Egypt. J. Chem. **Vol. 68,** SI: Z. M. Nofal, pp. 597 - 605 (2025)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Vitamin B12 Deficiency: Chemistry of Vitamin B12 and its Potential Effects

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Abstract

Background: Vitamin B12 (cobalamin) is an essential water-soluble vitamin crucial for DNA synthesis, fatty acid metabolism, and myelin sheath maintenance. Deficiency arises from dietary insufficiency, malabsorption (e.g., pernicious anemia, Crohn's disease), or toxin exposure (e.g., nitrous oxide). Long-term deficiency leads to megaloblastic anemia and irreversible neurological damage, including subacute combined degeneration of the spinal cord (SCDSC).

Aim: This review examines the biochemistry, pathophysiology, clinical manifestations, and management of vitamin B12 deficiency, emphasizing diagnostic challenges and therapeutic strategies.

Methods: A comprehensive analysis of B12 absorption, metabolic roles, and deficiency etiologies was conducted. Diagnostic approaches (serum B12, methylmalonic acid [MMA], homocysteine levels) and treatment modalities (parenteral/oral supplementation) were evaluated.

Results: Deficiency manifests as macrocytic anemia (elevated MCV, hypersegmented neutrophils) and neurological symptoms (neuropathy, ataxia, cognitive decline). Elevated MMA and homocysteine confirm diagnosis, particularly in borderline serum B12 cases. Treatment involves intramuscular B12 (1000 mcg/month) or high-dose oral therapy (1000–2000 mcg/day) for malabsorption. Early intervention improves hematologic recovery, but neurological damage may persist if treatment is delayed.

Conclusion: Vitamin B12 deficiency requires prompt recognition and lifelong management in malabsorptive etiologies. Interprofessional collaboration (clinicians, dietitians, pharmacists) optimizes outcomes, particularly in high-risk groups (vegans, post-gastrectomy patients, elderly). Proactive screening and patient education are critical to preventing irreversible complications.

Keywords: Vitamin B12 deficiency, cobalamin, megaloblastic anemia, subacute combined degeneration, methylmalonic acid, pernicious anemia.

1. Introduction

Vitamin B12, also known as cobalamin, is an essential water-soluble vitamin primarily obtained from dietary sources of animal origin, including red meat, eggs, and dairy products. The absorption of this vitamin depends on the presence of intrinsic factor, a glycoprotein secreted by the parietal cells of the stomach. This protein plays a vital role in facilitating the uptake of B12 in the terminal ileum, the specific site where absorption occurs. After absorption, vitamin B12 acts as a coenzyme in several crucial biochemical reactions, particularly in processes associated with the synthesis of deoxyribonucleic acid (DNA), the metabolism of fatty acids, and the maintenance of the myelin sheath that surrounds nerve fibers. The involvement of cobalamin in such fundamental physiological pathways highlights its importance in maintaining hematological stability and neurological integrity. Consequently, inadequate levels of this vitamin can manifest in disorders affecting the blood and nervous system, underscoring its clinical significance [1][2][3]. The body maintains relatively large reserves of vitamin B12, with the liver functioning as the main storage site. These stores typically provide sufficient amounts to meet metabolic needs for several years, thereby preventing rapid onset of deficiency even if intake decreases for a limited time. However, when absorption is persistently impaired, whether due to insufficient dietary intake, gastrointestinal malabsorption, or the absence of intrinsic factor, hepatic reserves become gradually exhausted. Once these stores are depleted, clinical manifestations of deficiency develop. This process explains why the symptoms of cobalamin deficiency may appear insidiously and remain unnoticed until they become more advanced.

Dietary insufficiency, although less common in populations consuming animal-based foods, remains a concern among individuals adhering to strict vegetarian or vegan diets, where natural food sources of B12 are absent. Malabsorption syndromes, such as those associated with celiac disease, Crohn's disease, or surgical resection of the ileum, also significantly compromise the uptake of this vitamin. Furthermore, conditions such as pernicious anemia, characterized by autoimmune destruction of parietal cells leading to intrinsic factor deficiency, serve as a classical example of impaired absorption resulting in cobalamin deficiency. These diverse etiological factors demonstrate that the development of deficiency is not limited to

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Receive Date: 23 June 2025, Revise Date: 25 August 2025, Accept Date: 05 September 2025
DOI: 10.21608/EJCHEM.2025.396874.11949

dietary restrictions but extends to a broad range of pathological mechanisms [1][2][3]. The clinical impact of vitamin B12 deficiency is broad due to its dual role in hematological and neurological functions. On the hematologic side, deficiency can cause megaloblastic anemia, characterized by the production of large, immature, and dysfunctional red blood cells. This leads to symptoms such as fatigue, pallor, and shortness of breath. From a neurological perspective, the lack of adequate B12 disrupts myelin synthesis, impairing nerve conduction and resulting in complications ranging from peripheral neuropathy and ataxia to cognitive decline and psychiatric disturbances. In severe or untreated cases, these neurological effects can progress irreversibly, highlighting the need for early detection and management. The overlapping nature of these hematologic and neurologic symptoms often complicates the diagnosis, requiring careful clinical and laboratory evaluation [1][2][3]. Overall, vitamin B12 plays a critical role in fundamental biological processes, and its deficiency is a significant medical condition with potentially severe outcomes if left unaddressed. The liver's ability to store excess B12 provides temporary protection against deficiency, but chronic disruptions in absorption or intake inevitably lead to clinical consequences. This emphasizes the necessity of awareness regarding the diverse causes of deficiency and the importance of timely identification to prevent long-term complications [1][2][3].

