



Review article

Vitamin B12 deficiency and depressive symptoms: A narrative review of the literature

Deficiencia de vitamina B12 y síntomas depresivos: una revisión narrativa de la literatura

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How to cite this article: Barliza-Quintana FA, Pachón CA. Vitamin B12 deficiency and depressive symptoms: A narrative review of the literature. Duazary. 2024;21:148-157. <https://doi.org/10.21676/2389783X.5828>

Received on March 20, 2024

Accepted on June 30, 2024

Posted online June 30, 2024

ABSTRACT

Depression has a complex origin that involves genetic, neurophysiological, hormonal, psychosocial, and environmental factors. There is a possible relationship between vitamin B12 deficiency and depression, with evidence that supplementation may alleviate symptoms in adults treated with selective serotonin reuptake inhibitors. Although this association has been found, a direct causal relationship has yet to be established, which requires more rigorous research. This article reviews and synthesizes the available evidence on this relationship and its clinical implications. More studies are needed to confirm the association and detection in at-risk populations.

Keywords: Vitamin B12 deficiency; Depression; Revision.

RESUMEN

La depresión tiene un origen complejo que involucra factores genéticos, neurofisiológicos, hormonales, psicosociales y ambientales. Existe una posible relación entre la deficiencia de vitamina B12 y la depresión, con indicios de que la suplementación puede aliviar los síntomas en adultos tratados con inhibidores selectivos de la recaptación de serotonina. Aunque se ha encontrado esta asociación, aún falta establecer una relación causal directa, lo que demanda investigaciones más rigurosas. Este artículo revisa y sintetiza la evidencia disponible sobre esta relación y sus implicaciones clínicas. Se requieren más estudios para confirmar la asociación, la detección en poblaciones de riesgo.

Palabras clave: deficiencia de vitamina B12; depresión; revisión.

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INTRODUCTION

The World Health Organization estimates that more than 264 million people worldwide suffer from major depressive disorder (depression) at some point in their lives.¹ This constitutes one of the leading causes of disease burden in terms of disability-adjusted for years of life.² Depression is one of the most frequent and costly mental disorders worldwide, with a current prevalence in adults between 5 and 19%.^{3,4} Approximately 75% of people with depression experience a second episode at some point in their lives. Depression contributes substantially to excess mortality, both directly due to suicide and indirectly due to concurrent chronic diseases that increase the risk of mortality between 60 and 80%.⁴ For these reasons, this disease is expected to be the primary disease burden worldwide in 2030.³

The etiology of depression constitutes a complex and dynamic enigma under constant investigation. Recent findings point to a multifaceted origin that may involve genetic, neurophysiological, and hormonal components, as well as stress-related triggers and psychological and social factors.⁵ The interaction between these genetic, psychosocial, environmental, and experiential elements is crucial to understanding the predisposition to depressive disorder throughout the life course.^{4,5} This understanding would broaden the vision of the etiopathogenesis of depression and direct our efforts toward more precise and effective preventive and therapeutic interventions.³⁻⁵

Simultaneously, research has investigated the relationship between depressive symptoms and the influence of vitamins for several decades.⁶⁻⁹ The possible deficiency of vitamin B12 and its correlation with depressive symptoms have been the subject of intense research in recent years. Experiments in animal models have shown encouraging results when supplementing with cobalamin, showing significant improvements in symptoms associated with depression.¹⁰ While most studies explore deficient levels of vitamin B12 in conjunction with other B vitamins, such as B6 or B9, and other biomarkers, such as homocysteine,¹¹⁻²¹ more recent research has highlighted the direct relationship between low levels of cobalamin and depressive symptoms in older adults, regardless of folate levels.²²⁻²⁴

The findings of Hutto *et al.*¹¹ point out that 31% of patients diagnosed with depression had deficient levels of vitamin B12. Additional research, such as that carried out by Ebesunun *et al.*¹⁴ and Syed *et al.*²⁴ supported this association by showing that low levels of B12 are linked to the manifestation of depressive symptoms. Likewise, it has been observed that the combination of selective serotonin reuptake inhibitors and B12 supplementation leads to significant improvements in patients diagnosed with depression.^{24,25}

Although a considerable number of studies highlight the relationship between vitamin B12 deficiency and major depressive disorder,^{11-20,23,25-27} None establishes a direct cause-and-effect relationship between both phenomena. The prevalence of vitamin B12 deficiency among patients with depression varies considerably across studies, highlighting the lack of consensus in the scientific community regarding this connection.¹⁸

Additionally, the diversity of the studies, ranging from geographic location to the diagnostic criteria used, indicates the need for a more homogeneous approach in future research.²⁰ Despite the promising findings, debate persists regarding the precise nature of the relationship between vitamin B12 deficiency and depression, underscoring the inherent complexity of this phenomenon and the urgency of conducting more rigorous research to understand its clinical implications fully.²⁰ This review aims to update knowledge on the relationship between vitamin B12 deficiency and depression.

