International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

CONSENSUS

DOI: 10.54448/ijn25103

Recommendations and guidance on Cobalamin (Vitamin B12) based on the Delphi method

Tiago Lazzaretti Fernandes[1], Dayse Maria Lourenço[2], Durval Ribas Filho[3], Glaucia Carneiro[2], Gustavo Loureiro[4], João Toniolo Neto[2], Luiz Claudio Cameron[5], Sonia Maria Dozzi Brucki[6], Nairo Massakazu Sumita[4], Henry Dan Kiyomoto[7*], André Pedrinelli[1]

[1] Institute of Orthopedics and Traumatology, Hospital das Clínicas, School of Medicine, University of São Paulo, Brazil.
[2] Federal University of São Paulo, São Paulo, Brazil.
[3] School of Medicine Padre Albino Foundation, Nutrology, São Paulo, Brazil,
[4] Fleury Laboratory, Brazil,
[5] Laboratory of Protein Biochemistry, University of Rio de Janeiro, Brazil.
[6] Cognitive and Behavioral Neurology, Hospital das Clínicas, School of Medicine, University of São Paulo, Brazil.
[7] University Center of the Americas, Brazil.

*Corresponding author: Henry Dan Kiyomoto.
University Center of the Americas, Brazil. Address: Embú Municipal Road, 1550, Guancan Residential - House 320.
Zip Code: 06713-100, Cotia, Sao Paulo, Brazil.
Phone: +55(11)983662078.
E-mail: pesquisa.dan@gmail.com

DOI: https://doi.org/10.54448/ijn25103
Received: 11-11-2024; Revised: 01-11-2025; Accepted: 01-12-2025; Published: 01-13-2025; IJN-id: e245103

Editor: Dr. Idiberto José Zotarelli-Filho, MSc, Ph.D., Post-Doctoral.

Abstract

Introduction: Vitamins are essential micronutrients for the body to function. Cobalamins (Cbls) are watersoluble compounds, acting as cofactors in enzymatic reactions. However, the use of Cbls in the clinical environment is still controversial. **Objective:** It was to discuss the topic and help guide different professionals, experts were brought together to discuss criteria concerning the diagnosis, indications, and use of cobalamin. **Methods:** The study was carried out using the Delphi method. Topics were initially created to direct the discussion and initial contributions. In the first meeting with the panelists, questions were formulated. The questions were distributed to all panelists. With the contributions, a text with the answers was created, and a third round to review the contributions and agree with the text was carried out. **Results:** The main topics related to the use of cobalamin were identified. **Conclusion:** The main topics related to this topic include risk groups of deficiency of ingestion or absorption by the gastrointestinal tract. The deficiency diagnosis must be made through laboratory tests, and early indication must be made when a significant cobalamin deficiency is identified, to avoid irreversible clinical conditions. A recommended practice is monitoring between 2 and 6 months after starting cobalamin replacement. Evidence Level:6.

Keywords: Cobalamin. Diagnosis. Indications. Guideline.

Introduction

Vitamins are essential micronutrients for the body. Cobalamins (Cbls) are water-soluble compounds that act as cofactors in enzymatic reactions in carbon transfer reactions through methylation and demethylation. Cbls act as cofactors in the conversion of methylmalonyl CoA to succinyl CoA, thus participating in the energy metabolism of fatty acids. Cbls are essential for the production of red blood cells [erythropoiesis] **[1,2]** and for normal neurological development **[3]**.

Also, Cbls are synthesized exclusively by some microorganisms that are members of the Bacteria and

Archaea kingdoms. Animals obtain these molecules from the consumption of vegetables and, consequently, foods of animal origin are the largest source of Cbls in the human diet **[4]**. Cbls deficiency manifests itself during increased demands and altered or reduced intake, such as in infants, pregnant women, the elderly **[5]**, vegan diets, or inadequate absorption.

During pregnancy, deficiency can result in decreased cobalamin levels in the embryo and fetus, resulting in higher rates of spontaneous abortion, intrauterine growth restriction, neural tube defects, and low birth weight **[6,7]**. In the elderly, some neurological manifestations appear to be associated with low serum Cbls concentrations **[8,9]**. Diabetes, as well as certain peripheral neuropathies, may be associated with inadequate Cbls levels **[10-12]** and benefit from cobalamin supplementation **[12-14]**.

The most common causes of Cbls deficiency are gastric disorders such as autoimmune pernicious anemia or gastrectomy **[15]**; ileal resection; pancreatic insufficiency; and malabsorption syndromes, including Crohn's disease **[16]** and celiac disease [gluten-induced enteropathy] **[17]**. Nutritional deficiency not associated with other diseases is rare and generally only occurs in vegans **[18]**. The prevalence is higher in elderly males and in some ethnic groups, such as in countries in the African and Asian continents **[5,8]**.

Diagnosis is based on measurements of serum Cbls concentrations **[19]** and is complemented by additional tests, including total homocysteine and methylmalonic acid levels, which are indirect indicators of Cbls deficiency **[20,21]**. The number of studies on Cbls-related disorders has increased in recent years **[22]**. However, uncertainties regarding treatment may be under or over-utilized, and the lack of clarity of criteria related to the topic should be investigated.

In order to guide and shed light on the discussion, a group was established, bringing together different experts, to discuss possible criteria for the diagnosis of deficiency, indications, and use of cobalamin.

Methods

The study was conducted using the Delphi method, which can be used in situations where there is no definitive answer or information is still scarce or uncertain, and can help mitigate individual biases by allowing experts to share their opinions and thus contribute to a panel in a more objective manner **[23,24]**. Medical professionals from various specialties participated. Professionals were invited who were known to have an interest in research and clinical practice in the use of CBLs. Our goal was to have representation of medical professionals from various specialties who use cobalamin in clinical practice, and we deliberately chose people who could have disparate points of view, representing the broadest possible spectrum of opinion. In total, nine physicians participated in the process and are the authors of this article.

A systematic literature review was conducted in databases (PubMed, EMBASE, and Cochrane Library), with no date restrictions until December 2021, using the descriptors cobalamin and vitamin B12. Panel members contributed spontaneously throughout the study and suggested additional studies that were not selected in the initial search of electronic databases. At this stage, the objective was to collect relevant literature and make it available to panelists, to standardize definitions and knowledge about CBLs among panelists, so that they could participate in the subsequent stage.

The research coordinator listed topics to guide the first meeting with panelists, which are described in Table 1. Thus, a first round of consultation with panelists was held in July 2021 and the responses were compiled and summarized anonymously.

