The role of vitamin $B_{12}$ in viral infections: a comprehensive review of its relationship with the muscle–gut–brain axis and implications for SARS-CoV-2 infection

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This comprehensive review establishes the role of vitamin $B_{12}$ as adjunct therapy for viral infections in the treatment and persistent symptoms of COVID-19, focusing on symptoms related to the muscle–gut–brain axis. Vitamin $B_{12}$ can help balance immune responses to better fight viral infections. Furthermore, data from randomized clinical trials and meta-analysis indicate that vitamin $B_{12}$ in the forms of methylcobalamin and cyanocobalamin may increase serum vitamin $B_{12}$ levels, and resulted in decreased serum methylmalonic acid and homocysteine concentrations, and decreased pain intensity, memory loss, and impaired concentration. Among studies, there is much variation in vitamin $B_{12}$ doses, chemical forms, supplementation time, and administration routes. Larger randomized clinical trials of vitamin $B_{12}$ supplementation and analysis of markers such as total vitamin $B_{12}$, holotranscobalamin, total homocysteine and methylmalonic acid, total folic acid, and, if possible, polymorphisms and methylation of genes need to be conducted with people with and without COVID-19 or who have had COVID-19 to facilitate the proper vitamin $B_{12}$ form to be administered in individual treatment.
INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), which was recognized by the World Health Organization as a pandemic in early 2020.1 This viral infection often causes respiratory-tract infection symptoms, but it is not limited to impairing lung function, because the infection can systematically affect the organism, undermining gastrointestinal,2 cardiovascular, and renal functions;3 or even the nervous4 and muscular systems.5,6 In addition to patient recovery, a growing concern has been that many patients have presented with post-acute COVID-19, long COVID-19, or persistent post-COVID-19 symptoms, which refer to effects or symptoms of this disease that continue for weeks or months beyond the initial illness.

Long COVID-19 appears to be a multisystem disease with varying symptoms.7,8 The main reported symptoms are shortness of breath, chest pain, headaches, neurocognitive difficulties, depression and other mental health conditions, muscle pain and weakness, gastrointestinal disorders, rashes, metabolic disruption, and thromboembolic conditions.9–11 The symptoms reported either during long COVID-19 seem to directly involve the skeletal muscle–gut–brain axis, which refers to the mutual interaction among these 3 systems.12–14 Even though relationships that consolidate this axis are not yet well established, there is a need to search for strategies that can strengthen it vis-à-vis this infectious disease.

Although population vaccinations are advancing in many countries, studies show that the virus has mutated, still infecting and reinfecting thousands of people, which has led to growing concern among health agencies.15 Nutritional status, chronic diseases, and age have been identified as important variables for the outcome of COVID-19.16,17 In this sense, the search for nutritional strategies that aim to reduce susceptibility to SARS-CoV-2 infection or the long-term complications of COVID-19 has been constant in several studies.16–18

In this scenario, vitamin B₁₂ (also known as cobalamin) is a water-soluble vitamin that is part of the group of vitamins in the B complex. It has important functions in the blood and cardiovascular system,19 also being involved with the regulation of the immune system and antiviral activity.20,21 Furthermore, this vitamin is an essential nutrient with markedly important functions in the skeletal muscle–gut–brain axis, such as maintenance of skeletal muscle and neurobehavioral parameters22–25 and modulation of gut microbiota.26 Vitamin B₁₂ was ranked among the top 4 substances for potential use in treatment for COVID-19, on the basis of findings from a study carried out with the help of molecular modelling and virtual screening tools, using data on US Food and Drug Administration–approved drugs.27 Thus, vitamin B₁₂ combined with a healthy diet can be an important adjuvant in treating COVID-19 and in patients treated after COVID-19 infection.

The subclinical deficiency rates of vitamin B₁₂ are high in developing countries and vegetarian populations because the main source of this vitamin are animal foods.28–30 In addition, older adults, people who have had bariatric surgery, and those are at increased risk of B₁₂ deficiency, and use of some medications also is a risk factor.31 Vitamin B₁₂ deficiency leads to hematologic, neuropathologic, and cardiovascular disorders, mainly by interfering in the homocysteine (Hcy) metabolism and the methylation reactions of the organism.32,33

Given that vitamin B₁₂ is involved in various functions in the body and is influenced by several clinical conditions known to be at risk, depending on the outcomes of COVID-19, identifying vitamin B₁₂ status is necessary for patients with current COVID-19 infection and those who have had COVID-19. Considering the relationship of vitamin B₁₂ with the muscle–gut–brain axis and its role in viral infections and the immune system, we aimed in this comprehensive review to provide evidence and novel insights into the role of B₁₂ during treatment and persistent symptoms of COVID-19.

SEARCH STRATEGY AND SELECTION CRITERIA

An online literature search was performed in the PubMed, Scopus, Web of Science, and Cochrane Library databases; on Google and ClinicalTrials.gov; and the International Clinical Trials Registry Platform to perform a comprehensive review about the role of vitamin B₁₂ in COVID-19 prognosis. The following Medical Subject Heading and free-text search terms associated with vitamin B₁₂ were input: “vitamin B12” OR “cobalamin” OR “cyanocobalamin” OR “methylcobalamin” OR “adenosylcobalamin” OR “hydroxycobalamin” OR “holotranscobalamin” OR “B12 deficiency” OR “vitamin B12 metabolism,” which were first used singly and then subsequently matched, in turn, with the terms associated with COVID-19 and other respiratory viral infections: “COVID” OR “COVID-19” OR “SARS-CoV-2” OR “SARS-CoV” OR “MERS” OR “respiratory infection” OR “viral infection” OR “viral disease.”34

The third round of searches ensued with terms referring to how the virus gains entry and causes damage in organs. Thus, “ACE-2” OR “gut” OR “brain” OR “muscle” OR “muscle-gut-brain axis” OR “COVID symptoms” OR “long-COVID” OR “post COVID” OR “persistent symptoms COVID” were added, in turn, to the first round of searches.34 The minimum eligible sample size of studies was 20 participants.
Only publications focusing on vitamin B<sub>12</sub> relative to COVID-19 prognosis, other viral infections, and diseases with similar symptoms were eligible for inclusion. All searches, including title and abstract screening, were performed by 2 investigators working independently. Any discrepancies were resolved through consensus. Only articles published in English were short-listed; all articles deemed potentially eligible were retrieved for full-text review, and preprint articles were excluded.

