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Effect of Vitamin D Deficiency on Fatigue in Systemic Sclerosis: A Cross-sectional Study

Sistemik Sklerozda D Vitamini Eksikliğinin Yorgunluk Üzerindeki Etkisi: Kesitsel Bir Çalışma

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Abstract

Objective: The purpose of this study was to explore the relationship between vitamin D deficiency (VDD) and fatigue severity, as well as its relationship with sleep quality, in subjects with systemic sclerosis (SSc).

Method: Our cross-sectional research included 98 subjects who were diagnosed with SSc according to EULAR/ACR 2013 classification criteria. Demographic, clinical, and laboratory data, including vitamin D (VitD) levels, were collected. Sleep quality was investigated with the Pittsburgh sleep quality index (PSQI) and fatigue severity with the multidimensional assessment of fatigue (MAF) scale.

Results: Subjects with VDD exhibited significantly poorer sleep quality as indicated by PSQI scores (12 vs. 8; p<0.001) and higher MAF scores (34.5 vs. 22.4; p<0.001). Multivariate analysis identified MAF score [odds ratio (OR): 1.204, 95% confidence interval (CI): 1.116-1.298, p<0.001] and disease symptom duration (OR: 1.009, 95% CI: 1.002-1.016, p=0.001) as independent predictors of VDD. ROC analysis demonstrated that an MAF score ≤27.7 and PSQI score ≤10.5 were optimal cut-off values for predicting VDD. Significant negative correlations were observed between VitD levels and MAF (r=-0.610, p<0.01) and PSQI (r=-0.346, p<0.01).

Conclusion: VDD is significantly associated with increased fatigue and poorer sleep quality in subjects with SSc. These signs indicate that addressing VDD through routine screening and supplementation may alleviate fatigue, enhance sleep quality, and raise the quality of life in SSc subjects.

Keywords: Multidimensional fatigue assessment (MAF) scale, Pittsburgh sleep quality index (PSQI), systemic sclerosis, vitamin D

Öz

Amaç: Bu çalışmanın amacı, sistemik skleroz (SSc) hastalarında D vitamini eksikliği ile yorgunluk şiddeti arasındaki ilişkinin yanı sıra uyku kalitesi ile ilişkisini değerlendirmektir.

Yöntem: Bu kesitsel çalışmaya EULAR/ACR 2013 sınıflandırma kriterlerine göre SSc tanısı konan 98 hasta dahil edilmiştir. D vitamini düzeyleri de dahil olmak üzere demografik, klinik ve laboratuvar verileri toplanmıştır. Yorgunluk şiddeti çok boyutlu yorgunluk değerlendirme (MAF) ölçeği kullanılarak, uyku kalitesi ise Pittsburgh uyku kalitesi indeksi (PSQI) kullanılarak değerlendirilmiştir.

Bulgular: D vitamini eksikliği olan hastalar anlamlı derecede daha yüksek MAF skorları (34,5'e karşı 22,4; p<0,001) ve PSQI skorlarına göre daha düşük uyku kalitesi (12'ye karşı 8; p<0,001) sergilemiştir. Çok değişkenli analiz, MAF skorunu [olasılık oranı (OR): 1,204, %95 güven aralığı (GA): 1,116-1,298, p<0,001] ve hastalık semptom süresini (OR: 1,009, %95 GA: 1,002-1,016, p=0,001) D vitamini eksikliğinin bağımsız belirleyicileri olarak tanımlamıştır. ROC analizi, MAF skoru ≤27,7 ve PSQI skoru ≤10,5'in D vitamini eksikliğini öngörmek için en uygun kesme değerleri olduğunu göstermiştir. D vitamini düzeyleri ile hem MAF (r=-0,610, p<0,01) hem de PSQI (r=-0,346, p<0,01) arasında anlamlı bir negatif korelasyon tespit edilmiştir.