Table 1. Topics addressed for initial discussion, with open-ended questions.

Topics covered – initial
1. What are the risk groups for Cbls deficiency that general practitioners should investigate?
2. What information is important for general practitioners and specialists who work with diseases related to the diagnosis of Cbls deficiency regarding dosage methods and reference values?
3. What are the most important clinical consequences related to Cbls deficiency? List all that you are aware of. Please discuss in depth the clinical presentation of the pathologies in your area of expertise.
4. What are the administration routes for the treatment of Cbls deficiency? Comment on the advantages and disadvantages of the formulations (bioavailability).
5. What are the advantages/disadvantages of the absorption routes of cobalamin present in the available formulations?
6. Treatment: for the pathologies selected and discussed in depth in item 3, please discuss the disease and how the treatment in question is monitored.
7. What is the level of evidence from the available scientific articles (on the pathologies discussed in depth) and your clinical practice that discusses the correlation of Cbls with the disease to be treated?

Source: Own authorship.

In the next round in October 2021, the panelists were sent the aggregated results of the first meeting, with closed questions added, and everyone was encouraged to comment on the questions. The panelists met for a convergence stage, in which opinions and comments could converge in light of the opinions among the panelists. Finally, the panel members answered

whether they agreed with the questions from the round for final validation. In the third stage, the statements constructed by the contributions of each panelist were sent to the panelists for a final correction of the text to finalize the final version of the document.

Results and Discussion

Tables 2 to 7 present the responses to each topic identified in the first meeting. In the round of topic validation, 89% of the panelists agreed with topic 1, which dealt with risk groups. Among the suggestions made, the term risk group should be added to the term clinical conditions, to characterize that these patients were deficient in Cbls. In addition, it was suggested that specific clinical conditions be added to the identified risk groups: strict vegetarians, patients with gastrectomy, such as ileal resections, post-bariatric surgery, angular stomatitis, and clinical conditions that indicated a possible Cbls deficiency.

Table 2. Results of the agreement between the text and the panelists' contributions, topic 1.

Question 1. What are the risk groups or clinical conditions for Cbls deficiency that Agreement the physician should investigate?	
Hematological diseases: anemia; patients with macrocytosis of any age group, with or without anemia; patients on hemodialysis.	100%
Malabsorption syndromes due to clinical conditions: atrophic gastritis; alterations of the small intestine; celiac disease, bacterial overgrowth syndrome, blind loop syndrome; patients with inflammatory bowel disease; dyspeptic syndrome; ulcerative disease; pancreatic insufficiency.	100%
Post-surgical syndromes: patients undergoing bariatric surgery; gastrectomy; patients undergoing intestinal resection; ileal resection or bypass.	100%
Nutritional deficiencies: patients with malnutrition of any etiology; vegetarians or vegans; nutritional deficiency; anorexia nervosa.	100%
Neurological diseases: patients with peripheral neuropathies or degenerative diseases; symmetrical paresthesias; cognitive deficits.	100%
Drug/food interactions: neomycin, biguanides (metformin), proton pump inhibitors (omeprazole), H2 receptor antagonists (cimetidine), alcohol use.	100%
Congenital defects: orotic aciduria, transcobalamin deficiency, Immerslund Grösbeck syndrome.	100%
Special populations: pregnant women, elderly, diabetics, HIV-positive patients.	100%
Autoimmune diseases: autoimmune diseases such as type 1 diabetes.	100%

Source: Own authorship.

In the second topic, which addressed the information that was important for professionals working with diseases related to Cbls deficiency, 89% of the panelists agreed that the topic was important. In the contributions, it was suggested that the term Cbls should be used instead of Vit.B12 and that questions about dosage methods, interferents, pre-analytical care, reference values, interpretation of results, tests that should be requested and correlated to aid in the diagnosis of Cbls deficiency, and when to request and how to interpret them, should be part of this topic. Table 3 shows the panelists' contributions to this topic.

Table 3. Results of the agreement between the text and the panelists' contributions, topic 2.

Question 2. What are the important tests and information for the laboratory Agreement diagnosis of cobalamin (B12) deficiency, the measurement methods, interfering agents, pre-analytical care, reference values , and interpretation of results?	
Request a B12 or cobalamin measurement. Competitive chemiluminescent immunoassay for cobalamin measurement, which has 95% sensitivity in symptomatic patients.	100%
Methylmalonic acid (MMA) and homocysteine, in case of borderline or unexpected Cbls values, or the presence of interfering agents. In cases with a suspicious clinical picture and hematological alteration, and if the serum cobalamin level is indeterminate, plasma homocysteine (nl 5-15 umol/L) and plasma methylmalonic acid (normal <0.28 umol/L) measurements may be considered as complementary tests, as they are functional markers of the Cbls status in the body. Less commonly, laboratory assays of MMA by liquid chromatography-mass spectrometry are available.	89%
MMA is an intermediate metabolite that accumulates in cases of cobalamin deficiency, leading to elevated concentrations. The same occurs with homocysteine. However, homocysteine may also be elevated in cases of folate deficiency, unlike MMA. Folate deficiency may lead to falsely low cobalamin levels, so folic acid dosage is recommended.	89%
In the laboratory evaluation of patients with suspected cobalamin deficiency, other tests may be used, such as complete blood count, reticulocyte count, DHL, bilirubin, antiintrinsic factor antibodies, and transcobalamin.	78%
Holotranscobalamin is the form of Cbls absorbed by cells to meet metabolic demand, and laboratory tests have recently become available.	56%
Radioimmunoassay, used in the past, is no longer routinely applied. The Schilling test, used to diagnose pernicious anemia, is also no longer applied and is only of historical interest.	78%
Determining the serum concentration of cobalamin (Cbls) has good specificity, but some situations may interfere with the determination of the concentration, reducing the concentration of cobalamin in a spurious manner, such as the presence of monoclonal protein (myeloproliferative diseases/multiple myeloma), and HIV infection. Other factors that interfere with falsely normal levels: diseases such as cancer, chronic liver disease, nephropathy, autoimmune diseases, physiological states such as pregnancy, presence of antibodies that can directly interfere with the assay. The presence of antiintrinsic factor antibodies present in pernicious anemia can influence the results of assays based on competitive binding luminescence technologies, making it difficult to diagnose cobalamin (B12) deficiency.	100%

