistry

Biochemically, vitamin B12 is the most complete of vitamins, with a molecular weight of 1.355kDa. The chemical structure of vitamin B12 composed of a tetrapyrrole ring that surrounds a central cobalt atom, a nucleotide group, which consists of the base 5,6-dimethylbenzimidazole and a phosphorylated ribose esterified with 1-amino, 2-propanol [12]. (Figure 1).

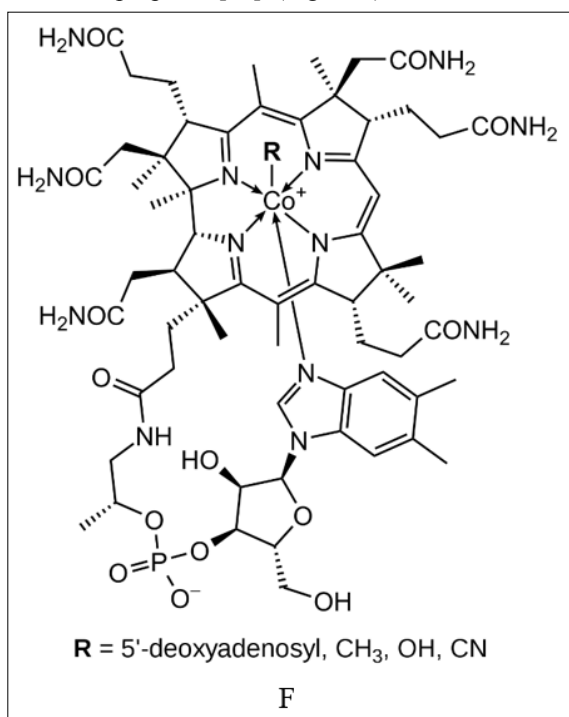


Figure 1: Vitamin structure B12

Adapted from Química Nova Interativa, Sociedade Brasileira de Química, 2011.

The bioavailability of vitamin B12 in healthy humans for beef, fish, chicken and sheep is on average 42%, 56 - 89% and 61 a 66%, respectively [13].

Serum Value of Vitamin B12

Literature considers values below 200pg/mL (148pmol/l) of vitamin B12 as low [7]. According to [14], in the presence of signs and symptoms of deficiency, in 97% of cases, vitamin B12 rates are below the reference value, demonstrating the importance of requesting this test, even in patients without symptoms. Serum

vitamin B12 measurement is the most commonly used test to diagnose vitamin B12 deficiency, due to its lower cost and already being better known [15].

Absorption Process

Vitamin B12 is present in animal protein, its absorption begins soon after the chewing process, where in saliva there is an R protein called haptocorrin serving as a protection mechanism, this complex being further degraded by hydrochloric acid (HCl) and pepsin with consequent transfer of the vitamin B12 molecule to a gastric intrinsic factor (IF), a protein produced by the stomach (Figure 2). The binding of vitamin B12 to FI forms a complex in the ileal mucosa that must resist proteolytic enzymes in the intestinal lumen and that, subsequently, FI binds to the cubillin receptor and is subsequently degraded, whereas vitamin B12 is absorbed and bound to a transporter plasma and released into the circulation and stored in the liver. Several hours are needed for its absorption (ULLELAND, 2002).

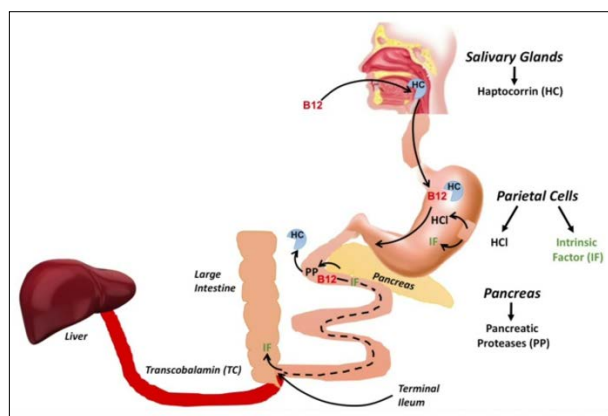


Figure 2: Vitamin B12 Absorption Process

Adapted from MARTIZES, Helena, Deficiencia de vitamina b12, causas, sintomas, prevención y tratamiento.