Table 1: Causes of Vitamin B12 Deficiency

Category	Examples
Autoimmune	Pernicious anemia (anti-intrinsic factor antibodies)
Malabsorption	Crohn's disease, celiac disease, gastric bypass, ileal resection
Dietary	Vegan diet, chronic alcoholism
Toxic/Drug-Induced	Nitrous oxide exposure, metformin, proton pump inhibitors

Etiology

Vitamin B12 deficiency arises from several distinct causes, with four major categories frequently identified in the literature. One of the most significant causes is autoimmune in origin, particularly in the form of pernicious anemia. This disorder develops when the body produces antibodies directed against intrinsic factor, the glycoprotein essential for cobalamin absorption in the terminal ileum. These antibodies either neutralize intrinsic factor directly or prevent its interaction with vitamin B12, thereby blocking its transport across the intestinal mucosa. Without this critical step, absorption becomes impossible despite adequate dietary intake. Pernicious anemia represents a classical example of how autoimmune mechanisms can interfere with normal physiological pathways and result in clinically significant deficiency [1]. A second important etiological pathway involves malabsorption syndromes. Since intrinsic factor is produced by parietal cells of the stomach, patients who undergo gastric bypass surgery are predisposed to vitamin B12 deficiency, as the surgical alteration of the gastrointestinal tract bypasses the site of intrinsic factor production. Even in cases where intrinsic factor secretion remains intact, damage to the terminal ileum compromises absorption. This is seen in conditions requiring surgical resection of the ileum, often performed in severe Crohn's disease, where the anatomical substrate necessary for uptake is removed. Beyond surgical causes, various pathological changes within the small intestine also contribute to malabsorption. Chronic inflammation from disorders such as celiac disease alters the intestinal mucosa, reducing absorption efficiency. Additionally, parasitic infections, particularly with Diphyllobothrium latum, a tapeworm acquired from consumption of undercooked fish, directly interfere with B12 uptake, further exemplifying the diversity of malabsorptive causes [1].

Dietary insufficiency represents another well-documented cause of vitamin B12 deficiency, although it is less common in individuals consuming animal-derived foods. Because cobalamin is stored in relatively large quantities within the liver, it typically takes years of inadequate intake for deficiency to manifest. However, individuals adhering to strict vegan diets, who exclude all animal products, are particularly at risk. Studies have shown that after approximately three years of such dietary restriction, hepatic stores may become depleted, resulting in symptomatic deficiency. This form of etiology highlights the importance of dietary sources in maintaining adequate levels and emphasizes the need for supplementation in populations with restrictive eating patterns [1]. Toxin exposure also plays a significant role in the development of vitamin B12 deficiency. Nitrous oxide, commonly used as an anesthetic agent, inactivates cobalamin by oxidizing the cobalt atom within its structure, thereby rendering it biologically inactive. Prolonged or repeated exposure can therefore lead to neurologic symptoms resembling those seen in dietary or malabsorptive deficiency. Similarly, long-term pharmacological use of certain agents contributes to deficiency. Metformin, a widely prescribed medication for type 2 diabetes mellitus, has been associated with impaired cobalamin absorption, leading to clinically relevant reductions in serum B12 levels over time. This drug-induced mechanism demonstrates how therapeutic interventions can unintentionally disrupt vitamin metabolism and result in adverse nutritional outcomes [1]. Taken together, the etiologies of vitamin B12 deficiency encompass autoimmune dysfunction, structural or functional malabsorption, inadequate dietary intake, and toxic or pharmacological interference. Each pathway reflects a distinct mechanism by which cobalamin availability to the body is reduced, either through impaired absorption, insufficient intake, or inactivation of the vitamin. Understanding these mechanisms is essential for accurate diagnosis and targeted management, as treatment must address the underlying cause to restore adequate B12 status and prevent the hematologic and neurological complications associated with deficiency [1].

Epidemiology

The epidemiology of vitamin B12 deficiency demonstrates variability that depends largely on the underlying etiology. In the general population, available data indicate that the condition is not rare among patients presenting with hematologic abnormalities. For example, research has shown that approximately 1% to 2% of cases of anemia can be attributed to B12 deficiency, underscoring its role as a notable though not predominant contributor to anemic disorders. When examining patients with macrocytosis, defined by an increased mean corpuscular volume (MCV) greater than 100 femtoliters, the prevalence of vitamin B12 deficiency is more pronounced. Studies have documented that 18% to 20% of macrocytosis cases are associated with insufficient B12 levels, emphasizing its relevance in differential diagnoses of enlarged red blood cells [4][5]. The condition also demonstrates a clear age-related trend, being more frequent among older adults regardless of the specific underlying cause. Age-associated factors, such as reduced gastric acid secretion, atrophic gastritis, and polypharmacy, contribute to the higher rates of deficiency in this population group. The accumulation of these risk factors makes elderly individuals particularly susceptible, which has important implications for screening and clinical management in geriatric care.

Genetic and ethnic differences further influence the epidemiological profile of vitamin B12 deficiency, particularly with respect to pernicious anemia. This autoimmune condition is observed more commonly among individuals of Northern European descent, suggesting a possible genetic predisposition or population-specific susceptibility. In contrast, the incidence of pernicious anemia has been reported to be lower among populations of African ancestry and individuals from other regions of Europe. These variations highlight the role of both hereditary and environmental factors in shaping disease prevalence and underscore the importance of considering demographic background when evaluating patients for potential deficiency [4][5]. Taken together, epidemiological evidence reflects that vitamin B12 deficiency is influenced by multiple determinants, including age, hematologic presentation, and ethnic background. Its higher prevalence among older adults and specific populations emphasizes the need for clinicians to maintain a high index of suspicion in these groups. The consistent association of B12 deficiency with anemia and macrocytosis also reinforces its clinical significance as a key condition in hematological practice. The documented differences in prevalence based on ancestry further illustrate that deficiency is not uniformly distributed, but rather shaped by a combination of biological and demographic variables [4][5].

