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Rapid communication

Efficacy of vitamin D replacement therapy on 28 cases of myalgic encephalomyelitis/chronic fatigue syndrome after COVID-19 vaccination

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ABSTRACT

Background: Prolonged symptoms have been reported following both COVID-19 infection and vaccination, with some cases leading to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Of 80 patients presenting to our hospital with postvaccination syndrome, 28 met the diagnostic criteria for ME/CFS. We conducted a retrospective study on these 28 patients.

Methods: We measured serum 25-hydroxyvitamin D levels in 28 patients who developed ME/CFS after COVID-19 vaccination between August 2022 and February 2024. Vitamin D replacement therapy included dietary counseling, sun exposure recommendations, and oral vitamin D supplementation. We evaluated changes in blood vitamin D levels and symptom improvement.

Results: At initial visit, 27 of 28 patients diagnosed with ME/CFS had insufficient or deficient serum 25-hydroxyvitamin D levels (16 ± 4 ng/mL, mean $\pm$ SD). Following vitamin D replacement therapy, we observed an increase in blood vitamin D levels (28 ± 5 ng/mL) associated with a decrease in ME/CFS diagnostic symptoms (from 10.3 ± 2.1 to 3.3 ± 2.0). Notably, 23 of 28 patients (82%) no longer met ME/CFS diagnostic criteria after the therapy. Among the symptoms, sleep problems showed the most improvement (71%), followed by autonomic symptoms (68%).

Conclusions: For patients developing ME/CFS after COVID-19 vaccination with insufficient or deficient vitamin D levels, appropriate vitamin D replacement therapy under medical guidance may lead to symptomatic relief. We are preparing a randomized controlled trial to evaluate the efficacy of vitamin D replacement therapy in individuals with ME/CFS who have developed vitamin D deficiency following COVID-19 infection or vaccination.

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Introduction

Since the COVID-19 pandemic began in 2020, a variety of post-COVID-19 symptoms have become known and have been reported by the World Health Organization as Post-COVID-19 conditions [1]. These symptoms are similar to those of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), including fatigue and symptoms of brain, autonomic, and neurological disorders [2].

Some COVID-19 patients reportedly suffer from prolonged post-COVID-19 symptoms, termed Long COVID [3]. Long COVID and ME/CFS share many clinical and biological similarities, leading to the hypothesis that SARS-CoV-2 infection may cause ME/CFS symptoms [4]. The prolonged sequelae after COVID-19 infection are also known as postacute sequelae of SARS-CoV-2 (PASC) and about half of patients with PASC are estimated to meet the criteria for ME/CFS [5]. Notably, symptoms similar to ME/CFS have also been observed after COVID-19 vaccination [6].

A wide range of symptoms has been reported following COVID-19 vaccination, particularly noted in literature from 2022 onwards

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[7]. Although the precise pathogenetic processes are not fully clarified to date and further investigation is needed to establish a causal relationship with COVID-19 vaccination [8], it is reported that the spike protein may exert pathophysiologic effects through several mechanisms leading to inflammatory responses, thrombus formation, and tissue damage associated with endothelialitis (a phenomenon termed "spikeopathy") [9]. These processes appear to be evolving as our understanding grows. However, in actual clinical practice, there are cases where the cause remains unknown and a definite diagnosis has not been made despite various tests conducted in hospitals for symptoms that suddenly occurred in patients after vaccination. At our hospital, we frequently encounter patients complaining of unexplained illnesses, with no previous diagnosis or resolution of their symptoms. Many of these patients ultimately receive a diagnosis of ME/CFS.

Despite the prevalence of ME/CFS worldwide, many clinicians lack the knowledge to manage it properly. The spread of COVID-19 has exacerbated this issue, with an increasing number of patients experiencing prolonged ME/CFS-like symptoms, posing a significant clinical challenge [10]. ME/CFS symptoms are diverse, including chronic severe fatigue, postexertional malaise, sleep disturbance, cognitive impairment, pain, and hyperesthesia, as well as neuroendocrine, autonomic, and immune function-related symptoms [11].

In our search for a safe and versatile treatment for ME/CFS patients, we found reports linking vitamin D deficiency to fatigue, immune and musculoskeletal pain, and headache [12–14]. Furthermore, vitamin D deficiency has been associated with neurologic disease and sleep disorders, with vitamin D supplementation shown to improve these symptoms [15,16]. After carefully examining these findings, we hypothesized that vitamin D might be effective for ME/CFS and conducted vitamin D replacement therapy based on this premise. This article reports our results.

Method

Intervention

This study included patients who developed ME/CFS after a COVID-19 vaccination and were either seen or admitted to Kodama Hospital/Kodama Clinic. The observational survey period ran from August 2022 to February 2024. The diagnostic criteria for ME/CFS used the "2003 Canadian Clinical Case" as described in the "Primer for Clinical Practitioners 2014 edition [17,18]" by the International Association for ME/CFS [19].

Dietary counseling

Patients were encouraged to consume foods high in vitamin D in their daily lives without undue stress. Generally, seafood and mushrooms are rich in vitamin D [20], but we instructed patients to investigate the details of food nutritional composition on their own and expected them to be health conscious about food.

