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# VITAMIN B 12 CAUSES AND TREATMENTS

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**Abstract:**

***Introduction:*** *In this article, seven questions answered about vitamin B12 deficiency. We will discusses the absorption of vitamin B12, the physiology, the importance and prevalence of the deficit, the way to recognize it early, and then we will talk about the several laboratory biomarkers to detect vitamin B12 deficiency, and the treatment.Dorothy Hodgkin and her collaborators had discovered the entire structure of vitamin B12 by means of X-ray crystallographic methods. They have showed that the vitamin was a cobalt-containing, cyanolated, amidated tetrapyrrole. The location of the cobalt is in the center of a ring-contracted modified tetrapyrrole macrocycle, coordinated via the four pyrrole nitrogen atoms. The cobalamin tetrapyrrole ring, exclusive of cobalt and other sidechains, is called a corrin. All of the compounds which contain this corrin nucleus are called corrinoids. Cobalamins is different in the nature from additional side groups bound to cobalt, like hydroxyl (Hydroxycobalamin-H- Cbl), deoxy-5'- adenosine (Deoxy-5'- adenosylcobalamin- Ado- Cbl), and cyanide (Cyanocobalamin Cn-Cbl), Methyl (methylcobalamin-Me- Cbl). The term vitamin B12 is used to identify the various forms of cobalamin, like Me-Cbl and Ado-Cbl, and they are also identified as complete corrinoids. Me-Cbl and Ado-Cbl are the active forms of vitamins that are used as coenzymes in the human cells.2 Vitamin B12 is needed in these coenzyme forms to convert L-methylmalonyl CoA to succinyl-CoA and homocysteine to mehionine. These pathways are important in the metabolism of branched-chain amino acids and fatty acid and to regenerate the methyl donor S-adenosylmethionine. Its malfunction causes a shortage, affecting DNA synthesis and the physiological processes such as hematopoietic process of the red blood cells* ***Aim of work:*** *In this review, we will discuss Vitamin B 12 causes and treatments****Methodology:*** *We did a systematic search for Vitamin B 12 causes and treatments using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.****Conclusions:*** *Vitamin B12 deficiency is a widespread disease and has serious irreversible clinical complications. There is no single widespread agreed diagnostic biomarker for vitamin B12 deficiency. Additional studies are required to define such standard marker, and to check whether positivity of APCA or AIFA can indirectly confirm the difficiency.The Clinical Laboratory plays a basic role in vitamin B12 deficiency. It should design and lead active screening strategies to increase its detection before the clinical symptoms arise, identify cases of autoimmune disease, and promote prompt treatment after abnormal serological tests.*

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## INTRODUCTION:

In this article, seven questions answered about vitamin B12 deficiency. We will discuss the absorption of vitamin B12, the physiology, the importance and prevalence of the deficit, the way to recognize it early, and then we will talk about the several laboratory biomarkers to detect vitamin B12 deficiency, and the treatment.

Dorothy Hodgkin and her collaborators had discovered the entire structure of vitamin B12 by means of X-ray crystallographic methods. They have showed that the vitamin was a cobalt-containing, cyanolated, amidated tetrapyrrole. [1] The location of the cobalt is in the center of a ring-contracted modified tetrapyrrole macrocycle, coordinated via the four pyrrole nitrogen atoms. The cobalamin tetrapyrrole ring, exclusive of cobalt and other sidechains, is called a *corrin*. All of the compounds which contain this corrin nucleus are called corrinoids. Cobalamins is different in the nature from additional side groups bound to cobalt, like hydroxyl (Hydroxycobalamin-H- Cbl), deoxy-5′- adenosine (Deoxy-5′- adenosylcobalamin- Ado- Cbl), and cyanide (Cyanocobalamin Cn-Cbl), Methyl (methylcobalamin-Me- Cbl).