B12 vitamin

Vitamins and minerals are essential for humans, playing important roles in various primary metabolic pathways that support fundamental cellular functions.^{9,28} In particular, their participation in energy metabolism, DNA synthesis, oxygen transport, and neuronal functions makes them critical for brain and muscle function.²⁸⁻³⁰

Cyanocobalamin is a water-soluble vitamin that is part of the B complex vitamins. Humans do not synthesize it. Therefore, it must be consumed through a diet of animal origin, such as fish, meat, dairy products, eggs, and certain fortified foods.^{29,30} The daily intake of vitamin B12 depends on age; the average amount recommended for an adult is 2.6 µg per day.²⁸ Absorption in the enterocyte of the distal ileum depends on the intrinsic factor.^{7,31}

The liver is the storage site for this vitamin (1,000-3,000 µg), so a deficiency in subjects with standard absorption mechanisms manifests between 3 and 6 years after a decline.³¹ The clinical manifestations that occur when serum vitamin B12 levels are below normal are hematological and neuropsychiatric changes.^{31,32}

Vitamin B12 is the largest of the B complex vitamins with a molecular weight of 1,355.3 daltons, which results from the asymmetric union of four pyrrolic rings, forming an almost planar macrocyclic group (Corrine nucleus) around a central cobalt atom, which is why this vitamin is also known as cobalamin.³³

Most vitamin B12 in cells and liver is found in the mitochondria as 5' deoxyadenosylcobalamin. At the same time, methylcobalamin is the main form of cobalamin in plasma, although small amounts of this coenzyme can be found in the cells.^{33,34} Cyanocobalamin (crystalline B12) is the most used medicinal form in most supplements and fortified foods, characterized by presenting a cyanide group in one of the axial positions. In the body, it is quickly converted into 5-deoxyadenosyl and methylcobalamin.²⁸

Vitamin B12 is bound to proteins in the diet, released by acidity and gastric proteolysis. Subsequently, it binds to the R protein, secreted by the salivary and esophageal glands. In the duodenum, the alkaline environment allows the release of B12, binding to intrinsic factor (IF), a protein secreted by gastric parietal cells.^{31,36,37}

In the enterocyte, the IF-B12 complex is taken up by endocytosis, adhering to cubilin receptors in the distal ileal mucosa.^{29,31} Once inside the cell, vitamin B12 is released from IF and subsequently linked to transport proteins: transcobalamin (TC) I, II, and III entering via portal circulation to the liver and all tissues.^{29,31} Transcobalamin II (TC-II) plays a vital role since the amount of TC-II-vitamin B12 complex known as holo-transcobalamin represents the biologically active fraction and is a reliable parameter of the amount of vitamin B12 usable in an individual.^{34,38}

Cyanocobalamin and hydroxycobalamin must be converted to 5' deoxyadenosyl and methylcobalamin, the coenzymatically active forms of cobalamin, to be helpful to the cell. The reduction and alkylation of the aforementioned pharmacological forms achieve this activation.^{35,36,38} This is achieved by reducing and alkylating the aforementioned pharmacological forms.³⁵ Cyanocobalamin and hydroxycobalamin are first reduced to Co²⁺ (cob(II)alanine) by NADPH- and NADH-dependent reductases in mitochondria and microsomes. During this reduction, the cyanide and hydroxyl are displaced from the metal.^{35,36} A portion of the cob(II) alanines are reduced in the mitochondria to the intensely reduced form Co⁺ (cob(I) alanine), which ATP alkylates to form 5' deoxyadenosylcobalamin in a reaction in which the 5' deoxyadenosyl portion of ATP is transferred to cobalamin and the three phosphates are released as inorganic triphosphate.^{37,39} The rest of

the cobalamin binds to the cytosolic 5-N-methyl-tetrahydrofolate-homocysteine methyltransferase, where it is converted to methylcobalamin.^{36,37,39}

Vitamin B12 has two critical metabolic roles in our body since it functions as an essential coenzyme for two enzymes: 1) cytoplasmic methionine synthetase, which catalyzes the methylation of homocysteine and its conversion to methionine, as well as the conversion of methyl-tetrahydrofolate to tetrahydrofolate and 2) the enzyme methyl malonyl-CoA mutase reductase, which catalyzes the conversion of methyl malonyl-CoA to succinyl-CoA in the mitochondria.^{34,40}

