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Maldigestion and malabsorption of cobalamins (Vitamin B12): Mechanisms, clinical spectrum, at-risk populations, and therapeutic approaches

Emmanuel Andrès*; Noel Lorenzo-Villalba

Service of Internal Medicine, Hautepierre Hospital, University Hospitals of Strasbourg, Strasbourg 67000, France.

***Corresponding Author: Emmanuel Andrès**
Service of Internal Medicine, Hautepierre Hospital, University Hospitals of Strasbourg, Strasbourg 67000, France.
Email: emmanuel.andres@chru-strasbourg.fr

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Abstract

Vitamin B12 (cobalamin) deficiency is a common but often underdiagnosed condition, particularly among older adults and patients with gastrointestinal disorders. Absorption of dietary cobalamin requires a complex sequence of gastric, pancreatic, and ileal processes. Disruption at any stage results in maldigestion or malabsorption, with hematologic and neurologic consequences. Biochemical deficiency prevalence ranges from 5-15% in community-dwelling older adults to 20-40% in institutionalized populations. Maldigestion of dietary cobalamins accounts for up to 60-70% of vitamin B12 deficiency in adults, often due to age-related gastric atrophy, H. pylori infection, long-term proton-pump inhibitor use, metformin therapy, or small intestinal bacterial overgrowth. Malabsorption arises in pernicious anemia and ileal resections, Crohn's disease, celiac disease, and congenital transport defects. High-dose oral crystalline cobalamin (≥1000 µg/day) is effective in most FCM cases, while parenteral therapy is indicated for severe neurologic involvement or often in case of severe malabsorption. Early recognition prevents irreversible complications. Identification of at-risk populations and mechanistic understanding enable targeted diagnosis, individualized therapy, and prevention of long-term morbidity.

Keywords: Vitamin B12; Cobalamin; Malabsorption; Maldigestion; Food-cobalamin malabsorption; Pernicious anemia; Biermer's disease; Gastric atrophy; Crohn's disease; Celiac disease; Metformin; Proton-pump inhibitors; Surgery; Helicobacter pylori.

Background

Vitamin B12 (cobalamin) is an essential water-soluble vitamin required for DNA synthesis, erythropoiesis, and the maintenance of nervous system integrity. Humans acquire vitamin B12 almost exclusively from animal-derived foods, where it is bound to dietary proteins. Absorption is a complex multistep process that includes gastric acid-mediated release from proteins, binding to haptocorrin, cleavage by pancreatic enzymes, association with Intrinsic Factor (IF), and active ileal uptake via the cubam receptor [1]. Disruption at any of these stages may result in deficiency, even in the presence of adequate intake.

Clinically, vitamin B12 deficiency manifests as megaloblastic anemia, peripheral neuropathy, cognitive impairment, and psychiatric disturbances, with neurological complications potentially irreversible if left unrecognized. Epidemiological studies estimate prevalence rates ranging from 5-15% in community-dwelling adults over the age of 60, increasing to 20-40% in institutionalized populations, thereby highlighting its major public health impact [2].

Two principal mechanisms underlie vitamin B12 deficiency. The first is malabsorption of food-bound cobalamins, often related to impaired digestion and release from dietary proteins.

The second is malabsorption of free cobalamin, representing true defects in absorption at the IF or ileal receptor stages. Understanding these distinct mechanisms is essential for accurate diagnosis, appropriate biomarker interpretation, and targeted therapeutic strategies [3].

The objective of this narrative review is to synthesize current evidence regarding these two mechanisms of vitamin B12 deficiency, with a particular focus on their pathophysiology, clinical implications, and relevance to diagnosis and management in older adults.

Pathophysiology of cobalamin absorption and deficiency

Dietary cobalamin is protein-bound and requires a series of tightly regulated steps for efficient absorption. In the stomach, hydrochloric acid and pepsin release cobalamin from dietary proteins. The free vitamin immediately binds to haptocorrin (R-protein), secreted by salivary glands and gastric mucosa, forming a complex resistant to gastric proteolysis [1]. Upon entry into the duodenum, pancreatic proteases degrade haptocorrin, thereby releasing cobalamin to bind IF, a glycoprotein produced by gastric parietal cells. The cobalamin–IF complex is highly stable and resistant to intestinal digestion, allowing safe passage to the terminal ileum.

