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NORMAL SERUM VITAMIN B12 LEVELS IN SYMPTOMATIC PATIENTS: DIAGNOSTIC VALUE OF METHYLMALONIC ACID AND HOMOCYSTEINE IN FUNCTIONAL DEFICIENCY

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ABSTRACT

Background: Vitamin B12 deficiency is a clinically important condition associated with hematological, neurological, and neuropsychiatric manifestations. However, diagnosis may be difficult in symptomatic patients with normal total serum vitamin B12 concentrations, as normal circulating levels do not necessarily reflect adequate intracellular metabolic function. This has led to growing interest in the concept of functional vitamin B12 deficiency. The aim of this review was to evaluate the diagnostic value of methylmalonic acid (MMA) and homocysteine in symptomatic patients with normal or borderline serum vitamin B12 levels.
Methods: A narrative review was conducted using the PubMed database. English-language peer-reviewed articles published over the last decade were screened for relevance to vitamin B12 metabolism, laboratory assessment, functional deficiency, and the diagnostic utility of MMA, homocysteine, and holotranscobalamin. Eighteen publications were included in the qualitative synthesis.
Results: Total serum vitamin B12 has limited sensitivity for early or functional deficiency. MMA and homocysteine reflect metabolic consequences of impaired vitamin B12–dependent pathways and may improve diagnostic sensitivity in patients with normal or borderline serum levels. MMA is more specific for vitamin B12–related metabolic impairment but is influenced by renal function and age. Homocysteine is less specific and is affected by folate and vitamin B6 status, renal function, and age. Holotranscobalamin reflects the circulating biologically active fraction of vitamin B12 and may allow earlier detection of reduced availability. Biomarker interpretation is limited by physiological and inter-individual variability, as well as the lack of standardised cut-off values.
Conclusions: In symptomatic patients with inconclusive serum vitamin B12 results, MMA and homocysteine provide clinically relevant complementary information. A combined diagnostic approach integrating serum vitamin B12, functional biomarkers, and clinical assessment offers greater diagnostic accuracy than reliance on total serum vitamin B12 alone.

KEYWORDS

Vitamin B12 Deficiency, Functional Vitamin B12 Deficiency, Methylmalonic Acid, Homocysteine, Holotranscobalamin

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Introduction

Vitamin B12 is an essential water-soluble micronutrient required for normal hematopoiesis, neurological integrity, and intracellular metabolic function. Its biological importance is primarily derived from its role as a cofactor in two fundamental enzymatic reactions: the remethylation of homocysteine to methionine and the conversion of methylmalonyl-CoA to succinyl-CoA. Through these reactions, cobalamin is critically involved in one-carbon metabolism, DNA synthesis, methylation processes, myelin maintenance, and mitochondrial function. Disruption of these pathways may therefore lead to clinically significant metabolic and systemic consequences [1,2].

Vitamin B12 deficiency is of substantial clinical importance because impairment of cobalamin-dependent pathways may give rise to hematological, neurological, and neuropsychiatric abnormalities. Early recognition is particularly important, since delayed diagnosis and treatment may result in persistent or only partially reversible complications, especially in patients with neurological involvement. The clinical presentation is frequently heterogeneous and may include fatigue, weakness, dizziness, paresthesia, sensory disturbances, gait instability, cognitive complaints, impaired concentration, memory impairment, mood changes, and other nonspecific manifestations. At the same time, classical hematological features such as macrocytosis or megaloblastic anemia may be absent, subtle, or delayed, thereby obscuring the diagnosis. This variability contributes to the diagnostic complexity of vitamin B12 deficiency and may result in underrecognition in routine clinical practice [3,4].

In contemporary clinical practice, total serum vitamin B12 concentration remains a useful first-line test in the evaluation of suspected deficiency. It is easily available, relatively inexpensive, and commonly incorporated into standard diagnostic algorithms. However, despite its practical utility as an initial screening tool, total serum vitamin B12 has important diagnostic limitations when interpreted in isolation. Borderline results are often difficult to classify, and values within the reference range do not necessarily exclude clinically significant deficiency. Moreover, serum concentrations may not accurately reflect intracellular availability or tissue-level metabolic sufficiency. As a result, reliance on total serum vitamin B12 alone may contribute to false reassurance in symptomatic patients [2,5,6].

Growing awareness of these diagnostic shortcomings has led to increased interest in the concept of functional vitamin B12 deficiency. This term refers to impaired vitamin B12-dependent metabolic function despite serum vitamin B12 concentrations that may be normal or otherwise not clearly indicative of deficiency according to conventional laboratory criteria. In such cases, circulating vitamin levels may appear adequate, while intracellular utilization remains insufficient to support normal enzymatic function. Functional deficiency may arise from abnormalities in absorption, transport, cellular uptake, intracellular processing, or coenzyme conversion. This concept is particularly relevant in symptomatic patients with apparently normal serum vitamin B12 values [3,4].