**VITAMIN B<sub>12</sub>: FUNCTIONS, SOURCES, AND DEFICIENCY**

The term vitamin B<sub>12</sub> is generally used to describe cobalamin, which is chemically composed by a heterocyclic corrin ring made up of 4 pyrroles with cobalt at the center of the ring. Vitamin B<sub>12</sub> comprises many forms, including cyanocobalamin, methylcobalamin, deoxyadenosylcobalamin, and hydroxy-cobalamin. Cyanocobalamin is the synthetic form of vitamin B<sub>12</sub> and can be found in supplements and fortified foods.

The biggest dietary sources of vitamin B<sub>12</sub> are viscera, such as liver (26–58 µg), meat (3–10 µg), dairy foods (0.3–2.4 µg), eggs (1–2.5 µg), poultry (trace amounts to 1 µg) in 100 g wet weight. Bonito fish and clam extracts contain considerable amounts of free vitamin B<sub>12</sub>, 41 µg and 132 µg/100 g wet weight, respectively. Gastrointestinal fermentation supports the growth of these vitamin B<sub>12</sub>-synthesizing microorganisms, and this vitamin is subsequently absorbed and incorporated into animal tissues, such as those of ruminants.

Vitamin B<sub>12</sub> is not synthesized by plants; therefore, low serum B<sub>12</sub> levels may be more prevalent among vegetarians, and especially vegans. Vegans and even lacto-ovo-vegetarians with only a small intake of eggs and dairy foods may require supplemental vitamin B<sub>12</sub> from fortified foods or supplements. Some foods, like cheddar cheese, “veggie burgers,” breakfast cereals, sunflower margarine, yeast extracts, vegetable stock, sausage mixes, and vegetable margarine are fortified with vitamin B<sub>12</sub>. The US Institute of Medicine has recommended that adults older than 51 years consume most of their vitamin B<sub>12</sub> from fortified foods or supplements, bearing in mind that older adults are at higher risk of B<sub>12</sub> deficiency due to the physiological reduction in intrinsic factor secretion necessary for absorbing this vitamin, as well as due to the use of drugs that can reduce the bioavailability of cobalamin.

Vitamin B<sub>12</sub> has also been reported to be present in lower levels in nonanimal foods, including edible algae, some mushrooms, and fermented foods such as tempeh, kimchi, miso, and tea. For example, Chlorella, Spirulina, and Porphyra yezoensis, commonly known as purple laver or nori, can produce a cobalamin-like compound, also called pseudo-cobalamin, which has an inactive corrinoid.

Bacterial vitamin B<sub>12</sub> is synthesized by the gut-resident Propionibacterium, Freudenreichii, Lactobacillus reuteri, L. corniformis, L. plantarum, L. coryniformis, Bifidobacterium animalis, B. infantis, and B. longum, among others, to produce adenosylcobalamin. The aforementioned bacteria are recognized for having probiotic activity, which points to the importance of the relationship between vitamin B<sub>12</sub> and the gut microbiota, because probiotics are defined as living microorganisms that provide benefits to the host’s health when administered in adequate doses.

The recommended daily allowance of vitamin B<sub>12</sub> is 3–5 µg/day (2.4 µg/day for adults, 1.2 µg/day for children up to 8 years of age, and 2.6 µg/day for pregnant women and breastfeeding mothers). The average, Western nonvegetarian diet will contain 5–7 µg/day of vitamin B<sub>12</sub>, which is sufficient to maintain normal cobalamin homeostasis.

Dietary cobalamin is released from food proteins by the action of stomach acid, where it is rapidly complexed to haptocorrin or transcobalamin I (a salivary B<sub>12</sub>-transfer protein). The haptocorrin-B<sub>12</sub> complex suffers proteolysis in the duodenum by pancreatic proteases. In the proximal ileum, B<sub>12</sub> is released to the gastric intrinsic factor, which is a B<sub>12</sub>-transfer protein essential for ileal cobalamin absorption. Next, the intrinsic factor-B<sub>12</sub> complex can enter mucosal cells in the distal ileum, and it again binds to transcobalamin (a serum B<sub>12</sub>-transfer protein). Finally, the transcobalamin-B<sub>12</sub> complex circulates in the blood and then enters target cells. Most of the circulating B<sub>12</sub> is bound to haptocorrin, which is unavailable for immediate delivery to cells. Between 10% and 30% of circulating B<sub>12</sub> is bound to transcobalamin, forming holotranscobalamin or transcobalamin II.

Specific blood-transport nonglycosylated protein is synthesized in most tissues that deliver cobalamin to cells by a receptor-mediated endocytosis. This protein binds to cobalamin with a high affinity and is encoded by a gene located on chromosome 22.

Evidence shows that transcobalamins can suppress systemic inflammation by modulating certain cytokines (ie, interleukin-6), growth factors and other substrates with anti-inflammatory properties under normal physiological conditions. Vitamin B<sub>12</sub> can be considered an endogenous negative regulator of nuclear transcription factor-κB (NFκB) through the regulation of nitric oxide, which plays a key role in regulating the immune response to infection. Vitamin B<sub>12</sub> contributes to improving the immune response via an increase in CD8+ T cells and natural killer T cells. In addition, this vitamin has antioxidant properties through the reduced glutathione-sparing effect: it is capable of increasing the cytosolic bioavailability of reduced glutathione and thus can promote the synthesis of oxidized...
In addition, vitamin B\textsubscript{12} is recognized to modulate the ecology of the gut microbiota.\textsuperscript{26}

Vitamin B\textsubscript{12} is essential for DNA synthesis and regulation. It is involved in many important metabolic pathways, especially in the metabolism of lipids, carbohydrates, and proteins, and plays a central role in hemopoesis. Methylcobalamin is a cofactor of 2 enzymes present in mammalian cells: methionine synthase and methylmalonyl-CoA mutase.\textsuperscript{33} When B\textsubscript{12} levels are too low in the body, the result is an increase in methylmalonic acid (MMA) and Hcy concentration due to inhibition of methylmalonyl-CoA mutase and methionine synthase, respectively.\textsuperscript{33} The increase in Hcy causes folate sequestration and interrupts DNA synthesis. Increased MMA levels cause demyelinating defects in the nervous system and elevate propionic acid, resulting in metabolic acidosis.\textsuperscript{30}