Pathophysiology

The pathophysiology of vitamin B12 deficiency is complex, involving multiple stages of absorption, transport, and utilization, each of which is critical for maintaining hematological and neurological function. In healthy individuals, dietary vitamin B12 enters the body bound to proteins present in food, and the process of absorption begins in the oral cavity. Salivary glands secrete a binding protein known as R-factor (also called haptocorrin), which has a high affinity for B12. Once swallowed, vitamin B12 remains attached to this protein as it passes through the stomach and into the small intestine. Upon reaching the duodenum, pancreatic proteolytic enzymes cleave the bond between B12 and R-factor, releasing free cobalamin. This liberated vitamin then binds to intrinsic factor, a glycoprotein produced by gastric parietal cells. The B12–intrinsic factor complex is essential because it is the only form of B12 that can be specifically recognized by receptors in the terminal ileum. After binding to these receptors, the complex is absorbed into enterocytes, enabling vitamin B12 to enter the bloodstream and perform its metabolic roles. Disruption of any step in this carefully regulated sequence—whether inadequate secretion of intrinsic factor, pancreatic enzyme deficiency, or ileal damage—results in impaired absorption and eventual deficiency [6][7].

Once absorbed, vitamin B12 participates in essential metabolic pathways that support both neurological integrity and hematologic stability. One of its primary functions is as a cofactor for the enzyme methionine synthase, which catalyzes the conversion of homocysteine into methionine. This reaction not only regulates homocysteine levels but also plays a key role in the folate cycle. During this process, methyl-tetrahydrofolate (methyl-THF) donates its methyl group and is converted to tetrahydrofolate (THF), which is then used to produce intermediates necessary for synthesizing pyrimidine bases required for DNA replication. In the absence of sufficient vitamin B12, methionine synthase activity declines, resulting in an accumulation of homocysteine and methyl-THF, while THF availability decreases. This reduction directly impairs DNA synthesis, particularly in rapidly dividing cells such as erythroid precursors in the bone marrow. The outcome is defective nuclear maturation relative to cytoplasmic development, a condition classically observed as megaloblastic anemia. The hematologic manifestation includes the production of abnormally large red blood cells with impaired function, which explains the clinical features of anemia such as fatigue, weakness, and pallor that are frequently observed in affected patients [6][7].

The impact of impaired DNA synthesis is not limited to red blood cells alone. Other rapidly dividing cell lines, including polymorphonuclear leukocytes (PMNs), are also affected by the disruption in nucleotide production. In particular, neutrophils display abnormal nuclear segmentation, leading to the characteristic finding of hypersegmented neutrophils on peripheral blood smears. This morphological abnormality serves as a useful diagnostic indicator of B12 deficiency. Thus, hematologic abnormalities in vitamin B12 deficiency are not solely restricted to anemia but extend to a broader dysregulation of cellular proliferation and maturation in multiple blood cell lineages [6][7]. Beyond its role in DNA synthesis, vitamin B12 also functions as a cofactor for methylmalonyl-CoA mutase, an enzyme responsible for converting methylmalonyl-CoA into succinyl-CoA, an intermediate of the Krebs cycle. In the setting of vitamin B12 deficiency, this conversion is impaired, leading to the accumulation of methylmalonic acid (MMA). Elevated levels of MMA, combined with the buildup of homocysteine from disrupted methionine synthase activity, contribute to neurological complications associated with deficiency. One proposed mechanism is that MMA interferes with fatty acid metabolism, resulting in the incorporation of abnormal fatty acids into neuronal lipids. This disrupts myelin synthesis and repair, leading to demyelination within both the central and peripheral nervous systems [6][7].

The neurological manifestations of B12 deficiency are often grouped under the condition termed subacute combined degeneration of the spinal cord (SCDSC). This disorder involves simultaneous degeneration of several critical neural pathways, including the dorsal columns, which are responsible for proprioception and vibration sense; the lateral corticospinal tracts, which mediate voluntary motor control; and the spinocerebellar tracts, which coordinate balance and movement. As these structures deteriorate, patients develop a constellation of neurological symptoms. Early manifestations may include paresthesias, numbness, and tingling in the extremities due to peripheral neuropathy. With progression, individuals often develop ataxia, spasticity, and impaired proprioception, making coordinated movement increasingly difficult. Cognitive disturbances, ranging from mild memory impairment to frank dementia, may also occur in advanced stages of deficiency. Importantly, these neurological deficits may arise independently of hematological abnormalities, meaning that patients can present with neurologic decline in the absence of anemia, complicating clinical recognition [6][7]. The mechanism linking homocysteine accumulation to neurological dysfunction has also been the subject of investigation. Elevated homocysteine levels are thought to exert direct neurotoxic effects through excitotoxicity and oxidative stress, damaging neurons and further contributing to cognitive decline. Additionally, impaired methionine synthesis reduces the availability of S-adenosylmethionine, a critical methyl donor for numerous biochemical reactions, including those involved in myelin maintenance and neurotransmitter regulation. Deficiency in this substrate exacerbates the demyelination process and contributes to the development of psychiatric symptoms such as depression, irritability, and mood disturbances. Therefore, the metabolic consequences of B12 deficiency extend well beyond simple biochemical imbalances, directly translating into structural and functional deterioration of the nervous system [6][7].