At the ileal mucosa, the cubam receptor complex, consisting of cubilin and amnionless, facilitates receptor-mediated endocytosis of the cobalamin-IF complex. Once internalized, cobalamin is released into the circulation, predominantly bound to transcobalamin II, which transports it to tissues with high metabolic demand. The liver serves as the principal storage organ, containing 2-5 mg of cobalamin-sufficient to cover physiological needs for several years [4].

Disruption of this pathway at any step-whether at the level of gastric acid secretion, pancreatic enzyme activity, IF production, or ileal receptor function-can result in deficiency, even in the presence of adequate intake. While some mechanisms are nutritional in origin, most are related to maldigestion or malabsorption [1]. These etiologies, which include gastric atrophy, autoimmune processes, gastrointestinal surgery, inflammatory diseases, and drug-induced interference, will be described in detail in the following section.

Age-related physiological changes amplify these risks. Hypochlorhydria and gastric atrophy are common in older adults, reducing the release of dietary cobalamin. Polypharmacy, including long-term metformin and Proton-Pump Inhibitor (PPI) use, further contributes to malabsorption. These factors help explain the high prevalence of subclinical and overt vitamin B12 deficiency in aging and frail populations, where even minor decrements in absorption can precipitate clinically meaningful declines in cognition, gait, and hematologic function [3].

Once absorbed, vitamin B12 is transported in the circulation bound primarily to transcobalamin II and delivered to tissues for intracellular utilization. Within the cell, cobalamin is converted into its two active coenzyme forms: methylcobalamin, required for methionine synthase activity in the cytosol, and adenosylcobalamin, necessary for methylmalonyl-CoA mutase function in mitochondria. These reactions are essential for DNA synthesis, myelin maintenance, and energy metabolism. Impairments in cellular uptake, lysosomal release, or enzymatic conversion-whether due to genetic defects, oxidative stress, or age-related decline-can result in functional vitamin B12 deficiency even when serum levels are normal, highlighting the importance of intracellular metabolism in tissue-level cobalamin sufficiency [4].

Pathophysiology: Maldigestion versus malabsorption

Cobalamin deficiency in older adults and at-risk populations can arise from two distinct mechanisms: maldigestion and malabsorption [3]. Maldigestion refers to the impaired release of cobalamin from dietary proteins, a process normally dependent on gastric acidity and pepsin activity. In this setting, patients are unable to extract cobalamin from food sources but can efficiently absorb crystalline (unbound) forms of the vitamin. This entity, termed Food-Cobalamin Malabsorption (FCM), is common in the elderly and is associated with age-related atrophic gastritis, chronic Helicobacter pylori infection, long-term PPI therapy, metformin use, and small intestinal bacterial overgrowth [5].

In contrast, true malabsorption of free cobalamins occurs when IF–dependent uptake in the ileum is impaired. Classic etiologies include autoimmune destruction gastric parietal cells and of presence of antibodies against IF in pernicious anemia (Biermer's disease), as well as structural loss of absorptive tissue following gastric or ileal resections, gastric bypass surgery, Crohn's disease with ileal involvement, and celiac disease [2]. Rare congenital disorders, such as Imerslund-Gräsbeck syndrome caused by mutations in the cubilin or amnionless genes, also lead to defective ileal transport.

Distinguishing between maldigestion and malabsorption has direct therapeutic implications: patients with FCM typically respond to high-dose oral or sublingual supplementation, whereas those with IF deficiency or ileal pathology usually require parenteral replacement to achieve adequate repletion (Table 1) [2].

Historically, the Schilling test was considered the gold standard for diagnosing vitamin B12 absorption disorders. In FCM, the standard Schilling test using free crystalline cobalamin is typically normal, since patients retain the ability to absorb non-protein-bound forms [3]. By contrast, the modified Schilling test, in which radiolabeled cobalamin is bound to food proteins, yields abnormal results, reflecting impaired release of cobalamin from dietary sources. In true malabsorption (pernicious anemia, ileal disease, or resection), both the standard and modified tests are abnormal.