The symptoms of subclinical B\textsubscript{12} deficiency are subtle and often not recognized. A B\textsubscript{12} deficiency can remain without symptoms for a long time, leading to a chronic deficiency. For many years, B\textsubscript{12} concentrations < 148 pmol/L in blood have been identified as being deficient. Nevertheless, due to the limitations of sensitivity and specificity of individual assays, 2 or more biomarkers should be used in combination to accurately diagnose vitamin B\textsubscript{12} deficiency, such as direct (total B\textsubscript{12} and holotranscobalamin) and functional (Hcy and MMA) biomarkers.\textsuperscript{31}

Vitamin B\textsubscript{12} deficiency occurs at all ages (but mainly in the older adult population) and in both sexes, especially in people who have a restricted diet in foods of animal origin either by choice or due to lack of financial resources to purchase these foods.\textsuperscript{52} Deficiency is much more common in developing countries, starting in early life and persisting across the life span,\textsuperscript{30} and can be associated with insufficient nutrition or microbial infections. Determining the prevalence of subclinical deficiency of vitamin B\textsubscript{12} is challenging, however.\textsuperscript{45}

Studies have shown a high prevalence of vitamin B\textsubscript{12} deficiency in populations with different types of vegetarian diets, specifically > 60% in vegans and > 40% in lacto- or ovolactovegetarians.\textsuperscript{53,54} Vegans have a higher prevalence of B\textsubscript{12} deficiency compared with other vegetarians that depends, in part, on dietary rigidity and length of time following this lifestyle.\textsuperscript{53,55} The lactovegetarian and ovolactovegetarian groups have intermediate vitamin B\textsubscript{12} status when compared with vegans and omnivores, because although milk, dairy products, and eggs contain some amount of vitamin B\textsubscript{12}, the intake of this vitamin through a lacto- or ovolactovegetarian diet is considered limited.\textsuperscript{53,54} The use of vitamin B\textsubscript{12} supplements may be necessary for these groups because the bioavailability of vitamin B\textsubscript{12} from supplements is greater than that from foods.\textsuperscript{53}

Low B\textsubscript{12} concentrations in the body may be present in different pathophysiological situations, including pregnancy, old age, smoking, and comorbidities such as hypertension, diabetes mellitus, pancreatic insufficiency, autoimmune gastritis, gastrectomy or gastric bypass, diseases or resection of the ileum, bacterial overgrowth, celiac disease, inflammatory bowel disease, or uremia-related malnutrition.\textsuperscript{22,23,56} Treatments such as antibiotics, proton pump inhibitor medications, anti-hyperglycemic medicines (eg, metformin), nitrous oxide anesthesia, a nonsteroidal anti-inflammatory drug, some anticonvulsants, and colchicine interfere with B\textsubscript{12} absorption and metabolism.\textsuperscript{33,45} Angiotensin-converting enzyme inhibitors have also been associated with low B\textsubscript{12} levels in older adults.\textsuperscript{57,58}

Cobalamin deficiency causes a decrease in hemoglobin levels, characterizing megaloblastic or pernicious anemia with manifestations that include skin pallor, decreased energy and exercise tolerance, fatigue, shortness of breath, and palpitations.\textsuperscript{59} Scientific evidence indicates that not necessarily the deficiency but the low status of the B\textsubscript{12} biomarker has been associated with increased total Hcy level, which is involved in increased generation of reactive oxygen species in lipid peroxidation and tissue damage to the endothelium vascular and thromboembolism.\textsuperscript{41,51} Hyperhomocysteinemia due to low B\textsubscript{12} status leads to an increased risk of several chronic diseases of aging, including cardiovascular disease and osteoporosis; however, these investigations are limited.\textsuperscript{41,51}

The neurologic complications of B\textsubscript{12} deficiency occur at a later stage of depletion than the indicators we discuss later in this article and are not specific for this deficiency. Alterations in peripheral nerves, followed by degenerative alterations of the posterior spinal cords and cortical spinal ducts, have been reported, in addition to sensory disturbances in the extremities (tingling and numbness). This deficiency was associated with severe symptoms of depression, suicidal behaviors, reduced cognition, mental fatigue, bad or depressed moods, mania, psychosis, and intense agitation.\textsuperscript{49}

Other symptoms related to cobalamin deficiency are elevated lactic dehydrogenase levels, mechanical hemolysis, thrombocytopenia, intravascular coagulation thrombosis, low reticulocyte count, vasoconstriction, and renal and pulmonary vasculopathy.\textsuperscript{60,61} Vitamin B\textsubscript{12} deficiency may induce macrocytosis, peripheral neuropathy, ataxia, dizziness, cognitive disturbances, depression, delirium, psychosis, paralysis, muscle cramps, fibromyalgia-like symptoms, and fatigue.\textsuperscript{22–25}

**ACTION OF VITAMIN B\textsubscript{12} ON THE SKELETAL MUSCLE–GUT–BRAIN AXIS**

Skeletal muscle, gut, and brain are tissues with a collaborative role in regulating physiological processes, including energy homeostasis. The skeletal muscle–gut–brain
axis is a recently introduced concept that is supported by increasing clinical and preclinical evidence showing a close relationship between the muscle–gut and gut–brain axes (Figure 1). The skeletal muscle–gut–brain axis is critically regulated by microbiota, a community of gut-resident microorganisms composed of ∼10^14 cells classified in > 1000 different bacterial species. Gut microbiota composition is regulated by several factors, such as diet, drugs, stress, and exercise. Homeostatic imbalance in this microbial composition, known as dysbiosis, is related to a sedentary lifestyle and some diseases like Alzheimer’s disease, colitis, and obesity in humans and rodents (Figure 1).

Gut microbiota modulate a wide range of functions in the host under normal conditions, including nutritional status, metabolism, and immunity, promoting physical and brain benefits (Figure 1). Microbiota exert their effects through direct cross-talk with tissues other than the intestine. A bidirectional communication linking gut microbiota and muscle, as well as gut microbiota and brain, has been demonstrated. Moderate physical activity and healthy diets promote a balanced microbiome (eg, a high Bacteroidetes to Firmicutes ratio) along with the production of neurotransmitters (eg, serotonin, dopamine), secondary bile acids, and short-chain fatty acids, including acetate, propionate, and butyrate (Figure 1). These bacteria-produced compounds positively affect both skeletal muscle and brain, decreasing inflammation and risk of psychiatric and neurodegenerative disorders, as well as increasing insulin sensitivity and glucose control (Figure 1). Opposite effects are observed in dysbiosis conditions (eg, a low Bacteroidetes to Firmicutes ratio), where high levels of lipopolysaccharides and pro-inflammatory cytokines (eg, interleukin-1β, interleukin-6, tumor necrosis factor α) are produced by gut bacteria (Figure 1). Skeletal muscle and brain effects on microbiota are exerted by direct physical activity and vagal colonic modulation.

