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THE EFFECT OF VITAMIN B_{12} DEFICIENCY ON NEUROLOGICAL AND COGNITIVE HEALTH OF THE ELDERLY: A REVIEW

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review paper

Summary

Vitamin B_{12} (cobalamin) is an essential nutrient necessary for DNA synthesis, fatty acid metabolism, and proper function of the nervous system. In the diet, it comes almost exclusively from foods of animal origin, while plant sources contain negligible amount or inactive forms of B_{12}. Elderly people are especially susceptible to the development of deficits due to reduced absorption, frequent chronic diseases, and use of medications that interfere with cobalamin metabolism. Subclinical deficit occurs in 15–40% of the elderly and often remains unrecognized, although it can gradually progress to neurological impairment. Absorption of vitamin B_{12} involves complex mechanisms that depend on the function of the stomach, pancreas, and distal ileum. Malabsorption occurs in atrophic gastritis, pernicious anemia, gastrointestinal diseases, and post-surgically. Bioavailability depends on the food source; it is the highest in meat and fish, while it is significantly lower in eggs and milk. Deficiency diagnosis is complex because neurological manifestations can occur even without the presence of anemia. Evaluation includes measurement of serum vitamin B_{12}, holotranscobalamin, homocysteine, and methylmalonic acid. Modern methods, such as the CobaSorb test, enable a more accurate assessment of absorption. Vitamin B_{12} deficiency can cause peripheral neuropathies, gait disorders, cognitive decline, psychiatric symptoms, and myelopathy, while excess often indicates more serious pathological processes such as liver, kidney, or malignancy. Timely recognition and adequate compensation are crucial in preventing permanent neurological damage, particularly among the elderly population.

Keywords: vitamin B12; food; deficiency; neurologic manifestations; elderly

Introduction

Vitamin B_{12} (cobalamin) is the most complex water-soluble vitamin of group B, necessary for DNA synthesis, nutrient metabolism, and normal functioning of the central and peripheral nervous system (Bundalo and Srkalović Imširagić, 2013; EFSA, 2015). In the diet, it is almost entirely found in foods of animal origin, since it is exclusively synthesized by certain microorganisms (some bacteria and archaea) in animal's gut (Watanabe and Bito, 2018). Therefore; the richest sources include liver and other offal, while plant foods contain negligible amounts of B_{12}, except for certain algae and fortified products like breakfast cereals or plant milks (Herbert, 1988; Carmel, 2011 b; Karakaš and Antonić, 2017; Nohr et al., 2016). The recommended daily intake is approximately 3 µg for adults, but the needs of older people are often increased due to reduced absorption and dietary restrictions (Miškulin et al., 2014; Wong, 2015; Vincenti et al., 2021). In addition to biological changes, the risk of deficiency is further increased by specific dietary patterns and socioeconomic factors (Porter et al., 2016). Subclinical vitamin B_{12} deficiency is particularly common, occurring in 15–40% of elderly, often without anemia, but with the possible gradual development of neurological damage (Clarke et al., 2007; Moore et al., 2012; Leishear et al., 2012). The use of more sensitive diagnostic methods, such as the determination of homocysteine and methylmalonic acid, enables earlier and more reliable recognition of this condition (Mathew et al., 2024).

This narrative review aims to synthesize current knowledge on the neurological manifestations of deficiency, outline the main diagnostic challenges, and highlight potential implications for clinical practice and public health.

Absorption and metabolism

Knowledge of the mechanisms of vitamin B_{12} absorption, transport, and metabolismis crucial for timely recognition of its deficiency, especially in at-risk populations. Maintaining an adequate nutritional status—by diet or supplementation—is necessary for the normal function of the nervous system and hematopoiesis. The entire path of cobalamin from intake to entry into the systemic circulation is shown in Figure 1. Vitamin B_{12} in foods is mostly bound to proteins. In the stomach, it is released by the action of hydrochloric acid and pepsin, after which it binds to

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R-protein. In the duodenum, pancreatic enzymes break down the complex with R-protein, which enables the binding of vitamin B_{12} to the intrinsic factor synthesized by the parietal cells of the stomach (Green et al., 2017; Vincenti et al., 2021; Čerkez Habek et al., 2023). The complex of intrinsic factor and vitamin B_{12} is absorbed in the distal ileum via specific receptors on enterocytes. After entering the portal circulation, most of the absorbed vitamin is bound to transcobalamin I and transported to the liver, while transcobalamin II enables transport to other tissues, where cobalamin is converted into its active coenzyme forms (Kirin, 2016; Krpan, 2024). The basic mechanism of absorption depends on the functionality of the receptor, but at an intake of ≥30 μg, passive diffusion also occurs, by which approximately 1–3% of the free vitamin is absorbed (Pawlak et al., 2013). The total absorption ranges between 11% and 65%, depending on the dose and the availability of receptors, whereby a small proportion of inactive analogues can be absorbed by passive diffusion (Nušinović, 2015). Vitamin B_{12} is predominantly stored in the liver and muscles, with its biological half-life estimated to be 1–4 years (Stahl and Heseker, 2007).