Sunbathing instruction

Since patients' physical conditions and ADLs vary, patients were instructed to take a walk or hold their face and palms up to the sun by a window, depending on their own physical condition and ADL, for 15 to 30 minutes once a day, which is the estimated time for adults to produce the daily required amount of vitamin D in their skin [21].

Oral vitamin D supplementation

Patients who were unable to participate in dietary or sunbathing interventions because of poor ADLs or lack of family support were actively given supplemental vitamin D. Meanwhile, patients who could intervene with diet and sunbathing guidance were also given supplemental vitamin D if they requested it after guidance. For vitamin D supplements, patients were asked to purchase over-the-counter supplements without any ingredients other than vitamin D on their own and to consume them in regular doses. More than half of the patients took one tablet (25 μg of vitamin D content) supplement once a day. The guidance for vitamin D intake is based on the report by the Study Group "Dietary reference intake in Japanese (2020 version)" [22] published by the Ministry of Health, Labour and Welfare (MHLW), which adopted recommendations from the Institute of Medicine's Dietary Reference Intakes for Calcium and Vitamin D [23]. They found that the recommended intake of vitamin D is 15 μg / d for people aged 70 and under and 20 μg/d for people aged 71 and over. It was determined that the amount of vitamin D taken in the replacement therapy would not cause toxicity even if dietary, sunbathing and supplementation guidance was provided simultaneously because 1) skin vitamin D production by ultraviolet rays is regulated, and more vitamin D than necessary is not produced; 2) the activation of vitamin D is regulated in the liver and kidneys, and the activation in the kidneys is strictly regulated in the event of hypercalcemia; and 3) even though the amount of vitamin D taken in dietary intake had a large day-to-day variation, the daily intake of vitamin D will not surpass the upper limit of 100 μg/d with the vitamin D supplementation of 25 μg/d.

Symptomatic treatment

Symptomatic treatment was provided, which included exercise therapy, drug therapy, and nutritional counseling. In exercise therapy (medical fitness), a custom-made exercise plan was prepared taking into account the age and condition of the patient, and exercise therapy was carried out in stages. Protein intake after exercise was also recommended to build muscle strength and aid in recovery from muscle fatigue. Taking into account that for patients with ME/CFS, daily activities are considered training, patients who were unable to integrate exercise into their daily routine were instructed to go about their daily activities as much as possible according to their physical condition.

Medications were basically selected from drugs other than those that the patient had taken before, and those that the patient did not feel the therapeutic effect from after starting use were discontinued as soon as possible. Upon patients' presentation at our hospital, medications prescribed at other hospitals were generally discontinued, unless they were for underlying medical conditions or psychiatric symptoms, and their discontinuation was thought to have the potential to exacerbate symptoms. Medications for which patients were aware of the treatment effect were continued.

Other therapeutic interventions

Because of the development of ME/CFS symptoms following COVID-19 vaccination, the COVID-19 vaccine was considered a suspect drug for ME/CFS, and patients were instructed not to receive future boosters.

Statistical analysis

In our study, all 25(OH) vitamin D measurements were performed by FALCO biosystems Ltd., an accredited clinical laboratory service in Japan with the Certificate of Accreditation from College of American Pathologists and the international standard ISO 15189 (Medical laboratories—Requirements for quality and competence), using the ECLIA method (Elecsys Vitamin D total II, Roche

Diagnostics). This method is approved by the Japanese MHLW as an insured diagnostics for 25(OH) vitamin D measurement and represents the standard testing method in Japanese clinical settings, which means that it has undergone rigorous evaluation and verification through the MHLW approval process, including thorough assessment of precision, accuracy, and calibration procedures.

The number of days from the initiation of vitamin D replacement therapy was divided into pretreatment (day 0) / 1 to 120 days / 121 days and beyond for serum 25(OH) vitamin D levels, and pretreatment (day 0) / 1 to 60 days / 61 to 120 days / 121 to 180 days / 181 days and beyond for the number of ME/CFS symptoms. Patients who had a measurement before vitamin D replacement therapy (baseline) and at least one measurement after the initiation of vitamin D replacement therapy were included in the analyses. If there were multiple values within the same time point category, the value at the last time point was used.

The mean and standard deviation of serum 25(OH) vitamin D levels (ng/mL) and the number of ME/CFS symptoms at each time point category were calculated, and spaghetti plots were used to show the longitudinal change of each measurement for each subject. A dashed line indicates a missing value at the intermediate time point. The change in each measurement at each time point category, its 95% confidence interval (CI), and the P value (null hypothesis: change from baseline equals 0) were estimated using mixed models for repeated measures with the change from baseline in each measurement as the response variable, the time point category as the fixed effect, and the patient as the random effect.

To explore factors associated with a change in the number of ME/CFS symptoms, we performed a survival analysis using time to have fewer than eight symptoms as a response variable and baseline characteristics and laboratory data as explanatory variables. Univariable screening (selection threshold: $P < 0.2$) and multivariable Cox regression analysis (backward stepwise selection method, selection threshold: $P < 0.1$) were used to identify potential risk factors.

All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant. All analyses used SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Result

Patient characteristics

During the study period, 28 cases of ME/CFS were diagnosed in our hospital. Patient characteristics are shown in Table 1. There were 11 men and 17 women. The average age of the patients was 47, ranging from 14 to 84 years old, and many of them were students or in the prime of life, which we considered a serious problem in the social context. Only 6 patients (21%) brought a letter of referral, and most of them visited our clinic on their own decision after their previous doctor's visit ended without a referral to another hospital.