For a good absorption of the vitamin, alcohol and tobacco consumption should be avoided, as they are related to interference with absorption. You should also avoid consuming foods rich in fiber along with sources of vitamin B12, as fiber can also interfere with the absorption of the vitamin. In addition to some drugs that interact with vitamin B12, namely: neomycin, colchicine, aminosalicylic acid and metformin, minimizing its effective effect on the absorption process.

Because the body's need is low, this vitamin needs little replacement. Its storage is relatively adequate and it has a very efficient enterohepatic circulation, recovering a large part of the vitamin B12 excreted in the bile [16]. However, because the absorption of vitamin B12 is a very complex, time-consuming and delicate process that can be interfered with by a variety of factors, malabsorption is a very common cause of vitamin B12 deficiency. Thus, in many cases, patients with malnutrition, the elderly, restricted vegans and vegetarians, patients with depressive disorders, alcoholics and who underwent bariatric surgery, it is necessary to replace serum vitamin B12 [17].

Clinical Manifestations

Vitamin B12 deficiency is a very common condition in the elderly and tends to increase with age. A very relevant factor that potentiates problems arising from its deficiency is the fact that it is asymptomatic, which can last for many years until the appearance of any clinical symptoms, and subsequent risk of causing a chronic

deficiency of vitamin B12, which, if maintained for a long time, can lead to irreversible neuropsychiatric manifestations [18].

The clinical manifestations of vitamin B12 deficiency can be characterized mainly by a picture of megaloblastic anemia, but in other patients it can present neurological symptoms (depressive and cognitive disorders), associated with the appearance of the triad (weakness, glossitis and paresthesia). The clinical manifestations of vitamin B12 deficit are classified as polymorphic, ranging from milder states to very critical conditions [19].

According to studies pointed out by the Washington Institute of Medicine, around 75% to 90% of people with clinically relevant vitamin B12 deficiency had neurological disorders, and in only 25% of cases they were only clinical manifestations of vitamin deficiency [20]. The main hematological alterations of vitamin B12 deficiency are characterized by a decrease in hemoglobin, causing a megaloblastic anemia, in addition to a low platelet count. Neurological changes are the most worrying, where they are noticed due to progressive damage of the central and peripheral nervous systems, manifesting with polyneuritis, mainly sensory, starting with demyelination, followed by axonal degeneration, which can lead to brain death. common reports of memory deficits, cognitive dysfunction, dementia, and depressive disorders. For these reasons, in recent decades studies have alerted to the importance of vitamin B12 deficiency in the development of neurological damage in the adult population and even in children [18]. Clinical manifestations are also associated with adverse maternal and neonatal outcomes, where children born to women with vitamin B12 deficiency can suffer damage to psychomotor function and brain development, making them even more worrying than those that occur in children adults or adults [21]. Its deficiency also contributes to the increase in plasma concentrations of homocysteine (Hcy), a condition called Hyperhomocysteinemia (HHcy), an independent risk factor for atherosclerosis, considered a marker of degenerative diseases in the brain and cardiovascular [22].

Laboratory Diagnosis and Available Methodologies

Due to the seriousness and numerous associated pathologies that this deficiency represents, an early and efficient laboratory diagnosis is of paramount importance, in order to minimize or even prevent many of the disorders that could be produced or triggered by the absence of vitamin B12 [22].

The initial laboratory diagnosis consists of vitamin B12 replacement, through the ingestion of rich sources of vitamin B12, for example: liver, cheese, meat (muscles), kidney, milk, eggs and fish, or through the prescription of oral cobalamin or injectable, for cases that seek better absorption. This diagnosis is based on serum levels of vitamin B12, which in most cases is reduced. In recent years, the search for the development of new, more efficient tests to diagnose vitamin B12 deficiency has been on the agenda among physicians and researchers. Currently, the laboratory tests available to diagnose this deficiency are routine, such as the serum dosage of vitamin B12, which in most cases is low, and serum Hcy (homocysteine), in addition to the holo-Tc (transport glycoprotein) tests and urinary excretion of MMA (methylmalonic acid) more used for research and/or more restricted to specialized laboratories. As tests to diagnose vitamin B12 deficiency still show uncertainties regarding their specificity and sensitivity, many laboratory diagnostic difficulties have been encountered and a consensus has not yet been established for a test that would be considered standard in the market for this diagnosis [7].