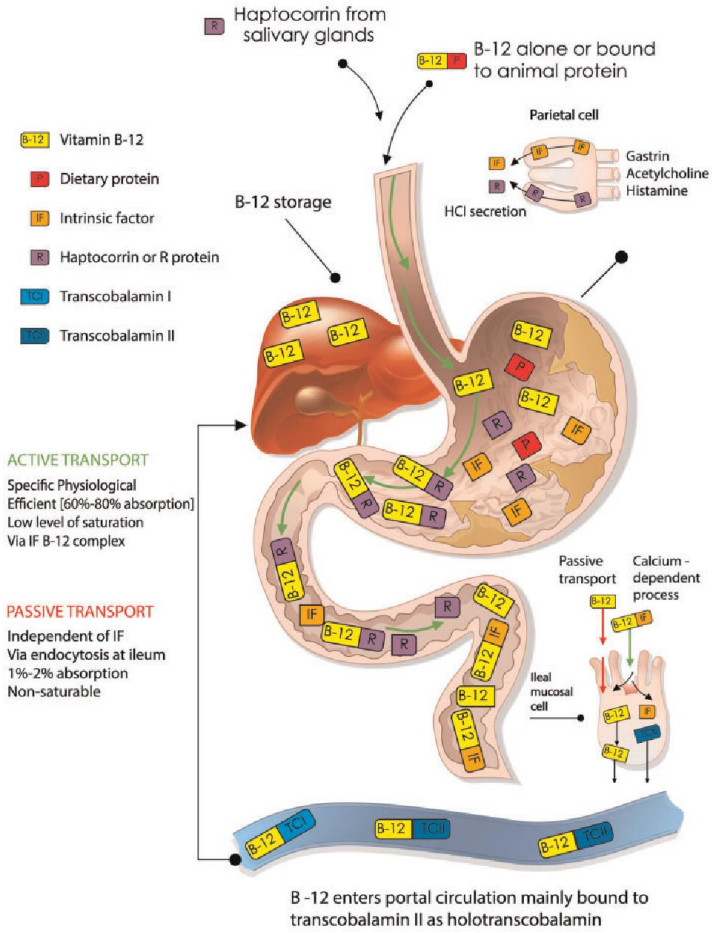

Figure 1. Mechanism of absorption and metabolism of vitamin B_{12} in the body (Brito et al., 2018)

Dietary sources of B_{12} and recommended intake

Vitamin B_{12} is present almost exclusively in foods of animal origin, while plant foods contain only minimal or inactive forms of cobalamin (Watanabe, 2007). In ruminants, vitamin B12 is synthesized by the action of microorganisms in the digestive system, and the amount of vitamin produced depends primarily on the intake of cobalt in the animal's diet (Kawashima et al., 1997; Ortigues-Marty et al., 2005). The most important dietary sources include liver, muscle tissue, fish, milk, and fermented milk products. As previously mentioned, cobalamin content in these foods depends on the diet and breeding conditions of the animals,including the technological processing of the food (Gille and Schmid, 2015). Their regular consumption is associated with higher serum concentrations of vitamin B12 (Barr et al., 2000; Stabler and Allen, 2004; Villamor et al., 2008;

Brouwer-Brolsma et al., 2015). However, different foods contain different forms of cobalamin, e.g. adenosylcobalamin and hydroxycobalamin are present in meat and fish, while methylcobalamin is mainly found in fermented milk products (Nušinović, 2015; Sobczyńska-Malefora et al., 2021). The recommended daily intake of vitamin B12 differs according to age and physiological needs and is defined by the guidelines of various institutions. According to the US Institute of Medicine (IOM, 1998) and the European Food Safety Agency (EFSA, 2015), the recommended values are several micrograms per day, which is sufficient to maintain normal metabolism and prevent deficits (Table 1).