Epidemiology and global burden

Vitamin B12 deficiency represents a significant and under recognized global health problem, particularly in older adults and populations with limited access to animal-derived foods. Prevalence estimates vary depending on diagnostic criteria, assays, and populations studied.

In the United States, NHANES (National Health and Nutrition Examination Survey) data suggest that biochemical deficiency, defined as serum vitamin B12<150 pmol/L, is present in approximately 6% of adults younger than 60 years and increases to nearly 20% in individuals older than 60 [6]. European cohorts report similar findings, with prevalence ranging from 5-15% in

Table 1: Comparison of maldigestion (Food-Cobalamin Malabsorption) versus true malabsorption of vitamin B12.

Feature	Maldigestion (Food-Cobalamin Malabsorption, FCM)	True malabsorption (Free cobalamin malabsorption)
Pathophysiology	Impaired release of cobalamin from dietary proteins due to reduced gastric acidity or pepsin activity.	Impaired absorption of free cobalamin–intrinsic factor complex in the terminal ileum.
Typical patient profile	Elderly, polymedicated, chronic gastritis, PPI or metformin users.	Patients with autoimmune gastritis, gastric/ileal resections, inflammatory bowel disease, celiac disease.
Main causes	- Atrophic gastritis (age-related) - Helicobacter pylori infection - Proton pump inhibitors, H2 blockers - Metformin therapy - Small intestinal bacterial overgrowth (SIBO)	- Pernicious anemia (Biermer's disease) - Gastrectomy, gastric bypass surgery - Ileal resection - Crohn's disease with ileal involvement - Celiac disease - Congenital defects (e.g., Imerslund–Gräsbeck syndrome)
Ability to absorb crystalline B12	Preserved → can absorb free vitamin B12 normally.	Impaired → cannot absorb crystalline B12 adequately.
Clinical presentation	Often mild, insidious, subclinical; anemia or neurologic symptoms develop gradually.	More severe deficiency; higher risk of megaloblastic anemia, neuropathy, neurocognitive decline.
Diagnostic clues	Low serum B12 despite normal diet; responds to oral crystalline B12 supplementation.	Very low B12, presence of intrinsic factor antibodies, history of surgery or ileal disease; poor response to oral therapy.
Treatment	High-dose oral, sublingual, or intranasal B12 (≥1000 µg/day).	Parenteral B12 (intramuscular or subcutaneous) usually required for long-term correction.

community-dwelling elderly to 35-38% in institutionalized populations [7].

FCM is estimated to account for 50-70% of non-pernicious anemia B12 deficiencies in the elderly, reflecting the high burden of atrophic gastritis, medication-related hypochlorhydria, and comorbid gastrointestinal disorders in this age group [8]. By contrast, pernicious anemia contributes less than 10% of cases, though it remains the leading cause of severe deficiency requiring lifelong parenteral supplementation.

Surgical interventions also play an important role: post–bariatric surgery patients demonstrate 15-30% prevalence of deficiency within one year, even when provided routine supplementation [9]. Similarly, ileal resection or inflammatory bowel disease involving the terminal ileum markedly increases risk [10].

Medications are a further driver of global prevalence. Metformin therapy is associated with biochemical vitamin B12 deficiency in 10-30% of long-term users, with risk proportional to dose and duration [11]. Chronic use of PPIs or H2-blockers is linked to impaired release of protein-bound vitamin B12, with studies showing up to 40% of elderly adults on long-term PPI therapy exhibiting low serum levels [12].

Beyond high-income countries, the burden is magnified in low- and middle-income regions where low intake of animal-derived foods and limited supplementation programs compound the risk. Prevalence exceeding 40-50% has been reported in South Asia, Latin America, and parts of Africa, highlighting the global scope of the problem [6].

Taken together, these data underscore the public health significance of vitamin B12 deficiency worldwide. The condition is particularly relevant in aging societies, where frailty, multimorbidity, and polypharmacy converge with high prevalence of malabsorption syndromes, amplifying clinical impact. Targeted screening, early detection, and preventive interventions are therefore essential to mitigate morbidity, functional decline, and healthcare burden.