Treatment and supplementation

The treatment for this deficiency is through the intake of sources rich in vitamin B12, such as liver, kidney, milk, eggs, fish, cheese and meat (mainly muscle), and oral or injectable cobalamin may also be prescribed, which are more recommended for get better food absorption. The response to treatment is related to the severity of the condition and the time between the first signs and the beginning of treatment [6].

After the diagnosis of vitamin B12 deficiency, even if associated with neuropsychomotor manifestations, treatment with administration of this nutrient is necessary, Cabrerizo- Garcia, et al. (2011), developed a treatment protocol in a 59-year-old male who presented complications related to vitamin B12 deficiency, after confirmation by blood dosage (30pg/dL). It was administered intramuscular injection of vitamin B12 at 1,000mcg/day and complex B orally twice/day ((0.5 mg) + B6 (250 mg) + B1 (250 mg)), after the first week of treatment, it was changed to same dosage, but 1x/week. Through this treatment, they observed, in the first week, an improvement in their cognitive status and re-establishment of the serum concentration of vitamin B12. After the first month, there was improvement in the rehabilitation of the lower limbs and tactile sensitivity, but there was no improvement in the depressive condition, nor in the impossibility of walking. In elderly people, the deficiency is usually caused by the difficulty in absorbing the vitamin mainly from meat, making them benefit from the intake of vitamin B12 supplements. Since they absorb the vitamin better through supplements than meat. This replacement can be performed through oral prescription and/or parenteral treatment [23].

For the treatment of pernicious anemia associated with lack of vitamin, it consists of supplements of high doses of vitamin B12, once diagnosed early, it has a good prognosis. In cases where people are deficient but are asymptomatic, the vitamin can be given orally. In addition, it is necessary to follow up with periodic exams to make sure that the vitamin B12 level has returned and remains normal [6]. For strict vegetarians, vegans, people who have undergone bariatric surgery, and for people who have very low levels of vitamin B12 or symptoms resulting from nerve damage, they are usually given an intramuscular injection of vitamin B12. These injections can be self-administered daily or weekly for several weeks until the vitamin B12 level normalizes. Only then can these injections be given once a month indefinitely, and can only be stopped when the deficiency is corrected. [24].

Conclusion

Vitamin B12, also known as cyanocobalamin is vital to the human body, being responsible for the formation and maintenance of essential components for the functioning of the human body, performing multiple functions in metabolic pathways (necessary for the central and peripheral nervous system) and neurotrophic, in addition to being important in the maturation of red blood cells. However, it is noteworthy that the lack of this vitamin can harm health, where patients with vitamin B12 deficiency can present various symptoms, such as pernicious anemia, hematological disorders and changes in the central nervous system, such as depression, peripheral neuropathy, behavioral changes and cognitive degeneration, which can lead to dementia. Serum levels of vitamin B12 below are common mainly in the elderly, vegans, restricted vegetarians, malnourished patients, with depressive disorders, alcoholics and who have undergone bariatric surgery. However, as seen in a review, there are cases of newborn children of mothers presenting vitamin B12 deficiency, especially mothers who adopt a low protein diet. Even today, there is no gold standard

test for diagnosing vitamin deficiency, pointing to the need for more research with defined standards in terms of time of use, dosage and best routes of administration for each population group. Tests available in the markets are based on serum and homocysteine (Hcy) levels. For this reason, it is very important that there is a more in-depth monitoring of vitamin B12 deficiency, first because it is a problem that in most cases is asymptomatic and that, if not treated correctly and early, can cause irreversible damage. Amid this scenario, pharmaceutical care would be of paramount importance in the early and correct diagnosis of this deficiency, and so patients who present any symptoms or signs can be referred to responsible physicians and treated correctly so that they achieve adequate levels of the vitamin in the body and they do not come to cause other major problems, and still can help in the development of new methodological researches.

Therefore, due to the serious problems that deficiency can bring to the human body, the importance of the vitamin must be elucidated so that in the future it does not become a public health problem [25-26].

Conflict of interest statement

The authors declare no conflict of interest.

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