Table 1. Recommended daily intakes of vitamin B_{12} (IOM, 1998; EFSA, 2015)

Ages	IOM (USA) RDA	EFSA (EU) PRI
Babies 0–6 months old	0.4 µg	0.4 µg
Babies 7–12 months old	0.5 µg	0.5 µg
Children 1–3 years old	0.9 µg	1.5 µg
Children 4–8 years old	1.2 µg	1.5 µg
Children 9–13 years old	1.8 µg	4.0 µg
Adolescents 14–18 years old	2.4 µg	4.0 µg
Adults (19+ years old)	2.4 µg	4.0 µg
Pregnant women	2.6 µg	4.5 µg
Nursing mothers	2.8 µg	5.0 µg

Bioavailability of B_{12}

The proportion of the ingested amount of cobalamin that is absorbed and becomes available for metabolic processes is bioavailable. It depends on the origin of the nutrient, the functional state of the digestive system, interactions with drugs and other nutrients, age, and food preparation methods. The content of vitamin B_{12} in meat varies depending on the age of an animal; younger animals have lower levels due to insufficiently developed storage capacities, so veal and lamb contain fewer amount than beef and mutton (Williams, 2007).

Bioavailability from chicken meat is about 61–65%, depending on the amount of intake (Doscherholmen et al., 1978). The concentration of the vitamin is also affected by the proportion of lipids in the meat, whereby lean parts contain more B12 (Ortigues-Marty et al., 2006). Thermal processing of meat products causes losses of 10% to 40%, which is particularly pronounced at high temperatures (Molonon et al., 1980; Gille and Schmid, 2015). Fish is a stable source of cobalamin, with minimal losses (2.3–14.8%) regardless of the method of preparation (Nishioka et al., 2006). In contrast, liver pate, although very rich in B_{12}, has low absorption (~10%) (Scott, 1997).

Absorption from eggs is extremely low (3.7–9.2%) due to the low availability of protein-bound vitamins (Squires and Naber, 1992). In milk, the concentration is stable, but cooking and microwave processing can cause losses of 30–50%, while pasteurization does not change the content of cobalamin (Watanabe et al., 1998). Fermentation of milk with bacteria *Lactobacillus bulgaricus* and *Streptococcus thermophilus* reduces B12 content, while *Propionibacterium shermanii* increases its concentration (Arkbåge et al., 2003).

The average absorption of vitamin B12 from a mixed diet is 35–40%, and it decreases with increased consumption of cobalamin per meal due to saturation of the absorption mechanism (Ströhle et al., 2019; Krpan, 2024).

Laboratory diagnostics of B_{12} status

Laboratory diagnosis of vitamin B_{12} deficiency is complex because neurological symptoms occur in 75–90% of patients, and in a quarter, those are the only symptoms, without macrocytic anemia (FNB, 1998). The basic assessment relies onserum vitamin B_{12}, with values <148 pmol/L (<200 pg/mL) considered the threshold for deficiency. The microbiological test is the most specific, while radiodilution and chemiluminescence offer faster, but less reliable results (Nemet, 2000). In pernicious anemia, a markedly reduced urinary excretion of vitamin B12 is a direct sign of low absorption in the gut (Sokoloff et al., 1952).

Considering possible falsely low values, simultaneous determination of folate is recommended (Vlasveld, 2003), especially since folate deficiency can mimic the clinical picture of B_{12} deficiency. Falsely reduced values also occur in multiple myeloma and in women using oral contraceptives (Shojania, 1982). Homocysteine and methylmalonic

acid (MMA) are typically elevated, while only homocysteine is elevated in folate deficiency. Autoimmune gastritis is accompanied by increased gastrin and decreased pepsinogen (Brinar, 2009).
Hematologic findings include macrocytic anemia (MCV 100–150 fL), reticulocytopenia, leukopenia, thrombocytopenia, with elevated LDH, bilirubin, iron, and ferritin, and decreased haptoglobin. In the bone marrow, there is a hypercellularity with megaloblastic hematopoiesis (Vrhovac et al., 2008). In the differential diagnosis, it is necessary to exclude infections (HIV-1, neurosyphilis) (Balt, 2000; Pandey, 2011), demyelinating diseases such as multiple sclerosis (Miller et al., 2005), and metabolic disorders (copper, vitamin E deficiency, exposure to N_2O).