In terms of past medical history, none of the patients had any serious underlying illness and all were socially independent. Of particular note, 15 patients (54%) were generally healthy before experiencing an onset of ME/CFS symptoms, which suddenly impacted their social functioning. At the time of the initial examination, patients received oral medication for underlying conditions that had existed before the onset of symptoms, as well as oral medication that had been prescribed and continued by previous physicians after the onset of symptoms. Some medications could be stopped or reduced from the start of treatment at our hospital, but some were difficult to stop because of underlying medical conditions, and some were difficult to stop or reduce because of psychoactive drugs or symptomatic treatments for pain.

Only 4 patients (14%) had a prior diagnosis of ME/CFS up to the time of the initial visit. In the remaining 24 cases (86%), the diagnosis was indeterminate or a suspected mental disorder. In all cases, patients were seen in multiple specialties of multiple healthcare organizations (eg, academic hospitals, regional core hospitals, private physicians) before presenting to our hospital. Some were referred for psychiatric care at the institution where they were seen, and some were further sickened by the psychoactive drugs prescribed. In some cases, patients were denied medical attention when they reported feeling unwell after receiving the COVID-19 vaccine. In other cases, upon examination, doctors concluded that patients' symptoms were unrelated to the COVID-19 vaccine.

Symptoms persisted for a minimum of 4 months and a maximum of 2 years and 4 months, with a median of 1 year and 3 months between the onset of symptoms and presentation to our hospital. All patients presented with long-term distress, uncertainty about their future, and mistrust of their healthcare. They were burdened physically, mentally, and financially.

The number of COVID-19 vaccinations ranged from one to six, with 13 cases (46%) occurring most commonly after three doses. Five cases (17%) had a history of COVID-19 infection and 23 cases (82%) had no history of infection; in most cases, there was no association between the onset of symptoms and coronavirus infection. Nineteen patients (68%) developed symptoms immediately after receiving the COVID-19 vaccine; the longest interval between vaccination and symptom onset was 6 months.

All patients believed their symptoms were caused by the COVID-19 vaccination. However, the doctors they had previously seen did not agree with this belief or did not provide clear evidence that the COVID-19 vaccination was not the cause of their symptoms. For the first time, patients received empathy for their opinions from their doctors after visiting our hospital. Before coming to our hospital, many patients felt psychologically driven away by their doctors.

There were 9 cases (32%) in which the family viewed the patient's symptoms as mental and did not understand the patient's behavior. In some cases, patients' subjective symptoms were understood by their families, but overreaction of the families to the illness made the patients even more exhausted.

Symptoms at initial presentation and end of observation

Based on the diagnostic criteria, an analysis of the symptoms of 28 patients in our hospital (Fig. 1) showed that in addition to pathological fatigue, postexertional malaise and worsening of symptoms, sleep problems, and pain, the most common neurocognitive symptoms was "muscle weakness" in 20 patients, followed by "confusion" in 17 patients and "impaired concentration" in 16 patients. "Orthostatic intolerance" was the most common autonomic symptom in 17 patients, followed by "light-headedness" in 12 patients. As for neuroendocrine symptoms, "other symptoms worsen with stress" was the most common in 12 patients, followed by "intolerance to heat or cold" in 11 patients, "reduced tolerance for stress" in 10 patients, and "cold extremities" in 7 patients. "recurrent flu-like symptoms" were the most common immune system symptom in 14 patients.

All patients visited our hospital after exclusion of any differential diseases. Some of the patients who brought a referral had already been diagnosed with ME/CFS, but most of the patients were diagnosed with ME/CFS after visiting our hospital. To be diagnosed with ME/CFS, a minimum of eight symptoms were required to meet the diagnostic criteria, with scores ranging from 8 to 18 based on the number of symptoms in each case, with one point for each criterion.

Table 2 shows the changes in patient symptoms from the initial visit to after vitamin D replacement therapy. At the end