Renal failure and the presence of inborn errors of metabolism can interfere with the dosage of MMA and homocysteine, respectively.	89%
In the laboratory evaluation of patients with suspected cobalamin deficiency, other tests may be used, such as complete blood count, reticulocyte count, DHL, bilirubin, antiintrinsic factor antibodies, and transcobalamin.	67%
The use of biotin in high doses (greater than 5000 micrograms per day), as well as the use of diphenylhydantoin and anticonvulsant medications may be associated with decreased serum values due to interference in the laboratory test.	89%
The increase in homocysteine is less specific, as it also increases in folate deficiency, vitamin B6 deficiency and hypothyroidism.	89%
Some pre-analytical precautions may be mentioned: type of sample (serum or plasma); centrifuge the sample within two hours after collection; after intramuscular application of Cbls, one must wait at least two weeks before collection; avoid drinking alcohol 24 hours before blood collection; discontinue use of biotin 72 hours before blood collection.	78%
The lower limit of normal may vary according to the kit used to measure cobalamin (B12), and the information on the kit leaflet must be followed. In general, the following reference values are recommended: Normal: above 300 pg/mL; Borderline: 200 to 300 pg/mL; Deficiency: below 200 pg/mL.	78%
Values slightly above the lower limit should be considered, especially in individuals at risk of deficiency.	78%
In cases of doubt between the clinical and laboratory findings, elevated plasma homocysteine and plasma MMA levels confirm the presence of cobalamin (B12) deficiency. A serum MMA concentration > 280 nmol/L may suggest a suboptimal status in young patients with normal renal function.	89%
Monitoring the cobalamin pool (always associated with measurements of folate, iron, hematocrit and reticulocyte count) is the best way to interpret the findings in a personalized manner.	78%
2.1 When to request and how to interpret?	**Agreement**
Cobalamin (B12) levels should be requested for risk groups or clinical conditions for cobalamin (B12) deficiency. Screening should be performed in all risk conditions to start early treatment and avoid complications.	89%
Based on current scientific knowledge, cobalamin levels should be routinely measured in all patients.	33%
For the nutritionist, cobalamin levels should always be measured.	67%

Source: Own authorship.

In the third topic, on the clinical consequences of Cbls deficiency, 100% of the panelists agreed that the topic was relevant. The first suggestion was to change the term pathology to disease, and it was important to discuss the disease in depth and correlate it with the clinical consequences of cobalamin deficiency.

Table 4. Results of the agreement between the text and the panelists' contributions, topic 3.

Question 3. What are the clinical consequences of Cbls deficiency? Please list all Agreement associated conditions and describe in detail the clinical presentation of the diseases within your area of expertise.	
Subacute combined degeneration of the spinal cord: progressive weakness of the lower limbs with signs of involvement of the pyramidal system and impairment of deep sensitivity (arthresthesia and paresthesia), with gait ataxia and imbalance that worsen when closing the eyes. It occurs due to the involvement of the corticospinal tracts and the posterior columns of the cervical and thoracic spinal cord.	89%
Reduced myelination with symptoms of peripheral neuropathy.	89%
Sensitive peripheral polyneuropathy with paresthesias, hyporeflexia, and decreased superficial sensitivity in the feet with progression to more proximal regions of the lower and upper limbs. It is a symmetrical axonal neuropathy. Optic neuropathy appears as a progressive visual deficit.	89%
Autonomic dysfunction with orthostatic hypotension and syncope are also associated with B12 deficiency.	78%
Cognitive impairment, generally with memory complaints that may worsen over time and be accompanied by progressive cognitive deterioration of other functions, may occur, sometimes indistinguishable from degenerative dementia, such as Alzheimer's disease. There may be mood and behavioral changes accompanying the condition.	78%
Psychiatric conditions such as depression or psychotic symptoms may also be secondary to cobalamin deficiency. Neurological or psychiatric conditions may be found in the absence of megaloblastic anemia.	89%
Anemias: the clinical consequences of reduced hematopoiesis, with anemia and its effects on reduced tissue oxygenation, such as fatigue, asthenia, adynamia, difficulty concentrating, and reduced physical and mental work capacity.	89%
Elevated homocysteine levels are observed in patients with arterial thrombosis resulting from atherosclerotic disease and in individuals with venous thromboembolism. These levels are usually normalized only with the administration of folic acid so it is rarely necessary to use B complex in this clinical situation. Note: Normalization of homocysteinemia is not associated with a reduction in the frequency of recurrence of venous thrombosis.	89%
Low back pain, neuropathic pain, low back pain, Carpal tunnel syndrome, Adhesive capsulitis/rotator cuff	78%
Hepatic steatosis, glossitis.	67%

Source: Own authorship.

The fourth and fifth topics were about the route of administration and the understanding of the advantages and disadvantages of the routes of administration and absorption. 100% of the panelists agreed that this was an important issue to be discussed, due to the various presentations, injectable intramuscular, oral, and sublingual, and that the topic permeated the issue of adherence to treatment.

Table 5. Results of the agreement of the text with the aggregate contributions of the panelists, topic 4.