Sonuç: D vitamini eksikliği, SSc'li hastalarda artmış yorgunluk ve daha kötü uyku kalitesi ile önemli ölçüde ilişkilidir. Bu bulgular, rutin tarama ve takviye yoluyla D vitamini eksikliğinin giderilmesinin SSc hastalarında yorgunluğu hafifletebileceğini, uyku kalitesini iyileştirebileceğini ve yaşam kalitesini artırabileceğini düşündürmektedir.

Anahtar kelimeler: Çok boyutlu yorgunluk değerlendirme (MAF) ölçeği, D vitamini, Pittsburgh uyku kalitesi indeksi (PSQI), sistemik skleroz

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Introduction

Systemic sclerosis (SSc) is a chronic autoimmune disease involving immune dysregulation and vascular damage that is characterised by diffuse fibrosis of the skin and internal organs such as the lung and gastrointestinal tract (1). In SSc, systemic involvement and various clinical problems such as Raynaud's phenomenon, ischaemic digital ulcers, the thickening of inelastic skin due to tissue degradation, and joint contractures are associated. Fatigue is a common and debilitating symptom among various clinical manifestations of SSc, which significantly affects subjects' quality of life (2). Fatigue, which has multiple dimensions including social, physiological, and psychological, is a common presenting complaint in patients with various rheumatological conditions, including Sjögren's disease, ankylosing spondylitis, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) (3,4). In spite of its prevalence, the underlying mechanisms contributing to fatigue in SSc are poorly understood and effective management strategies are limited.

Vitamin D (VitD), with well-documented roles in calcium homeostasis and bone metabolism, has immunomodulatory and anti-inflammatory activity, playing an important role in both innate and adaptive immunity. Several studies have described vitamin D deficiency (VDD) as a common comorbidity in autoimmune diseases, including SSc (5). The pathophysiological overlap between VDD and features of SSc, such as immune activation, chronic inflammation, and musculoskeletal involvement, raises the possibility that suboptimal VitD levels may contribute to fatigue in this patient population (6).

More recent evidence from other rheumatic diseases, such as RA and SLE, suggests a possible association between low VitD levels and increased fatigue (7). Nevertheless, studies specifically examining this association in SSc are rare. In view of the unique pathophysiology of SSc, characterised by vascular damage and fibrotic processes, it is essential to understand the role of VitD in fatigue in the context of this disorder.

The aim of this study was to evaluate the relationship between VitD concentrations and fatigue in subjects with systemic sclerosis. Through investigating this interaction, we aim to clarify an overlooked contribution of VDD to fatigue in SSc.

Materials and Methods

Study Design and Participants

We included in this cross-sectional study all consecutive subjects who were diagnosed with SSc according to EULAR/ACR 2013 classification criteria, and presented to our outpatient clinic between October 2024 and December 2024, who gave written informed consent after being fully informed about the aims of the study and evaluation methods (8). Patients with known malignancy, liver failure, chronic kidney disorder or other autoimmune diseases, endocrine or metabolic disorders affecting VitD metabolism; chronic infections; or comorbid conditions that may cause fatigue, such as recent surgery, trauma, or haemorrhagic events in the last three months, were excluded. We also excluded current VitD supplementation, pregnancy and breastfeeding, severe psychiatric or musculoskeletal disorders, and significant sunlight or ultraviole exposure in the past three months to minimise confounding factors. Additionally, we excluded patients who had a diagnosis of fibromyalgia according to the 1990 American College of Rheumatology fibromyalgia criteria from our study (9).

Ethics committee approval was obtained from the Research Ethics Committee of Marmara University Faculty of Medicine (approval no: 09.2024.1166, dated 18/10/2024). The study was conducted in accordance with the Declaration of Helsinki.

Data Collection

A combination of clinical assessments and patient-reported outcome measures was used for data elicitation. Demographic data (e.g. age, gender, disease duration) and clinical characteristics, including SSc-specific parameters (e.g., organ involvement, modified Rodnan skin score, serological markers), were collected from subjects' medical records and verified with a clinical examination. Additionally, acute phase values [such as erythrocyte sedimentation rate (ESR) (mm/h) and C-reactive protein (mg/L)] and VitD levels (ng/mL) were recorded from regular controls. 25-hydroxyvitamin D (25[OH]D) was used in measuring VitD levels. Since 25(OH)D <20 ng/mL is defined as VDD, and 25(OH)D 21-29 ng/mL is defined as insufficient, we included those with 25(OH)D <30 ng/mL in the VDD group and those with 25(OH)D ≥30 ng/mL in the non-VDD group (10).