The first is directly involved with folic acid; cobalamin is necessary for transforming methyl-tetrahydrofolate to tetrahydrofolate, the active form of folic acid. Therefore, low levels of vitamin B12 also generate a functional depletion of available folic acid, a phenomenon known as the "folate trap."^{7,32,41} Both vitamins promote the synthesis of tetrahydrobiopterin, which in turn participates as a cofactor in the tyrosine and tryptophan pathway, necessary for producing the neurotransmitters norepinephrine and serotonin.^{41,42} Folate facilitates the generation of S-adenosyl methionine, a donor of methyl groups necessary for forming the previously mentioned neurotransmitters. In addition, it promotes the synthesis of DNA and membrane phospholipids, receptors, channels, and second messengers.^{7,32,43} These metabolic alterations are reflected in myelin lesions, decreased myelotrophic growth factor, endothelial injury, cell apoptosis, decreased GABA, blood-brain barrier dysfunction, and phospholipid methylation in neuronal membranes.^{32,43}

The second is related to lipid metabolism.^{28,40} Disruptions in any of these metabolic pathways result in elevated levels of homocysteine and methylmalonic acid.^{28,40,44} Traditionally, it has been known that the most frequent cause of deficiency is poor absorption, but possibly in underdeveloped countries, nutritional deficiency is a more relevant factor.³⁰ Other causes that must be taken into account during the study of a patient with vitamin B12 deficiency are being a strict vegetarian or vegan, use of metformin, gastric diseases (atrophic gastritis, absence of intrinsic factor, pernicious anemia, infiltrative disorders of the stomach), mixed problems (post-gastrectomy disease, gastric bypass, bariatric surgery), intestinal disorders (luminal defects, bacterial overgrowth in the small intestine, parasite infestation, Zollinger-Ellison syndrome, pancreatic insufficiency), ileal defects (ileal resection, ileal disease, malabsorption induced by drugs, alcohol or congenital cobalamin malabsorption), plasma transport disorders (congenital transcobalamin II deficiency, protein R deficiency) and alterations in tissue metabolism (exposure to nitrous oxide, or inborn errors of metabolism).^{36,45-49}

Depression

The pathophysiology of depression is not yet fully understood, as it is believed to involve a complex interaction between biological, psychological, and environmental factors. However, several theories try to explain how this disease develops.⁵⁰

The monoaminergic hypothesis of depression suggests that the disease is due to a deficiency of monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) due to an unknown pathological process, stress, or drugs, which would directly affect neuronal communication and emotional regulation, causing depressive symptoms.⁵⁰

Due to the difficulties of the monoaminergic hypothesis, the attention of theories about the origin of depression focused on its receptors and the subsequent molecular events that they trigger; the monoamine

receptor and gene expression hypothesis proposes that an abnormality in monoamine receptors leads to depression: neurotransmitter depletion causes compensatory upregulation of post-synaptic receptors for these neurotransmitters.⁵⁰

Finally, the neurotrophic hypothesis of depression states that the disease would be caused by a reduction in the synthesis of proteins involved in neurogenesis and synaptic plasticity, such as brain-derived neurotrophic factor (BDNF).⁵⁰⁻⁵² Stress can reduce serotonin levels, acutely increase, and deplete norepinephrine and dopamine.⁵⁰ These changes in monoamine neurotransmitters, together with deficient amounts of BDNF, can lead to atrophy and possible apoptosis of vulnerable neurons in the hippocampus and prefrontal cortex; this could generate overactivity of the hypothalamic/pituitary/adrenal axis and increased levels of glucocorticoids that They could be toxic to neurons and contribute to their atrophy under chronic stress, generating known depressive symptoms.⁵⁰⁻⁵²

Vitamin B12 and depression

The relationship between depressive symptoms and vitamins has been the subject of research in recent years. The history of the relationship between hypovitaminosis and neuropsychiatric symptoms is not new.^{6,53} The discussion has changed since the discovery of vitamins in 1940 and has migrated from hypotheses that strongly link them with psychiatric symptoms to more antivitamin theories.⁷

Numerous studies have been conducted to determine the relationship between vitamin B12 and depression and whether supplementation with this vitamin can slow the progression of depression or prevent it.^{8,23} To date, there is little evidence showing the benefits of this behavior. However, some studies have shown positive effects in patients with the disease.²³⁻²⁵