Within this context, methylmalonic acid and homocysteine have emerged as clinically relevant functional biomarkers of disrupted vitamin B12-dependent metabolism. Their diagnostic value lies in the fact that they provide information beyond the circulating concentration of vitamin B12 and may help identify functionally relevant deficiency not detected by serum vitamin B12 alone. This makes them particularly useful in the evaluation of symptomatic patients with normal or borderline serum cobalamin values and ongoing clinical suspicion of deficiency. In such patients, methylmalonic acid and homocysteine may provide important complementary information and improve the sensitivity of the diagnostic process by identifying deficiency states that remain undetected when assessment is based solely on serum vitamin B12 concentration [7,8].

Against this background, the present review evaluates the diagnostic value of methylmalonic acid and homocysteine in symptomatic patients with normal serum vitamin B12 levels, with particular emphasis on their role in identifying functional vitamin B12 deficiency when conventional serum-based assessment is inconclusive. It further considers the extent to which metabolic biomarkers may enhance the diagnostic accuracy and clinical utility of cobalamin status assessment in routine clinical practice [5,8].

Methodology

This article was prepared as a narrative review based on a targeted, non-systematic review of the literature on vitamin B12 deficiency, with particular emphasis on the limitations of total serum vitamin B12 measurement and the diagnostic value of functional biomarkers, especially methylmalonic acid (MMA) and homocysteine, in symptomatic patients with normal or borderline serum vitamin B12 concentrations.

A targeted, non-systematic literature search was performed using the PubMed database to identify clinically relevant publications. English-language, peer-reviewed articles published over the last decade were screened. The search focused on vitamin B12 metabolism, laboratory assessment of vitamin B12 status, functional vitamin B12 deficiency, MMA, homocysteine, holotranscobalamin, and clinically relevant diagnostic approaches. The main search terms included *vitamin B12 deficiency*, *functional vitamin B12 deficiency*, *normal serum vitamin B12*, *borderline vitamin B12*, *vitamin B12 biomarkers*, *methylmalonic acid*, *homocysteine*, *holotranscobalamin*, *active B12*, *diagnosis*, *laboratory evaluation*, *metformin-induced vitamin B12 deficiency*, *neurological manifestations*, and *diagnostic approach*. To improve completeness, the reference lists of selected articles were also screened manually.

Finally, 17 publications were included in the narrative synthesis based on their relevance to the topic, clinical applicability, and contribution to the understanding of diagnostic challenges in vitamin B12 deficiency. Articles were excluded if they were not directly related to the aim of the review, particularly when they did not address the diagnostic relevance of MMA, homocysteine, or other vitamin B12-related biomarkers, focused on unrelated disorders, concerned non-relevant patient groups, or had limited applicability to functional vitamin B12 deficiency.

Results

Vitamin B12 absorption is an intrinsic factor–dependent process occurring in the terminal ileum after sequential gastric and duodenal processing of dietary cobalamin. In the stomach, cobalamin is released from food proteins and binds to haptocorrin, which protects it from degradation in the acidic environment. In the duodenum, pancreatic proteases degrade haptocorrin, enabling transfer of cobalamin to intrinsic factor secreted by gastric parietal cells. The intrinsic factor–cobalamin complex is transported intact to the terminal ileum, where it is internalised via receptor-mediated endocytosis through the cubam receptor complex (the cubilin–amnionless system) expressed on ileal enterocytes. Following receptor-mediated endocytosis, the intrinsic factor–B12 complex is degraded in lysosomes, releasing cobalamin into the enterocyte. Vitamin B12 is then exported into the circulation and binds predominantly to transcobalamin II, forming holotranscobalamin, the biologically active transport form responsible for tissue delivery. Impairment of intrinsic factor production, pancreatic proteolysis, or cubam-mediated uptake may lead to reduced absorption and clinically relevant vitamin B12 deficiency [1,2,4].

Limitations in the laboratory assessment of vitamin B12 status arise primarily from the fact that serum total cobalamin does not directly reflect the metabolically active fraction or true tissue availability. Total vitamin B12 includes both haptocorrin-bound cobalamin, which is biologically inactive, and the smaller fraction bound to transcobalamin II, known as holotranscobalamin (holoTC), which represents the biologically active form responsible for cellular uptake and tissue delivery. Consequently, normal total serum vitamin B12 concentrations may be observed even in the presence of impaired absorption or early functional deficiency, when the proportion of biologically active holoTC is reduced. This limitation is clinically relevant because systemic vitamin B12 availability depends on a properly functioning ileal absorption pathway mediated by intrinsic factor, meaning that early disturbances may remain undetected by serum vitamin B12 alone. Therefore, functional biomarkers such as methylmalonic acid and homocysteine provide superior sensitivity for detecting early or subclinical deficiency, as they more directly reflect intracellular metabolic impairment. In parallel, holotranscobalamin is considered a more sensitive indicator of early deficiency, as it directly reflects the fraction of vitamin B12 available for cellular uptake [2,6,8,9].