Table 1
Patient characteristics

Patient No.*	Age	Sex	Letter of Referral	Medical history	Medications	Diagnosis before initial visit	No. of visited health care facilities	Period between onset of symptoms and initial visit	No. of COVID-19 vaccinations	History of COVID-19 infection	Period between COVID-19 vaccination and onset of symptoms	Family members' acknowledgment of patient's illness	Initial visit date
1	55	Female	No	No	No	Unknown	3	4 mo	2	No	6 mo	No	August 5, 2022
2	36	Female	No	Hypertension, insomnia	Amlodipine besilate, atenolol, triazolam, clonazepam	Psychosomatic disorder, cervico-omo-brachial syndrome, cervical spine osteoarthritis, positional vertigo	7	11 mo	2	No	0 d	Yes	September 16, 2022
3	25	Female	No	No	No	Lower extremity peripheral neuritis	3	5 mo	3	No	5 mo	Yes	December 26, 2022
4	36	Female	Yes	Bipolar disorder	No	Unknown	2	4 mo	4	No	0 d	No	November 17, 2022
5	49	Male	No	Panic disorder, sleep apnea	Alprazolam, domperidone, paroxetine hydrochloride hydrate, quetiapine fumarate, brotizolam, loxoprofen sodium hydrate	Unknown	3	9 mo	3	No	0 d	No	January 13, 2023
6	24	Male	No	Asthma	No	Unknown	10	1 y and 7 mo	2	No	0 d	Yes	April 17, 2023
7	71	Male	No	No	No	Unknown	4	1 y and 9 mo	2	No	0 d	No	April 18, 2023
8	36	Male	No	No	No	Unknown	1	1 y and 4 mo	3	No	0 d	Yes	April 24, 2023
9	65	Female	No	Myasthenia gravis	Ambenonium chloride, prednisolone	Unknown	1	8 mo	4	No	0 d	Yes	May 15, 2023
10	36	Female	No	Myofascial pain syndrome	No	Chronic fatigue syndrome, fibromyalgia	7	2 y and 4 mo	1	No	0 d	No	May 22, 2023
11	20	Female	No	No	Chinese herbal medications (details unknown)	Unknown	2	1 y and 1 mo	3	No	1 d	Yes	June 5, 2023
12	82	Female	No	Insomnia	Hypnotics (details unknown)	Insomnia, dementia	2	1 y and 4 mo	3	No	0 d	Yes	June 9, 2023
13	47	Male	Yes	No	Multiple medications, Chinese herbal medications (details unknown)	COVID-19 vaccine sequelae	multiple	1 y	4	No	0 d	Yes	June 19, 2023
14	49	Female	Yes	No	Prednisolone, polaprezinc	Chronic fatigue syndrome	multiple	1 y and 9 mo	2	No	0 d	Yes	June 23, 2023
15	47	Male	Yes	No	Sulpiride, polaprezinc, ivermectin (once a week)	Chronic fatigue syndrome, parasympathetic paralysis	multiple	1 y and 5 mo	3	Yes	3 d	Yes	June 23, 2023
16	50	Male	No	No	No	Sinusitis, migraines	7	1 y and 5 mo	3	No	14 d	Yes	July 14, 2023
17	49	Male	No	Depression	No	Unknown	6	1 y and 3 mo	3	No	0 d	No	July 24, 2023
18	28	Male	Yes	No	Prednisolone, polaprezinc	Chronic fatigue syndrome, encephalitis	multiple	1 y and 8 mo	2	No	1 d	Yes	August 1, 2023
19	19	Female	No	No	Loxoprofen sodium hydrate, lemborexant	Unknown	3	1 y and 3 mo	3	No	0 d	No	September 11, 2023
20	34	Female	No	Graves disease	Levothyroxine sodium hydrate	Unknown	4	1 y and 6 mo	3	No	5 mo	Yes	September 15, 2023

(*continued on next page*)

Table 1 (*Continued*)

Patient No.*	Age	Sex	Letter of Referral	Medical history	Medications	Diagnosis before initial visit	No. of visited health care facilities	Period between onset of symptoms and initial visit	No. of COVID-19 vaccinations	History of COVID-19 infection	Period between COVID-19 vaccination and onset of symptoms	Family members' acknowledgment of patient's illness	Initial visit date
21	14	Male	No	No	Chinese herbal medications (details unknown), multiple supplements	Postural orthostatic tachycardia syndrome, orthostatic dysregulation, chronic fatigue syndrome	multiple	2 y	5	No	1 d	Yes	October 16, 2023
22	86	Female	No	Bronchiectasis, stomach cancer, gallbladder cancer	Clonazepam, bromazepam, arotinolol hydrochloride, mecobalamin, *Daikenchuto, Daiokanzoto*, camostat mesilate, *Bifidobacterium* products	Drug allergy	2	5 mo	6	No	0 d	Yes	October 23, 2023
23	69	Male	No	Hypertension	Antihypertensives, antidepressants (details unknown)	Depression	3	10 mo	5	Yes	14 d	Yes	October 23, 2023
24	37	Female	No	No	Multiple Chinese herbal medications, psychoactive medications, various supplements, multiple hypnotics	COVID-19 sequelae	multiple	1 y and 1 mo	3	Yes	0 d	No	October 27, 2023
25	64	Female	No	No	No	Unknown	4	1 y and 9 mo	3	No	0 d	No	November 6, 2023
26	71	Female	No	Lumbar spinal stenosis, reflux esophagitis	No	Right shoulder arthritis, asthma	3	6 mo	6	No	0 d	Yes	December 8, 2023
27	80	Female	No	Hepatitis B, liver cancer, arrhythmia, generalized anxiety disorder, emphysema	Valsartan, rivaroxaban, ursodeoxycholic acid, eszopiclone, lorazepam, *Bifidobacterium* products	COVID-19 sequelae	3	1 y and 9 mo	3	Yes	0 d	Yes	November 28, 2023
28	46	Female	Yes	No	*Hochuekkito*, polaprezinc	COVID-19 vaccine sequelae	6	1 y and 1 mo	1	Yes	0 d	Yes	July 24, 2023

*Patients are numbered in order of date of first visit (with some exceptions).

