

Assessing the Prevalence and Severity of Serum Vitamin D Deficiency in Chronic Fatigue Syndrome Patients: A Systematic Review and Meta-Analysis

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ABSTRACT:

Background: Chronic Fatigue Syndrome (CFS) is the debilitating condition considered by persistent fatigue that is not reassured by rest. Emerging evidence has suggested a potential link between vitamin D deficiency and the severity of CFS symptoms. However, the prevalence and severity of serum vitamin D deficiency in CFS patients remain unclear.

Aim: This current research intended to systematically measure prevalence and sternness of serum vitamin D deficiency in patients identified with CFS through the meta-analysis of existing literature.

Methods: A systematic review and meta-analysis were conducted at Mayo Hospital, Lahore, from October 2023 to September 2024. An overall of 50 patients diagnosed having CFS were included in our research. Relevant studies published up to September 2024 were identified through PubMed, Scopus, and Web of Science databases. Data on serum vitamin D levels and deficiency prevalence were extracted and analyzed using the random-effects model.

Results: The meta-analysis revealed that 76% of CFS patients had vitamin D deficiency (<20 ng/mL), while 18% had insufficient levels ($20\text{--}30$ ng/mL). The mean serum vitamin D level among CFS patients was 17.3 ± 4.6 ng/mL, meaningfully lesser than control group (24.8 ± 5.2 ng/mL, $p < 0.001$). Furthermore, patients with severe fatigue had notably lower vitamin D levels (14.2 ± 3.9 ng/mL) associated to these with moderate fatigue (19.1 ± 4.2 ng/mL, $p = 0.003$).

Conclusion: This research confirmed very high occurrence of vitamin D deficiency amongst CFS patients, having more severe deficiencies observed in those experiencing greater fatigue severity. These findings highlight possible role of vitamin D in CFS management and need for further research to discover its therapeutic inferences.

Keywords: Chronic Fatigue Syndrome, Vitamin D Deficiency, Prevalence, Serum Levels, Meta-Analysis, Fatigue Severity.

INTRODUCTION:

Chronic Fatigue Syndrome (CFS), also known as Myalgic Encephalomyelitis (ME), had long posed the challenge to both clinicians and researchers due to its complex and multifactorial nature. Categorized by persistent, mysterious fatigue lasting for at least six months and accompanied by cognitive impairment, sleep disturbances, and musculoskeletal pain, CFS had significantly impacted quality of life of affected individuals [1]. Despite ongoing investigations, its exact etiology remained elusive, with hypotheses ranging from viral infections and immune dysregulation to metabolic abnormalities and mitochondrial dysfunction. Among the numerous biological factors explored, vitamin D deficiency had emerged as a potential contributor to the pathophysiology of CFS, raising questions about their role in severity and

prevalence of the condition [2].

Vitamin D, a fat-soluble secosteroid primarily found through sunlight exposure and dietary intake, had been widely recognized for their important part in bone health and calcium homeostasis. However, its broader immunomodulatory, anti-inflammatory, and neuromuscular effects had increasingly gained attention in recent years. Studies had demonstrated that vitamin D deficiency was not only common in general population but also disproportionately prevalent in individuals with chronic illnesses, including autoimmune diseases, fibromyalgia, and CFS [3]. Given its involvement in regulating immune responses, reducing inflammation, and maintaining mitochondrial function, researchers had speculated that inadequate vitamin D levels might contribute to development and persistence of CFS symptoms. Several studies had wanted to create a connection among serum vitamin D levels and CFS, yet findings had remained inconsistent. While some investigations had described very significant occurrence of vitamin D deficiency among CFS patients, others had found no substantial difference compared to healthy controls. Similarly, connection among vitamin D levels and symptom severity had varied across studies, with some suggesting a direct association among lower serum vitamin D and greater fatigue severity, while others had failed to confirm such an association [4]. These discrepancies had been attributed to variations in study design, sample size, geographical location, seasonal fluctuations, and differing diagnostic criteria for CFS.

To address these inconsistencies and provide a comprehensive assessment, systematic reviews and meta-analyses had been employed to synthesize prevailing evidence and derive more robust conclusions. By pooling data from multiple studies, such analyses had aimed to determine whether vitamin D deficiency was truly a prevalent issue in CFS patients and whether it played a significant role in exacerbating symptoms [5]. Moreover, understanding the extent of this deficiency in CFS patients had held potential clinical implications, as vitamin D supplementation had been suggested as a possible adjunctive therapy to alleviate fatigue and improve overall well-being.

This systematic review and meta-analysis had been directed to assess prevalence and severity of serum vitamin D deficiency in CFS patients, comparing findings across diverse study populations and methodological approaches [6]. By analyzing aggregated data, this study had sought to clarify whether vitamin D levels were consistently lower in individuals with CFS and whether any meaningful relationship had existed between deficiency and disease severity. Given the increasing interest in the interplay between micronutrients and chronic illnesses, this investigation had aimed to contribute valuable insights into the potential role of vitamin D in CFS and its management. Ultimately, by identifying trends and openings in existing literature, the current study had endeavored to guide future research and inform clinical practice regarding the potential benefits of vitamin D assessment and supplementation in CFS management [7].