The term vitamin B12 is used to identify the various forms of cobalamin, like Me-Cbl and Ado-Cbl, and they are also identified as complete corrinoids. Me-Cbl and Ado-Cbl are the active forms of vitamins that are used as coenzymes in the human cells. [2] Vitamin B12 is needed in these coenzyme forms to convert L-methylmalonyl CoA to succinyl-CoA and homocysteine to mehionine. These pathways are important in the metabolism of branched-chain amino acids and fatty acid and to regenerate the methyl donor S-adenosylmethionine. Its malfunction causes a shortage, affecting DNA synthesis and the physiological processes such as hematopoietic process of the red blood cells. [3]

In article, we will talk about the most recent evidences regarding Vitamin B 12 causes and treatments.

## METHODOLOGY:

We did a systematic search for Vitamin B 12 causes and treatments using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.
The terms used in the search were: Vitamin B 12 causes, presentation, manifestations and treatments.

## HOW IS DIETARY VITAMIN B 12 ABSORBED?

Dietary vitamin B12 requires gastric acid and pepsin in the stomach to separate the proteins that normally bound to it. Salivary haptocorrin (HC) attaches vitamin B12 when it is free, to protect the vitamin from the low PH environment of the stomach while it is transported to the small intestine. In the small intestine, vitamin B12 binds to intrinsic factor (IF) that gastric parietal cells produce. In ileum, the cubam receptor binds the complex of IF-vitamin B12, which facilitates the endocytosis into the lysosome. In the lysosome, IF is degraded and the separated vitamin B12 is released into the cytosol and then transported to the circulation. HC bind about 80% of vitamin B12, whereas transcobalamin (TC) bind the remainder. IF and TC bind only vitamin B12. TC is the only one that is able to facilitate uptake into cells via the TC receptor-mediated endocytosis. [4]

## WHAT ARE THE KEY PHYSIOLOGICAL ROLES OF VITAMIN B 12?

Intracellular vitamin B12 is metabolized into adenosylcobalamin or methylcobalamin. Inside the cells, vitamin B12 acts as a coenzyme for 2 different enzymes, methylmalonyl-CoA mutase, and methionine synthase. [5] Vitamin B12 is vital for appropriate red blood cell formation, neurological function, and DNA and RNA synthesis. Impaired DNA synthesis can cause cell arrest in the DNA replication or S phase of the cell cycle, resulting in errors in DNA replication, and/or apoptotic death. [6]

## WHAT A RE T HE D IE TARY REQUIREMENTS OF VITAMIN B12?

As described in the vitamin B12 Dietary Fact Sheet from the National Institutes of Health (NIH), the sufficient daily intake of vitamin B12 ranges from 0.4 mcg in young infants to 2.4 mcg in adults; during pregnancy and breastfeeding, a slightly higher amounts might be needed.7 Half of total body storage of vitamin B12 is stored in the liver, the total ranges from 2 to 5 mg. deficiency of vitamin B12 usually do not develop for at least 1-2 years after intake ceases, and sometimes it takes longer. [7]

## WHAT IS T HE P RE VALENCE O F VITAMIN B 12 D EFICIENC Y?

Vitamin B12 deficiency prevalence varies among different populations and depends on the definition of deficiency and the threshold used to define it. Generally, vitamin B12 storage decreases with age so prevalence of vitamin B12 deficiency is increased in the elderly. The prevalence of vitamin B12 deficiency in the elderly differs depending on the

definition of vitamin B12 deficiency used and can range between 5% and 40%. [8]

Nearly 6% of people over 60 years in the western has vitamin B12 deficiency and as many as 20% may have marginal vitamin B12 status.10 In a 2016 series,249 patients had macrocytosis among 3324 patients with anemia in a general practice population in the Netherlands. [9] Of these, 46 had vitamin B12 deficiency (1.4% of all individuals with anemia; 18% of those with macrocytic anemia).

The groups at risk of vitamin B12 deficiency are [10]:
• The elderly (>65 years).
• Low absorption (eg, gastrectomy, celiac disease, Crohn's disease, bariatric surgery, pancreatic insufficiency, bacterial overgrowth, fish tapeworm infection).
• Autoimmune diseases (thyroid disease).
• Medication that intermediate vitamin absorption, metabolism or stability: proton pump inhibitors, nitrous oxide, and metformin.