Assessment of vitamin B_{12} absorption

The vitamin B_{12} absorption assessment has evolved from traditional radioisotope methods to safer and more accurate techniques. The Schilling test, although historically important, is rarely used today due to limitations in assessing protein-bound B_{12} and radioactivity (Vuk, 2016). Similar limitations are present in the yolk absorption test.
More modern approaches include CobaSorb, a non-radioactive method that measures the increase in holotranscobalamin after low oral doses and is effective in detecting malabsorption (Brito et al., 2018). A highly sensitive but technically demanding alternative is the ^{14}C-labeled B_{12} assay analysed by accelerator mass spectrometry (Brito et al., 2018).
In addition to diagnostics, strategies to improve absorption are being developed, including preparations linked to transport proteins or peptides, excipients such as SNAC, and probiotic and fermented products as potential sources and modulators of bioavailability (Brito et al., 2018).

Vitamin B_{12} status and neurological manifestations of deficit

The prevalence of vitamin B_{12} deficiency varies significantly among populations and is most often associated with limited intake of animal foods, economic and social factors, as well as dental and gastrointestinal problems that reduce intake or absorption (Baik and Russell, 1999). The elderly and patients with chronic malabsorption are the most at-risk groups. Epidemiological data consistently confirm the high prevalence of deficits in elderly people. In Nepal, 33.5% of $\geq$ 60-year-olds had a laboratory-confirmed deficiency (Gjawali et al., 2023), while in India the prevalence was 42.3%, especially pronounced in women over 75 years of age (Kumar et al., 2021). Data from the US (NHANES 2023) indicate a prevalence of approximately 20% among people over 60 years of age (CDC, 2023). In Croatia, Miškulin et al. (2014) found a deficit in 7.1% of the respondents, all of whom had concurrent symptoms of depression. Subclinical vitamin B_{12} deficiency, defined by reduced biochemical values without hematological or neurological manifestations, has particular clinical importance because it can progress to serious neurological damage before the appearance of clear symptoms (Carmel, 2011 b). Evidence suggests that subclinical deficiency is associated with cognitive decline, dementia, and depression (Bailey et al., 2015), and is most common in the elderly due to reduced absorption and metabolic changes (Allen et al., 2018). Evidence supports the need to introduce routine screening for vitamin B_{12} deficiency in ederly (Wong, 2015).
Unlike deficiency, vitamin B_{12} excess is much less common, but its clinical significance is becoming increasingly clear. Elevated serum concentrations do not usually reflect excessive dietary intake, but can be a marker of serious pathological conditions, including liver disease, renal failure, hematological disorders, and malignant diseases (Zulfiqar et al., 2019). In the geriatric population, excess is a strong predictor of mortality and is associated with more pronounced comorbidities. In a French geriatric acute care setting, 25.3% of hospitalized elderly patients had elevated levels of vitamin B_{12}, which were associated with acute renal failure, liver disease, and solid neoplasia (Zulfiqar et al., 2017).
Lack of vitamin B_{12} is most often the result of reduced intake, impaired absorption, or increased consumption of vitamins, whereby the elderly population is at the highest risk. Reduced intake occurs especially in people who do not consume products of animal origin;therefore, the prevalence of the deficit reaches more than 60% in vegans and about 40% in lacto- and ovo-lactovegetarians (Herrmann and Obeid, 2017). In the elderly population, primary causes include age-related changes in the gastrointestinal tract, such as hypochlorhydria and atrophic gastritis (Baik and Russell, 1999; Andrès et al., 2004), and pernicious anemia caused by a deficiency of intrinsic factor required for the absorption of vitamin B_{12}. Chronic gastrointestinal diseases, including Crohn's disease, celiac disease, and the post-gastrectomy condition, further impair the absorption of vitamin B_{12} (Allen, 2008). The status of vitamin B_{12} is significantly affected by numerous drugs, among which proton pump inhibitors and H_2-blockers (Lam et al., 2013),

metformin (de Jager et al., 2010; Ting et al., 2006), colchicine (Penniston et al., 2010), and anticonvulsants (Selby et al., 1998) stand out. Less common but clinically significant causes include parasitic infections such as *Diphyllobothrium latum*, which competitively consume vitamin B_{12} (Allen, 2009), and malnutrition and adverse social determinants of health, including poor appetite, dental problems, and depression in the elderly (Herrmann and Obeid, 2017). Autoimmune diseases (e.g., Hashimoto thyroiditis, vitiligo) and chronic inflammatory diseases can further impair the absorption and metabolism of vitamin B_{12} (Andrès et al., 2004), whereas liver and kidney diseases reduce the body's ability to store and recycle vitamin B_{12} (Herrmann and Obeid, 2017). Understanding a wide range of etiological factors is crucial for timely diagnosis and multidisciplinary management of subclinical and clinical vitamin B deficiency in the elderly population.