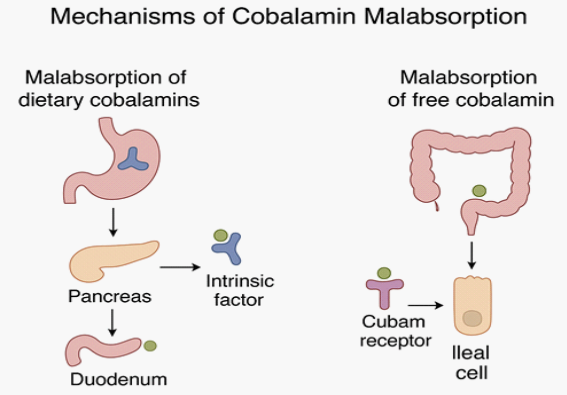

Figure 1: Mechanisms of cobalamin malabsorption.

Schematic representation of vitamin B12 absorption: (1) release from food protein in the stomach, (2) binding to intrinsic factor, (3) transport through the small intestine, and (4) absorption in the terminal ileum. Defects at any step can lead to cobalamin malabsorption.

Maldigestion of food-bound cobalamin (Food-Cobalamin Malabsorption, FCM)

FCM occurs when patients are unable to release cobalamin from dietary proteins in the stomach due to impaired gastric acidity or enzymatic activity (Table 1) [8]. Importantly, absorption of crystalline or unbound cobalamin (as in supplements) remains intact. This mechanism accounts for 50-70% of vitamin B12 deficiency cases in older adults.

Historically, the Schilling test-particularly its modified version using food-bound radiolabeled cobalamin-demonstrated this functional deficit, whereas the standard test with free cobalamin appeared normal [3].

Atrophic gastritis and aging

Age-related gastric atrophy leads to reduced secretion of hydrochloric acid and pepsin, impairing the release of protein-bound cobalamin [2]. This hypochlorhydric state is highly prevalent among elderly individuals and represents the most common cause of FCM in community-dwelling older adults.

Helicobacter pylori Infection

Chronic infection with Helicobacter pylori induces hypochlorhydria and gastric mucosal atrophy. Several studies, including Kaptan et al. (2000), have demonstrated that eradication therapy restores normal cobalamin absorption in 20-40% of affected patients, underscoring the causal relationship between H. pylori and vitamin B12 deficiency [13].

Chronic use of acid-suppressing drugs

PPIs and H2 receptor antagonists reduce gastric acid secretion, thereby impairing protein-bound cobalamin release [12]. Long-term therapy, particularly in older adults, has been consistently linked to an increased prevalence of biochemical deficiency.

Metformin therapy

Metformin, widely prescribed for type 2 diabetes, interferes with the calcium-dependent endocytosis of the IF-cobalamin complex at the ileal level. Chronic use is associated with biochemical deficiency in 10-30% of patients. This effect is cumulative with duration of therapy and dose, making long-term monitoring essential [14].

Small Intestinal Bacterial Overgrowth (SIBO)

Excessive colonization of the small intestine increases competition for luminal cobalamin, as bacteria actively consume vitamin B12. SIBO is more common in older adults, particularly those with motility disorders or chronic PPI use, and contributes to FCM [15].

Exocrine pancreatic insufficiency

Pancreatic proteases are required to degrade haptocorrin, releasing cobalamin to bind IF in the duodenum. Chronic pancreatitis and cystic fibrosis reduce protease secretion, resulting in partial malabsorption. This mechanism is typically corrected by pancreatic enzyme replacement therapy [16].

Bariatric surgery

Roux-en-Y gastric bypass and sleeve gastrectomy alter the normal physiology of vitamin B12 absorption by reducing gastric acid production and bypassing IF-producing mucosa. Prevalence of deficiency is 15-35% within one year of surgery, even with supplementation. These patients require lifelong monitoring and replacement [17].

Malabsorption of free cobalamins

True malabsorption involves impaired uptake of the IF-cobalamin complex at the ileal level (Table 1). In this context, both the standard and modified Schilling's tests are abnormal.

