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Prevalence of Vitamin B12 Deficiency in Patients with Depressive Symptoms: Clinical and Biochemical Correlations

Roberto Lozano [1,*] and Carina Bona [2]

[1] *Department of Pharmacy, University clinical hospital"Lozano Blesa", Zaragoza, Spain.*
[2] *Unit for the Rational Use of Medicines, Aragon Health Service, Zaragoza, Spain.*

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Abstract

Objective: To evaluate the prevalence of vitamin B12 deficiency in patients presenting with depressive symptoms and to explore its biochemical and clinical implications. Methods: Observational study assessing serum vitamin B12, folate, ferritin, thyroid function, and homocysteine in patients with depressive symptoms. Results: Vitamin B12 deficiency was identified in a significant proportion of patients, with associated elevations in homocysteine and frequent comorbid deficiencies in ferritin and thyroid dysfunction. Conclusion: Vitamin B12 deficiency is a common yet underrecognized contributor to depressive symptomatology, and routine screening should be integrated into psychiatric evaluations.

Keywords: Vitamin B12 deficiency; Depression; Homocysteine; Ferritin; Thyroid function

1. Introduction

Depression is a prevalent and disabling psychiatric disorder, affecting more than 280 million people worldwide. It is characterized by persistent low mood, anhedonia, cognitive impairment, and somatic symptoms that significantly impair daily functioning [1]. Despite extensive research, the etiology of depression remains multifactorial, encompassing genetic, neurobiological, psychosocial, and nutritional factors. Among the nutritional contributors, deficiencies in essential vitamins, particularly vitamin B12, have gained increasing attention due to their role in neuropsychiatric functioning [2].

Vitamin B12 (cobalamin) is an essential water-soluble vitamin that serves as a cofactor in DNA synthesis, fatty acid metabolism, and the methylation cycle. Its deficiency results in impaired synthesis of methionine and S-adenosylmethionine (SAMe), leading to hyperhomocysteinemia and disrupted methylation of neurotransmitters [3]. This biochemical disturbance has been implicated in mood disorders, cognitive decline, and neurodegeneration. Low levels of vitamin B12 have been reported in 10–30% of psychiatric populations, with higher prevalence among elderly patients, vegetarians, and those with malabsorption syndromes [4].

The neuropsychiatric manifestations of vitamin B12 deficiency extend beyond classic megaloblastic anemia. Patients may present with depression, irritability, memory loss, psychosis, and neuropathy, often in the absence of hematological abnormalities [5]. This dissociation between psychiatric and hematological features can delay recognition and diagnosis in psychiatric settings. Moreover, vitamin B12 deficiency frequently coexists with other biochemical alterations, including folate deficiency, iron deficiency (low ferritin), and thyroid dysfunction, all of which may independently or synergistically exacerbate depressive symptoms [6].

* Corresponding author: Roberto Lozano

Epidemiological studies have demonstrated a bidirectional relationship between depression and nutritional deficiencies. Depressive symptoms may lead to poor dietary intake and malabsorption, while vitamin deficiencies may worsen mood and cognitive performance. For example, folate deficiency impairs methylation reactions in the central nervous system, potentiating the effects of B12 deficiency. Iron deficiency contributes to fatigue, poor concentration, and anhedonia, overlapping with depressive features [7]. Thyroid dysfunction, particularly hypothyroidism, is another established risk factor for depressive symptoms, highlighting the importance of an integrative biochemical approach.

Hyperhomocysteinemia, a metabolic consequence of B12 deficiency, has been consistently linked to depression and cognitive impairment. Elevated homocysteine exerts neurotoxic effects through excitotoxicity, oxidative stress, and endothelial dysfunction, contributing to neuronal injury and cerebral small vessel disease [8]. Clinical studies have reported that elevated homocysteine is associated with poorer antidepressant response and increased risk of treatment-resistant depression [9]. Thus, measuring homocysteine alongside vitamin B12 provides additional insight into the metabolic basis of depressive symptoms.

Despite these associations, screening for vitamin B12 deficiency is not routinely performed in psychiatric practice. Standard evaluations often overlook nutritional biomarkers, focusing instead on neurochemical hypotheses of depression. This gap in practice delays diagnosis and potentially deprives patients of simple, effective, and inexpensive interventions such as vitamin supplementation. The present study aims to evaluate the prevalence of vitamin B12 deficiency in patients with depressive symptoms and to analyze its biochemical and clinical correlates, thereby emphasizing the relevance of integrated nutritional assessment in psychiatric care.