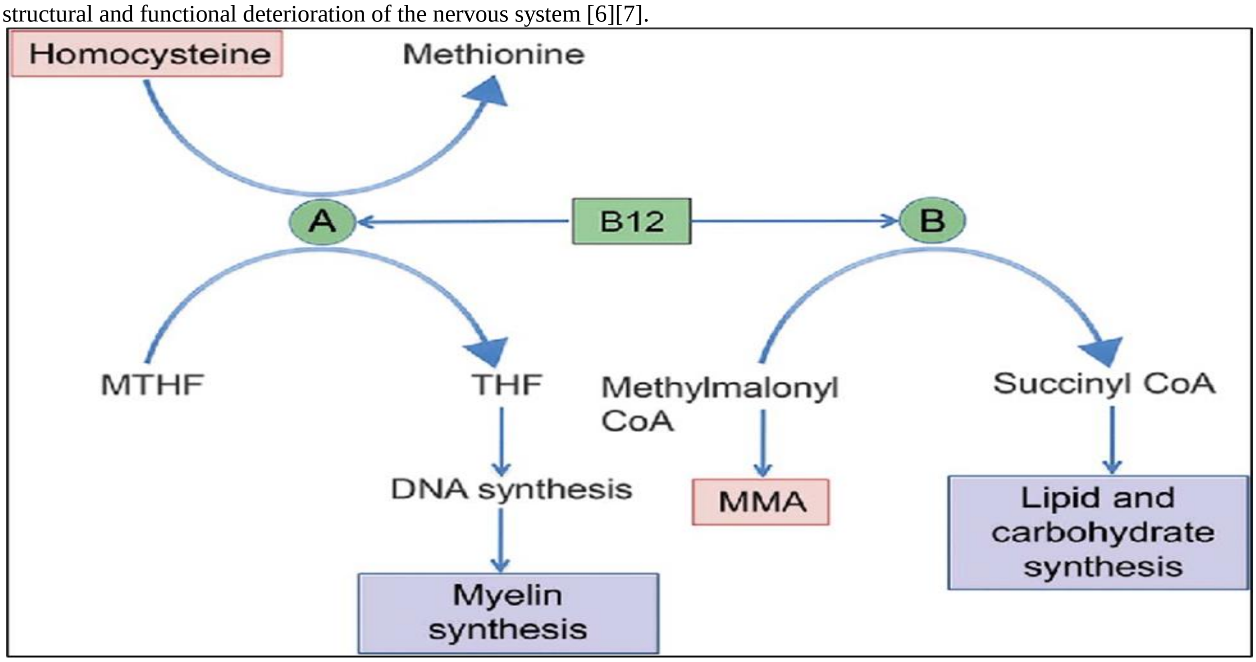

Figure-1: Vitamin B12 Biochemistry.

Another noteworthy aspect of the pathophysiology is the temporal relationship between hematological and neurological manifestations. While anemia may take months or even years to manifest due to the body's ability to recycle B12 and utilize hepatic stores, neurological complications can sometimes arise more insidiously and with less obvious laboratory markers. This discrepancy highlights the importance of early recognition and intervention, as neurological deficits may become irreversible if deficiency persists for prolonged periods. The dual impact on both rapidly proliferating cells and nervous tissue underscores why vitamin B12 occupies such a central role in human physiology and why its deficiency carries significant clinical consequences [6][7]. Overall, the pathophysiology of vitamin B12 deficiency reflects a cascade of interconnected disruptions beginning with impaired absorption and extending to downstream effects on DNA synthesis, hematopoiesis, and nervous system function. The vitamin's essential role as a cofactor in both methionine synthase and methylmalonyl-CoA mutase links its deficiency to distinct biochemical abnormalities—homocysteine accumulation, impaired nucleotide synthesis, and elevated methylmalonic acid. These abnormalities in turn explain the characteristic hematologic finding of megaloblastic anemia and the neurological syndrome of subacute combined degeneration of the spinal cord. The convergence of hematological and neurological dysfunction highlights the importance of recognizing and treating deficiency promptly. Failure to intervene not only prolongs symptomatic anemia but also risks permanent neurological damage that profoundly impacts quality of life [6][7].

History and Physical

The evaluation of vitamin B12 deficiency requires a comprehensive history and physical examination, with particular attention given to gastrointestinal and neurological systems, as these are most frequently implicated in the disease process. One of the earliest and most common manifestations of deficiency is macrocytic anemia, which typically presents general symptoms of anemia such as persistent fatigue, reduced exercise tolerance, shortness of breath, and noticeable pallor. These features often lead patients to seek medical attention and provide the first clue to an underlying hematologic disorder. In some cases, due to ineffective erythropoiesis and the premature destruction of defective red blood cells, increased hemolysis occurs. This process contributes to the development of jaundice, which may be detected during a dermatologic examination as yellowing of the skin and sclera. Because of this overlap between hematologic and dermatologic findings, a careful physical inspection of skin, mucous membranes, and nail beds may yield important diagnostic insights [6][7]. Patients may also present with a constellation of non-hematologic symptoms that reflect the diverse roles of vitamin B12 in neurological and gastrointestinal health. Neurological complaints are often among the most concerning, with peripheral neuropathy being a frequent feature. Patients describe tingling, numbness, or burning sensations in the extremities, often starting in the feet and progressing proximally. Glossitis, characterized by a swollen, painful, or smooth tongue, is another recognized feature, reflecting the impact of deficiency on rapidly dividing epithelial cells. Gastrointestinal manifestations may include diarrhea or nonspecific abdominal discomfort, both of which contribute to reduced quality of life. Headaches are also reported and may coexist with neuropsychiatric disturbances such as mood swings, irritability, memory impairment, or even frank depression. Taken together, these symptoms emphasize the multisystemic nature of vitamin B12 deficiency and reinforce the need for a broad clinical perspective during evaluation [6][7].

