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RESEARCH ARTICLE

The relationship between vitamin D supplementation and symptoms, sleep, depression, and fatigue in restless legs syndrome

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ABSTRACT

Background: Restless Legs Syndrome (RLS) is a neurological disorder primarily linked to dopaminergic dysfunction. Since vitamin D plays a role in modulating the dopaminergic system, this study aimed to evaluate the impact of vitamin D supplementation on symptom severity, sleep quality, depression, and fatigue in patients with idiopathic RLS and vitamin D deficiency.

Methods: This study retrospectively evaluated patients with idiopathic RLS and vitamin D deficiency who presented to our clinic between April 2022 and March 2023. Participants received weekly oral supplementation of 50,000 IU vitamin D and were assessed at baseline and at 3 months using the International Restless Legs Syndrome Study Group (IRLS) Symptom Scale, Fatigue Severity Scale (FSS), Beck Depression Inventory (BDI), and Pittsburgh Sleep Quality Index (PSQI).

Results: Twenty-five patients (10 females and 15 males) meeting the eligibility criteria were enrolled. Following vitamin D replacement, mean serum 25-hydroxyvitamin D [25(OH)D] levels increased significantly from 16.91 ± 8.09 ng/mL to 38.08 ± 9.58 ng/mL ($p< 0.001$). A statistically significant reduction was observed in IRLS symptom severity scores (15.36 ± 6.75 vs. 14.28 ± 6.22, $p = 0.019$). However, no statistically significant changes were found in FSS, PSQI, and BDI scores ($p = 0.058$, 0.242, and 0.846, respectively).

Conclusion: Vitamin D supplementation appears to reduce symptom severity in patients with idiopathic RLS and vitamin D deficiency; however, its impact on sleep quality, depression, and fatigue warrants further investigation. Large-scale, randomized controlled trials are necessary to confirm these preliminary findings and define the role of vitamin D in RLS management.

Keywords: depression, fatigue, restless legs syndrome, sleep quality, vitamin D

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INTRODUCTION

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a neurological disorder characterized by an urge to move the legs, typically accompanied by uncomfortable sensations (1). These sensations usually occur during rest, where movement is limited, especially in sitting or lying positions, and may worsen in the evening or night hours (2). Most patients report experiencing this discomfort deep within their limbs rather than superficially. Although symptoms typically present bilaterally, they can be asymmetrical or, less frequently, unilateral (3). In patients with RLS, the exacerbation of symptoms upon lying down and the subsequent urge to move the legs significantly impair sleep duration, daily quality of life, and occupational performance (3,4).

The prevalence of RLS in the general population ranges from 1% to 13%, with higher rates observed in women and older populations (5). The condition is classified into primary and secondary forms. Primary RLS is largely considered a genetic disorder, with a positive family history reported in 50% to 70% of cases (6). Conversely, secondary RLS is associated with underlying conditions such as iron deficiency, renal failure, anemia, diabetes mellitus, and pregnancy (7).

The underlying pathophysiological mechanism of RLS involves a decrease in striatal D2 receptor binding potential and circadian fluctuations in extracellular dopamine levels, which lead to sensorimotor disinhibition in susceptible individuals. Rather than a structural loss of dopaminergic neurons, this dysfunction represents a modulation error (2,5). Emerging research suggests that vitamin D plays a critical role in the central dopaminergic system, which is central to the pathophysiology of RLS. Specifically, vitamin D has been shown to exert regulatory effects on the nigrostriatal pathway, increasing dopamine levels and modulating dopaminergic transmission (8). While several studies have demonstrated that low serum vitamin D levels correlate with increased symptom severity and impaired sleep quality, the literature remains inconsistent. Some cross-sectional studies have reported that although RLS prevalence may be higher in vitamin D-deficient cohorts, symptom scores do not differ significantly from those with normal vitamin D levels (9-11).

Given these conflicting findings in the literature, further investigation into the therapeutic impact of vitamin D supplementation is required. Therefore, this study aimed to evaluate the effects of vitamin D replacement therapy on disease symptoms, sleep quality, depression, and fatigue in patients diagnosed with idiopathic RLS and vitamin D deficiency.

METHODS

Study design and population

This study was conducted following approval from the Düzce University Clinical Research Ethics Committee (Decision No: 2023/51). A retrospective review was performed on the medical records of patients who visited the Neurology Outpatient Clinic at Düzce University Hospital between April 2022 and March 2023.

In the movement disorders department of our clinic, vitamin D levels are routinely checked alongside other biochemical parameters. Additionally, patient follow-up routinely includes the assessment of IRLS symptom scale (3), Beck Depression Inventory (BDI) (12), Fatigue Severity Scale (FSS) (13), and Pittsburgh Sleep Quality Index (PSQI) (14) scores. In patients presenting with low vitamin D levels, these parameters are re-evaluated three months after initiating replacement therapy.