In 65-year-old and above patients, the autoimmune disorders are common and associated with presence of anti-parietal cell antibodies (APCA), and anti-intrinsic factor antibody (AIFA); which leads to autoimmune-based gastric atrophy (ABG) with severe injury of the oxyntic gastric mucosa. The damage of parietal cells that produce hydrochloric acid in normal subjects, as well as IF, causes vitamin B12 deficiency. If this co-exists with anemia and macrocytosis, it is called pernicious anemia (PA), defined as the presence of hemoglobin concentration <13 g/dL for men and <12 g/dL for women, mean corpuscular volume ≥100 fL, low levels of vitamin B12, along with concomitant ABG and IF deficiency.

The definition of pernicious anemia is a macrocytic anemia caused by deficiency of vitamin B12, which, is caused by IF deficiency, IF is a protein that binds strongly to food vitamin B12 and facilitates its transport to the terminal ileum for absorption.14 The average age of patients with pernicious anemia can range between 59 and 62 years, that challenges the common understanding that pernicious anemia is an exclusive condition of older individuals, and suggests that, in everyday practice, pernicious anemia is likely under diagnosed among older individuals and younger individuals.16 Its prevalence is around two percent in people over sixty years and is not common before that age; with only ten percent of cases happening in individuals who are younger than forty years. It seems to be more common among females when compared to males, proven in a study of individuals older than sixty years, where the prevalence of pernicious anemia was 2.7 percent in females and 1.4 percent in males. [11]

Classically, vitamin B12 deficiency is associated to pernicious anemia. But, individuals with decreased serum vitamin B12 concentrations rarely have anemia or macrocytosis. Actually, early diagnosis and treatment leads to a decreased percentage of vitamin B12 deficiency in patients with pernicious anemia. [12]

## WHAT A RE T HE M AIN C LINIC AL MANIFESTATIONS O F V ITAMIN B 12 DEFICIENCY?

Vitamin B12 deficiency is usually silent and under-diagnosed, because of its slow beginning and development patients might get used to the symptoms. None the less, the clinical outcomes of undetected vitamin B12 deficiency might be critical and may include a plenty of neurological and mood disorders.

Vitamin B12 deficiency usually causes three major possible complications: haematological disorders like macrocytosis, anemia,hypersegmentation of neutrophils, leukopenia, thrombocytopenia, and of course megaloblastic changes in bone marrow. demyelinating disorder of the central nervous system that might results in critical and sometimes irreversible neurological problems. Gastric tumors when vitamin B12 deficiency is caused by autoimmune-based gastric atrophy. Of the three major complications of vitamin B12 deficiency, haematological condition may be cured with treatment, as opposed to neurological problems and gastric malignancy.

The most common conditions in primary care practice are subtle neurologic, cognitive, or psychiatric changes. In general, symmetric paresthesias or numbness and gait problems are the most common neurologic disorders found in vitamin B12 deficiency. The neuropathy is usually symmetrical and most of times affects the lower limps more than the upper. The usual neurologic signs in vitamin B12 deficiency, sub-acute combined degeneration of the dorsal (posterior) and lateral columns (white matter) of the spinal cord caused by demyelination, is distinctive if exist, but might not appear in all patients, especially if the diagnosis was made early in the course of the deficiency. In vitamin B12 deficiency patients, neuropsychiatric symptoms may exist even if there is no anemia or macrocytosis, and the absence of these hematologic changes can't be used in vitamin B12 deficiency exclusion. [13]

Other neurological-psychological symptoms include20
Depression or mood impairment

• Irritability
• Insomnia
• Cognitive slowing
• Forgetfulness
• Dementia
• Psychosis
• Visual problems, that might be associated with optic atrophy
• Peripheral sensory loss.
• Weakness that might developes to paraplegia and incontinence if
severe
• Impaired position sense
• Impaired vibration sense
• Lhermitte's sign, a shock-like sensation that radiates to the feet
during neck flexion
• Ataxia or positive Romberg test
• Abnormal deep tendon reflexes
• Extrapyramidal signs (eg, dystonia, dysarthria, rigidity)
• Restless legs syndrome