Pernicious anemia

Pernicious anemia, also known as Biermer's disease, is an autoimmune disorder that primarily targets the gastric parietal cells. These cells are responsible for producing IF and gastric acid, both essential for vitamin B12 absorption [18]. The autoimmune process leads to the destruction of parietal cells and the production of antibodies against IF. As a result, affected individuals experience hypochlorhydria, or reduced stomach acid, and a deficiency of IF. This dual deficit severely impairs the absorption of cobalamin (vitamin B12) in the terminal ileum. Without adequate vitamin B12, patients gradually develop megaloblastic anemia, characterized by large, immature red blood cells. Although pernicious anemia accounts for less than 10% of all vitamin B12 deficiency cases in older adults, its clinical significance is disproportionate. It is particularly notable for causing severe neurological complications, including peripheral neuropathy and cognitive disturbances. Early recognition and treatment with parenteral or high-dose oral vitamin B12 are crucial to prevent irreversible damage.

Gastric resections

Partial or total gastrectomy greatly reduces gastric acid and IF secretion, both essential for vitamin B12 absorption. As a result, patients are at high risk of developing B12 deficiency within a few years post-surgery [9]. Early signs include fatigue, pallor, and neurological symptoms such as numbness or tingling. Without treatment, severe anemia and irreversible neurological damage can occur. Lifelong vitamin B12 supplementation, usually via injections or high-dose oral therapy, is essential. Regular monitoring of B12 levels is recommended to prevent complications and ensure adequate replacement.

Ileal resections and crohn's disease

The terminal ileum is the exclusive site for absorption of the IF-cobalamin complex. Surgical resection or inflammatory destruction of this region, as in Crohn's disease, results in impaired absorption. Studies have shown that up to 29% of Crohn's patients with ileal resection develop vitamin B12 deficiency [10].

Celiac disease

Celiac disease causes villous atrophy of the proximal small intestine, leading to generalized malabsorption. Although the ileum is not primarily affected, extensive mucosal involvement can impair vitamin B12 absorption in addition to iron and folate.

Congenital defects

Rare genetic disorders such as Imerslund–Gräsbeck syndrome result from mutations affecting the cubam receptor (cubilin and amnionless), which mediates ileal uptake of the IF–cobalamin complex [19]. These patients present with lifelong deficiency requiring parenteral therapy.

Medication-induced malabsorption

Beyond PPIs and metformin, other medications interfere with cobalamin absorption or utilization:

- Nitrous oxide anesthesia, which inactivates vitamin B12 through oxidation of its cobalt center [20].

- Methotrexate and hydroxyurea, which interfere with DNA synthesis pathways dependent on folate/vitamin B12.

Populations at risk

Recognizing these high-risk groups is essential to guide targeted screening, early detection, and preventive supplementation to mitigate hematologic, neurologic, and cognitive sequelae.

Vegetarian and vegan populations

Strict vegetarians and vegans are highly vulnerable to vitamin B12 deficiency, as cobalamin is almost exclusively found in animal-derived foods. Without fortified products or supplements, deficiency can develop within years, especially in pregnant or lactating women. Studies report suboptimal B12 status in 30-80% of long-term vegans and 10-20% of vegetarians, with

Table 2: Screening, prediction, and prevention of vitamin B12 deficiency in at-risk populations.

Domain	Strategy	Target population	Methods / Tools	Evidence / Notes
Screening	Serum B12 measurement	Elderly (>60 years), vegetarians/ vegans, patients with GI surgery, long-term PPI/metformin users	Serum cobalamin, holotranscobalamin, methylmalonic acid (MMA), homocysteine	Routine screening recommended for high-risk groups; serum B12 alone may miss functional deficiency
Prediction / Risk Assessment	Identify risk factors	Elderly, patients with autoimmune gastritis, malabsorption syndromes, chronic pancreatic insufficiency	Clinical history, medication review, dietary assessment	Risk stratification helps prioritize screening and early intervention
Prevention	Dietary counseling	Vegetarians, vegans, elderly	Encourage B12-rich foods (meat, fish, dairy, fortified foods)	Regular dietary intake may suffice if absorption is intact
Prevention	Oral supplementation	Elderly, FCM, limited dietary intake	Daily or weekly oral cyanocobalamin/ methylcobalamin (e.g., 250–1000 µg/day)	Effective in mild-to-moderate deficiency and functional malabsorption
Prevention	Parenteral supplementation	Severe deficiency, malabsorption (pernicious anemia, post-gastrectomy)	IM or SC B12 injections (1000 µg every 1–3 months)	Rapid correction of hematologic and neurologic deficits
Follow-up / Monitoring	Re-assess biochemical and clinical response	All treated patients	Serum B12, MMA, hematology, neurologic evaluation	Ensures efficacy, adjusts dose, prevents relapse