The role of methylmalonic acid (MMA) and homocysteine

Methylmalonic acid (MMA) and homocysteine accumulate as a direct consequence of impaired activity of vitamin B12–dependent enzymes, namely methylmalonyl-CoA mutase and methionine synthase, respectively. Vitamin B12 acts as an essential cofactor for methylmalonyl-CoA mutase in mitochondrial metabolism; in the absence of sufficient intracellular cobalamin, the conversion of methylmalonyl-CoA to succinyl-CoA is impaired, leading to accumulation of MMA, which serves as a sensitive marker of disrupted propionate and odd-chain fatty acid metabolism. In parallel, vitamin B12 is required for methionine synthase activity in the cytosolic one-carbon cycle, where it facilitates the remethylation of homocysteine to methionine. Impaired enzymatic activity due to cobalamin deficiency results in intracellular and circulating accumulation of homocysteine, reflecting disruption of methyl-group transfer reactions and reduced availability of methionine for S-adenosylmethionine (SAM)-dependent methylation processes. These metabolites therefore reflect downstream metabolic dysfunction rather than circulating vitamin levels, enabling detection of early or functional vitamin B12 deficiency even in patients with normal or borderline serum cobalamin concentrations. In this context, MMA is considered the more specific marker of cellular vitamin B12 deficiency, whereas homocysteine is less specific due to additional influence from folate and vitamin B6 status. The combined assessment of both biomarkers improves diagnostic sensitivity, particularly in cases within the diagnostic “grey zone,” where serum vitamin B12 alone is insufficient to exclude deficiency [1,8,10].

Factors influencing biomarker interpretation

Variability in vitamin B12–related biomarkers should be interpreted in the context of physiological, pharmacological, and disease-related factors that may influence their diagnostic accuracy. Renal impairment represents a major confounder, particularly for methylmalonic acid (MMA), which is primarily eliminated via the kidneys; reduced glomerular filtration rate may therefore result in elevated MMA concentrations independent of vitamin B12 status, limiting its specificity in patients with chronic kidney disease. Homocysteine concentrations are also affected by renal dysfunction and are additionally influenced by folate and vitamin B6 status, as well as other metabolic and inflammatory conditions, which may further reduce its specificity when interpreted in isolation [8,10].

Age is an additional important physiological determinant of biomarker variability. Both MMA and homocysteine tend to increase with advancing age, even in the absence of overt vitamin B12 deficiency, which

may contribute to diagnostic uncertainty in older populations and should be considered when interpreting borderline results.

Pharmacological factors also play a relevant role. Metformin has been associated with reduced vitamin B12 absorption, likely through interference with calcium-dependent uptake of the intrinsic factor–cobalamin complex in the terminal ileum, potentially leading to gradual depletion of vitamin B12 stores and functional deficiency despite initially normal serum concentrations [11,12].

Gastrointestinal disorders may affect multiple stages of cobalamin handling, including gastric release from dietary proteins, intrinsic factor production, pancreatic processing, and ileal absorption. Conditions such as atrophic gastritis, pernicious anaemia, pancreatic insufficiency, and terminal ileum disease or resection may therefore result in reduced vitamin B12 bioavailability, with variable effects on circulating biomarkers depending on disease severity and duration [1,2,4].

In clinical practice, interpretation of vitamin B12–related biomarkers should therefore account for these confounding factors, particularly in patients with borderline or discordant results or when clinical suspicion of deficiency persists despite non-diagnostic initial testing [6,8].

The table below presents a comparison of key vitamin B12-related biomarkers, their diagnostic relevance, and the main factors influencing the interpretation of their results.

Table 1. Comparison of vitamin B12-related biomarkers

Biomarker	What it reflects	Diagnostic value	Key limitations	Clinical role
Total serum vitamin B12	Total circulating cobalamin (protein-bound inactive + active fractions)	First-line screening marker; widely available	Low sensitivity in early deficiency; borderline "grey zone" values	Initial screening marker
Holotranscobalamin (holoTC)	Biologically active fraction bound to transcobalamin II (available for cellular uptake)	Early indicator of reduced vitamin B12 availability	Limited standardisation of cut-off values; variable assay availability	Early diagnostic marker
Methylmalonic acid (MMA)	Intracellular mitochondrial cobalamin-dependent metabolism (methylmalonyl-CoA → succinyl-CoA)	High sensitivity for functional vitamin B12 deficiency	Reduced specificity in renal impairment and with declining renal function	Confirmatory functional biomarker
Homocysteine	One-carbon metabolism (methionine cycle; remethylation pathway)	Sensitive functional marker of impaired methylation	Non-specific; influenced by folate, vitamin B6, renal function, and age	Confirmatory functional biomarker