The aforementioned evidence shows the close relationship among muscle, gut, and brain, supporting the concept of the muscle–gut–brain axis. Thus, its modulation can be used as a valuable strategy to develop therapies against diseases related to the brain and muscle, such as psychiatric disorders and neurodegenerative and muscular diseases.

Vitamin B12 is exclusively produced by archaea and bacteria and is required for DNA and methionine synthesis, as well as catabolism of fatty acids and amino acids. This vitamin emerges as a serious candidate to modulate the muscle–gut–brain axis, because of its ability to modulate functions at the muscular, intestinal,
and cerebral levels. Treatment with cobalamin improves skeletal muscle dysfunction in patients with hyperhomocysteinemia\(^71\) and reduces formalin-induced muscle pain.\(^72\) Vitamin B\(_{12}\) deficiency at the brain level is associated with affective disorders, behavior changes, psychosis, cognitive impairment or decline, and dementia (including Alzheimer’s disease and vascular dementia protection).\(^73\)

Treatment with vitamin B\(_{12}\) in rats with experimental autism improved impaired markers of this neurologic condition.\(^74\) Modulation of the muscle–gut–brain axis by vitamin B\(_{12}\) is also possible by acting on gut microbiota. This is based on the fact that resident bacteria in the colon produce cobalamin, which regulates gene expression in gut Bacteroidetes.\(^26\) Moreover, vitamin B\(_{12}\) protects from dysbiosis and promotes different microbial responses in a murine model of colitis.\(^83\)

That vitamin B\(_{12}\) can act at any level of the skeletal muscle–gut–brain axis makes its use an interesting option to treat associated diseases. Thus, cobalamin may be an important agent to prevent or improve neurologic consequences of COVID-19.

**Vitamin B\(_{12}\) Antiviral Role**

Adaptive immunity has been associated with low levels of vitamin B\(_{12}\) involving viral infection.\(^75\) It seems plausible that severe vitamin B\(_{12}\) deficiency can also be associated with increased risk and severity of infections, because this deficiency affects the functions of phagocytes, production of interferon, replication of viruses, and maturation of T lymphocytes.\(^76–78\) In 9 studies, researchers reported the effects of vitamin B\(_{12}\) supplementation on viral diseases (Table 1).\(^79–87\)

In this respect, it is useful to note that most studies to date have looked at the association between vitamin B\(_{12}\) levels and the anti-inflammatory and immunomodulating properties of patients infected with HIV. First, a randomized controlled trial (RCT) showed the relationship of a continuous measure of cobalamin level to psychological distress in bereaved HIV-1(+) and HIV-1(-) patients. The mood outcomes in this study were inversely related to levels of serum vitamin B\(_{12}\). Moreover, the lower plasma cobalamin levels also were associated with the presence of symptoms consistent with major depressive disorder.\(^80\)

The second study was a cross-sectional study\(^81\) including antiretroviral therapy (ART)-naïve adults. Logistic regression was used to determine factors associated with suboptimal vitamin B\(_{12}\) levels. Compared with people with normal concentrations of B\(_{12}\), individuals with vitamin B\(_{12}\) deficiency had a longer known duration of HIV infection. In addition, participants eligible for ART (ie, those with CD4 count < 350 cells/μL) with suboptimal B\(_{12}\) had a higher mean rate of CD4 cell population decline than counterparts with normal B\(_{12}\) levels.

In the third study, researchers performed a multicenter clinical trial in asymptomatic patients with HIV with a CD4 T-cell count between 375 and 750 cells/μL at screening evaluation.\(^83\) The authors evaluated the effect of high-dose micronutrient supplements (16 capsules/day) on measures of HIV disease progression used to guide ART initiation. The weak but significant correlation of levels of serum vitamin B\(_{12}\) levels with CD4 count observed in this study may suggest either that low B\(_{12}\) levels may predict CD4 decline, or that B\(_{12}\) and CD4 count decline in concert.

More recently, Shivakoti et al\(^86\) conducted a secondary analysis of a random subcohort sample from a multinational randomized trial of a combination ART regimen efficacy among 1571 combination-ART-naïve adults. The researchers aimed to investigate the relationship of micronutrients and inflammation with CD4 cell recovery. The results showed that small numbers of participants (17.1%) were deficient in vitamin B\(_{12}\). Therefore, the analysis was not powered to detect significant differences in CD4 count among participants who were B\(_{12}\) deficient and those who were not.

In the same period, Tenford et al\(^85\) performed a case-cohort design study to evaluate the association between micronutrient deficiencies and incident tuberculosis in a diverse population with high incidence of HIV, particularly in low- and middle-income countries. The vitamin A and vitamin D levels at ART initiation were independently associated with increased risk of incident tuberculosis in the ensuing 96 weeks. The median values of vitamin B\(_{12}\) did not differ significantly between groups.

In addition, 2 different viral conditions were included in this review: hepatitis and norovirus infection. Three studies investigated the ability of vitamin B\(_{12}\) to repair tissue damage and compensate for diminished hepatic storage during viral hepatitis. In the first RCT, researchers reported the therapeutic effect of coenzyme-B\(_{12}\) in hepatitis A compared with that of hydroxocobalamin after the 1972 epidemic.\(^79\) Admitted patients who were born in even-numbered years received hydroxocobalamin. Patients born in odd-numbered years were treated with coenzyme B. All patients had to rest during the period of abnormal serum bilirubin levels. The group treated with coenzyme B showed a tendency to more rapid normalization of aminotransferases than did the patients treated with hydroxocobalamin.