risks of megaloblastic anemia, neuropathy, and cognitive impairment [21]. In elderly vegetarians, age-related malabsorption and polypharmacy further exacerbate deficiency. Compared with omnivores, vegetarians have lower serum B12 and holotranscobalamin, higher methylmalonic acid and homocysteine, highlighting the need for routine screening, education, and supplementation, particularly in older adults and women of childbearing age.

Other populations at risk

Populations at increased risk for cobalamin deficiency extend beyond community-dwelling older adults to include those with gastrointestinal disorders, prior gastric or ileal surgery, chronic medication use, or strict dietary restrictions [2]. Institutionalized elderly populations are particularly vulnerable, with prevalence rates approaching 38%, reflecting the cumulative effects of multimorbidity, polypharmacy, and limited dietary diversity.

Clinical manifestations

Vitamin B12 deficiency presents a wide clinical spectrum ranging from asymptomatic biochemical abnormalities to severe hematologic and neurologic syndromes. Hematologic manifestations classically include macrocytic anemia, hypersegmented neutrophils, pancytopenia, and megaloblastic bone marrow changes. Neurologic features may be equally prominent and encompass peripheral neuropathy, posterior column degeneration with impaired proprioception and vibration sense, gait ataxia, cognitive decline, and psychiatric disturbances. Importantly, neurologic signs may precede hematologic abnormalities in up to one-quarter of patients, underscoring the need for early recognition [2].

The underlying clinical presentation is often influenced by the mechanism of deficiency: in maldigestion syndromes, impaired gastric acid or IF secretion leads to gradual and insidious deficiency, whereas true malabsorption may cause earlier and more severe manifestations (Table 1). Chronic untreated deficiency, irrespective of mechanism, may result in irreversible neurologic injury if not corrected within six months.

A particular challenge is the recognition of subtle or subclinical cobalamin deficiency, a state characterized by biochemical evidence of low or borderline vitamin B12 with absent or nonspecific clinical symptoms. This form is especially common in the elderly and in patients with FCM due to hypochlorhydria, atrophic gastritis, or chronic PPI and metformine therapy [22]. While these patients may initially lack overt anemia or macrocytosis, they remain at risk for progressive neurologic impairment if unrecognized. In our experience, however, the FCM syndrome can also lead to true vitamin B12 deficiency with clinical manifestations that are indistinguishable from those observed in pernicious anemia.

Diagnostic approach

Initial evaluation of suspected vitamin B12 deficiency begins with serum cobalamin measurement, although its sensitivity is limited, particularly when values are near the lower reference range. Functional biomarkers such as methylmalonic acid (MMA) and total homocysteine rise earlier in the course of deficiency, improving diagnostic accuracy, especially in patients with borderline serum B12 [5]. Holotranscobalamin, which represents the fraction of bioavailable cobalamin, may further aid in detecting subclinical or subtle deficiency before overt hematologic or neurologic manifestations appear.

Once vitamin B12 deficiency is confirmed, a comprehensive etiologic workup is warranted to guide long-term management [2]. This evaluation includes testing for IF and parietal cell antibodies to identify pernicious anemia, with IF antibodies being highly specific for autoimmune destruction of gastric parietal cells and parietal cell antibodies being more sensitive but less specific. Serologic testing also encompasses detection of IgG antibodies against H. pylori, which may contribute to chronic gastritis and secondary maldigestion of vitamin B12, and, when celiac disease is suspected, measurement of anti-gliadin or anti-transglutaminase antibodies. Structural or functional causes of malabsorption should be evaluated through ileal imaging or endoscopy for Crohn's disease, surgical resection, or other ileal pathology, as well as assessment of pancreatic exocrine function in cases of suspected insufficiency. A thorough medication review is essential, as long-term use of PPIs, H2-receptor antagonists, or metformin may impair cobalamin absorption.