Question 4. Regarding the routes of administration (parenteral, oral, and Agreement sublingual) for the treatment of cobalamin (B12) deficiency: comment on the advantages and disadvantages of the formulations (bioavailability).	
Do you agree with the statement: "The intramuscular route can be administered into different muscles of the body, including the deltoid, dorsogluteal, ventrogluteal, rectus femoris, or vastus lateralis muscles? It can be used when oral absorption of the drug is erratic or incomplete; the drug has high first-pass metabolism; or when the patient is noncompliant. A depot preparation of the drug can be administered intramuscularly, and the medication dissolves slowly in the circulation to provide a sustained dose over a longer period. The intramuscular route is contraindicated in an active infection or inflammation at the site of drug administration, myopathies, muscle atrophy, thrombocytopenia, or coagulopathy."	78%
Do you agree with the statement: "The sublingual route is a form of medication administration that offers the benefit of bypassing the first-pass effect and the problems of interference with absorption in the lower gastrointestinal tract? By placing the medication directly under the tongue (sublingual), the drug is absorbed by passive diffusion, going directly to the systemic circulation without entering the portal system, thus escaping first-pass metabolism. The sublingual tissue has a highly permeable mucosa with rapid access to the underlying capillaries. It has the advantage of rapid absorption, convenience, and low incidence of infection."	89%
Do you agree with the statement: "Oral administration of medications is a convenient, economical, and most commonly used route? The primary site of drug absorption is usually the small intestine, and the bioavailability of the drug is influenced by the amount of drug absorbed across the intestinal epithelium. The first-pass effect is an important consideration for medications administered by this route. It refers to metabolism by which the concentration of the drug is significantly decreased before it reaches the systemic circulation, often due to metabolism in the liver. It is contraindicated in patients who cannot tolerate oral drugs, such as those who have altered mental status or have nausea or vomiting that prevents them from safely taking the drug orally."	89%
In neurological conditions, we always start parenterally. *	78%
In cases of combined degeneration, treatment generally begins with the patient hospitalized and is administered intramuscularly.	78%
In cases of altered cobalamin (B12) absorption or accelerated food transit through the small intestine, for example after bariatric surgery, parenteral supplementation may be necessary. Parenteral (intramuscular) B12 supplementation is recommended, 1,000 µg/month or 1,000 to 3,000 µg every 6 to 12 months, and is indicated if B12 levels cannot be maintained orally.	67%
In my opinion, severe or acute cobalamin deficiency should initially be treated by the intramuscular route.	67%
The advantage of the injectable route is a higher concentration and a longer interval between doses; some patients prefer this. In practice, it is observed that the injectable route favors a greater increase in plasma serum levels in a shorter period of time. Therefore, it is interesting to make a comparative analysis between the three forms of administration. The bioavailability of the parenteral route appears to be faster than that of the sublingual and oral routes.	33%
Current scientific knowledge seems to show that sublingual cobalamin supplementation is a comparable or even superior alternative, in certain cases, to the use of the parenteral route. Studies comparing different supplements of different forms of cobalamin are still limited and will need to take into account the different polymorphisms described that are related to the metabolism and functions of cobalamin in the future.	67%
I believe that studies comparing administration routes are the most relevant for defining therapeutic conduct. They demonstrate that sublingual replacement is as effective as intramuscular replacement and more convenient for the patient.	78%
In our setting, the unavailability of the sublingual route has led medical professionals to always use the oral or parenteral routes, which of course have their indications and good responses, despite the discomfort of the parenteral route. Issues related to practicality, absorption, and efficacy should soon make this route the preferred route for prescriptions.	89%
With the advent of the sublingual route, it is also possible to use it to maintain neurological conditions.	78%
Sublingual replacement therapy requires daily use, although it can be done more spaced out depending on the degree and reason for the deficiency.	89%
The sublingual route of administration of B12 is preferred because it facilitates adherence and avoids the use of injectables. The recommended dosage is 1000 µg/day for one week and then 1000 µg per week for 4 weeks. The replacement therapy should be maintained according to the clinical and laboratory conditions.	89%
The bioavailability of the sublingual route is greater than that of the oral route.	89%
The sublingual route is requested by patients who are afraid of injections. Individualization of the patient is the most appropriate for adherence.	89%
The disadvantage of the sublingual route is that it must be administered daily or, at least, more frequently than the intramuscular route.	89%
The sublingual form may be more costly for the patient, depending on the type of health system in which he or she is enrolled.	78%
The oral route of administration is preferred because it facilitates adherence and avoids the use of injectables. The recommended dosage is 1000 µg/day for one week and then 1000 µg per week for 4 weeks. Continue the replacement according to the clinical and laboratory conditions.	78%
The oral route is requested by patients who are afraid of injections. Individualizing the patient is the most appropriate for adherence.	89%
In less severe or chronic deficiency, the oral formulation may be the route of choice.	78%

Source: Own authorship.

The sixth topic was about the treatment itself, such as dosage and monitoring of the disease. The majority, 89%, agreed that the topic was important and that it should be separated by systems: hematologic, neurological, psychiatric, cardiovascular, digestive (post-bariatric surgery) diseases and that after the diagnosis of Cbls deficiency, a treatment plan is initiated, monitoring is necessary to determine the patient's response to therapy, such as serum levels of Cbls, homocysteine and methylmalonic acid, in two to three months after the start of treatment.

Table 6. Results of the agreement of the text with the aggregated contributions of the panelists, topic 4.

Question 5. For the diseases discussed above, please discuss the treatment and clinical Agreement follow-up of each condition in question.	
The administration of cobalamin (Cbls) should replenish depleted stocks and the continuity of treatment depends on the underlying cause that determines the deficiency.	100%
Once Cbls deficiency is detected, treatment should be initiated using the most appropriate route, tailored to each patient, until at least international equilibrium levels are achieved, and follow-up should be performed every 6 months.	67%
Permanent replacement in the case of pernicious anemia, gastrointestinal resections, or permanent conditions, such as the use of metformin, or veganism.	78%
Monitoring involves periodic measurement of serum cobalamin, including measurements of folate, iron, hematocrit, and reticulocyte count. Measurement of homocysteine and methylmalonate may be useful. Platelet pool and potassium levels should also be monitored during cobalamin therapy.	67%
Even after replacement therapy, despite the normalization of laboratory tests, sometimes the changes are irreversible. Cases of anemia tend to have a faster response, both clinically and laboratory-wise. In psychiatric cases, together with specific medication, replacement therapy plays a supporting but important role in treatment.	89%

Source: Own authorship.

The last topic was related to the scientific evidence available on the indication of cobalamin. 89% of the panelists agreed that it was an important issue that the question should ask about the level of evidence for the use of cobalamin in various diseases and that the evidence should come from clinical trials.

Table 7. Results of the agreement between the text and the aggregate contributions of the panelists, topic 5.

Question 6. What are the levels of evidence described, based on available scientific Agreement publications, regarding the correlation of cobalamin (B12) with the disease to be treated (discussed in the previous question)?	
The correlation is well described. It is important to note that cause and consequence are not necessarily synonymous with correlation. However, scientific evidence points to and has been revealing the physiological and pathophysiological mechanisms of the abovementioned treatment.	89%
The levels of evidence in publications on various pathologies vary significantly, and it is not possible to analyze them in a generalized manner, but there is evidence of increased mortality in severe cases of deficiency.	67%
Patients with type 2 diabetes taking metformin should have their cobalamin levels measured if there is strong clinical suspicion (Grade 2B).	67%
Patients after bariatric surgery should have their cobalamin levels measured every 6 months (Grade 1B) and replaced as needed.	89%
Vegetarians should monitor their cobalamin levels according to their clinical condition (Grade 2C).	67%
The association of autoimmune diseases such as pernicious anemia secondary to autoimmune gastritis and celiac disease, which lead to cobalamin (B12) deficiency, should be considered in cases of strong clinical suspicion, especially in individuals with DM1 (Grade 2C).	78%
6.1. How much does this influence your decision-making?	
Decision-making should always be based on scientific knowledge and physiological and pathophysiological mechanisms. Bibliographic references are the structural basis of evidence-based medicine.	100%
Regardless of the level of evidence, I believe that early screening and detection of cobalamin (B12) deficiency in high-risk patients can prevent many clinical complications, which are often irreversible.	78%
Always, but there must be an adequate balance between evidence and the specific condition to be treated, assessing the benefit of treatment to time, medication dosage, and route of administration.	89%

Source: Own authorship.