This study retrospectively included patients with baseline vitamin D deficiency who started 50,000 IU/week replacement therapy, completed a 3-month follow-up showing normalization of vitamin D levels, and underwent complete BDI, IRLS, FSS, and PSQI evaluations.

Inclusion criteria were: diagnosis of RLS according to the 2014 International Restless Legs Syndrome Study Group (IRLS) criteria (3), receiving a stable dose of RLS medication for at least three months, laboratory-confirmed vitamin D deficiency (serum 25(OH)D levels <30 ng/mL), age of 18 years or older, literacy, and provision of written informed consent.

Patients with renal failure, iron deficiency, liver dysfunction, osteoporosis, secondary RLS due to pregnancy, or polyneuropathy were excluded from the study.

Statistical analysis

Statistical analyses were performed using IBM SPSS version 21 software. The Shapiro-Wilk test was applied to evaluate the normality of data distribution. For normally distributed continuous variables, the Paired Sample T-test was used to compare consecutive measurements between dependent groups. For non-normally distributed data, the Wilcoxon signed-rank test was utilized. Statistical significance was defined as $p < 0.05$.

RESULTS

A total of 25 patients (10 females, 15 males) with a mean age of 45.96 ± 15.41 years were included in the study. Baseline serum 25(OH)D levels ranged from 3.48 ng/mL to 29.48 ng/mL, with a mean baseline concentration of 16.91 ± 8.09 ng/mL. Following three months of vitamin D replacement therapy, post-treatment levels ranged from 30.00 to 61.24 ng/mL, yielding a mean concentration of 38.08 ± 9.58 ng/mL (Figure 1).

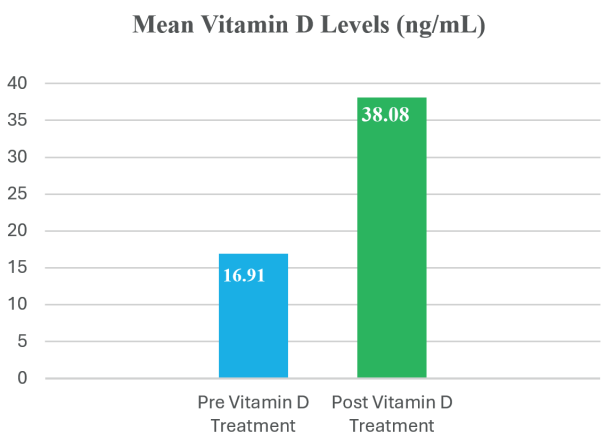

Figure 1. Vitamin D Levels before and after treatment.

RLS symptom severity

At baseline, the mean IRLS Severity Scale score was 15.36 ± 6.75. After three months of vitamin D replacement therapy, the mean IRLS score decreased to 14.28 ± 6.22. Post-replacement IRLS scores were statistically significantly lower than baseline values ($p = 0.019$). This suggests that vitamin D supplementation may reduce clinical symptoms in restless legs syndrome patients with concomitant vitamin D deficiency, although the reduction in symptom scores is modest.

Fatigue

The mean baseline FSS score was 19.32 ± 12.34. After three months of vitamin D replacement therapy, the mean FSS score was 18.24 ± 11.32. Comparing baseline and 3-month values, a slight numerical decrease in FSS scores was observed; however, this change did not reach statistical significance ($p = 0.058$).

Depression and sleep quality

The mean baseline BDI score was 6.80 ± 5.64. Following three months of vitamin D replacement, the mean BDI score was 6.84 ± 5.91, representing no statistically significant change ($p = 0.846$).

The mean baseline PSQI score was 11.76 ± 1.98. The mean post-treatment PSQI score was 11.52 ± 2.30, showing no statistically significant difference between baseline and 3-month follow-up values ($p = 0.242$). A comprehensive comparison of clinical scores (depression, symptom severity, sleep quality, and fatigue) at baseline and at three months is summarized in Table 1.

DISCUSSION

This study demonstrated that three months of vitamin D replacement therapy may have a symptom-reducing effect in patients with idiopathic restless legs syndrome (RLS) and concomitant vitamin D deficiency. However, no statistically significant improvements were observed in sleep quality, depression, or fatigue during the same period.