2. Materials and Methods

This observational cross-sectional study was conducted at a tertiary care psychiatric hospital. Patients presenting with depressive symptoms were consecutively recruited from outpatient clinics. Inclusion criteria included: (i) clinical diagnosis of depressive disorder based on DSM-5 criteria, (ii) age between 18 and 75 years, and (iii) informed consent to participate. Exclusion criteria comprised recent vitamin supplementation (within the past 3 months), chronic gastrointestinal disease affecting absorption (e.g., celiac disease, Crohn's disease), renal failure, or ongoing chemotherapy.

Clinical assessments included psychiatric evaluation, structured symptom rating scales (Hamilton Depression Rating Scale, HDRS), and physical examination. Sociodemographic data (age, sex, dietary habits, alcohol use, smoking status) and comorbid medical conditions were recorded. Medication history, including antidepressants, mood stabilizers, and antipsychotics, was documented.

Laboratory investigations included serum vitamin B12, folate, ferritin, thyroid-stimulating hormone (TSH), free T4, and plasma homocysteine levels. Vitamin B12 deficiency was defined as serum B12 <200 pg/mL, borderline deficiency as 200–300 pg/mL, and normal as >300 pg/mL. Folate deficiency was defined as serum folate <4 ng/mL. Iron deficiency was defined as ferritin <30 ng/mL. Thyroid dysfunction was defined based on abnormal TSH or free T4 levels. Hyperhomocysteinemia was defined as plasma homocysteine >15 µmol/L.

Kernel density estimation was applied to analyze population distributions of B12, ferritin, and TSH values, enabling identification of subgroups within the sample. Comparisons between groups were performed using Student's t-test for continuous variables and chi-square tests for categorical variables. Correlation analyses were conducted between serum B12 and homocysteine levels, as well as between B12 and HDRS scores. Statistical significance was set at $p<0.05$. Analyses were performed using SPSS version 25.0.

The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants. Patient confidentiality was strictly maintained throughout the study.

3. Results

The study cohort consisted of 80 patients (52 females, 28 males) with a mean age of 44 ± 13 years. All patients presented with depressive symptoms, with mean HDRS scores of 23 ± 6, indicative of moderate to severe depression.

Serum vitamin B12 levels showed a mean of 280 ± 110 pg/mL. According to established thresholds, 18 patients (22.5%) had deficiency (<200 pg/mL), 25 patients (31.2%) had borderline levels (200–300 pg/mL), and 37 patients (46.2%)

had normal levels (>300 pg/mL). Kernel density analysis revealed three distinct subpopulations of B12 distribution, suggesting heterogeneity in metabolic vulnerability.

Plasma homocysteine levels were elevated (>15 μmol/L) in 20 patients (25%), with mean levels of 14.8 ± 6.2 μmol/L across the cohort. There was a significant inverse correlation between serum B12 and homocysteine ($r = -0.46$, $p<0.01$), confirming the metabolic impact of B12 deficiency. Patients with homocysteine elevation reported higher HDRS scores, consistent with more severe depressive symptoms.

Folate deficiency was identified in 12 patients (15%), while iron deficiency (ferritin <30 ng/mL) was present in 16 patients (20%). Thyroid dysfunction was observed in 10 patients (12.5%), predominantly hypothyroidism. Subgroup analysis indicated that patients with combined deficiencies (e.g., low B12 plus low ferritin) exhibited significantly higher depression severity compared to those with isolated or no deficiencies ($p<0.05$).

Gender-specific analysis showed that females were more likely to present with low ferritin (25% vs. 10% in males), while males exhibited higher rates of hyperhomocysteinemia (30% vs. 23%). No significant sex differences were observed in B12 deficiency prevalence.

Overall, the findings underscore the substantial prevalence of vitamin B12 deficiency and related biochemical abnormalities among patients with depressive symptoms. These deficiencies appear to contribute to depression severity and may represent modifiable risk factors amenable to targeted intervention.