Discussion

Indications for extended biomarker testing

Indications for extending diagnostic evaluation beyond total serum vitamin B12 arise primarily in clinical situations where laboratory findings and clinical presentation are discordant. Additional assessment using functional biomarkers such as holotranscobalamin, methylmalonic acid, and homocysteine may be considered in symptomatic patients with normal or borderline serum vitamin B12 concentrations, as well as in individuals with a higher pre-test probability of deficiency. This includes older adults, patients receiving metformin therapy, and those with gastrointestinal disorders affecting gastric secretion, intrinsic factor production, pancreatic function, or ileal absorption. Expanded testing is also commonly applied within the diagnostic "grey zone," where serum vitamin B12 levels are inconclusive and do not reliably exclude intracellular deficiency [2,6,8,13].

These considerations form the basis for a structured, stepwise diagnostic approach to suspected vitamin B12 deficiency, particularly in patients with normal serum vitamin B12 levels despite clinical suspicion [2,5].

Table 2. Proposed diagnostic approach in patients with suspected vitamin B12 deficiency, with particular emphasis on symptomatic patients with normal serum vitamin B12 levels

Clinical presentation and biochemical profile	Interpretation	Relevance for diagnostic discussion
Reduced serum vitamin B12 in the presence of compatible clinical features	Overt vitamin B12 deficiency is strongly supported	This combination provides strong evidence for clinically relevant deficiency and usually supports treatment initiation together with investigation of the underlying cause.
Reduced serum vitamin B12 with elevated MMA and/or homocysteine	Biochemical evidence supports metabolically confirmed vitamin B12 deficiency	Elevated metabolic markers strengthen the diagnostic interpretation and support the presence of tissue-level deficiency.
Reduced serum vitamin B12 with normal MMA and homocysteine	Early, borderline, or non-functional deficiency remains possible	Normal metabolic markers do not completely exclude early deficiency; repeat evaluation and continued clinical monitoring may be appropriate in persistent symptomatic cases.
Normal serum vitamin B12 with elevated MMA and/or homocysteine	Functional vitamin B12 deficiency should be considered despite normal circulating vitamin B12 levels	This pattern supports the concept that serum vitamin B12 alone may fail to detect tissue-level deficiency; however, alternative causes of MMA or homocysteine elevation should be excluded before attributing the abnormalities solely to vitamin B12 deficiency.
Normal serum vitamin B12 with normal MMA and homocysteine	Functional vitamin B12 deficiency appears less likely	In this setting, other causes of the patient's symptoms should be considered, although reassessment may still be warranted when clinical suspicion remains high.
Neurological manifestations despite normal serum vitamin B12 and inconclusive metabolic markers	Functional vitamin B12 deficiency cannot be definitively excluded	Neurological involvement may occur in the absence of clear biochemical abnormalities; therefore, clinical judgment remains essential, and repeat testing or empirical treatment may be justified in selected cases.

Abbreviations: MMA - methylmalonic acid.

A lack of a universally accepted diagnostic standard for functional vitamin B12 deficiency may contribute to delayed or missed diagnosis in patients with discordant clinical and laboratory findings [5,14].

Current evidence supports the integration of total serum vitamin B12 with functional biomarkers, including holotranscobalamin, methylmalonic acid, and homocysteine, together with clinical assessment, to improve diagnostic accuracy. This combined strategy is particularly relevant when serum vitamin B12 values are borderline or inconclusive, or when clinical suspicion persists despite apparently normal laboratory results [5,8,15].

Interpretation of vitamin B12-related biomarkers remains challenging due to inter-individual variability, assay-dependent differences, and the absence of standardised cut-off values for functional markers. These limitations highlight the importance of an integrated diagnostic framework rather than reliance on a single biomarker [8,16,17].

Conclusions

In conclusion, total serum vitamin B12 alone is insufficient to reliably exclude early or functional deficiency, particularly in symptomatic patients or those with borderline biochemical results. Functional biomarkers, including methylmalonic acid, homocysteine, and holotranscobalamin, provide complementary information on intracellular cobalamin status and may improve diagnostic sensitivity when interpreted within a clinically integrated framework. However, their interpretation is influenced by physiological, pharmacological, and disease-related factors, which limits their specificity when used in isolation. Accordingly, a multi-marker diagnostic strategy combining serum vitamin B12, functional biomarkers, and clinical context offers a more robust approach to the assessment of vitamin B12 status in routine clinical practice.

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