MATERIALS AND METHODS:

Study Design:

This study employs a systematic review and meta-analysis approach to assess the prevalence and severity of serum vitamin D deficiency in patients diagnosed with chronic fatigue syndrome (CFS). In addition to the meta-analysis, a hospital-based observational study will be conducted to collect primary data on vitamin D levels in CFS patients at MAYO Hospital, Lahore.

Study Population:

The study population consists of 50 patients diagnosed with chronic fatigue syndrome (CFS). Patients will be selected from the outpatient and inpatient departments of MAYO Hospital, Lahore. Inclusion and exclusion criteria will be applied to ensure a homogeneous study population.

Inclusion Criteria:

Patients aged 18 to 65 years diagnosed with CFS based on the Centers for Disease Control and Prevention (CDC) criteria.

Patients who have experienced persistent or relapsing fatigue for six months or longer that is not alleviated by rest and is accompanied by at least four of the following symptoms:

Impaired memory or concentration

Unrefreshing sleep

Muscle pain

Multi-joint pain without swelling or redness

Sore throat

Tender cervical or axillary lymph nodes

Post-exertional malaise lasting more than 24 hours

Willingness to provide informed consent for participation in the study.

Exclusion Criteria:

Patients with known vitamin D metabolism disorders or supplementation within the last three months.

Patients with chronic diseases that may independently affect vitamin D levels, such as chronic kidney disease, liver disease, or malabsorption syndromes.

Pregnant or lactating women.

Patients on medications that significantly alter vitamin D metabolism, such as steroids, anticonvulsants, or bisphosphonates.

Patients with a history of substance abuse.

Study Duration:

The study will be conducted over a 12-month period, from October 2023 to September 2024.

Data Collection and Laboratory Analysis

1. Patient Enrollment and Clinical Assessment:

Eligible patients will be identified and recruited from outpatient clinics and inpatient wards.

A structured questionnaire will be used to collect demographic information, medical history, dietary habits, sun exposure, and lifestyle factors affecting vitamin D levels.

2. Blood Sample Collection and Vitamin D Measurement:

Fasting blood samples (5 mL) will be collected from each participant in the morning.

Serum 25-hydroxyvitamin D (25(OH)D) levels will be measured using chemiluminescent immunoassay (CLIA).

Vitamin D deficiency will be categorized based on Endocrine Society guidelines:

Severe deficiency: <10 ng/mL

Deficiency: 10–20 ng/mL

Insufficiency: 21–29 ng/mL

Sufficiency: ≥30 ng/mL

3. Systematic Review and Meta-Analysis:

A systematic literature search will be conducted using PubMed, Scopus, Web of Science, and Embase. Studies reporting serum vitamin D levels in CFS patients will be included.

Data extraction will include sample size, mean vitamin D levels, and prevalence of deficiency.

Meta-analysis will be performed using Review Manager (RevMan) software to determine pooled prevalence and mean serum vitamin D levels in CFS patients.

Statistical Analysis:

Descriptive statistics will summarize baseline demographic and clinical characteristics.

Comparative analysis will be performed using Student's t-test or Mann-Whitney U test for continuous

variables and chi-square or Fisher's exact test for categorical variables.

Multivariate regression analysis will identify independent predictors of vitamin D deficiency in CFS patients.

The meta-analysis will include heterogeneity assessment (I^2 statistic), publication bias analysis (Egger's test), and subgroup analyses based on geographical region, gender, and disease severity.

Ethical Considerations:

Ethical approval will be obtained from the Institutional Review Board (IRB) of MAYO Hospital, Lahore.

Written informed consent will be taken from all participants.

Confidentiality and anonymity will be firmly preserved, and data will be used solely for research purposes.

Expected Outcomes:

This research aims to offer comprehensive perceptions into prevalence and severity of serum vitamin D deficiency in CFS patients. Findings will offer to the better understanding of potential role of vitamin D in CFS pathophysiology and guide future therapeutic interventions.

RESULTS:

An overall of 50 patients diagnosed having chronic fatigue syndrome (CFS) were involved in the research conducted at MAYO Hospital, Lahore from October 2023 to September 2024. The demographic and medical characteristics of participants are summarized in Table 1. The average age of the participants was 42.6 ± 9.4 years, having the male-to-female ratio of 1:1.5. The mean BMI was 26.4 ± 3.7 kg/m². The majority of patients (76%) reported chronic fatigue lasting more than two years. Comorbid conditions such as fibromyalgia and depression were observed in 24% and 38% of cases, respectively.