In the second randomized controlled study, researchers compared pegylated interferon-α plus
| Reference                              | Design                | Target condition               | No. of participants | Population (age)                          | Dose and time       | Main results                                                                                                                                 |
|----------------------------------------|-----------------------|-------------------------------|---------------------|-------------------------------------------|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Iwarson and Lindberg (1977)            | RCT                   | Acute viral hepatitis         | 40                  | 2 groups of patients from the 1972 epidemic with short-incubation hepatitis A (aged 15–45 y) | 1 mg HOCbl, IM, per d for 12 d, followed by 1 mg of oral HOCbl per d for 23 d | A significant return of serum aminotransferase levels to normal was observed in the group treated with coenzyme-B₁₂. |
| Baldewicz et al (2000)                 | RCT                   | HIV                           | 159                 | Bereaved HIV-1(+) and HIV-1(−) homosexual men (aged 30–40 y) | Observational study | Serum cobalamin level was inversely related to self-reported overall distress level and specifically to depression, anxiety, and confusion subscale scores, as well as to clinically rated depressed and anxious mood. |
| Semeere et al (2012)                   | Cross-sectional study | HIV                           | 204                 | ART-naïve adults (34.4 [SD ± 9.4] y)        | 3 doses of 1 mg of parenteral vitamin B₁₂³ | HIV-infected, ART-naïve individuals had a lower mean vitamin B₁₂ level (384 pg/mL) than the mean B₁₂ level reported in a population of healthy university students (469 pg/mL). Vitamin B₁₂ supplementation significantly improved sustained viral response rates in patients with HCV naïve to antiviral therapy. |
| Rocco et al (2013)                     | RCT                   | Chronic viral hepatitis       | 94                  | Patients with chronic hepatitis, naïve to antiviral therapy (51–53 y) | 5000 µg of IM vitamin B₁₂³ for 4 wk | Lower baseline levels of B₁₂ (<133 pmol/L) correlated with lower baseline CD4 count (r = 0.2; P = 0.007) in multiple linear regression adjusted for sex and body mass index, as well as in unadjusted analysis (r = 0.21; P = 0.02). |
| Balfour et al (2014)                   | Multicenter RCT       | HIV                           | 218                 | Asymptomatic patients with HIV (38.1 [SD ± 8.9] y). | Vitamin B₁₂³ divided into 16 capsules of micronutrient supplements per day for 2 y. | The serum vitamin B₁₂ level was a significant independent predictor for overall survival in patients with chronic viral liver disease. Falsely elevated serum vitamin B₁₂ levels (584.5 pg/mL) were associated with severity and prognosis in viral liver disease. |
| Sugihara et al (2017)                  | Prospective cohort study | Chronic viral hepatitis     | 90                  | Patients with chronic viral hepatitis and viral-induced cirrhosis (30–88 y) | Observational study | (continued)                                                                                                    |
EFFECTS OF VITAMIN B12 ON SYMPTOMS DURING AND AFTER COVID-19

COVID-19 affects people of all ages and sexes, but the severity of COVID-19 symptoms predominantly increases in elderly individuals, men, and people with comorbidities such as obesity, malnutrition, and chronic hepatitis B virus (HBV) infection. The results showed that, in patients with chronic hepatitis B virus (HBV) infection, vitamin B12 supplementation improved the overall rate of sustained viral response to pegylated interferon-α and ribavirin (standard of care) with the standard of care plus ribavirin (standard of care).
hypertension, and diabetes mellitus who generally have inadequate nutritional status and inflammation.

Patients with COVID-19 may present acute polyneuropathy such as Guillain–Barré syndrome and variants, which affect the peripheral nervous system due to an exacerbated immune response to infection or also as a postinfectious immune-mediated response. The most common Guillain–Barré syndrome and variants symptoms are severe back pain and muscle weakness, and there may be long-term complications, including severe disability, pain, and fatigue.

Some COVID-19 symptoms can persist for weeks or months after symptoms onset; this condition is called acute post–COVID-19 (from week 5 to week 12), long COVID-19 (from week 12 to week 24), or persistent post–COVID-19 symptoms (lasting >24 weeks). The symptoms include gastrointestinal symptoms (eg, diarrhea, nausea and vomiting, abdominal pain); neurologic manifestations (eg, concentration impairment, anxiety and depression symptoms, headache, migraine, memory or cognition loss, hallucinations, sleep disturbances, post-traumatic stress disorder, loss of taste (anosmia); neuromuscular disorders (eg, fatigue); and muscular disorders (eg, muscle weakness, myalgia).92–98

Various vitamin B12 deficiency symptoms are similar to those found in patients with COVID-19 and post–COVID-19.22–25 Studies tested vitamin B12 supplementation to alleviate some of the symptoms of various diseases that are also present in COVID-19 (Table 2). Two RCTs and 5 meta-analyses reported benefits of vitamin B12 supplementation in methylcobalamin (0.5–1mg orally or local injection for 2 weeks to 1 year) and cyanocobalamin (2000mg orally or 1–1000mg via intramuscular route for 90 days and 4 months) forms. The benefits were mainly in analgesic action and attenuation of neurologic symptoms.

Other meta-analyses and RCTs did not indicate significant results in relieving pain, fatigue, or neurologic symptoms by supplementation with these vitamin B12 forms. However, the authors of these meta-analyses listed some limitations that open the way for carrying out more RCTs to answer questions: a small number of available trials and high heterogeneity between included studies; a long time difference between the start of vitamin B12 supplementation and the appearance of measurable benefits; heterogeneity in the included studies; only 1 high-quality RCT evaluated the effects on fatigue, making it impossible to estimate the meta-analysis; small variations in combined estimates in sensitivity and subgroup analysis; and a low number of studies for subgroup analyses.

A meta-analysis of observational studies (n = 21,837 people 12–90 years old) revealed a significant inverse association between dietary intake of vitamin B12 and/or vitamin B12 supplementation and the risk of depression in women. The most used vitamin B12 forms in the included studies were methylcobalamin and cyanocobalamin. There is still controversy regarding the effectiveness of vitamin B12 used in supplementation; some scientists claim that natural methylcobalamin and adenosylcobalamin forms may have greater vitamin B12 activity than the synthetic cyanocobalamin form.

Nevertheless, Obeid et al proposed that cyanocobalamin supplementation (the most stable and inexpensive form) is as effective as the cobalamin coenzyme forms methylcobalamin and adenosylcobalamin. Methylmalonic aciduria and homocystinuria type C protein convert cyanocobalamin into the active methylcobalamin and adenosylcobalamin forms in cells, as long as there is no remethylation disorder cblC in methylmalonic aciduria and homocystinuria type C protein, cblF and cblJ in the protein integral membrane of lysosomal cobalamin transport-escort protein LMBD1 and ATP-binding cassette subfamily D member 4—required for lysosomal release of transport of cobalamin.

The guidelines for diagnosis and management of the cobalamin-related remethylation disorders recommend treatment with parenteral hydroxylcobalamin in suspected cases of remethylation disorder, the incidence of serious complications, and for significant improvement in patient survival.

Thus, vitamin B12 can be used in adjunct treatment of mild to severe COVID-19 symptoms, because of its analgesic function and role in neuromuscular disorders (Figure 2). The appropriate choice of the chemical form of vitamin B12, the dose, and treatment time will depend on individual factors such as the type of vitamin B12 deficiency, age, preexisting diseases, type of methylation gene, and medication used.