Vitamin B12 deficiency is basically a benign disease for most of patients. But, when deficit is caused by pernicious anemia, patients are Known to be at high risk for a gastric adenocarcinoma and gastric carcinoid type I. [14] Chronic hypergastrinemia in patients with pernicious anemia is Known to be associated with Enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids. It has been informed that nearly 4%-5% of individuals with pernicious anemia gets gastric carcinoids. Furthermore, the hypochlorhydria role in the progression of gastric malignancy has been highlighted. At last, ascorbic acid decreases in the condition of gastric atrophy and also its protective role. A prospective study had shown a gastric malignancy incidence in individuals with pernicious anemia of 0.1% to 0.5%. A study of individuals with autoimmune-based gastric atrophy during a montoring period of 6.7 years, has shown an annual incidence risk of 0.14 percent for developing gastric malignancy. [15]

It is necessary to increase our sensibility of this disease, whose definite diagnosis might be made by reliable and non-invasive serological screening. [16]

## WHAT B IOMARKERS A RE A VAIL ABLE TO D IAG NOSE V ITAMIN B 12 D EFICIENC Y?

Symptoms and signs of vitamin B12 deficiency are usually unclear and very often cannot be recognized. Early diagnosis and treatment are necessary before the development of irreversible or permanent neuropsychological symptoms. Number of scientists suggest vitamin B12 deficiency screening in the older people. But this strategy is not recommended in general and only focuses on individuals who have one or more risk factors, like gastric or small intestine resections, the exist of inflammatory bowel disease, long-term use of proton pump inhibitors, metformin, or histamine H2 blockers, vegans or strict vegetarians, and individuals older than 75 years. [17] Although there is no official recommendation for screening in asymptomatic individuals, the increased risk of incidence in older people, and easy and safe replacement therapy, more testing and treatment is recommended in older individuals. There are different serum biomarkers that may be beneficial in the work-up of a patient with vitamin B12 deficiency. Beside the vitamin B12 serum level test, holoTC is another biomarker that is reduced in the serum in vitamin B12 deficiency. high levels of total homocysteine (tHcy) and methylmalonic acid (MMA) are markers for intracellular vitamin B12 difficiency.

There is an association between serum vitamin B12 levels neurological symptoms like memory impairment and cognitive impairment. But the associations are stronger between cognitive impairment and holoTC and other metabolites of vitamin B12 (tHcy and MMA). This submit that holoTC may be a more credible index of intracellular vitamin B12 status than the standard vitamin B12 assay, although availability and cost would also have to prove its superiority. Despite this evidence, the request of vitamin B12 keeps increasing.

There are multiple limitations regarding the use of biomarkers in the identification of Vitamin B12 deficiency. Serum vitamin B12 assay is not standardized, [18] and there is no agreed upon cut-off to make a definition of deficiency. The World Health Organization recommended the use of 150 pmol/L (200 pg/ mL) in the year 2008; but, total vitamin B12 levels of 156-450 pmol/L could not exclude the presence of vitamin B12 deficiency, and some researchers even suggest those latter measurements to be too low. however, plasma MMA and tHcy are generally more expensive, not always available and reference intervals are not always standardized.

As the only part of dietary vitamin B12 that is bioavailable for systemic distribution is available in the form of holoTC, the levels of holoTC in blood has been efficiently used as a surrogate of bioactive vitamin B12.31 Holo-TC represents about twenty percent of total vitamin B12 present in serum. This marker is more accurate in estimating the biologically active part of vitamin B12 in bloodstream than serum vitamin B12 itself, and its level is associated with the concentrations of serum vitamin B12 in the erythrocytes. However, the diagnostic level of holoTC—the normal value in healthy people is between 20-125 pmol/L31—has shown superior to Hcy and MMA
for the estimating of vitamin B12 levels in older people. But an extra research is needed to clarify the mechanisms that control holoTC homeostasis in the healthy people and in pathophysiologies that change vitamin B12 transport and utilization. For example, the abnormal decreased levels of holoTC have been detected in individuals on chemotherapy, with macrocytosis, and in patients carrying the TC polymorphism 67A>G, with no strong proof of vitamin B12 deficiency. In addition, the insufficiency of the sensitivity (44 percent) of holoTC as a marker of vitamin B12 status was seen in a cohort of 218 institutionalized older individuals. [19] At present, it is still unknown whether holoTC levels change in individuals harboring inborn problems affecting intracellular vitamin B12 metabolism. So, the diagnostic value of holoTC as a first line test still requires more researches.