Table 1. Comparison of clinical assessment scores at baseline and post-treatment (3rd month)

Assessment Scale	Baseline (Mean ± SD)	3rd Month (Mean ± SD)	p-value
IRLS (Symptom Severity)	15.36 ± 6.75	14.28 ± 6.22	0.019*
FSS (Fatigue)	19.32 ± 12.34	18.24 ± 11.32	0.058
PSQI (Sleep Quality)	11.76 ± 1.98	11.52 ± 2.30	0.242
BDI (Depression)	6.80 ± 5.64	6.84 ± 5.91	0.846

*Statistically significant at $p < 0.05$. Abbreviations: BDI: Beck Depression Inventory; IRLS: International Restless Legs Syndrome Study Group Symptom Scale; PSQI: Pittsburgh Sleep Quality Index; FSS: Fatigue Severity Scale.

Although the exact pathophysiology of RLS remains partially understood, dopaminergic dysfunction is widely accepted as the primary mechanism. Vitamin D is known to exert neuroprotective effects on dopaminergic neurons in the nigrostriatal pathway and plays a vital role in modulating dopamine synthesis (8,15,16). The reduction in symptom severity observed in our cohort may be attributed to the supportive role of vitamin D in maintaining the functional integrity of the dopaminergic system.

In a study conducted by Atalar involving 152 patients, 25(OH)D levels were low in 89 patients and normal in 63 (9). RLS symptom scores were significantly higher in the vitamin D-deficient cohort. Similar to our findings, their study demonstrated that RLS severity is heightened in patients with 25(OH)D deficiency. Furthermore, Atalar reported significantly higher PSQI scores in patients with low 25(OH)D levels (9). In contrast, our study did not find a significant change in PSQI scores. In a study by Wali et al., which included 78 patients with primary RLS and 123 controls, vitamin D deficiency was detected in 75.6% (n = 59) of RLS patients compared to 42.3% (n = 52) of control subjects. The risk of developing RLS was significantly higher in individuals with vitamin D levels < 50 nmol/L (< 20 ng/mL) than in those with levels ≥ 50 nmol/L. RLS symptom severity was also greater in vitamin D-deficient patients than in those with normal levels (11). In a cross-sectional study of 102 cases by Cakir et al., the prevalence of RLS was significantly higher in patients with vitamin D deficiency; however, contrary to our findings, no significant differences in symptom severity scores were found when comparing RLS patients with low and normal vitamin D levels (17).

In a study by Liu et al., serum vitamin D levels in 57 patients with primary RLS were significantly lower than those of healthy controls. Additionally, a negative correlation was observed between serum vitamin D levels and IRLS scores, with symptom severity being significantly higher in patients with insufficient vitamin D levels (18). Similarly, a prospective study by Tutuncu and Tutuncu reported that vitamin D replacement led to significant improvements in both total IRLS scores and symptom severity sub-scores (19). Nevertheless, the literature contains conflicting findings. A randomized controlled trial by Wali et al. indicated no significant difference in RLS symptom severity between the group receiving vitamin D supplementation and the placebo cohort (10). These discrepancies suggest that clinical response to vitamin D replacement may depend on the baseline severity of the deficiency or specific patient cohort characteristics.

Regarding secondary outcomes, the lack of significant changes in sleep quality (PSQI) and depression (BDI) scores in our study contrasts with some existing reports. While Liu et al. suggested that low vitamin D levels correlate with poor sleep quality and depressive symptoms (18), our data did not show a statistically significant shift. This lack of change may be explained by the stable baseline treatment of our patients with pramipexole, which potentially masked the additional therapeutic benefits of vitamin D on sleep and mood. Additionally, psychological parameters and sleep architecture often require follow-up periods longer than three months to show measurable clinical recovery.

Although our study demonstrated a downward numerical trend in fatigue scores, this reduction did not achieve statistical significance. Future investigations

with larger sample sizes or extended intervention periods may demonstrate a significant impact of vitamin D replacement on fatigue, potentially offering a valuable adjunctive therapeutic avenue.

Despite the importance of our findings, several limitations must be acknowledged. First, the study was conducted with a relatively small sample size at a single center, which limits the generalizability of the results. Second, the retrospective design and the absence of a control group make it difficult to rule out placebo effects or external variables. Finally, the short follow-up duration prevents assessment of the long-term sustainability of the observed improvements. To confirm these findings and establish definitive causality, prospective, multicenter randomized controlled trials are warranted.

In conclusion, while our study indicates that vitamin D supplementation may improve restless legs syndrome symptoms, the small cohort and lack of a comparative control arm preclude broad clinical application. To validate these preliminary results and optimize therapeutic protocols, more robust, large-scale randomized controlled trials are necessary.

Ethical approval

This study has been approved by the Düzce University Clinical Research Ethics Committee (approval date 20/03/2023, number 2023/51). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: OZ, AY, HŞ; Concept: OZ, AY; Design: OZ, AY; Data Collection or Processing: OZ, AY, HŞ; Analysis or Interpretation: OZ, AY; Literature Search: OZ, AY; Writing: OZ, AY, HŞ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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