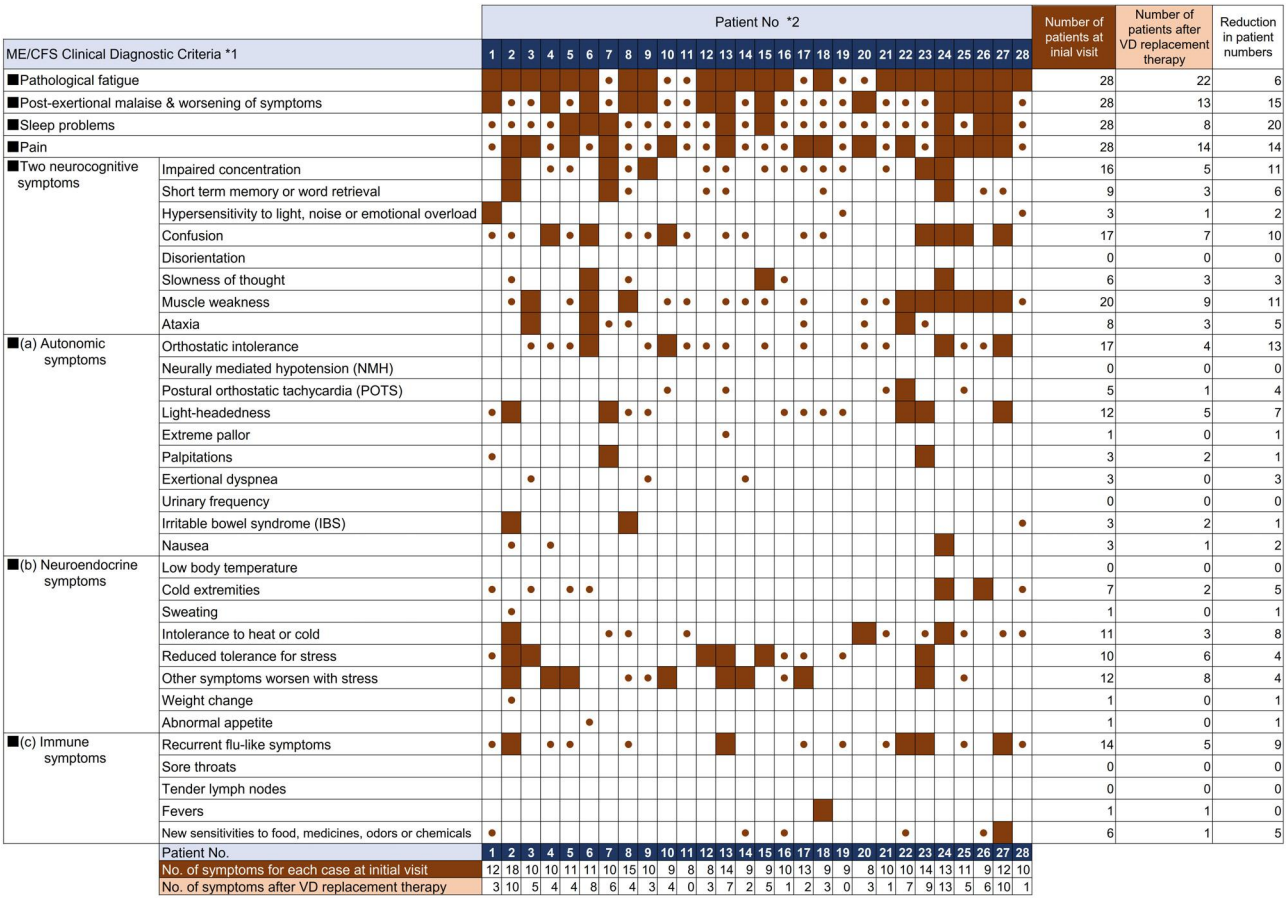


Fig. 1. Symptoms observed at initial visit and after vitamin D replacement therapy. Both ■ and ● represent symptoms observed at initial visit. Among the symptoms, ● represents symptoms which disappeared at the end of the observation period. *1 Referred from ME/CFS Clinical Diagnostic Criteria Worksheet in ME/CFS: A Primer for Clinical Practitioners [17]. *2 Patients numbered sequentially based on initial visit date (with some exceptions).

of observation, 23 of the 28 patients (82%) no longer met the diagnostic criteria for ME/CFS. The most notable improvements were in sleep problems and autonomic symptoms of neurocognitive symptoms (71% and 68% improvement, respectively). Pathologic fatigue, an essential symptom of the ME/CFS diagnostic criteria, was less likely to improve with vitamin D supplementation. No instances of vitamin D toxicity occurred.

Serum vitamin D level at initial visit

Blood tests done before presenting to the hospital showed that 27 of the 28 patients had insufficient or deficient blood levels of vitamin D (25(OH) vitamin D) (Table 3) . The remaining patient was in a satisfactory condition. There were no common abnormalities in other blood test parameters (Supplementary Table 1).

Vitamin D was measured as 25(OH) vitamin D in serum. A 25 (OH) vitamin D concentration of 30 ng/mL or more was considered a sufficient condition, a concentration equal to or greater than 20 ng/mL and less than 30 ng/mL was considered an insufficient condition, and a concentration of less than 20 ng/mL was considered a deficient condition [24].