After the conclusion of this stage, 6 questions were formulated, aggregating the contributions of each panelist, and a final round of questions was carried out for the final review of the text. The questions and final contributions of the panelists are described below:

❖ **Question 1.** What are the risk groups or clinical conditions for Cbls deficiency that the physician should investigate?

Panelists' Contribution 1: Pregnancy, elderly, vegans/strict vegetarians, pancreatic insufficiency, HIV-positive patients, neurological and hematological conditions, gastrointestinal conditions (gastrectomy, atrophic gastritis, intestinal resection, bariatric surgeries, malabsorption syndromes, ileal resection or bypass, inflammatory bowel diseases, celiac disease, bacterial overgrowth syndrome, blind loop syndrome, Helicobacter pylori infection, patients on chronic use of proton pump inhibitors or with dyspeptic syndrome, abrupt changes in the microbiota), patients with malnutrition of any etiology, diabetic patients and/or on metformin, alcoholism, patients with macrocytosis, with or without anemia, pernicious anemia, Diphyllobothrium latum infection, pancreatic insufficiency, folate deficiency, cyanide poisoning, inhalation of smoking, vasoplegia associated with surgery, patients on hemodialysis and congenital deficiencies (orotic aciduria, transcobalamin deficiency, Immerslund

Grösbeck syndrome).

❖ **Question 2.** What are the important tests and information for the laboratory diagnosis of Cbls deficiency, to the methods of measurement, interferents, pre-analytical care, reference values , and interpretation of results? 2.1 When to request and how to interpret?

Contribution of panelists 2 and 2.1: The request can be considered when faced with patients in the risk group and with the clinical conditions that were presented in item 1. Laboratory tests (based on chemiluminescent immunoassay) measurement of serum cobalamin, folic acid, blood count, reticulocyte count, DHL, bilirubin, methyl malonate (MMA), homocysteine, anti-intrinsic factor antibodies, and transcobalamin.

Reference values may vary depending on the laboratory and the immunoassays used. In general, the values listed in Table 1 are recommended.

Table 8. Reference values for Cbls in laboratory tests **[9]**.

Normal	Borderline	Deficiency
300 pg/mL	200 a 300 pg/mL	< 200 pg/mL

Some precautions during the exam were recommended, such as avoiding alcohol consumption 24 hours before the blood collection, stopping the use of biotin 72 hours before the blood collection, and after intramuscular administration of cobalamin, a minimum of two weeks before a new control exam is collected.

Some precautions in interpreting the results were suggested:

- A blood count showing the presence of a high mean corpuscular volume (MCV) may alert the physician to the presence of cobalamin deficiency.

- Folate deficiency may lead to falsely low cobalamin levels, therefore folic acid dosage is recommended.

- In cases with a suspicious clinical picture and hematological alteration, but the serum cobalamin level is undetermined, the measurement of plasma homocysteine (normal 5-15 umol/L) and elevated plasma methyl malonate -MMA (normal <0.28 umol/L, very specific) can be considered as complementary tests because they are functional markers of the Cbls status in the organism.

- Holotranscobalamin is the form of Cbls absorbed by cells to meet metabolic demand and laboratory tests have recently become available.

- The presence of anti-intrinsic factor antibodies and anti-parietal cell antibodies should be investigated when there is no apparent cause for very low Cbls levels and may be present in pernicious anemia that can influence the results of tests based on competitive binding luminescence technologies, making the diagnosis of Cbls deficiency difficult. - Renal failure and the presence of inborn errors of metabolism may interfere with the measurement of MMA and homocysteine, respectively.

- Increased homocysteine is less specific, as it also increases in cases of folate deficiency, vitamin B6 deficiency, and hypothyroidism. They are very useful when there is a clinical picture suggestive of Cbls deficiency but with normal levels. Falsely normal or borderline levels may occur in chronic liver disease or myeloproliferative diseases.

- For patients with borderline cobalamin concentrations (between 200 and 300 pg/mL), the interpretation of additional deficiency markers is recommended. The main marker used in these situations is MMA. MMA is an intermediate metabolite that accumulates in cases of cobalamin deficiency, presenting an increase in its concentration. The same occurs with homocysteine. However, homocysteine can also increase in cases of folate deficiency, unlike MMA.

- Elevated homocysteine levels may be observed in patients with arterial thrombosis resulting from atherosclerotic disease, and in individuals with venous thromboembolism. These levels are usually normalized only with the administration of folic acid, so I rarely need to use B complex in this clinical situation. Unfortunately, normalization of homocysteinemia is not associated with a reduction in the frequency of recurrence of venous thrombosis.

Serum cobalamin levels should be monitored periodically, including folate, iron, hematocrit, and reticulocyte counts. Homocysteine and MMA levels may be useful. Platelet pool and potassium levels should also be monitored during cobalamin therapy. Serial follow-up should be 2 to 6 months, depending on the clinical picture.

❖ **Question 3.** What are the clinical consequences of Cbls deficiency? Please list all associated conditions and describe in detail the clinical presentation of the diseases within your area of expertise.

Panelists' contributions 3. As a consequence of Cbls deficiency, megaloblastic anemia may occur, as well as reduced myelination with symptoms such as peripheral neuropathy or polyneuropathy (tingling, changes in sensitivity, decreased reflexes, and neuromuscular control). Combined with some form of subacute spinal degeneration, this may lead to progressive weakness of the lower limbs with signs of involvement of the pyramidal system and impairment of deep sensitivity (arthritis and palsy), with gait ataxia and imbalance that worsen when closing the eyes, which occurs due to impairment of the corticospinal tracts and the posterior

columns of the cervical and thoracic spinal cord. Autonomic dysfunction with orthostatic hypotension and syncope may also be associated with Cbls deficiency.

Cognitive impairment, generally with memory complaints that may worsen over time, is sometimes indistinguishable from degenerative dementia, such as Alzheimer's disease. Mood and behavior changes may occur. Psychiatric conditions such as depression or psychotic symptoms may also be secondary to Cbls deficiency. Neurological or psychiatric conditions may be found in the absence of megaloblastic anemia. Cognitive, psychiatric, polyneuropathy, or spinal cord conditions require investigation of Cbls dosage. Optic neuropathy may appear as a progressive visual deficit.