Together, this integrated approach-combining serologic, structural, functional, and pharmacologic evaluation—facilitates accurate etiologic diagnosis and guides appropriate long-term management.

Management and monitoring

Oral high-dose crystalline cobalamin (1000-2000 µg/day) is effective in FCM and many cases of pernicious anemia, relying on passive diffusion (~1% absorption) to achieve sufficient systemic levels. Parenteral therapy with cyanocobalamin (1 mg/day for 7 days, then 1 mg/week for 4 weeks then 1 m monthly) or hydroxocobalamin (1 mg intramuscularly every 2-3 days for two weeks, followed by monthly maintenance) is indicated for patients with severe neurologic involvement, extensive malabsorption, or unreliable adherence to oral therapy [5]. Comparative studies have demonstrated equivalent hematologic and neurologic responses between oral cyanocobalamin and parenteral hydroxocobalamin, although hydroxocobalamin offers longer tissue retention. Methylcobalamin may confer specific neurotrophic benefits, particularly in peripheral neuropathy, but robust clinical evidence remains limited.

Monitoring response to therapy includes assessment of reticulocyte count at 7-10 days, normalization of hemoglobin and Mean Corpuscular Volume (MCV) within 6-8 weeks, and biochemical reassessment of serum vitamin B12, methylmalonic acid, or homocysteine at 3-6 months. In cases of permanent malabsorption, such as Biermer's disease or extensive ileal resection, lifelong replacement therapy is mandatory to prevent recurrence and irreversible neurologic damage.

Knowledge gaps and future research

Further research on vitamin B12 deficiency increasingly leverages advanced technologies such as Artificial Intelligence (AI), Machine Learning (ML), and multi-omics approaches. AI and ML can analyze large, complex datasets to identify patterns and predict which patients are at highest risk of deficiency. Genomics, proteomics, and metabolomics ("omics") help uncover novel biomarkers, such as holotranscobalamin, and elucidate pathways involved in cobalamin absorption and metabolism. Integrating microbiome data with metabolomic profiles can reveal how gut flora influence vitamin B12 bioavailability. ML models can optimize screening intervals by combining clinical, laboratory, and omics data. Comparative studies using these tools can refine oral versus parenteral therapy recommendations for post-surgical or inflammatory bowel disease patients. Longitudinal multi-omics studies can link subclinical deficiency to cognitive decline, frailty, and cardiovascular outcomes. These approaches allow for precision medicine strategies, tailoring supplementation and monitoring to individual risk profiles. AI-driven predictive models also facilitate early intervention before overt anemia or neurological damage occurs. Overall, integrating AI, ML, and omics holds great promise to improve understanding, diagnosis, and management of vitamin B12 deficiency [23].

Conclusion and clinical implications for internists

Maldigestion and malabsorption of cobalamin are frequent causes of deficiency, many of which are potentially reversible with proper intervention. Elderly patients, those with gastrointestinal disorders, individuals who have undergone bariatric or gastric surgery, and patients on chronic PPIs or metformin are at particularly high risk. Clinicians should maintain a high index of suspicion to identify deficiency early, even before clinical symptoms appear. Laboratory evaluation, including serum B12 and potentially holotranscobalamin or methylmalonic acid, aids in accurate diagnosis. Prompt initiation of oral or parenteral vitamin B12 therapy is critical to prevent irreversible hematologic and neurological complications. Monitoring B12 levels over time ensures treatment efficacy and adjusts supplementation as needed. Personalized strategies based on patient risk factors enhance prevention and long-term outcomes. Awareness of reversible causes allows targeted interventions to restore normal cobalamin metabolism. Integration of precision medicine approaches, including AI and omics data, may further refine risk stratification and management. Overall, proactive recognition, tailored supplementation, and vigilant follow-up are essential components of preventive internal medicine in at-risk populations.

Declarations

Conflicts of interest: None declared.

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