Changes in serum 25(OH) vitamin D levels and number of symptoms after vitamin D replacement therapy

At each time point category after the initiation of vitamin D replacement therapy, there was a statistically significant increase

Table 2
Number of patients per ME/CFS diagnostic criteria (at initial visit vs. after vitamin D replacement therapy) and symptom resolution rate

ME/CFS clinical diagnostic criteria	Number of patients at initial visit	Number of patients after VD therapy	Change in number	Symptom resolution rate
Pathological fatigue	28	22	6	21%
Postexertional malaise and worsening of symptoms	28	13	15	54%
Sleep problems	28	8	20	71%
Pain	28	14	14	50%
Two neurocognitive symptoms	28	16	12	43%
(a) Autonomic symptoms	28	9	19	68%
(b) Neuroendocrine symptoms	26	14	12	46%
(c) Immune symptoms	18	6	12	67%

Table 3
Initial laboratory values before vitamin D replacement therapy

Patient No.	Laboratory test items					
	25 hydroxyvitamin D (ECLIA) (ng/mL)		estimated GFR (eGFR)		Complete blood count: erythrocyte mean corpuscular hemoglobin (MCH) (pg)	
1	14	↓	80		30	
2	10	↓	101		31	
3	12	↓	171		30	
4	12	↓	108		33	
5	12	↓	65		28	
6	20	↓	127		31	
7	19	↓	81		33	
8	*		*		*	
9	11	↓	60		31	
10	16	↓	103		31	
11	13	↓	110		30	
12	20	↓	57	↓	32	
13	21	↓	97		31	
14	11	↓	78		31	
15	15	↓	71		30	
16	26	↓	81		30	
17	23	↓	72		31	
18	14	↓	112		31	
19	15	↓	106		27	
20	11	↓	64		26	↓
21	26	↓	n/a		29	
22	19	↓	79		31	
23	21	↓	67		29	
24	14	↓	86		31	
25	16	↓	78		29	
26	15	↓	101		30	
27	20	↓	77		30	
28	16	↓	76		31	

↑ represents over the reference value and ↓ represents below the reference value
*Data for patient no. 8 is missing.

in serum 25(OH) vitamin D from the baseline: an increase of 11 ng/mL for the day 1 to 120 days category and an increase of 13 ng/mL for the 121 days and beyond category from the start of vitamin D supplementation (Fig. 2). Moreover, the change in the number of ME/CFS symptoms was a 2.9 decrease for the day 1 to 60 days category, 4.8 decrease for the 61 to 120 days category, 5.5 decrease for the 121 to 180 days category, and 7.0 decrease for the 181 days and beyond category, all of which were statistically significant decreases (Fig. 3).

Variables affecting time to ME/CFS number of symptoms less than 8

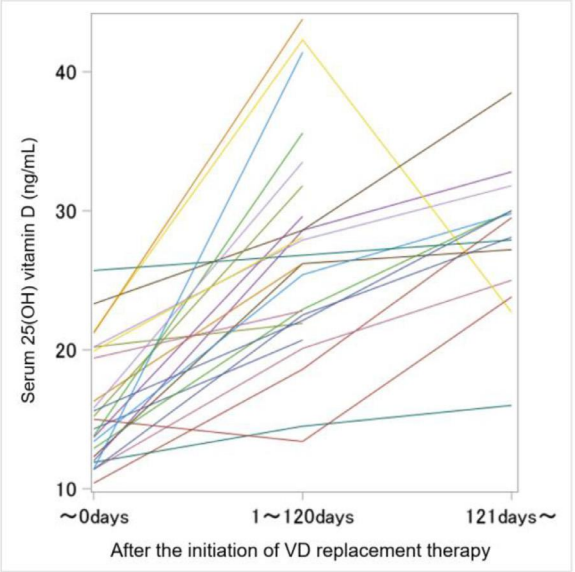
In an attempt to identify factors associated with a change in the number of ME/CFS symptoms in an exploratory manner, a multivariable Cox regression analysis for time to symptoms <8 identified the number of baseline serum 25(OH) vitamin D levels (hazard ratio per 1 ng/mL increase, 1.20; 95% CI, 1.02 to 1.40) as factors favoring improvement in symptoms and the number of baseline symptoms (hazard ratio per symptom, 0.57; 95% CI, 0.39−0.83), presence or absence of past medical history (hazard ratio for present vs. absent, 0.24; 95% CI, 0.07−0.77), eGFR (hazard ratio per 1 unit increase, 0.98; 95% CI, 0.96−1.00), and MCH (hazard ratio per 1 pg increase, 0.58; 95% CI, 0.39−0.87) as factors inhibiting improvement in symptoms (Table 4).

Discussion

This article provides a quantitative analysis of how vitamin D replacement therapy in patients with ME/CFS that developed after COVID-19 vaccination results in a reduction of symptoms listed as diagnostic criteria for ME/CFS and leads to a significant proportion of patients no longer meeting the full diagnostic criteria for ME/CFS. ME/CFS has been reported to be potentially triggered by chronic viral infections or immune disorders [25]. Interestingly, prolonged sequelae after COVID-19 infection, known as Long COVID or PASC, are estimated to meet the criteria for ME/CFS in about half of patients with PASC [5]. Also, a systemic review comparing the clinical findings and symptoms of Long COVID and ME/CFS suggests many similarities in their clinical manifestations and pathogenesis [26].

There has been much speculation about the etiology of PASC, including recent speculation that the spike protein of SARS-CoV-2 may be associated with the immune system, causing neuroinflammation [27], and that the spike protein contains an extended amino acid sequence characteristic of prion-like proteins, which may lead to neurodegenerative disorders [28]. Other reports indicated that the spike protein caused vascular endothelial disorder [29] and that vascular endothelial disorder was associated with reduced erythrocyte deformability [30].