The clinical consequences of reduced hematopoiesis, with anemia, and its effects on reduced tissue oxygenation may generate clinical signs and symptoms such as fatigue, adynamia, pallor, asthenia, cognitive deficit conditions, from difficulty concentrating to depression (mainly in the elderly) as a differential diagnosis, with reduced physical and mental work capacity.

Glossitis may be present in Cbls deficiency conditions.

❖ **Question 4.** Regarding the administration routes (parenteral, oral, and sublingual) for the treatment of Cbls deficiency: comment on the advantages and disadvantages of the formulations (bioavailability).

Panelists' contributions 4. From the patients' perspective, there is great variability in the preference for taking medications, some prefer the oral route, others the injectable route, and others the sublingual route.

From the medical perspective, the advantage of the injectable route is a higher concentration and longer intervals between doses. The oral route requires greater discipline in adherence to treatment and may be indicated for patients who are afraid of injections, and the sublingual route is similar. These factors of individualizing patient preferences are suitable for improving treatment adherence.

Some panelists said that the lack of access to the sublingual route has led medical professionals to prescribe the oral or injectable route, which has a good response, despite the discomfort of the injectable route. However, issues related to practicality, absorption, and efficacy should soon make the sublingual route the preferred route for prescriptions. However, the sublingual route has the disadvantage of being used daily or at least more frequently than the intramuscular route and may be more costly for the patient, depending on the type of health system in which they are included, as there does not appear to be a difference in benefits/efficacy between the administration routes in the medium and long term. Except for cases involving speed of bioavailability, with the injectable route being faster than the sublingual route, and the sublingual route faster than the oral route.

In general, the oral or sublingual routes of administration of cobalamin replacement are preferred by patients, as they facilitate adherence and avoid the use of injectables that require availability and greater complexity of application. However, in cases of altered absorption, such as in bariatric surgeries or accelerated food transit through the gastrointestinal system, parenteral supplementation is necessary.

❖ **Question 5.** For the diseases discussed above, please discuss the treatment and clinical monitoring of each condition in question.

Contribution from panelists 5. Once a Cbls deficiency has been identified, cobalamin replacement should be implemented to replenish depleted stocks and the continuation depends on the underlying cause that determines the deficiency. Replacement is necessary in proportion to the severity of the clinical condition and mainly to the time of exposure to the deficiency. Cobalamin can be administered orally or intramuscularly depending on the cause and patient demands. Thus, severe or acute cobalamin deficiency can be treated initially by the intramuscular route. In less severe or chronic deficiency, the oral formulation may be the route of choice.

Regarding dosage, panelists usually use a dosage of 1000 µg/day for one week, followed by 1000 µg per week for 4 weeks. Continue the replacement according to clinical and laboratory conditions.

In parenteral (intramuscular) cobalamin supplementation, 1,000 µg per month or 1,000 to 3,000 µg every 6 or 12 months is recommended, and is indicated if CBL levels cannot be maintained orally.

Replacement should be continued in cases of pernicious anemia, gastrointestinal resections, or permanent conditions, such as the use of metformin or veganism. It is important to note that, characteristically in neurological conditions, even after replacement, and despite laboratory indicators returning to normal, sometimes the clinical condition may be irreversible. Anemia tends to have a faster response, both clinically and in laboratory terms.

In psychiatric conditions, along with specific medication, replacement plays a supporting but important role in treatment. Periodic monitoring of serum cobalamin levels should include measurements of folate, iron, hematocrit, and reticulocyte count. Measurement of homocysteine and methyl malonate may be useful. Platelet count and potassium should also be monitored during cobalamin therapy. Clinical and

laboratory tests for monitoring after replacement of B12 are necessary and follow-up can be done every 2 to 6 months, depending on the clinical conditions of each patient.

❖ **Question 6.** What are the levels of evidence described, based on available scientific publications, on the correlation of cobalamin (B12) with the disease to be treated (discussed in the previous question)? 5.1. How much does this influence your decision-making?

Contribution of panelists 6 and 6.1. Some panelists collaborated by citing some studies, with specific studies that presented a high level of evidence, such as systematic review studies of clinical trials. It was mentioned that treatment with cobalamin is mainly focused on the aforementioned specialties, despite being present in the offices of all medical professionals, and that the lack of knowledge of the levels of scientific evidence or in chronic cases, mainly neurological, in practice discourages professionals from further investigating and using cobalamin replacement.

The levels of scientific evidence in the various diseases vary, and it is not possible to analyze in a generalized way, from scenarios that question the use of replacement to evidence of increased mortality in severe cases of deficiency. A larger group of studies **[25-27]** compare the routes of administration, which are relevant to define the therapeutic approach, and the studies demonstrate that sublingual replacement is as effective as intramuscular replacement and more convenient for the patient.

There are some recommendations already based on, for example, patients with type 2 diabetes using metformin should perform cobalamin dosage if there is strong clinical suspicion **[10]**, patients after bariatric surgery should perform cobalamin dosage every 6 months and replace as needed **[28]**. Vegetarians should monitor cobalamin levels according to their clinical condition **[29]**. The association of autoimmune diseases such as secondary pernicious anemia, autoimmune gastritis, and celiac disease that lead to Cbl deficiency should be considered in cases of strong clinical suspicion **[30]**.

Correlation studies were also cited, but it is important to note that cause and consequence are not necessarily synonymous with correlation. However, scientific evidence points to and has been analyzing the physiological and pathophysiological mechanisms involved in cobalamin deficiency **[31-33]**. Regarding how much current scientific evidence influences clinical decision-making, the panelists' opinions were diverse, since scientific evidence always or significantly influences clinical decision-making, and even regardless of the evidence, when Cbls deficiency is identified, it should be treated with replacement. However, in general, it was clear that an adequate balance between evidence, pathophysiology, and the specific clinical condition is necessary, always assessing the benefit of replacement to time, medication dosage, and route of administration. Early cobalamin replacement, especially in cases of severe deficiency, can prevent many clinical complications that may become irreversible.

Study Limitations

It is worth noting that this study aimed to discuss the use of cobalamins from various perspectives in the health field, with panelists who were selected by convenience with limited specialties, and without any intention of exhausting or closing the subject, on the contrary, to shed light and open the discussion on the topic. Therefore, the Delphi method was chosen as the method, and reservations and limitations of the method should be taken into account when interpreting the results.

