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NEUROLOGICAL SYMPTOMS AND SERUM VITAMIN B12 LEVELS CORRELATE IN COVID-19 PATIENTS

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ნევროლოგიური სიმპტომებისა და შრატში ვიტამინ B12-ის დონის კორელაცია კოვიდ-19 პაციენტებში

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რეზიუმე

კოვიდ-19 პანდემიის დასაწყისში პაციენტებში ხშირი იყო სმენისა და ყნოსვითი მგრძნობელობის ცვლილებები და B12 ვიტამინის უკმარობასთან ასოცირდებოდა. ადრეული 2022-დან ჩვენ ვაკვირდებოდით პოსტ-კოვიდის ნევროლოგიულ სიმპტომებს, რომლებიც მნიშვნელოვნად აუარესებდნენ პაციენტთა ცხოვრების ხარისხს, რის გამოც პაციენტები პირველად სამედიცინო დახმარებას მიმართავდნენ. ჩვენი კვლევა მიზნად ისახავდა, დაგვედგინა B12 ვიტამინის უკმარობის კორელაციური კავშირი პოსტ-კოვიდის ნევროლოგიურ სიმპტომებთან. კვლევაში ჩართული იყო 312 პაციენტი ლაბორატორიულად დადასტურებული კოვიდ-19-ით. ყველა პაციენტი უჩიოდა მეხსიერების პრობლემებს, გაუარესებულ კონცენტრირების უნარს, გუნება-განწყობის ცვალებადობას, წვა-ქავილის შეგრძნებებს და/ან კუნთების სისუსტეს. ყველა პაციენტი უარყოფდა აღნიშნული სიმპტომების არსებობას კოვიდ-19-ით დაავადებამდე, ან ამტკიცებდა, რომ ამ სიმპტომების არსებობა გავლენას არ ახდენდა მათი ცხოვრების ხარისხზე. პაციენტებში B12 ვიტამინის დონე შრატში გაზომილი იქნა სტანდარტული ენზიმასოცირებული იმუნოფერმენტული ანალიზის (ELISA) მეშვეობით. კვლევამ აჩვენა, რომ პაციენტთა 85%-ს ჰქონდა B12 ვიტამინის დაბალი დონე. ლაბორატორიულ შედეგებზე დაყრდნობით, პაციენტებს დაენიშნათ B12 ვიტამინის პერორალური დღიური თერაპიული დოზა 2 თვით. ღრმა დეფიციტის მქონე პაციენტები, პირველი 10 დღის განმავლობაში იღებდნენ B12 ვიტამინს ინექციური ფორმით, და შემდეგ - აბებით. მკურნალობის ჩამთავრების შემდეგ, ყველა პაციენტს სიმტომები მნიშვნელოვნად შეუმცირდა ან გაუქრა. მოცემული კვლევის საფუძველზე, მიზანშეწონილად მიგვაჩნია ვიტამინ B12-ის დონის მონიტორინგი იმ პაციენტებში, რომლებსაც კოვიდ-19-ის შემდგომ განვითარებული ნევროლოგიური სიმპტომები აღენიშნებათ. კვლევამ ასევე გვიჩვენა, რომ ყველა პაციენტისთვის შრატში B12-ის სასურველ დონის მისაღწევად მხოლოდ ორალური დანამატი შეიძლება არ იყოს საკმარისი.

Introduction. The 2019 novel coronavirus (2019-nCoV), also known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first appeared in China in Wuhan in December 2019. Since then, this new virus, also known as coronavirus disease 2019 (COVID-19), has dramatically spread across all national boundaries, and on March 11, 2020, the World Health Organization (WHO) declared it to be a pandemic disease [1]. The lower respiratory tract-related symptoms of the novel COVID-19, such as fever, coughing, dyspnea, and tightness in the chest, can develop rapidly into acute respiratory distress syndrome (ARDS) [2]. However, COVID-19 can also cause a variety of upper respiratory tract-related symptoms, such as a sore tongue, difficulty breathing and nasal congestion [3]. In the early stages of the infection, olfactory and gustatory changes are common [2–5].