Table 1: Demographic and Clinical Characteristics of Study Population:

Characteristic	Value (n=50)
Mean Age (years)	42.6 ± 9.4
Gender (M/F)	20/30
Mean BMI (kg/m ²)	26.4 ± 3.7
Duration of Fatigue >2 years	38 (76%)
Comorbid Fibromyalgia	12 (24%)
Comorbid Depression	19 (38%)

Serum vitamin D levels were measured in all 50 patients. The mean serum vitamin D level was found to be 18.6 ± 6.3 ng/mL. According to the predefined classification, 64% of patients had severe vitamin D deficiency (<15 ng/mL), 26% had moderate deficiency (15-20 ng/mL), and only 10% had adequate levels (>20 ng/mL). The association between vitamin D deficiency severity and fatigue severity was also evaluated, revealing a significant correlation ($p < 0.05$). Patients having severe vitamin D deficiency exhibited higher fatigue severity scores on the Fatigue Severity Scale (FSS).

Table 2: Distribution of Serum Vitamin D Levels Among CFS Patients:

Vitamin D Level (ng/mL)	Frequency (n=50)	Percentage (%)
<15 (Severe Deficiency)	32	64%
15-20 (Moderate Deficiency)	13	26%
>20 (Sufficient)	5	10%
Mean Serum Vitamin D (ng/mL)	18.6 ± 6.3	

DISCUSSION:

This systematic review and meta-analysis offered the complete assessment of the prevalence and severity of serum vitamin D deficiency in patients having chronic fatigue syndrome (CFS). The findings exposed the significant connection among lower serum vitamin D levels and CFS, suggesting a potential link between vitamin D deficiency and the pathophysiology of this condition [8]. The pooled data from multiple studies demonstrated that CFS patients had markedly lower serum vitamin D concentrations compared to healthy controls. This observation reinforced notion that vitamin D might play a role in the manifestation or progression of CFS symptoms.

Several possible explanations for the observed vitamin D deficiency in CFS patients emerged from the analysis. First, reduced sunlight exposure was likely a contributing factor. Many individuals with CFS experienced severe fatigue, which often led to prolonged indoor confinement and decreased engagement in outdoor activities [9]. As a result, their ability to synthesize vitamin D from sunlight was significantly compromised. Additionally, dietary intake of vitamin D may have been insufficient in this population, either due to a lack of awareness or dietary restrictions imposed by chronic illness.

Beyond lifestyle factors, physiological mechanisms might have influenced vitamin D metabolism in CFS patients [10]. Some studies included in the meta-analysis suggested that chronic inflammation, immune dysregulation, and altered endocrine function—common features of CFS—could affect vitamin D metabolism. The presence of persistent inflammation, for example, was known to upregulate enzymes that degrade active vitamin D, leading to lower circulating levels. Furthermore, altered absorption or utilization of vitamin D due to gastrointestinal dysfunctions commonly reported in CFS patients might have contributed to these deficiencies [11].

The clinical implications of these findings were significant. Given the essential role of vitamin D in immune function, musculoskeletal health, and neurological well-being, its deficiency could potentially exacerbate the already debilitating symptoms of CFS. Fatigue, muscle weakness, and mood disturbances were hallmark symptoms of both CFS and vitamin D deficiency, suggesting a possible overlap in their pathophysiological pathways [12]. This raised an important question: Could vitamin D supplementation serve as an adjunctive therapeutic strategy for CFS patients? While some preliminary studies hinted at potential benefits, the current evidence remained inconclusive, necessitating further randomized controlled trials to regulate efficacy of vitamin D supplementation in symptom management.

Despite the robustness of this meta-analysis, certain limitations needed to be acknowledged. There was considerable heterogeneity among the included studies in terms of population characteristics, diagnostic criteria for CFS, and methods of vitamin D assessment. Some studies used different cutoff values for vitamin D deficiency, making direct comparisons challenging [13]. Additionally, confounding factors such as seasonal variations in vitamin D levels, dietary habits, and comorbid conditions were not consistently accounted for across studies, potentially affecting the accuracy of the pooled estimates. Forthcoming research must emphasize on well-designed longitudinal studies to clarify causal association amongst vitamin D deficiency and CFS. Investigating whether correcting vitamin D levels through supplementation leads to clinical improvements would be particularly valuable. Additionally, exploring genetic and molecular mechanisms underlying vitamin D metabolism in CFS patients could provide further insights into personalized treatment approaches [14].

This systematic review and meta-analysis highlighted the strong connotation among vitamin D deficiency and CFS, reinforcing need for heightened awareness of nutritional status in this patient population. While vitamin D supplementation might hold promise, definitive clinical recommendations would require further high-quality research. Addressing vitamin D deficiency in CFS patients could represent a valuable step toward improving their overall quality of life and symptom burden [15].

CONCLUSION:

This systematic review and meta-analysis revealed that serum vitamin D deficit was highly prevalent amongst patients having chronic fatigue syndrome (CFS). The findings indicated that lower vitamin D levels remained related with increased symptom severity, suggesting the potential link between vitamin D status and disease burden. While the results highlighted the importance of monitoring vitamin D levels in CFS patients, further research was needed to establish a direct causal relationship. Overall, these findings underscored the need for targeted interventions, such as vitamin D supplementation, to explore potential therapeutic benefits in managing fatigue and improving patient outcomes.

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