Many protocols performed in hospitals in Brazil that receive patients affected by COVID-19 recommend supplementation or intramuscular injection of vitamin B12 in cases where a deficiency or subclinical deficiency of vitamin B12 is identified. This clinical practice may be related to the increase in Hcy in patients with severe COVID-19. Pharmacological treatment with B12 usually implements high doses (1000–2000 µg/day) for an average of 1–3 months. Vitamin B12 therapy reduces oxidative damage and inflammation levels,
Table 2  Effects of vitamin B₁₂ treatment on symptoms related to COVID-19 prognosis

| Reference                      | Design                 | Target condition                                      | No. of participants | Population (age)                                                                 | Dose and time                                      | Main results                                                                                                                                                  |
|--------------------------------|------------------------|-------------------------------------------------------|---------------------|---------------------------------------------------------------------------------|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mauro et al (2000)⁹⁹           | Randomized, double-blind, placebo-controlled trial | Low back pain                                         | 60                  | Patients with a proven medical history for back pain, without vitamin B₁₂ deficiency (18–65 y) | 1000 mg daily of cyanocobalamin IM for 2 wk       | Alleviating the low back pain and related functional disability, decreasing the consumption of paracetamol                                               |
| Sun et al (2005)¹⁰⁰             | Meta-analysis of RCTs   | DN                                                    | 231                 | Patients with diabetic PN, without vitamin B₁₂ deficiency (53–56 y)            | 0.5 mg of methylcobalamin injection 3 times per week for 4 wk; or 0.5–500 mg of oral methylcobalamin 3 times a day for 4–16 wk | Improved somatic symptoms, such as pain and paresthesia. In 3 studies, methylcobalamin therapy improved autonomic symptoms (peripheral neurophysiology, oral dryness, and dysuria). |
| Vidal-Alaball et al (2005)⁶¹; ⁹⁲ | Meta-analysis of RCTs   | Oral vs IM vitamin B₁₂ to treat vitamin B₁₂ deficiency | 153                 | Patients with megaloblastic anemia, (16–86 y)                                   | 1000 µg daily of oral vitamin B₁₂⁶²; 2000 µg daily of oral cyanocobalamin, 1000 µg daily IM cyanocobalamin or vitamin B₁₂⁶³ for 90 d and 4 mo | In both times: All doses increased serum vitamin B₁₂ levels. Dose of 1000 µg (oral and IM) improved cognitive function (ie, loss of memory, impaired concentration), sensory neuropathy, and vibration sense. Doses of 2000 µg (orally) and 1000 µg (IM) decreased serum methylenetetrahydrofolate acid and serum homocysteine concentrations; improved or clearing of paresthesia, ataxia, or memory loss. |
| Talaei et al (2009)¹⁰³          | RCT, single-blind       | DN                                                    | 100                 | Patients with diabetes (duration > 3 years; 18–53 y old) with DN, and without vitamin B₁₂ deficiency | 2 mg IM vitamin B₁₂⁶⁴ twice weekly for 3 mo       | Decrease in pain and paresthesia scores, and tingling sensation; no changes in vibration, position, pinprick, and nerve conduction parameters |
| Reference                  | Design                                      | Target condition                                           | No. of participants | Population (age)                                           | Dose and time                        | Main results                                                                 |
|---------------------------|--------------------------------------------|------------------------------------------------------------|---------------------|------------------------------------------------------------|--------------------------------------|--------------------------------------------------------------------------------|
| Volkov et al (2009)       | RCT, double-blind                          | RAS                                                        | 58                  | Patients with RAS and without vitamin B₁₂ deficiency (22.54–42.67 y) | 1000 µg daily of sublingual vitamin B₁₂ for 6 mo | Decreases in pain level, number of ulcers, and duration of outbreaks at 5 and 6 mo of treatment, regardless of initial vitamin B₁₂ levels in the blood. |
| Syed et al (2013)         | RCT                                        | Major depressive disorder                                  | 73                  | Patients with depression and low to normal B₁₂ levels (24.28–51.06 y) | 1000 µg IM vitamin B₁₂ every week in addition to the antidepressants (imipramine 100–250 mg/d and fluoxetine 20–40 mg/d) during the 6 wk | Improved depressive symptoms. |
| Taneja et al (2013)       | RCT, double-blind                          | Diarrhea and acute lower respiratory tract infections      | 1000                | North Indian children with or without B₁₂ deficiency (6–30 mo) | 1.8 µg of oral vitamin B₁₂ for 6 mo | The supplementation significantly improved vitamin B₁₂ status, but vitamin B₁₂ administration did not reduce the incidence of diarrhea or lower respiratory infections. |
| Almeida et al (2015)      | Meta-analysis of RCTs                       | Major depressive episodes                                  | 1695                | Patients with major depression with or without B₁₂ deficiency (16–85 y) | 0.1–0.5 mg daily of oral vitamin B₁₂ for 52 wk to 7 y, or 1 mg local injection of cyanocobalamin for 4 wk | Vitamin B₁₂ did not decrease the severity of depressive symptoms. |
| Scholten et al (2018)     | RCT, double-blind                          | Severe fatigue                                             | 95                  | Patients with irritable bowel syndrome or inflammatory bowel disease, and normal vitamin B₁₂ blood levels (18–65 y) | 1000 µg daily of oral vitamin B₁₂ for 8 wk | Increased vitamin B₁₂ blood levels, but not improved fatigue, quality of life, or depressive or anxiety symptoms. |
| Wang et al (2018)         | Meta-analysis of RCTs                       | Herpetic neuralgia                                          | 383                 | Patients with postherpetic neuralgia and with or without B₁₂ deficiency (47.01–74.70 y) | 1 mg daily of methylcobalamin, local injection, for 2–4 wk | Improved the quality of life, decreased pain intensity and analgesics use. |
| Didangelos et al (2021)  | Randomized, double-blind, placebo-controlled trial | Neurophysiological parameters, pseudomotor function, life quality, and level of pain | 90                  | Patients with DN, metformin use, and low vitamin B₁₂ levels (53.4–71.8 y) | 1000 µg daily of oral methylcobalamin for 1 y | Increased plasma B₁₂ levels and improved all neurophysiological parameters, pseudomotor function, pain score, and quality of life, but it did not improve cardiovascular autonomic reflex tests and MNSI. |
| Reference                  | Design                         | Target condition                                      | No. of participants | Population (age)                                                                 | Dose and time                                                                 | Main results                                                                                                                                 |
|----------------------------|--------------------------------|-------------------------------------------------------|---------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Markun et al (2021)¹¹¹      | Meta-analysis of RCTs          | Cognitive function, depressive symptoms, and fatigue  | 6276                | Patients with or without mild cognitive impairment, with or without vitamin B₁₂ deficiency (66–82 y) | 0.1–1 mg daily of oral cyanocobalamin or methylcobalamin; or 1 mg IM cyanocobalamin once or twice weekly up to 2 y | Vitamin B₁₂ supplementation did not improve cognitive function and depressive symptoms, and idiopathic fatigue analysis was not possible. |
| Stein et al (2021)¹¹²       | Meta-analysis of RCTs          | PN                                                   | 2948                | Patients with PN and lowered plasma vitamin B₁₂ level (33–86 y)                  | 0.75–2 mg daily of oral methylcobalamin for 28–168 d                          | The presence of PN was associated with lowered B₁₂ levels. B₁₂ treatment showed a nonsignificant association with symptom improvement (eg, numbness, paresthesia, pain, and/or dysesthesia), perhaps due to the low number of studies included in the meta-analysis (n = 4). |