Clinical Measurement

Active and inactive disease states were evaluated in detail using the indices of the European Scleroderma Study Group (EScSG) for disease activity. The calculation is made with a method consisting of ten elements, where each element is evaluated on a 10-point scale. Upon initial assessment, the index reflects activity levels in various organs or systems by assigning specific weights to each criterion. Subjects with a score of 2.5 or higher, based on the activity scoring and EScSG assessments conducted in accordance with the study's measurement protocol, were classified as having active disease (11).

The 17 regions of the modified Rodnan Skin Score (mRSS) include the feet, lower legs, upper arms, fingers, forearms, chest, hands, face, abdomen. All skin areas are palpated by squeezing or rolling between the thumbnail and pointer finger, respectively, but not excessively. The maximum mRSS score is 51, with 0 corresponding to normal thickness, 1 mild, 2 moderate, and 3 severe thickening, and the individual score is obtained by summing the scores obtained at 17 points (12).

Overall quality of life, general health, role-physical, vitality, social function, physical function, mental health, role-emotional, and bodily pain were assessed using the Turkish version of the 36-item short form (SF-36) covering these eight domains. The total score ranges from 0 to 100. Higher scores refer to a slightly better quality of life (13,14).

HADS is a self-report scale consisting of 14 questions measuring anxiety and depression. All questions are marked on a scale of 0 (no impairment) to 3 (severe impairment), with a mark of 0-7 considered normal, 8-10 considered borderline, and 11 and greater considered considered abnormal (15).

Patients' sleep quality was examined in the previous month with the Pittsburgh sleep quality index (PSQI), a 19-item questionnaire grouped into seven component scores, each with equal weight. When we look at the seven components of the PSQI: Sleep disorders, sleep medication use, daytime activity disorder and quality, onset, delay, duration, and efficiency of sleep, we can better understand overall sleep health. A global PSQI score (0-21) is calculated by summing the seven components, with higher scores indicating worse sleep quality and more sleep disturbances (16). The validity and reliability of the PSQI were confirmed in a study conducted in 1996 (17).

Multidimensional Fatigue Assessment (MAF) Scale

We evaluated fatigue utilizing the MAF scale, assessing various dimensions of fatigue, including its severity, frequency, timing, impact on daily activities, and overall quality of life. The MAF scale is a validated instrument that provides a comprehensive measurement of fatigue. It consists of 16 items covering four primary domains: Fatigue severity, timing, interference with activities, and global impact. The scores from each domain are summed to create a global fatigue index. The total score ranges from 1 to 50, with higher scores indicating greater fatigue. The MAF scale has demonstrated reliability and validity in assessing fatigue across various patient populations, including those with autoimmune diseases (18).

Statistical Analysis

Analysis of the data was performed using SPSS 26.0 statistical software (IBM, Chicago, USA). We assessed the normality of the data sets using the Shapiro-Wilk test. While categorical variables are presented as numbers and percentages, quantitative variables are summarised as mean ± standard deviation for normally distributed data, and for non-normally distributed data as median [25% (Q1) - 75% (Q3) quartiles]. For normally distributed parameters, independent t-tests were used to compare the two groups. Group comparisons were made using Mann-Whitney U tests for parameters not showing normal distribution. Categorical variables were analysed either using Fisher's exact test or the chi-square test. Spearman correlation tests were performed for parameters not showing normal distribution, and Pearson correlation tests were performed for parameters showing normal distribution to examine correlations between variables. Variables predicting VDD were primarily evaluated using binary logistic regression analysis, and those with significant p-values then included in multivariate analysis. The 95% confidence interval (CI) and odds ratio (OR) were estimated. Receiver operating characteristic (ROC) curve analyses were used to evaluate disease-related clinical variables for predicting VDD with the best specificity and sensitivity. The effect size (Cohen's d), power value (1-ß), and total sample size of MAF scale comparison between subjects with and without VDD were calculated using G*Power software (V3.1.9.2). The effect size, power value and total sample size were 1.07, 0.95 and 40, respectively. A statistically significant p-value of <0.05 was considered.