Reduced erythrocyte deformability has also been reported in patients with ME/CFS [31], suggesting that the spike protein may also affect erythrocyte deformability. It has been proposed that the reduced deformability of erythrocytes is determined by geometric factors (surface area / volume ratio, morphological change), the internal viscosity of erythrocytes, and the viscoelasticity of their membranes [32]. Interestingly, our study revealed a significant association between higher mean corpuscular hemoglobin (MCH) levels and slower improvement in ME/CFS symptoms following vitamin D replacement therapy. Furthermore, it has been reported that increases in MCH and mean corpuscular hemoglobin concentration (MCHC), which are



	N=25	mean ± SD	Change from baseline	95%CI	P-value*
~0 days	25	16 ± 4		N/A	
1~120days	25	27 ± 8	11	8 , 14	<0.001
121days~	14	28 ± 5	13	9 , 17	<0.001

Fig. 2. Longitudinal change in serum 25(OH) vitamin D and MMRM estimates for change from baseline. CI, confidence interval. *The null hypothesis is change from baseline = 0.

associated with a decrease in erythrocyte deformability, have been identified as variables with a high discriminative diagnostic ability for ME/CFS [33]. Although the factors affecting increases in MCH and MCHC have not been examined in detail, it is possible that the effects of the spike protein on erythrocytes are responsible for the development of ME/CFS. Taken together, the symptoms of ME/CFS after COVID-19 vaccination and post-COVID-19 can be considered a Spikeopathy manifestation [9].

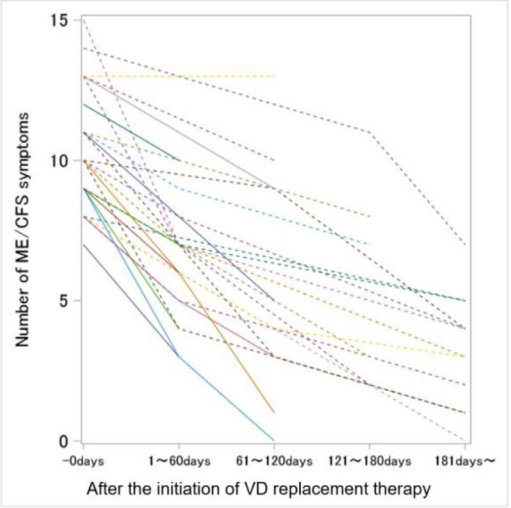
Given these findings, we believe that ME/CFS after COVID-19 vaccination and PASC may be caused by similar mechanisms and that vitamin D may have an effect on PASC, as it did on ME/CFS after COVID-19 vaccination in our study. Despite the highly debilitating neuropsychiatric symptoms identified in PASC, vitamin D, with its favorable properties in neurologic, psychiatric, cardiac, and immune domains, has been shown to potentially provide a pathophysiological defense against PASC [34]. In addition, there is a report that COVID-19 infection causes systemic inflammation, which leads to a decrease in 25(OH) vitamin D [35]. There is also a report that after COVID-19 infection, vitamin D receptor expression in blood cells decreases, leading to reduced vitamin D activity, which normally suppresses the release of cytokines and chemokines, consequently resulting in increased production of inflammatory cytokines [36]. The process of decrease in vitamin D needs to be examined in more detail in the future. It is important for each person to determine their baseline vitamin D level during times of health.

Furthermore, daily supplementation with 600 IU of vitamin D3 has been reported to reduce adverse effects of COVID-19 vaccination [37], suggesting a possible link between vitamin D deficiency and the development of PASC and adverse effects following COVID-19 vaccination. While vitamin D supplementation was used as treatment in this study, future research may help clarify whether prophylactic vitamin D supplementation could help reduce symptoms associated with COVID-19 infection and vaccination side effects.

The optimal dosing regimen for vitamin D supplementation remains a subject of discussion in the field. While high-dose bolus vitamin D administration has been reported to rapidly increase vitamin D levels and decrease inflammatory cytokines [38], this approach is not currently approved for clinical use in Japan. Future studies may help determine the potential role of different dosing strategies in vitamin D supplementation.

In this study, there were fewer patients with a history of COVID-19 infection, but there was no difference in the degree of vitamin D insufficiency or deficiency at presentation and in the effectiveness of vitamin D replacement therapy between post-COVID-19 infection and post-COVID-19 vaccination patients.

COVID-19 vaccine toxicity has also been reported to cause neurodegenerative disorders [28], and COVID-19 vaccination can cause widespread neurologic damage and neurologic symptoms. In fact, in this retrospective study, patients with ME/CFS had many neurologic symptoms. Regarding the relationship between neurological symptoms and vitamins, there are reports that ultra-high-dose methylcobalamin has been effective in amyotrophic lateral sclerosis (ALS) [39] and that vitamin D and vitamin B12 have been



	N=28	mean ± SD	Change from baseline	95%CI	P-value*
~0 days	28	10.3 ± 2.1		N/A	
1～60days	20	6.7 ± 2.3	-2.9	-3.9 , -1.9	<0.001
61～120days	12	5.5 ± 3.9	-4.8	-6.0 , -3.7	<0.001
121～180days	5	6.2 ± 3.7	-5.5	-7.1 , -3.9	<0.001
181days～	12	3.3 ± 2.0	-7.0	-8.2 , -5.8	<0.001

Fig. 3. Longitudinal change in the number of ME/CFS symptoms and MMRM estimates for change from baseline. CI, confidence interval. *The null hypothesis is change from baseline = 0, dashed line indicates a missing value at the intermediate time point.

effective to some extent in patients with COVID-19 vaccine sequelae [40]. The effects of vitamins related to the pathogenesis of ME/CFS require further comprehensive investigation.