A detailed gastrointestinal history is especially valuable in determining possible causes of deficiency. Clinicians should inquire about conditions such as celiac disease or Crohn’s disease, both of which can impair absorption in the small intestine and predispose patients to B12 deficiency. Past surgical history is equally important, particularly in cases involving gastrectomy or intestinal resection. Resection of the terminal ileum, the primary site of cobalamin absorption, is strongly associated with the development of deficiency, and gastric surgeries that reduce intrinsic factor production create similar risks. These associations highlight the need to correlate surgical and medical history with present clinical findings to avoid missed diagnoses [6][7]. Dietary history provides another essential dimension in the assessment. Vitamin B12 is derived almost exclusively from animal products, and although the liver stores significant reserves, prolonged restriction of intake can lead to deficiency. Patients adhering to strict vegan diets for several years, without supplementation, are at particular risk. In clinical practice, patients may report recent dietary changes or long-standing avoidance of animal products, both of which should raise suspicion when evaluating unexplained anemia or neurological complaints. This emphasizes the need for physicians to integrate nutritional assessment into routine history-taking, particularly in populations at higher risk due to lifestyle or dietary practices [6][7].

Neurological complications represent some of the most serious outcomes of untreated vitamin B12 deficiency. In advanced stages, the condition may progress to subacute combined degeneration of the spinal cord (SCDSC), which results from demyelination of critical pathways within the central nervous system. These include the dorsal columns, responsible for proprioception and vibration sense, the lateral corticospinal tracts, and the spinocerebellar tracts. Damage to these systems produces a distinctive neurological profile, characterized by ataxia, impaired balance, peripheral neuropathy, and loss of proprioception. As the disease advances, patients may also develop cognitive impairment, ranging from mild memory difficulties to dementia, significantly affecting daily functioning. Thus, a thorough neurological evaluation is mandatory in patients suspected of B12 deficiency, with particular attention to reflexes, coordination, gait, and sensory function [6][7]. A mental status examination is also a valuable component of the assessment, especially in patients presenting with neuropsychiatric symptoms. Mood disturbances, changes in affect, or alterations in cognitive performance may all represent subtle manifestations of deficiency. Identifying such signs early is important, as neurological deficits caused by prolonged deficiency can become irreversible even after treatment. Careful documentation of baseline mental status also assists in monitoring the effectiveness of therapy over time. In this way, clinical assessment extends beyond immediate diagnosis, playing a critical role in both prognosis and ongoing management [6][7]. In summary, the history and physical examination of a patient with suspected vitamin B12 deficiency should encompass hematologic, gastrointestinal, neurologic, and psychiatric domains. Clues may be uncovered in dietary practices, surgical history, or chronic gastrointestinal illness, while physical findings such as pallor, jaundice, glossitis, or neuropathic changes provide important diagnostic confirmation. The recognition that this deficiency produces a spectrum of symptoms—from anemia and jaundice to neuropathy and cognitive decline—underscores the necessity of a holistic, systems-based approach to evaluation. A meticulous history and detailed examination not only facilitate timely diagnosis but also help prevent the progression of disease to its more severe and potentially irreversible neurological sequelae [6][7].

Evaluation

The evaluation of suspected vitamin B12 deficiency requires a systematic approach that integrates clinical suspicion with appropriate laboratory testing. The first step in assessment involves ordering a complete blood count (CBC), a peripheral smear, and measurements of serum vitamin B12 and folate levels. These tests provide essential baseline information and frequently establish the diagnosis. In patients with B12 deficiency, the CBC often reveals anemia characterized by reductions in both hemoglobin and hematocrit. The mean corpuscular volume (MCV), which measures the average size of red blood cells, is typically elevated above 100 femtoliters, consistent with macrocytic anemia. This finding directs attention to the possibility of deficiencies in either folate or vitamin B12. A peripheral blood smear provides additional supportive evidence, as it frequently demonstrates hypersegmented neutrophils, defined by the presence of neutrophils with five or more nuclear lobes. The presence of these cells is a classic morphological feature of B12 deficiency and is an important diagnostic clue when laboratory data are inconclusive [8][9][10]. Serum B12 and folate levels are central to the differentiation between vitamin B12 deficiency and folate deficiency, as both conditions present with macrocytic anemia. Establishing the distinction is critical because treatment with folic acid alone in patients with underlying B12 deficiency may correct the hematologic abnormalities but allow irreversible neurological damage to progress. In laboratory interpretation, a serum B12 concentration above 300 pg/mL is generally regarded as normal, while values between 200 and 300 pg/mL fall into a borderline range. Patients with serum B12 levels below 200 pg/mL are considered deficient. However, isolated serum B12 values may be misleading, as they do not identify the underlying etiology of deficiency, and borderline results may require confirmation through further biochemical testing.

Additional enzymatic assays are particularly valuable in cases where serum B12 levels fall into the borderline range. Since B12 functions as a cofactor in key enzymatic pathways, its deficiency results in the accumulation of specific metabolites. Measurement of methylmalonic acid (MMA) and homocysteine levels provides critical diagnostic clarity. In vitamin B12 deficiency, both MMA and homocysteine concentrations are elevated, reflecting impaired enzymatic function. In contrast, folate deficiency produces elevated homocysteine levels without a concurrent increase in MMA. This distinction makes enzymatic assays a powerful tool not only for confirming deficiency but also for differentiating it from folate-related disease processes [8][9][10]. Once the diagnosis of vitamin B12 deficiency is established, determining the underlying cause becomes the next essential step in patient evaluation. A thorough surgical history often provides critical insights, as many cases are related to procedures that compromise absorption. Gastrectomy, resection of the terminal ileum, and gastric bypass surgeries are well-documented causes because they interfere with either intrinsic factor production or the absorption of the vitamin in the ileum. If a surgical explanation is absent, further investigation of gastrointestinal disorders is necessary. Conditions such as Crohn’s disease and celiac disease are strongly associated with malabsorption and should be considered through appropriate diagnostic workup, including endoscopy, serological testing, or biopsy as clinically indicated.