Vitamin B12 (also identified as cobalamin) is a water-soluble vitamin that is part of the set of vitamins in the B complex. It has crucial roles in the blood and cardiovascular system [6], also being implicated with the regulation of the immune system and antiviral activity [7,8]. Additionally, this

vitamin is an indispensable nutrient with distinctly significant roles in the skeletal muscle–gut–brain axis, such as the maintenance of skeletal muscle and neurobehavioral parameters [9,10] and modulation of gut microbiota [11]. Vitamin B12 was ranked among the top 4 substances for potential use in treatment for COVID-19, based on findings from a study conducted with the assistance of molecular modeling and virtual screening tools, using data on US Food and Drug Administration–approved drugs [12]. Therefore, vitamin B12 combined with a nutritious diet can be an important adjuvant in treating COVID-19 and in patients treated after COVID-19 infection.

The subclinical inadequacy rates of vitamin B12 are high in developing countries and vegetarian populations because the primary source of this vitamin is animal-based foods [13,14]. Additionally, older adults, people who have had bariatric surgery, and those at increased risk of B12 deficiency, and use of some medications also pose a risk factor [15]. Vitamin B12 deficiency leads to hematologic, neuropathologic, and cardiovascular disorders, mainly by interfering with the homocysteine (Hcy) metabolism and the methylation reactions of the organism [16,17].

Since vitamin B12 is engaged in diverse roles in the organism and is impacted by various medical conditions, identifying vitamin B12 status is vital for patients with ongoing COVID-19 infection and those who underwent COVID-19. Based on the association of vitamin B12 with the muscle-intestinal-cerebral axis and its function in viral infections and the immune system, we aimed to offer verification and innovative perspectives with respect to B12 during management and persistent manifestations of COVID-19.

Vitamin B-12 deficiency effects on COVID-19 patients. 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 [18,19,20]. The most common Guillain–Barré syndrome are severe back pain and muscle weakness, and there may be long-term complications, including severe disability, pain, and fatigue [19,20].

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) [8]. The symptoms include gastrointestinal symptoms (eg, diarrhea, nausea and vomiting, abdominal pain); neurologic manifestations (eg, concentration impairment, anxiety and depression symptoms, headache, migraine, dementia, stroke, obsessive-compulsive disorder, anorexia, apathy, executive deficits, vertigo, memory or cognition loss, hallucinations, sleep disturbances, post-traumatic stress disorder, loss of taste (ageusia) or of smell (anosmia); neuromuscular disorders (eg, fatigue) and muscular disorders (eg, muscle weakness, myalgia).

Various vitamin B12 deficiency symptoms are like those found in patients with COVID-19 and post-COVID-19 [9,10]. Studies tested vitamin B12 supplementation to alleviate some of the symptoms of various diseases that are also present in COVID-19 [21-23]. Two RCTs [22,24] and 5 meta-analyses [21,25,26,27,28] reported benefits of vitamin B12 supplementation in methylcobalamin (0.5–1 mg orally or local injection for 2 weeks to 1 year) and cyanocobalamin (2000 mg orally or 1–1000 mg via intramuscular route for 90 days to 4 months) forms. The benefits were mainly in analgesic action and attenuation of neurologic symptoms.

Methods. At the beginning of 2022 after recovering from the virus, most of the patients addressed us with a neurological symptom which usually developed in 1 or 2 weeks after recovery and got worse over time.

From April to November of 2022, we started collecting data from 312 patients who had laboratory confirmed COVID-19 for the last three months and neurological symptoms. Most patients were women. These subjects were not receiving treatments and did not have any diseases that may potentially cause a vitamin B12 insufficiency; they had not undergone bariatric surgical procedures, and did not follow a vegetarian dietary pattern. All these patients presented with at least one of these symptoms:

1. Memory problems such as short-term memory impairment.
2. Depressive syndrome.
3. Mood changes, easily irritated and agitated (especially in children).
4. Lack of concentration.