We have shown that vitamin D replacement therapy is effective in patients with ME/CFS throughout the course of our treatment. This finding aligns with reports that vitamin D replacement therapy is also effective in preventing severe disease in COVID-19 infection [41], suggesting that vitamin D plays an important role in immune and neurologic function in the body. Despite this growing recognition of the importance of vitamin D, it is estimated that more than 1 billion people worldwide are deficient or insufficient in vitamin D [42], and about 75% of adults worldwide have serum 25(OH)D levels <30 ng/mL [43].

The prevalence of vitamin D deficiency is further highlighted by recent studies. During the COVID-19 pandemic, a study in a single institution in Japan found that more than 90% of healthcare workers had blood vitamin D levels below normal [44], and another study in Tokyo between April 2019 and March 2020 found that vitamin D blood levels were measured in 5,518 participants who had health examinations, and surprisingly, vitamin D insufficiency or deficiency was found in 5,396 of them (98% of the total) [45]. This finding suggests that vitamin D deficiency may have been at the root of the spread, onset, severity, and persistence of symptoms during the COVID-19 pandemic. Given these findings, the nutritional status of modern humans may require further investigation.

Many cases of ME/CFS have been difficult to diagnose due to the absence of abnormalities in blood tests or imaging studies, which has limited the search for causes and development of treatments [18]. However, the recent discovery of increased levels of specific B-cell receptors in patients with ME/CFS has led to the application of B-cell receptor repertoire analysis as a potential biomarker for ME/CFS [46]. It has also been reported that diffusion tensor imaging parameters, used to study microstructural changes in neurodegenerative disorders, are sensitive to ME/CFS microstructural changes (particularly in the brain stem) and may serve as imaging biomarkers of the abnormal pathophysiology of ME/CFS [47].

In our study, we measured serum 25(OH) vitamin D levels in patients with ME/CFS and found a significantly high prevalence of vitamin D insufficiency or deficiency. Improvement in these levels through vitamin D replacement therapy was associated with significant improvement in ME/CFS symptoms. Based on this result, vitamin D levels may serve as another possible biomarker for ME/CFS.

Overall, the results of our retrospective study show that a future challenge is to understand the underlying pathological mechanisms that may contribute to the development of ME/CFS symptoms and their relationship to vitamin D. As a first step, these findings warrant a pivotal randomized controlled trial to prove the

Table 4
Multivariable Cox regression analysis for time to number of symptoms <8 (*N* = 26)

Factor		Hazard ratio	95% CI	*P* value
Number of baseline symptoms	Per symptom	0.57	0.39–0.83	0.003
Medical history	Yes	0.24	0.07–0.77	0.02
25(OH) vitamin D	Per 1 ng/mL	1.20	1.02–1.40	0.03
eGFR	Per unit	0.98	0.96–1.00	0.03
MCH (mean corpuscular Hb)	per 1 pg	0.58	0.39–0.87	0.009

effectiveness of vitamin D replacement therapy in ME/CFS patients with vitamin D insufficiency or deficiency.

Conclusions

In a single-center, real-world clinical environment, we observed that vitamin D replacement therapy for ME/CFS cases that developed after COVID-19 vaccination reduced ME/CFS symptoms as vitamin D insufficiency or deficiency status improved. Notably, 82% of patients no longer met the diagnostic criteria for ME/CFS after treatment. Based on these promising results, we recommend that patients who report feeling unwell after receiving a COVID-19 vaccine should have their serum 25(OH) vitamin D levels measured and be given vitamin D replacement therapy if found to be insufficient or deficient. To further validate these findings, a protocol for a randomized controlled study to investigate the effectiveness of vitamin D replacement therapy in patients with PASC or ME/CFS developed after COVID-19 vaccination has recently been submitted to the Ethics Committee of Hamamatsu University School of Medicine.

Declaration of competing interest

The authors have no conflicts of interest directly relevant to the content of this article. All authors have read and agreed to the published version of the manuscript.

CRediT authorship contribution statement

Shinichiro Kodama: Writing – original draft, Methodology, Conceptualization. **Nafuko Konishi:** Writing – review & editing, Writing – original draft, Investigation. **Yuriko Hirai:** Visualization, Data curation. **Akinori Fujisawa:** Methodology. **Mitsuko Nakata:** Writing – original draft, Visualization, Formal analysis. **Satoshi Teramukai:** Validation, Supervision, Formal analysis. **Masanori Fukushima:** Validation, Supervision, Project administration.

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Data availability

The authors have made efforts to share data while maintaining patient privacy and adhering to ethical guidelines. A subset of the data that supports the findings of this study is available in the Supplementary Materials accompanying this article. This includes laboratory test values (blood) before vitamin D replacement therapy.

Ethics statement

This study was approved by the Ethics Committee of Hamamatsu University School of Medicine (Study No. 24-075).

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During the preparation of this work, the authors used a generative AI, Claude, in order to improve the readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2025.112718.

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