¹Vitamin B₁₂ form not mentioned.

Abbreviations: DN, diabetic neuropathy; IM, intramuscularly; MNSI, Michigan Neuropathy Screening Instrument Examination; PN, peripheral neuropathy; RAS, recurrent aphthous stomatitis; RCT, randomized controlled trial.
both systemically and in the central nervous system, especially associated with folate; it improves microvascular disease associated with hyperhomocysteinemia and can alleviate COVID-19 symptoms, thereby improving the prognosis either during or in the post–acute COVID-19 syndrome.

In a cohort study by Tan et al. older patients (≥50 years; n = 43) with COVID-19 received a daily oral combination of 500 mg methylcobalamin, 1000 IU of cholecalciferol (vitamin D₃), and 150 mg of magnesium oxide before the onset of the primary outcome and during 14 days. These patients had lower required need of oxygen therapy during hospitalization than did the control group (which did not receive the combination).

Jang et al. evaluated in 6 hospitals in South Korea 80 patients (median age, 63 years) with COVID-19 receiving mechanical ventilatory support, 19 of whom were treated with extracorporeal membrane oxygenation (9.8 days; interquartile range, 7.0–13.7 days). Five patients (31.58%) received vitamin B₁₂ therapy and were successfully weaned off extracorporeal membrane oxygenation (P = 0.013). However, they did not specify the chemical form of vitamin B₁₂ used in hospital treatment. The resolution of lung injury by vitamin B₁₂ may be associated with its reduced glutathione-sparing effect to maintain the antioxidant status, as well as its role as a regulator of NFκB levels affecting the expression of genes encoding pro-inflammatory cytokines.

The daily oral supplementation of vitamin B₁₂ (250 μg) in women immunized against influenza A (H1N1) during pregnancy and 3 months postpartum increased the vitamin B₁₂ values in plasma, colostrum, and breast milk; increased H1N1-specific immunoglobulin A responses in the plasma and colostrum of mothers, but not in babies; decreased MMA in mothers and children; and reduced the number of babies with high levels of C-reactive protein. The C-reactive protein levels may have an inverse correlation with vitamin B₁₂ concentration.

Vitamin B₁₂ can block factors that facilitate infection with SARS-CoV-2. Kandeel and Al-Nazawi conducted a virtual screening study of the Food and Drug Administration–approved drugs against COVID-19 main protease 3-C-like protease, which plays a key role in viral replication and transcription. Vitamin B₁₂ was in the fourth position of docking scores (relative docking score, 1.99) against COVID-19 main protease 3-C-like protease. The authors suggested combining vitamin B₁₂ with nicotinamide (vitamin B₃) or drugs...
against COVID-19, such as ribavirin (an potent antiviral drug, especially vs RNA viruses), and telbivudine (used to treat hepatitis B virus) to treat COVID-19.

Methylcobalamin has a significant affinity to bind to the active site of the nsp12 protein of SARS-CoV-2, with a docking score of −8.193, Glide gscore of −8.263, and Glide energy of −75.794 (Schrodinger, New York, NY). Thus, vitamin B₁₂ may inhibit the RNA-dependent RNA polymerase activity of nsp12 responsible for the replication of the viral genome. In an in silico study by Narayanan and Nair, the docking score of −10.008, Glide gscore of −10.008, and Glide energy of −86.131 indicated that vitamin B₁₂ has an affinity for binding with the active site of nsp14 protein from SARS-CoV-2.

The nsp14 protein has 3′ to 5′ exoribonuclease activity responsible for removing mismatches that arise during genome duplication; this action may impair the inhibitory effect of drugs used to treat COVID-19. Furthermore, Kaur et al proposed that the entry of SARS-CoV-2 facilitated by nsp14 protein in the host cell allows the use of cell S-adenosylmethionine for viral RNA capping, culminating in an increase in the Hcy production and angiotensin-converting enzyme-2 activation, which will facilitate greater viral entry into cells. It is important to note that the prolonged use of angiotensin-converting enzyme inhibitors to reduce viral infection can reduce vitamin B₁₂ levels (< 200 pmol/L) in older adult patients aged ≥ 65 years.

In data from 24 262 participants with a mean age of 48.0 (SD, ± 19.0) years, Wolffenbuttel et al found that low serum B₁₂ concentrations (< 140 pmol/L) were associated with a moderate increase in all causes of death (eg, chronic lower respiratory diseases, Alzheimer’s disease, influenza and pneumonia, cerebrovascular diseases, diabetes mellitus) and high serum concentrations of MMA and Hcy; the increase in cardiovascular causes of death was associated with both low (< 140 pmol/L) and high (> 700 pmol/L) serum B₁₂ levels.

On the other hand, excess vitamin B₁₂ in the body was also associated with poor outcomes of diseases. Ersöz and Yılmaz reported poor prognostic factors (eg, death of patients in the intensive care unit and intubated) in 310 patients from Turkey with COVID-19 (mean age ± SD, 57.02 ± 18.28 years) with high blood vitamin B₁₂ concentration (> 911 pg/mL), and low folate, iron, vitamin D, and hemoglobin levels. Some studies indicated an association between higher B₁₂ levels (1000–1719 pg/mL) and the death of critically ill adult patients in the intensive care unit (mean age ± SD, range, 53.5 ± 12.0 to 66.7 ± 20.0 years). Flores-Guerrero et al showed that a plasma vitamin B₁₂ concentration > 455.41 pg/mL was associated with a higher risk of all-cause mortality in 1394 adults (mean age ± SD, 54.6 ± 11.6 years). Excess vitamin B₁₂ is still controversial, and other authors have used distinct values for high plasma B₁₂ levels: > 950 pg/mL or 701 pmol/L, > 771 pg/mL, > 203 pg/mL or > 601 pmol/L.