Results

A total of 98 subjects, 80.6% of whom were female, were evaluated. The average age was 49.99±13.15 years. The median EScSG activity index, MAF scale, and PSQI of all subjects were 2.0, 27.9, and 11, respectively. Baseline characteristics, clinical presentations, outcome measures, and treatment status of all subjects were presented in Table 1. The variables found to be significantly increased in the VDD group were disease symptom duration, number of digital ulcers, proximal muscle weakness, MAF scale (34.5 vs. 22.4), and PSQI (12 vs. 8). There was no difference between the groups in the drug treatments used. Autoantibodies and laboratory parameters are given in Table 2. ESR was significantly higher in the VDD group (33 vs. 16). In multivariate analysis, the independent predictors of VDD were MAF scale (OR: 1.204, 95% CI 1.116-1.298; p<0.001) and disease symptom duration (OR: 1.009, 95% CI 1.002-1.016; p=0.001). The results of the regression analysis are given in Table 3. The ROC analysis is given in Figure 1. The best cut-off value for predicting VDD using the MAF scale and PSQI obtained by the ROC curve analysis was ≤27.7 (sensitivity: 78.7%, specificity: 74.5%) and ≤10.5 (sensitivity: 70.2%, specificity: 66.7%), respectively. The correlation analysis between VitD level and admission characteristics, and SF-36 parameters is given in Table 4. There was a significant negative correlation between VitD level and the MAF scale (r=-0.610, p<0.01) and the PSQI (r=-0.346, p<0.01).

Table 1. Baseline characteristics, clinical manifestations and outcome measures of patients with systemic sclerosis according to the vitamin D deficiency

	All patients n=98	Non-vitamin D deficiency n=51	Vitamin D deficiency n=47	p-value
Age (years; mean SD)	49.99 SD 13.15	50.37 SD 12.29	49.57 SD 14.16	0.766
Female, gender, n (%)	79 (80.6%)	42 (82.4%)	37 (78.8%)	0.650
Disease symptoms duration (month)	**82 (38-168)**	**50 (31-125)**	**90 (50-170)**	**0.015**
EScSG activity indexes	2.0 (1.0-4.0)	1.5 (1.0-2.5)	2.0 (1.5-4.0)	0.160
Limited cutaneous SSc, n (%)	48 (49.0%)	27 (52.9%)	21 (44.7%)	0.414
Diffuse cutaneous SSc, n (%)	45 (45.9%)	22 (43.1%)	23 (48.9%)	0.565
The overlap of systemic sclerosis, n (%)	5 (5.1%)	2 (3.9%)	3 (6.4%)	0.669
Clinical manifestations				
Raynaud's phenomenon, n (%)	90 (91.8%)	46 (90.2%)	44 (93.6%)	0.717
Digital ulcers, n (%)	**38 (38.8%)**	**14 (27.5%)**	**24 (51.1%)**	**0.016**
Telangiectasias, n (%)	87 (88.8%)	44 (86.3%)	43 (91.5%)	0.411
Scleredema, n (%)	31 (31.6%)	17 (33.3%)	14 (29.8%)	0.706
Calcinosis cutis, n (%)	23 (23.5%)	10 (19.6%)	13 (27.7%)	0.347
Synovitis, n (%)	36 (36.7%)	17 (33.3%)	19 (40.4%)	0.467
Flexion contractures, n (%)	14 (14.3%)	5 (9.8%)	9 (19.1%)	0.185
Tendon friction rubs, n (%)	8 (8.2%)	3 (5.9%)	5 (10.6%)	0.475
Proximal muscle weakness, n (%)	**9 (9.2%)**	**1 (2.0%)**	**8 (17.0%)**	**0.013**
Upper GI symptoms, n (%)	68 (69.4%)	32 (62.7%)	36 (76.6%)	0.135
Lower GI symptoms, n (%)	34 (34.7%)	16 (31.4%)	18 (38.3%)	0.472
Pulmonary hypertension, n (%)	22 (22.4%)	8 (15.7%)	14 (29.8%)	0.093
Interstitial lung disease, n (%)	39 (39.8%)	21 (41.2%)	18 (38.3%)	0.771
Arrhythmia, n (%)	7 (7.1%)	2 (3.9%)	5 (10.6%)	0.255
Outcome measures				
Digital ulcers count	**0 (0-1)**	**0 (0-0)**	**0 (0-5)**	**0.001**
Pitting scars count	0 (0-3)	0 (0-3)	1 (0-3)	0.133
Modified Rodnan skin score	16 (8-26)	15 (9-26)	18 (8-30)	0.345
HAQ-DI	1.95 (0.85-7.00)	1.5 (0.70-7.0)	1.95 (1.40-9.0)	0.193