Dietary history is another important component of evaluation. Patients who report strict adherence to a vegan diet over several years are at particular risk because vitamin B12 is found almost exclusively in animal-derived foods. In such cases, the absence of supplementation often explains the deficiency. If both gastrointestinal and dietary evaluations fail to provide an explanation, attention shifts toward autoimmune etiologies. The most prominent of these is pernicious anemia, which results from antibodies directed against intrinsic factor. Testing for anti–intrinsic factor antibodies remains a reliable diagnostic approach, as their presence confirms an autoimmune mechanism for deficiency [8][9][10]. Historically, the Schilling test was the standard method for identifying pernicious anemia, though it is no longer performed in clinical practice. This test involved administering an oral dose of radiolabeled vitamin B12 and subsequently measuring its excretion in the urine. Adequate urinary excretion of the labeled vitamin indicated normal absorption, whereas low excretion pointed to impaired absorption due to either intrinsic factor deficiency or other malabsorptive processes. Although informative, this test has been replaced by more practical and less invasive diagnostic methods, such as antibody assays and direct measurement of serum metabolites [8][9][10]. In summary, the evaluation of vitamin B12 deficiency involves a stepwise approach that begins with basic laboratory tests, progresses to confirmatory enzymatic assays when necessary, and culminates in an etiological investigation guided by surgical history, dietary practices, gastrointestinal disorders, and autoimmune markers. The integration of these diagnostic modalities ensures not only accurate identification of deficiency but also recognition of its cause, which is essential for tailoring appropriate therapy and preventing recurrence. This thorough and systematic process is vital because the consequences of untreated B12 deficiency extend beyond hematologic abnormalities to irreversible neurological damage, making timely diagnosis and intervention a clinical priority [8][9][10].

Table 2: Diagnostic Biomarkers in B12 Deficiency

Biomarker	Normal Range	Deficiency Threshold	Clinical Utility
Serum B12	200–900 pg/mL	<200 pg/mL	Initial screening; limited sensitivity
Methylmalonic Acid (MMA)	<0.4 μmol/L	>0.4 μmol/L	Confirms functional deficiency
Homocysteine	5–15 μmol/L	>15 μmol/L	Elevated in B12/folate deficiency; CVD risk marker
Peripheral Smear	—	Hypersegmented neutrophils (>5 lobes)	Supports megaloblastic anemia

Treatment / Management

The management of vitamin B12 deficiency is centered on correcting the deficiency through B12 replacement, with the specific approach determined by the underlying cause. In cases where the deficiency results from dietary insufficiency, such as in individuals who follow a strict vegan diet, oral supplementation with vitamin B12 is usually sufficient to restore normal levels. However, when the deficiency is caused by impaired absorption related to intrinsic factor deficiency, as occurs in pernicious anemia or following gastric bypass surgery, oral therapy alone is not adequate. In such cases, parenteral replacement is recommended because oral vitamin B12 cannot be effectively absorbed without intrinsic factor. The standard parenteral regimen involves intramuscular administration of 1000 mcg of vitamin B12 once per month. For newly diagnosed patients, an initial intensive regimen is advised, consisting of 1000 mcg intramuscularly once weekly for four weeks, which serves to rapidly replenish depleted body stores. After this initial phase, the regimen is adjusted to monthly maintenance dosing. This approach ensures both the correction of anemia and the reversal or prevention of neurological complications.

Evidence has also indicated that very high oral doses of vitamin B12 can be effective, even in individuals lacking intrinsic factor, as such doses saturate intestinal receptors and allow sufficient passive absorption. This finding has expanded therapeutic options, particularly for patients who prefer to avoid injections. Nevertheless, parenteral therapy remains the standard in cases of severe deficiency or when rapid correction is needed. For individuals with chronic gastrointestinal conditions associated with malabsorption, such as Crohn disease or celiac disease, routine monitoring of vitamin B12 levels is recommended. This surveillance helps detect declines in B12 levels before clinical manifestations become significant. Treatment is initiated once laboratory evidence of deficiency or symptomatic presentation is documented. Importantly, prophylactic therapy in individuals at risk is not routinely recommended unless deficiency has been confirmed. Overall, the treatment strategy for vitamin B12 deficiency balances the etiology, severity, and clinical context. Parenteral therapy is prioritized when absorption is impaired, while oral therapy is sufficient in diet-related cases or when high doses can overcome limited absorption. Long-term management requires continuous follow-up to monitor B12 status, ensure adequate repletion, and prevent recurrence of deficiency and its associated complications [11][12][13].

Differential Diagnosis

The differential diagnosis of vitamin B12 deficiency is broad and requires careful clinical evaluation, as several disorders can present with overlapping neurological and hematological features. Lead toxicity represents one important consideration, as chronic exposure to lead can produce anemia and neurological dysfunction that may mimic the clinical manifestations of B12 deficiency. Patients with lead toxicity may develop cognitive disturbances, peripheral neuropathy, and fatigue, all of which overlap with the presentation of cobalamin deficiency. The presence of occupational or environmental exposure history is often crucial in distinguishing between the two conditions. Syphilis is another disorder that must be considered in the differential diagnosis, particularly neurosyphilis, which can cause sensory deficits, gait instability, and ataxia. These manifestations are similar to the neurological impairments seen in patients with subacute combined degeneration resulting from vitamin B12 deficiency. A history of risk factors for syphilis, along with confirmatory serological testing, is required to establish the correct diagnosis and avoid misclassification.