Dalbeni et al exposed that 9 of 49 patients with COVID-19-associated pneumonia who did not receive vitamin B₁₂ by any route had excess vitamin B₁₂ in plasma (median, 1315 ng/mL), low arterial oxygenation (median, 202 partial pressure of oxygen/% inhaled oxygen) and were transferred to the intensive care unit or died. Some factors in this study limit the establishment of the relationship between the high blood levels of vitamin B₁₂ and intensive therapy or death resulting from COVID-19: 1) 9 patients (small sample size) were older than the 40 recovered patients by an average of 13 years (83.3 vs 70.2 years old, respectively); 2) the increase in vitamin B₁₂ level did not interfere with Hcy values, which were similar between groups (11 μmol/L vs 9 μmol/L) and are within the normal range, 5–15 μmol/L; and 3) the authors did not verify the values of other vitamin B₁₂ biomarkers, such as MMA. Aging itself predisposes to lower resistance to viral infections.

The mechanism by which blood excess vitamin B₁₂ occurs in patients in the intensive care unit is not clear, but some factors that may partially explain it include: 1) the elevated plasma levels of the cobalamin-carrier proteins, the transcobalaminbs I and III; 2) elevated release of vitamin B₁₂ from liver storage and decreased vitamin B₁₂ hepatic clearance; and 3) decreased hepatic production of transcobalamin II with reduction of vitamin B₁₂ peripheral tissues uptake, or reduced affinity of carrier proteins for vitamin B₁₂.

Transcobalamin II gene polymorphisms can decrease tissue distribution of cobalamin, even with high serum cobalamin levels. The 776GG homozygous variant of 776C>G polymorphism encodes a transcobalamin 2 with a lower binding affinity to vitamin B₁₂, whereas polymorphisms in the FUT 6 gene (ie, rs708686, rs78060698, rs3760775, and rs7788053) elevate vitamin B₁₂ status. It is interesting to note that polymorphisms in the ATP-binding cassette subfamily D member 4 protein will affect the transporting vitamin B₁₂ out of lysosomes, and thus intracellular processing of vitamin B₁₂, which may increase serum levels of vitamin B₁₂.

Several conditions may also result in higher vitamin B₁₂ concentrations in critically ill patients, especially in older adults, such as preexisting diseases (eg, renal failure, hepatic diseases, cancer, Alzheimer’s disease), nutritional status, and inflammatory status (eg,
sepsis.\textsuperscript{44,135} Acute uncontrolled systemic inflammation in severe COVID-19 induces sepsis and multiple organ failure, and can lead to an elevation of vitamin B\textsubscript{12} level due to higher levels of transcobalamin I and II, their receptors, and unsaturated B\textsubscript{12} binding capacity in the blood.\textsuperscript{141,143} The inactive form of vitamin B\textsubscript{12} bound to transcobalamin I is the main factor that elevates blood vitamin B\textsubscript{12} levels.\textsuperscript{84} However, the mechanisms by which excess vitamin B\textsubscript{12} is associated with sepsis remain poorly elucidated and, in these cases, supplementation with vitamin B\textsubscript{12} should be individually evaluated considering the aforementioned metabolic and genetic factors.

Patients with severe COVID-19 have elevated levels of high mobility group box 1,\textsuperscript{144} a potential biomarker of sepsis that is modulated by NF\textsubscript{kB}.\textsuperscript{141} The active form of this vitamin in patients with functional transcobalamin II and normal B\textsubscript{12} cell metabolism can inhibit production of this biomarker by indirect mechanisms, that is, through downregulation of NF\textsubscript{kB} levels and increased acetylcholine synthesis, which positively modulates the neuro-immune cholinergic anti-inflammatory pathway.\textsuperscript{141}

Some interventional clinical trials on the effects of vitamin B\textsubscript{12} supplementation in combination with other micronutrients and/or medications in cases of COVID-19 are currently being recorded in the International Clinical Trials Registry Platform and ClinicalTrials.gov databases registration numbers NCT04395768 (500 µg methylcobalamin orally, daily, for 14 days), NCT04751669 (9.6 mg cyanocobalamin orally, once a day, for 14 days), and NCT04828538 (1 mg daily oral B\textsubscript{12} supplementation for up to 60 days). In addition, 2 registered observational clinical studies will investigate the B\textsubscript{12} levels in patients positive for COVID-19 (age range, 21–60 years; Clinical Trials Registry India identification number CTRI/2021/02/030946) and in pregnant women positive for COVID-19 (ClinicalTrials.gov registration number NCT04407572).

However, more RCTs of vitamin B\textsubscript{12} supplementation and analysis of various markers (eg, total B\textsubscript{12}, holotranscobalamin, total Hcy and MMA, total folic acid, and if possible, polymorphism and/or methylation of genes) are needed to precisely identify the status of this micronutrient (before and after) in people with or without COVID-19 and thus facilitate the proper choice of vitamin B\textsubscript{12} form to be administered in treatment.

**CONCLUSIONS**

The evaluation of parameters that determine the deficiency or subclinical levels of vitamin B\textsubscript{12} deficiency can be an ally in treating patients affected by COVID-19 or in persistent symptoms of the disease, given the important functions of this vitamin in the skeletal muscle–gut–brain axis.

Vitamin B\textsubscript{12} plays an important role in viral infections. The consumption of a healthy diet containing vitamin B\textsubscript{12} sources, and especially supplementation with methylcobalamin and cyanocobalamin, are promising alternatives as adjuvants in the treatment of COVID-19, especially in patients with B\textsubscript{12} deficiency or deficiency risk. However, establishing doses, intervention times, and mechanisms of action of vitamin B\textsubscript{12} against COVID-19 can be a great challenge.

Researchers are encouraged to identify whether the subclinical deficiency or deficiency itself of this vitamin is a risk factor for COVID-19 complications, and it is necessary to carry out intervention studies with vitamin B\textsubscript{12} supplementation in both the adjuvant treatment of mild, moderate, and severe COVID-19 and post-COVID-19, with a focus on minimizing symptoms related to the muscle–gut–brain axis.

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