Table 1. Continued

	All patients n=98	Non-vitamin D deficiency n=51	Vitamin D deficiency n=47	p-value
MAF scale (mean SD)	**27.9 (19.3-35.1)**	**22.4 (15.5-28.0)**	**34.5 (28.1-38.6)**	**<0.001**
Pittsburgh sleep quality index	**11 (7-14)**	**8 (5-13)**	**12 (10-15)**	**0.001**
36-item short-form health survey (SF-36)				
Physical functioning	**50 (25-70)**	**55 (35-80)**	**35 (20-65)**	**0.015**
Role functioning/physical	**25 (0-50)**	**25 (0-75)**	**0 (0-50)**	**0.034**
Role functioning/emotional	33.3 (0-66.7)	33.3 (0-100)	0 (0-66.7)	0.073
Energy/fatigue	**50 (25-60)**	**55 (40-65)**	**45 (20-55)**	**0.010**
Emotional well-being	**52 (32-64)**	**56 (40-68)**	**48 (24-52)**	**0.010**
Social functioning	50 (25-62.5)	50 (25-75)	50 (25-62.5)	0.108
Pain	**45 (22.5-57.5)**	**45 (22.5-67.5)**	**45 (22.5-45)**	**0.036**
General health	36.3 SD 20.0	39.8 SD 19.6	32.5 SD 19.9	0.073
Health change	**50 (25–50)**	**50 (25 – 50)**	**50 (25 – 50)**	**0.037**

Values are presented as mean ± standard deviation (SD), number (%), or median (interquartile range). EScSG: The European systemic sclerosis study group, SSc: Systemic sclerosis, GI: Gastrointestinal, HAQ-DI: Health assessment questionnaire-disability index, MAF: Multidimensional assessment of fatigue

Table 2. Laboratory findings of patients with systemic sclerosis according to the vitamin D deficiency

	All patients n=98	Non-vitamin D deficiency n=51	Vitamin D deficiency n=47	p-value
Serum 25-hydroxyvitamin D levels, mg/L	30.9 (19-38)	37 (34-45)	19 (15-23)	<0.001
ESR, mm/h	23 (12-37)	16 (7-30)	33 (21-40)	<0.001
CRP, mg/L	2.96 (1.46-5.70)	3.10 (1.36-4.81)	2.96 (1.60-7.30)	0.408

Values are presented as mean ± standard deviation or median (interquartile range). ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

Table 3. The independent effects of some possible predictors in relation to vitamin D deficiency according to univariate/multivariate analysis