Vitamin B12 deficiency and depression are two prevalent conditions in the general population. Vitamin B12 deficiency affects 2.5% and 26% of adults over 18.^{26,27,42,46} Depression occurs in around 3.8% to 5% of the world's population.^{1, 54, 55} Although the relationship between the two is still not entirely clear, some studies suggest that vitamin B12 deficiency could be associated with the clinical presentation of depression.^{11,13,14,16,17,19,21,23-25}

A possible mechanism that could explain this relationship is the accumulation of homocysteine since higher levels of homocysteine are associated with a phenomenon called "methionine loading": A deficiency of vitamin B12 along with B6 and folate generally prevents the conversion of homocysteine into methionine, increasing homocysteine levels.^{23,44} Homocysteinemia can also occur in patients with kidney disorders or genetic alterations of methyl-tetrahydro-folate reductase or cystathionine beta-synthetase, which are necessary for homocysteine metabolism.^{8,41,44} Higher homocysteine levels affect DNA formation and overall red blood cell turnover, leading to the development of megaloblastic or pernicious anemia and ultimately affecting the cognitive ability and mood of the patient.²³

However, in recent years, it has been known that clinical disorders associated with deficiency of this vitamin, especially neuropsychiatric disorders, can occur with serum vitamin B12 values within limits accepted as normal-low and with the absence of hematological alterations.⁵³

Vitamin B12 is interdependent with other micronutrients, mainly vitamin B6 and folate.^{8,27} This interdependence affects multiple neuronal pathways not directly controlled by vitamin B12. Neurotransmitters are required to conduct signals from one neuron to another with the help of pre- and post-synaptic junctions. A malfunction of any of these pathways can lead to depression.²³

Clinical implications

The request for vitamin B12 levels is expected in the clinical practice of psychiatry and, according to current evidence, it is recommended to screen in risk populations: adults over 65 years of age, diagnosis of major neurocognitive impairment (dementia), alterations in intestinal absorption and intrinsic factor production, history of bariatric surgery, genetic deficiency, inadequate intake, *Helicobacter pylori* infection, prolonged use of drugs such as H2 antagonists, proton pump inhibitors, anticonvulsants, metformin, alcoholism or use of psychoactive substances) and not routinely in all people who meet the criteria for a mental disorder.^{7,56}

According to the measurement of serum levels of vitamin B12,⁷ the following classification has been established:

- Normal: when they are above 350 pg /ml.
- Low normal: between 200 and 350 pg /ml.
- Low: when they are less than 150-200 pg /ml
- Serious: when they are less than 50 pg /ml.

Initial laboratory evaluation should include a complete blood count and serum vitamin B12 level. Additionally, serum measurement of methylmalonic acid is recommended to confirm the deficiency, especially in asymptomatic high-risk patients.^{48,57} The traditional treatment of clinical manifestations associated with vitamin B12 deficiency is vitamin replacement through oral or parenteral routes. The most used strategy is parenteral replacement, in which it is recommended to administer 1000 µg of cyanocobalamin weekly for eight weeks and then monthly until the deficiency is corrected,⁴⁷ The recommended oral dose varies between 1 and 2 mg/day for three or four months and is indicated for patients who reject the intramuscular route.⁴⁹

Although vitamin replacement is essential for treating vitamin B12 deficiency and its clinical manifestations,^{47,49} the growing evidence on the relationship between this deficiency and depression in adults has generated the need to understand this association better and its underlying biological mechanisms.²⁰

CONCLUSIONS

Although some studies support the association between low levels of cobalamin and depressive symptoms, the exact nature of this connection and its role in the pathophysiology of depression is unknown. The complexity of the phenomenon is reflected in the variety of factors that can influence vitamin B12 levels and predisposition to depression.

The current findings suggest that vitamin B12 deficiency could contribute to the onset or exacerbation of depressive symptoms, possibly through homocysteine accumulation and alterations in neurotransmitter synthesis. However, the lack of consensus in the scientific community highlights the need for more rigorous research to understand the clinical implications of this relationship fully.

In clinical practice, it is recommended to consider evaluating vitamin B12 levels in at-risk populations and patients with depressive symptoms, especially those with known risk factors for vitamin B12 deficiency. Vitamin replacement is the primary treatment for correcting the clinical manifestations of vitamin B12 deficiency. A deeper understanding of this relationship may open new opportunities for more precise preventative and therapeutic interventions in the future.

ACKNOWLEDGEMENTS

We want to thank all those who participated directly or indirectly in this study.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

AUTHORS' CONTRIBUTION

FABQ participated in the conceptualization and design of the study, bibliographic review, writing, and final approval of the manuscript.

CAP collaborated in the conceptualization and design of the study, writing, and final approval of the manuscript.

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