HIV myelopathy also represents an important diagnostic consideration. Individuals with HIV infection may develop progressive myelopathy characterized by spastic paraparesis, weakness, and bladder dysfunction, which closely resemble the spinal cord involvement associated with vitamin B12 deficiency. Differentiating these two conditions often requires laboratory evaluation of vitamin B12 levels in combination with imaging and virologic testing for HIV. Multiple sclerosis constitutes another key differential diagnosis. It frequently presents with demyelinating lesions that result in sensory loss, weakness, and impaired coordination. These clinical findings can overlap substantially with those observed in B12 deficiency–related neurological disease. Magnetic resonance imaging and the identification of demyelinating plaques are useful in distinguishing multiple sclerosis from vitamin B12 deficiency. Therefore, accurate diagnosis relies on a comprehensive clinical history, targeted laboratory investigations, and imaging studies to correctly differentiate vitamin B12 deficiency from these other disorders.

Prognosis

The prognosis of vitamin B12 deficiency largely depends on the timeliness of diagnosis and initiation of treatment. Patients who receive prompt therapy with vitamin B12 generally achieve favorable outcomes, with most hematological abnormalities resolving completely. Younger individuals often experience better recovery compared to older patients, as age-related comorbidities and slower regenerative capacity may limit the extent of improvement. The degree of neurological involvement at the time of treatment initiation also plays a critical role in determining prognosis. Patients without severe neurological impairment typically demonstrate the most favorable responses, while those presenting with advanced complications such as profound neuropathy, ataxia, or cognitive decline may have only partial recovery despite adequate repletion. Thus, early recognition and treatment of vitamin B12 deficiency remain central to optimizing patient outcomes and preventing irreversible damage.

Complications

Vitamin B12 deficiency, if left untreated or diagnosed late, can lead to a wide range of complications that affect both hematological and systemic functions. One of the most significant complications is the development of heart failure, which occurs secondary to severe and chronic anemia. The deficiency impairs normal red blood cell production, leading to ineffective erythropoiesis and reduced oxygen-carrying capacity. Over time, the heart is forced to work harder to deliver sufficient oxygen to body tissues, which can ultimately result in cardiomegaly, left ventricular dysfunction, and progression to congestive heart failure. This risk is particularly heightened in patients with pre-existing cardiovascular disease, where the additive burden of anemia accelerates cardiac decompensation. Neurological complications are another major consequence, often presenting as severe and disabling deficits. Prolonged vitamin B12 deficiency can damage the myelin sheath surrounding nerve fibers, especially within the spinal cord, peripheral nerves, and brain. This process leads to sensory and motor impairments, including peripheral neuropathy, loss of proprioception, and ataxia. In advanced cases, patients may develop spasticity, cognitive impairment, or even dementia-like syndromes. The progression of these deficits can be debilitating, significantly impairing quality of life, and in some cases, the damage may become irreversible despite repletion therapy. Thus, neurological sequelae remain one of the most feared complications of untreated deficiency.

Another important complication is the increased risk of gastric cancer. Patients with pernicious anemia, a common cause of vitamin B12 deficiency, develop chronic atrophic gastritis due to autoimmune destruction of gastric parietal cells. This process not only reduces intrinsic factor production but also creates a state of gastric mucosal atrophy and achlorhydria. Long-standing mucosal changes predispose these individuals to gastric carcinoma, particularly adenocarcinoma, as well as gastric carcinoid tumors. Surveillance and careful monitoring are therefore advised in patients with pernicious anemia to identify malignant transformation at earlier stages. Finally, vitamin B12 deficiency, especially when linked to autoimmune mechanisms such as pernicious anemia, increases susceptibility to other autoimmune disorders. Patients may develop comorbid conditions like type 1 diabetes mellitus, myasthenia gravis, Hashimoto thyroiditis, or rheumatoid arthritis. The clustering of these conditions reflects a shared underlying autoimmune predisposition, suggesting that B12 deficiency may be part of a broader autoimmune syndrome. Recognition of this association underscores the importance of monitoring patients for multisystem involvement, as timely detection of coexisting autoimmune diseases can influence overall prognosis and management strategies.

Patient Education

Patient education plays a central role in the management and long-term outcomes of vitamin B12 deficiency. Patients need to understand the importance of strict adherence to prescribed supplementation regimens, whether oral or parenteral, as non-compliance can result in recurrence of deficiency and the re-emergence of complications. Clear communication about the chronic nature of certain etiologies, such as pernicious anemia or post-gastric bypass states, helps patients recognize that supplementation is not temporary but a lifelong necessity to maintain adequate B12 levels and prevent irreversible damage. Individuals who follow a strict vegan diet should receive targeted counseling on the risk of developing vitamin B12 deficiency due to the lack of natural animal-derived sources in their diet. They should be informed that supplementation is not optional but essential to prevent hematological and neurological complications. In this context, education should also include practical advice on supplement options, such as fortified foods and oral B12 tablets, to encourage sustained compliance.

Patients with identifiable risk factors for vitamin B12 deficiency, including those with gastrointestinal disorders like Crohn disease, celiac disease, or chronic gastritis, as well as individuals on long-term medications such as metformin or proton pump inhibitors, should be counseled on the importance of routine laboratory monitoring. Regular testing allows early detection of declining B12 levels before the onset of symptoms, ensuring that timely intervention can be initiated. Follow-up with primary care clinicians should also be emphasized, as ongoing medical supervision ensures that the supplementation strategy remains effective, dosages are adjusted when necessary, and potential complications are identified early. Education should also address the long-term health implications of untreated deficiency, reinforcing the connection between adherence, monitoring, and preservation of quality of life. By equipping patients with knowledge about their condition and the role they play in its management, healthcare providers can improve compliance, reduce the risk of relapse, and promote better overall outcomes.