Neurological changes often appear independently or in combination with other symptoms; they are present in 4–50% of patients, and without timely vitamin supplementation, demyelination, axonal degeneration, and neuronal death occur, resulting in permanent damage to the nervous system. Table 2 shows the most common symptoms associated with B_{12} deficiency.

Table 2. Overview of symptoms of vitamin B_{12} deficiency in the peripheral, central, and autonomic nervous system

Symptom	Description of symptoms	Referrence
Peripheral neuropathy	Tingling, prickling, burning in hands and feet (symmetrical)	Allen et al., 2018; Carmel, 2011 b
Ataxia	Unsteady gait, balance disorder (especially in the dark)	Baik & Russell, 1999;Langan & Goodbred, 2017
Spasm	Stiffness and increased muscle tone	Mikkelsen & Apostolopoulos, 2018; Carmel, 2011b
Muscle weakness	Usually in the lower extremities	Baik & Russell, 1999; Mikkelsen & Apostolopoulos, 2018
Subacutecombined degeneration	Degeneration of the posterior and lateral columns of the spinal cord	Carmel, 2011b; Langan & Goodbred, 2017
Optical neuropathy	Blurred vision, central scotoma, reduced colour vision	Calderón-Ospina & Nava-Mesa, 2020; Allen et al., 2018
Positive Babinski reflex	Pathological reflex - a sign of upper motor neuron lesion	Baik & Russell, 1999; Carmel, 2011a
Autonomousdysfunction(rarely)	Orthostatic hypotension, urination disorders	Baik & Russell, 1999; Calderón-Ospina & Nava-Mesa, 2020

Aging, itself causes changes in the gastrointestinal tract which directly imapacts vitamin B_{12} absoprtion – from reduced consumption of meat to dental issues, to lower acidity in the stomach and atrophy of the stomach that affects intrinsic factor, to impaired motility. When combined with underlaying chronic health issues and (multi)mediaction use, the risk of deficiency among elderly is especially high (Mouchaileh, 2023).

Concluding remarks

Available literature proves that vitamin B_{12} deficiency is frequent, but insufficiently recognized in routine clinical practice among elderly. This may be due to methodological differences between studies, including the definition of deficiency (serum B_{12} cut-offs), the biomarkers assessed (serum B_{12}, holotranscobalamin, methylmalonic acid), participant selection, age groups, as well as geographic, and socio-economic factors.

While some studies focus on laboratory-confirmed deficiencies in older adults, others address subclinical deficiency or populations with specific risk factors, such as users of metformin or proton pump inhibitors. This heterogeneity complicates direct comparison of results and underscores the need for standardized protocols in future research. Currently, there is no recommendation for mass screening for vitamin B12 in the elderly, and given the increased number of elderly in the global population (WHO, 2025) and high burden of neurodegenerative disorders (GBD 2021 Nervous System Disordes Collaborators, 2024), there is an evident need to improve current practice. Based on the literature reviewed, we found sparse evidence from long-term studies that focused on early detection of vitamin B_{12} deficiency, and targeted replacement to prevent neurological damage among elderly. Particularly underexplored areas include interactions of vitamin B_{12} with medications and nutritional factors, as well as strategies to optimize early detection of subclinical deficiency in older

populations. Because symptoms often develop gradually and can be nonspecific including peripheral neuropathies, balance disturbances, cognitive decline, and mood changes the deficit is often misattributed to aging processes or other comorbidities. Additionally, the fact that neurological changes can occur even at serum levels of vitamin B_{12} within the reference range highlights the limitations of conventional diagnostic criteria. In this context, the use of more specific biomarkers, such as holotranscobalamin and methylmalonic acid, represents a significant advance in assessing the functional status of B_{12}. These markers enable early detection of cobalamin metabolism disorders, especially in risk groups such as the elderly, people with chronic gastrointestinal diseases, patients after bariatric procedures, and users of metformin and proton pump inhibitors. Including these parameters in diagnostic algorithms can significantly improve the timely recognition of deficits and reduce the risk of irreversible neurological consequences.

It is necessary to educate healthcare professionals about the need for early screening for vitamin B_{12} status, while older adults, especially those with chronic conditions known to affect vitamin B_{12} bioavailability need specific education on risks of low vitamin B_{12} status and its neurological consequences. The proactive implementation of targeted supplementation and preventive strategies, based on insights from the reviewed studies, may reduce the incidence of neurological complications, improve quality of life in older adults, and optimize healthcare system resources.

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