Conclusion

The Delphi panel identified the main topics related to cobalamins, from risk groups that may benefit from investigation of conditions resulting from deficiency in intake or absorption by the gastrointestinal tract, diagnosis that should be made by laboratory tests that correlate with clinical conditions, taking into account other laboratory markers and that the indication should be early when a significant cobalamins deficit is identified to avoid irreversible clinical conditions, and monitoring that should occur between 2 and 6 months after starting cobalamin replacement.

CRediT

Author contributions: **Conceptualization** - Tiago Lazzaretti Fernandes, Dayse Maria Lourenço, Durval Ribas Filho, Glaucia Carneiro, Gustavo Loureiro, João Toniolo Neto, Luiz Claudio Cameron, Sonia Maria Dozzi Brucki, Nairo Massakazu Sumita, Henry Dan Kiyomoto, André Pedrinelli; **Data curation -** Tiago Lazzaretti Fernandes, Dayse Maria Lourenço, Durval Ribas Filho, Glaucia Carneiro, Gustavo Loureiro, João Toniolo Neto, Luiz Claudio Cameron, Sonia Maria Dozzi Brucki, Nairo Massakazu Sumita, Henry Dan Kiyomoto, André Pedrinelli; **Formal Analysis** -Tiago Lazzaretti Fernandes, Henry Dan Kiyomoto; **Investigation -**Tiago Lazzaretti Fernandes, Dayse Maria Lourenço, Durval Ribas Filho, Glaucia Carneiro, Gustavo Loureiro, João Toniolo Neto, Luiz Claudio Cameron, Sonia Maria Dozzi Brucki, Nairo Massakazu Sumita, Henry Dan Kiyomoto, André Pedrinelli; **Methodology -**Tiago Lazzaretti Fernandes, Dayse Maria Lourenço, Durval Ribas Filho, Glaucia Carneiro, Gustavo Loureiro, João Toniolo Neto, Luiz Claudio Cameron, Sonia Maria Dozzi Brucki, Nairo

Massakazu Sumita, Henry Dan Kiyomoto, André Pedrinelli; **Project administration -**Tiago Lazzaretti Fernandes; **Supervision -**Henry Dan Kiyomoto; **Writing- original draft -**Tiago Lazzaretti Fernandes, Henry Dan Kiyomoto; and **Writing-review & editing-** Tiago Lazzaretti Fernandes, Dayse Maria Lourenço, Durval Ribas Filho, Glaucia Carneiro, Gustavo Loureiro, João Toniolo Neto, Luiz Claudio Cameron, Sonia Maria Dozzi Brucki, Nairo Massakazu Sumita, Henry Dan Kiyomoto, André Pedrinelli.

Acknowledgment

Not applicable.

Ethical Approval

Not applicable.

Informed Consent

It was applicable.

Funding

All authors were eventually remunerated by the Marjan Farma Group for the development of this study using the Delphi methodology.

Data Sharing Statement

No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate[@].

Peer Review Process

It was performed.

References

1. Green R, Allen LH, Bjørke-Monsen AL, Brito A, Guéant JL, Miller JW, et al. Vitamin B12 deficiency. Nat Rev Dis Primers [Internet]. 2017 Jun 29 [cited 2023 Apr 9];3. Available from: https://pubmed.ncbi.nlm.nih.gov/28660890/
2. Abboud Leon C, Georges P, Zaeeter W. Vitamin B12 deficiency. N Engl J Med [Internet]. 2013 May 23 [cited 2023 Apr 9];368(21):2041. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23697528
3. Venkatramanan S, Armata IE, Strupp BJ, Finkelstein JL. Vitamin B-12 and Cognition in Children. Adv Nutr [Internet]. 2016 [cited 2023 Apr 9];7(5):879–88. Available from: https://pubmed.ncbi.nlm.nih.gov/27633104/
4. Devalia V, Hamilton MS, Molloy AM. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol [Internet]. 2014 [cited 2023 Apr 9];166(4):496–513. Available from: https://pubmed.ncbi.nlm.nih.gov/24942828/
5. Allen LH. How common is vitamin B-12 deficiency? Am J Clin Nutr [Internet]. 2009 Feb 1 [cited 2023 Apr 9];89(2). Available from: https://pubmed.ncbi.nlm.nih.gov/19116323/
6. Finkelstein JL, Layden AJ, Stover PJ. Vitamin B-12 and Perinatal Health. Adv Nutr [Internet]. 2015 [cited 2023 Apr 9];6(5):552–63. Available from: https://pubmed.ncbi.nlm.nih.gov/26374177/
7. Chandyo RK, Kvestad I, Ulak M, Ranjitkar S, Hysing M, Shrestha M, et al. The effect of vitamin B12 supplementation during pregnancy on infant growth and development in Nepal: a community-based, double-blind, randomised, placebo-controlled trial. The Lancet [Internet]. 2023 Apr [cited 2023 Apr 9];0(0). Available from: http://www.thelancet.com/article/S01406736230 0346X/fulltext
8. High prevalence of cobalamin deficiency in elderly outpatients - PubMed [Internet]. [cited 2023 Apr 9]. Available from: https://pubmed.ncbi.nlm.nih.gov/1447433/
9. Soh Y, Lee DH, Won CW. Association between Vitamin B12 levels and cognitive function in the elderly Korean population. Medicine [Internet]. 2020 Jul 7 [cited 2023 Apr 9];99(30):e21371. Available from: /pmc/articles/PMC7387066/
10. Sublingual vitamin B12 compared to intramuscular injection in patients with type 2 diabetes treated with metformin: a randomised trial - PubMed [Internet]. [cited 2023 Apr 9]. Available from: https://pubmed.ncbi.nlm.nih.gov/27355231/
11. Haeusler S, Parry-Strong A, Krebs JD. The prevalence of low vitamin B12 status in people with type 2 diabetes receiving metformin therapy in New Zealand—a clinical audit. New Zealand Medical Journal. 2014;127(1404):8–16.
12. Biemans E, Hart HE, Rutten GEHM, Cuellar Renteria VG, Kooijman-Buiting AMJ, Beulens JWJ. Cobalamin status and its relation with depression, cognition and neuropathy in patients with type 2 diabetes mellitus using metformin. Acta Diabetol

[Internet]. 2015 Oct 15 [cited 2023 Apr 9];52(2):383–93. Available from: https://pubmed.ncbi.nlm.nih.gov/25315630/