5. Tingling sensation and/or weakness (especially in the upper limb).
6. General weakness, drowsiness.

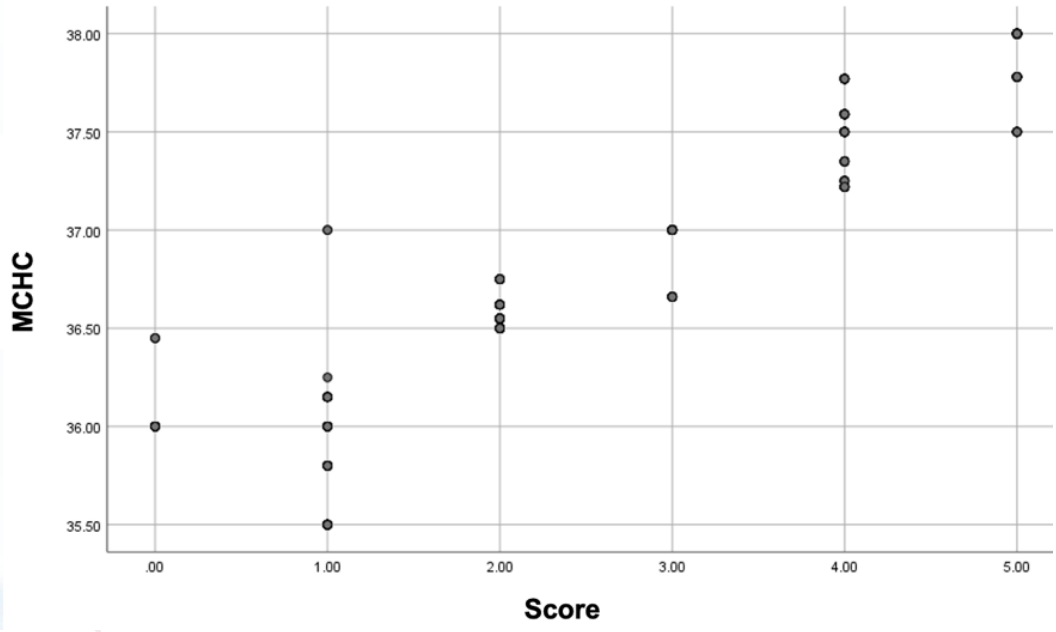
CBC, TSH and Serum vitamin B12 levels were measured in all these patients. Studies have shown that 288 of them had vitamin B-12 levels below 200 pg/ml (with a slightly elevated MCHC), 8 patients had a high level of TSH, in 17 cases they had both B12 deficiency and high level of TSH.

PERCENTAGE DISTRIBUTION OF SYMPTOMS

Memory problems	92%
Impaired concentration	62%
Tingling sensation	64%
Mood changes	90%
Weakness of muscles	89%

For each symptom, we give 1 point to assign with MCHC level.

MCHC LEVEL CORRELATION WITH SYMPTOMS



Correlations

		MCHC	Score
MCHC	Pearson Correlation	1	.941**
	Sig. (2-tailed)		.000
	N	288	288
Score	Pearson Correlation	.941**	1
	Sig. (2-tailed)	.000	
	N	288	288

**. Correlation is significant at the 0.01 level (2-tailed).

Methods: A total of 288 patients diagnosed with vitamin B12 deficiency were enrolled in this study. Each patient was given the option to choose their preferred treatment plan. The patients were divided into two groups based on their choices. The first group, comprising 208 of the participants, opted for an oral dosage of 1000 mg per day, to be taken once in the morning on an empty stomach for a duration of 2 months. The second group, 80 of the participants, initially chose a 10-day intramuscular injection regimen followed by the same oral dosage of 1000 mg per day.