4. Discussion

This study highlights the high prevalence of vitamin B12 deficiency among patients with depressive symptoms, with nearly one-quarter of participants exhibiting frank deficiency and an additional one-third presenting with borderline levels. These findings are consistent with previous studies reporting elevated rates of B12 deficiency in psychiatric populations [2,4]. The correlation between low B12 and elevated homocysteine further supports the mechanistic link between nutritional status and mood disorders.

Vitamin B12 deficiency has been implicated in depression through multiple pathways. Elevated homocysteine, a direct consequence of impaired B12-dependent remethylation, induces neurotoxicity via excitotoxicity, oxidative stress, and endothelial dysfunction [8]. Homocysteine also disrupts monoamine neurotransmitter synthesis, thereby compromising serotonergic and dopaminergic function, which are central to mood regulation [9]. In addition, B12 deficiency impairs myelin synthesis, potentially contributing to cognitive and affective symptoms.

The co-occurrence of B12 deficiency with folate and iron deficiency in our cohort underscores the multifactorial nutritional vulnerability of depressed patients. Both folate and iron play crucial roles in neurotransmitter synthesis and energy metabolism. Folate deficiency exacerbates hyperhomocysteinemia, while iron deficiency impairs dopamine metabolism, leading to fatigue, cognitive slowing, and anhedonia [7]. Similarly, thyroid dysfunction was observed in 12.5% of patients, reinforcing the importance of endocrine evaluation in depression.

Our findings also suggest a dose-response relationship between metabolic abnormalities and depression severity. Patients with multiple deficiencies demonstrated higher HDRS scores, highlighting the cumulative impact of nutritional and endocrine imbalances on mental health. These results emphasize the need for comprehensive biochemical screening in psychiatric populations.

From a clinical perspective, routine evaluation of vitamin B12 and related biomarkers should be incorporated into standard diagnostic protocols for depression. Simple and inexpensive laboratory tests can identify deficiencies amenable to supplementation. Randomized controlled trials have demonstrated that vitamin B12 supplementation, alone or in combination with folate, improves depressive symptoms and enhances response to antidepressants, particularly in deficient individuals [10]. Similarly, correction of iron and thyroid abnormalities can improve energy, cognition, and mood.

The overlap between psychiatric and somatic symptoms poses diagnostic challenges. Fatigue, poor concentration, and irritability are characteristic of both depression and B12 deficiency. Without laboratory evaluation, clinicians may attribute these symptoms solely to psychiatric illness, delaying recognition of treatable deficiencies. This highlights the importance of interdisciplinary care, integrating psychiatry, primary care, and laboratory medicine.

Limitations of this study include its cross-sectional design, which precludes causal inference, and the relatively small sample size. Additionally, dietary intake and absorption status were not assessed, limiting interpretation of underlying etiologies. Nevertheless, the use of biochemical markers, correlation analyses, and kernel density estimation strengthens the validity of the findings.

Future research should focus on prospective studies evaluating the impact of B12 supplementation on depressive outcomes, as well as mechanistic studies clarifying the interplay between nutritional, endocrine, and psychiatric factors. Genetic studies examining polymorphisms in one-carbon metabolism may also provide insights into individual susceptibility.

Overall, our results reinforce the role of vitamin B12 deficiency as a modifiable contributor to depressive symptoms and advocate for its systematic evaluation in psychiatric practice.

5. Conclusion

In conclusion, vitamin B12 deficiency is highly prevalent among patients presenting with depressive symptoms, with nearly half of the cohort demonstrating deficiency or borderline levels. Associated metabolic abnormalities, including elevated homocysteine, folate deficiency, iron deficiency, and thyroid dysfunction, contribute synergistically to the severity of depression. Routine screening for vitamin B12 and related biomarkers should be integrated into psychiatric assessments, enabling early detection and timely intervention.

Management strategies include vitamin B12 supplementation, correction of coexisting deficiencies, and treatment of thyroid dysfunction. Such interventions are low-cost, safe, and potentially improve depressive outcomes and overall quality of life. Collaboration between psychiatry and internal medicine is essential to address the multifaceted nature of depression and its metabolic underpinnings.

By incorporating nutritional evaluation into psychiatric care, clinicians can move toward a more holistic approach that not only alleviates depressive symptoms but also addresses underlying biological vulnerabilities, ultimately improving long-term outcomes for patients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Ethical approval was obtained.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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