13. Sawangjit R, Thongphui S, Chaichompu W, Phumart P. Efficacy and Safety of Mecobalamin on Peripheral Neuropathy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Altern Complement Med [Internet]. 2020 Dec 1 [cited 2023 Apr 9];26(12):1117–29. Available from: https://pubmed.ncbi.nlm.nih.gov/32716261/
14. Julian T, Syeed R, Glascow N, Angelopoulou E, Zis P. B12 as a Treatment for Peripheral Neuropathic Pain: A Systematic Review. Nutrients [Internet]. 2020 Aug 1 [cited 2023 Apr 9];12(8):1–16. Available from: https://pubmed.ncbi.nlm.nih.gov/32722436/
15. Kornerup LS, Hvas CL, Abild CB, Richelsen B, Nexo E. Early changes in vitamin B12 uptake and biomarker status following Roux-en-Y gastric bypass and sleeve gastrectomy. Clin Nutr [Internet]. 2019 Apr 1 [cited 2023 Apr 9];38(2):906–11. Available from: https://pubmed.ncbi.nlm.nih.gov/29506877/
16. Gomollón F, Gargallo CJ, Muñoz JF, Vicente R, Lue A, Mir A, et al. Oral Cyanocobalamin is Effective in the Treatment of Vitamin B12 Deficiency in Crohn's Disease. Nutrients [Internet]. 2017 Mar 20 [cited 2023 Apr 9];9(3). Available from: /pmc/articles/PMC5372971/
17. Andrès E, Zulfiqar AA, Serraj K, Vogel T, Kaltenbach G. Systematic Review and Pragmatic Clinical Approach to Oral and Nasal Vitamin B12 (Cobalamin) Treatment in Patients with Vitamin B12 Deficiency Related to Gastrointestinal Disorders. J Clin Med [Internet]. 2018 Oct 1 [cited 2023 Apr 9];7(10). Available from: /pmc/articles/PMC6210286/
18. Watanabe F, Yabuta Y, Tanioka Y, Bito T. Biologically active vitamin B12 compounds in foods for preventing deficiency among vegetarians and elderly subjects. J Agric Food Chem [Internet]. 2013 Jul 17 [cited 2023 Apr 9];61(28):6769–75. Available from: https://pubmed.ncbi.nlm.nih.gov/23782218/
19. Willis CD, Elshaug AG, Milverton JL, Watt AM, Metz MP, Hiller JE. Diagnostic performance of serum cobalamin tests: a systematic review and meta-analysis. Pathology [Internet]. 2011 [cited 2023 Apr 9];43(5):472–81. Available from: https://pubmed.ncbi.nlm.nih.gov/21716160/
20. Quadros E V. Advances in the understanding of cobalamin assimilation and metabolism. Br J Haematol [Internet]. 2010 Jan [cited 2023 Apr 9];148(2):195–204. Available from: https://pubmed.ncbi.nlm.nih.gov/19832808/
21. Tavares J, Baptista B, Gonçalves B, Horta AB. Pernicious Anaemia with Normal Vitamin B12. Eur J Case Rep Intern Med [Internet]. 2019 Feb 18 [cited 2023 Jun 19];6(2). Available from: /pmc/articles/PMC6432825/
22. Pubmed. https://pubmed.ncbi.nlm.nih.gov/?term=cobalamin+or+vitamin+b12. 2024. cobalamin or vitamin b12.
23. McPherson S, Reese C, Wendler MC. Methodology Update: Delphi Studies. Nurs Res [Internet]. 2018 Sep 1 [cited 2023 Aug 15];67(5):404–10. Available from: https://pubmed.ncbi.nlm.nih.gov/30052591/
24. Romero-Collado A. Essential elements to elaborate a study with the (e)Delphi method. Enferm Intensiva [Internet]. 2021 Apr 1 [cited 2023 Aug 15];32(2):100–4. Available from: https://pubmed.ncbi.nlm.nih.gov/33008751/
25. Bensky MJ, Ayalon-Dangur I, Ayalon-Dangur R, Naamany E, Gafter-Gvili A, Koren G, et al. Comparison of sublingual vs. intramuscular administration of vitamin B12 for the treatment of patients with vitamin B12 deficiency. Drug Deliv Transl Res [Internet]. 2019 Jun 15 [cited 2023 Aug 15];9(3):625–30. Available from: https://pubmed.ncbi.nlm.nih.gov/30632091/
26. Wang H, Li L, Qin LL, Song Y, Vidal-Alaball J, Liu TH. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database of Systematic Reviews. 2018 Mar 15;2018(3).
27. Tuğba-Kartal A, Çağla-Mutlu Z. Comparison of Sublingual and Intramuscular Administration of Vitamin B12 for the Treatment of Vitamin B12 Deficiency in Children. Rev Invest Clin. 2020 Dec 22;72(6):380–5.
28. Lewis CA, de Jersey S, Seymour M, Hopkins G, Hickman I, Osland E. Iron, Vitamin B12, Folate and Copper Deficiency After Bariatric Surgery and the Impact on Anaemia: a Systematic Review. Obes Surg [Internet]. 2020 Nov 1 [cited 2023 Aug 15];30(11):4542–91. Available from: https://pubmed.ncbi.nlm.nih.gov/32785814/
29. Craig WJ. Nutrition concerns and health effects of vegetarian diets. Nutr Clin Pract [Internet]. 2010 Dec [cited 2023 Aug 15];25(6):613–20. Available from: https://pubmed.ncbi.nlm.nih.gov/21139125/
30. Guéant JL, Guéant-Rodriguez RM, Alpers DH. Vitamin B12 absorption and malabsorption. Vitam Horm [Internet]. 2022 Jan 1 [cited 2023 Aug

15];119:241–74. Available from: https://pubmed.ncbi.nlm.nih.gov/35337622/

31. Smith AD, Warren MJ, Refsum H. Vitamin B12. Adv Food Nutr Res [Internet]. 2018 Jan 1 [cited 2023 Aug 15];83:215–79. Available from: https://pubmed.ncbi.nlm.nih.gov/29477223/
32. Vitamin B12 deficiency - PubMed [Internet]. [cited 2023 Aug 15]. Available from: https://pubmed.ncbi.nlm.nih.gov/12643357/
33. Shipton MJ, Thachil J. Vitamin B12 deficiency - A 21st century perspective. Clin Med (Lond) [Internet]. 2015 Apr 1 [cited 2023 Aug 15];15(2):145–50. Available from: https://pubmed.ncbi.nlm.nih.gov/25824066/.