Results: After the 2-month treatment period, the outcomes of the two groups were assessed, particularly regarding serum vitamin B12 levels. Among the patients who observed the oral dosage regimen (Group 1), 85% displayed a significant improvement in their vitamin B12 levels, and the neurological symptoms they had been complaining of, practically disappeared (only memory problems remained as the main complaint), with values approaching 300 pg/ml. The rest of the patients in this group still maintained serum B12 levels below the desirable threshold of 300 pg/ml, but these patients also reported a reduction or complete disappearance of symptoms.

In contrast, the group of patients who underwent the combination therapy (intramuscular injection followed by oral dosage) (Group 2) displayed varying results. After the initial 10-day intramuscular treatment, all patients transitioned to the oral dosage of 1000 mg per day. At the end of the 2-month treatment period, it was observed that 90% of patients in this group achieved serum B12 levels close to 400 pg/ml. The rest of the patients in this group still had vitamin B12 levels below the target threshold (450-500 pg/ml). In the case of this treatment regimen, patients reported the disappearance and reduction of symptoms after 14 days of treatment.

Discussion: The findings of this study highlight the influence of patient preferences on treatment outcomes in individuals with vitamin B12 deficiency. While the majority of patients preferred the convenience and ease of the oral dosage, only part of them demonstrated a substantial improvement in their vitamin B12 levels after 2 months of treatment. This suggests that oral supplementation alone may not be sufficient for all patients to reach the desired serum B12 levels.

On the other hand, the combination therapy involving intramuscular injections followed by oral dosage showed comparable results to the oral-only regimen. However, it should be noted that the majority of patients in this group still did not reach the target serum B12 levels after the 2-month treatment period. This indicates the need for further investigation into alternative or adjunctive treatment approaches to optimize outcomes for patients with persistent vitamin B12 deficiency.

These findings emphasize the importance of personalized treatment plans tailored to individual patient preferences. Factors such as patient's compliance, convenience, and tolerability should be taken into consideration when designing treatment strategies for vitamin B12 deficiency. Future research could focus on exploring novel administration methods, optimizing dosing regimens, and investigating the potential benefits of adjunctive therapies to enhance the effectiveness of B12 supplementation in patients with persistent deficiency.

This study demonstrates the varying outcomes of different treatment strategies for vitamin B12 deficiency based on patient preferences. While oral dosage and combination therapy showed promising results for a subset of patients, a significant proportion still did not achieve optimal serum B12 levels. These findings call for further research and the development of personalized approaches to address the diverse needs of patients with vitamin B12 deficiency.

In conclusion, we recommend monitoring vitamin B12 levels in patients presenting with neurological symptoms developed after COVID-19 infection.

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SUMMARY

At the beginning of the COVID-19 pandemic, olfactory and gustatory changes were common, and they were associated with vitamin B12 deficiency. From early 2022 we observed post-COVID neurological symptoms that significantly worsened the patient's quality of life, and because of this, the patients were referred to primary care. The objective of our research was to evaluate the vitamin B12 deficiency correlation to post-COVID neurological symptoms. 312 patients with laboratory-confirmed COVID-19 were included in the research. All the patients suffered from self-rated symptoms such as memory problems, impaired concentration, mood changes, tingling sensation, and/or weakness of muscles. All patients either denied having these symptoms before the COVID-19 infection or claimed that having these symptoms did not affect their quality of life. Using standard enzyme-linked immunosorbent assay (ELISA) serum vitamin B12 levels in the patients were measured. The study showed that 85% of patients had low levels of vitamin B12. Based on the laboratory results, patients have been prescribed a daily dose of peroral vitamin B12 therapy for 2 months. Patients with a severe deficiency were initially given the injectable form for the first ten days, followed by a switch to the tablet form. Upon completing the treatment, all patients reported a significant reduction or complete disappearance of their symptoms. Based on our study we recommend the monitoring of vitamin B12 levels in patients presenting with neurological symptoms developed after COVID-19 infection. The study also showed that oral supplementation alone may not be sufficient to achieve the desirable level of vitamin B12 in all patients.

Keywords: Covid 19, Vitamin 12, Neurology