Anti-parietal cell antibodies (APCA), and anti-intrinsic factor antibody (AIFA) must be measured in the individuals with vitaminB12 deficiency. The sagnificance of evaluating Anti-parietal cell antibodies APCA in all B12 deficient individuals appears in that positivity is associated with increased risk of gastric carcinoma and gastric carcinoid tumor. Anti-parietal cell antibodies (APCA) are present in 90 percent of individuals with pernicious anemia but have low specificity and are found in autoimmune-based gastric atrophy (ABG) without megaloblastic anemia as well as in different autoimmune disorders. Anti-intrinsic factor antibody (AIFA) are Known to be less sensitive, have been found in only 60 percent of individuals with pernicious anemia, however they are considered highly specific for pernicious anemia.28 Actually, once the pernicious anemia is diagnosed in a patient, single endoscopic screening for gastric carcinoma and gastric carcinoid tumor is needed.

The diagnosis of intrinsic factor (IF) deficiency might be difficult, and excessing confidence is placed on detecting anti-intrinsic factor antibody (AIFA) for the diagnosis of pernicious anemia, which is considered as a beneficent marker of the disease. Previous studies have viewed that 40-60 percent of individuals with pernicious anemia have positive anti-intrinsic factor antibody (AIFA), which increases to 60-80 percent with prolonged duration of disease,35 which yielded for anti-intrinsic factor antibody (AIFA) , a sensitivity and specificity of 37percent and 100 percent, respectively, and for Anti-parietal cell antibodies (APCA), a sensitivity and specificity of 81 percent and 90 percent, respectively. The combination of the two autoantibodies in the assessment rises the diagnostic performance, with 73 percent sensitivity and 100 percent specificity.

Additional researches should study the presence of anti-intrinsic factor antibody (AIFA) in vitamin B12 deficient individuals without anemia. Actually, in addition of being a specific hallmark of pernicious anemia, anti-intrinsic factor antibody (AIFA) and Anti-parietal cell antibodies (APCA) might be explained as an expression of injury to the oxyntic mucosal, given the connection between histological score of autoimmune-based gastric atrophy (ABG) and the titer of both antibodies. Anti-parietal cell antibodies (APCA), were detected in thirteen of the ninety-five individuals examined, and anti-intrinsic factor antibody (AIFA) indicative of pernicious anemia in three of the thirteen individuals. As APCA and AIFA indicate autoimmune-based gastric atrophy (ABG), in an individual with a positive test might be an indirect indicator to diagnose vitamin B12 deficiency, which solve, at least in these conditions the problem of the lack of a reliable serum marker for diagnosis.

## WHAT I S T HE T RE ATMENT O F VITAMIN B 12 D EFICIENC Y ?

Vitamin B12 replacement therapy allows to repair the anemia, whereas the neurological disorders might be reversed only if replacement therapy is given early after onset. The classic treatment of vitamin B12 deficiency is the intramuscular (IM) injection of cyanocobalamin, in general, 1 mg/d for 1 week, followed by 1 mg/wk for 1 month, and then 1 mg every 1 or 2 months ad perpetuum.
Oral administration of high-dose vitamin B12 (1 to 2 mg daily) is known to be as effective as IM for repairing anemia and neurologic disorders.27 But, in spite of multiple researches suggesting oral administration of vitamin B12 to be easy, effective and cheaper than IM, argument surrounds the efficacy of the oral administration. This might help clarify why it is not generally used by physicians.

## CONCLUSIONS:

Vitamin B12 deficiency is a widespread disease and has serious irreversible clinical complications. There is no single widespread agreed diagnostic biomarker for vitamin B12 deficiency. Additional studies are required to define such standard marker, and to check whether positivity of APCA or AIFA can indirectly confirm the difficiency.

The Clinical Laboratory plays a basic role in vitamin B12 deficiency. It should design and lead active screening strategies to increase its detection before the clinical symptoms arise, identify cases of autoimmune disease, and promote prompt treatment after abnormal serological tests.

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