Enhancing Healthcare Team Outcomes

Management of vitamin B12 deficiency requires a coordinated interprofessional approach to ensure optimal outcomes and prevent long-term complications. If untreated, the condition can lead to profound neurological damage, making collaborative care essential. A multidisciplinary team comprising a primary clinician, gastroenterologist, neurologist, surgeon, pharmacist, dietitian, and nurse plays a critical role in both prevention and treatment [14]. The current emphasis in healthcare is not only on early treatment but also on prevention. Nurses, dietitians, and pharmacists have a pivotal role in patient education, particularly in raising awareness about familial risk. Patients should be informed that relatives may also have an elevated likelihood of deficiency, warranting screening and monitoring. Similarly, individuals who have undergone gastric resection or bypass surgery face impaired absorption of vitamin B12 and should be placed under regular surveillance.

Pharmacists contribute by identifying at-risk patients through medication review. Those receiving long-term therapy with metformin or proton pump inhibitors, both of which interfere with B12 absorption, should be advised to undergo periodic laboratory evaluation. This proactive approach enables earlier detection and intervention before significant clinical consequences arise. Older adults represent another high-risk group due to factors such as dietary insufficiency, dementia, limited healthcare access, and strict vegetarian or vegan diets. For this population, proactive screening strategies can help mitigate the high prevalence of deficiency. Once treatment is initiated, ongoing follow-up is essential. A visiting home care nurse can play a crucial role in ensuring adherence to therapy, monitoring clinical improvement, and documenting recovery from neurological manifestations. An integrated strategy that combines medical oversight with patient-centered education and monitoring not only improves compliance but also enhances clinical outcomes. By leveraging the strengths of each professional discipline, the healthcare team can reduce disease burden, prevent complications, and promote sustainable recovery in individuals with vitamin B12 deficiency.

Outcomes

The clinical outcomes of vitamin B12 deficiency depend largely on the timing of diagnosis and initiation of treatment. Patients who receive prompt therapy often experience partial resolution of neurological manifestations such as subacute combined degeneration, with further progression of the disease halted [15][16]. However, the degree of recovery varies, and in many cases, residual deficits may persist despite adequate replacement therapy. Age is a critical factor influencing prognosis. Younger individuals tend to respond more favorably to treatment compared to older adults, who often present with more advanced disease and reduced capacity for neurological recovery. The extent of neurological involvement at the time of diagnosis also significantly affects outcomes. Patients without severe or long-standing neurological impairment demonstrate the best therapeutic response, while those with profound deficits frequently show only limited improvement. Radiological findings provide additional prognostic insights. Magnetic resonance imaging (MRI) features such as mild cord swelling or involvement of fewer than seven spinal segments are associated with a more favorable outcome. In contrast, patients with extensive spinal cord lesions usually exhibit slower and less complete recovery. Even in cases with a good prognosis, clinical improvement may require prolonged periods of therapy, often extending over several months or even years, highlighting the chronic and slowly reversible nature of neurological injury linked to B12 deficiency [15][16]. Ultimately, early recognition and timely intervention are decisive in improving neurological recovery and preventing permanent disability. Regular monitoring and follow-up are essential to ensure sustained response and to reduce the long-term burden of disease.

Conclusion:

Vitamin B12 deficiency is a multifaceted disorder with hematologic and neurologic consequences stemming from impaired DNA synthesis and myelin maintenance. Its etiology spans dietary insufficiency (e.g., strict veganism), malabsorption (pernicious anemia, Crohn's disease), and iatrogenic causes (gastric surgery, metformin use). The liver's extensive B12 stores delay symptom onset, often leading to late diagnosis with advanced complications. Clinically, deficiency presents as macrocytic anemia (fatigue, pallor) and neurological dysfunction (peripheral neuropathy, SCDSC). The latter, characterized by dorsal column and corticospinal tract demyelination, underscores the vitamin's role in neuronal integrity. Notably, neurological symptoms may precede anemia, complicating diagnosis. Elevated MMA and homocysteine levels are pivotal for confirming deficiency, especially in borderline serum B12 cases (200–300 pg/mL). Treatment hinges on etiology: parenteral B12 (1000 mcg/month) is first-line for malabsorption (e.g., pernicious anemia), while high-dose oral therapy (1000–2000 mcg/day) suffices for dietary deficiency. Hematologic abnormalities typically resolve within weeks, but neurological recovery is slower and often incomplete, particularly in elderly patients or those with prolonged deficits. This highlights the importance of early intervention to mitigate irreversible damage. The condition's systemic impact extends beyond anemia and neuropathy. Chronic deficiency exacerbates cardiovascular risk (via hyperhomocysteinemia) and increases gastric cancer risk in pernicious anemia due to atrophic gastritis. Furthermore, autoimmune associations (e.g., thyroiditis, type 1 diabetes) necessitate screening for comorbid conditions. Prevention and education are paramount. High-risk groups—vegans, post-bariatric surgery patients, and elderly individuals—require routine B12 monitoring. Pharmacists and dietitians play key roles in identifying at-risk patients (e.g., long-term PPI users) and promoting adherence to supplementation. Interprofessional collaboration ensures holistic management, combining clinical oversight with patient empowerment. Future directions include refining diagnostic biomarkers and exploring novel formulations (e.g., nasal B12) to improve compliance. Public health initiatives should prioritize awareness, particularly in populations with dietary restrictions. By integrating early screening, targeted therapy, and multidisciplinary follow-up, healthcare systems can reduce the burden of B12 deficiency and its debilitating sequelae.

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