	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, years	0.995 (0.966-1.026)	0.763		
EScSG activity indexes	1.270 (1.006-1.603)	0.044		
Disease symptoms duration (month)	1.006 (1.001-1.010)	0.016	1.009 (1.002-1.016)	0.001
Female, gender	1.261 (0.463-3.439)	0.650		
MAF scale	1.187 (1.106-1.274)	<0.001	1.204 (1.116-1.298)	<0.001
Pittsburgh sleep quality index	1.166 (1.060-1.281)	0.002		
Digital ulcers	2.758 (1.191-6.387)	0.018		
HAQ-DI	1.023 (0.978-1.070)	0.316		
36-item short-form health survey (SF-36)				
Physical functioning	0.982 (0.967-0.997)	0.022		
Role functioning/physical	0.987 (0.975-0.999)	0.030		
Role functioning/emotional	0.991 (0.982-1.001)	0.086		
Energy/fatigue	0.977 (0.958-0.997)	0.023		
Emotional well-being	0.973 (0.952-0.995)	0.016		
Social functioning	0.990 (0.976-1.004)	0.168		

Table 3. Continued

	Univariate	Multivariate
Pain	0.981 (0.963-1.000)	0.050
General health	0.981 (0.961-1.002)	0.075
Health change	0.980 (0.963-0.998)	0.025

OR: Odds ratio, CI: Confidence interval, EScSG: The European systemic sclerosis study group, MAF: Multidimensional assessment of fatigue, HAQ-DI: Health assessment questionnaire-disability index

Table 4. Correlation of clinical variables, MAF scale, Pittsburgh sleep quality index, 36-item short-form health survey and laboratory finding with serum 25-hydroxyvitamin D levels

	r/rho	
Age (years)	0.222*	r
EScSG activity indexes	-0.123	rho
Pittsburgh sleep quality index	-0.346**	rho
Modified Rodnan skin score	-0.108	rho
HAQ-DI	-0.057	rho
MAF scale	-0.610**	rho
ESR, mm/h	-0.312**	rho
36-item short-form health survey (SF-36)		
Physical functioning	0.238*	rho
Role functioning/physical	0.229*	rho
Role functioning/emotional	0.169	rho
Energy/fatigue	0.233*	rho
Emotional well-being	0.199*	rho
Social functioning	0.172	rho
Pain	0.182	rho
General health	0.086	r
Health change	0.241*	rho

MAF: Multidimensional assessment of fatigue, EScSG: The European systemic sclerosis study group, HAQ-DI: Health assessment questionnaire-disability index, ESR: Erythrocyte sedimentation rate, *: p<0.05, **: p<0.01, r: Pearson corelation /rho Spearman's corelation

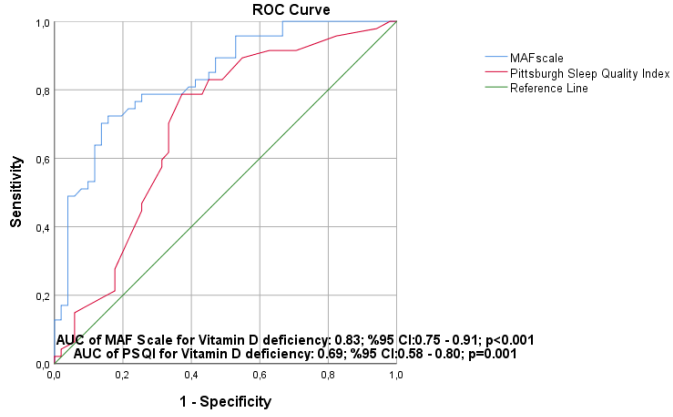

Figure 1. In ROC analysis, area under the ROC curve value of MAF scale and PSQI for vitamin D deficiency

ROC: Receiver operating characteristic, MAF: Multidimensional assessment of fatigue, PSQI: Pittsburgh sleep quality index, AUC: Area under the curve, CI: Confidence interval

Discussion

The present study demonstrates a significant association between VDD and fatigue severity as measured by the MAF scale in subjects with SSc. Subjects with VDD reported higher fatigue scores and worse sleep quality compared to those with adequate VitdD levels, emphasizing the potential role of VitD in the pathophysiology of fatigue in this population. Furthermore, MAF score and disease symptom duration were detected to be independent determinants of VDD among these subjects.

Fatigue is a widespread and debilitating sign in subjects with rheumatic diseases such as RA, SLE, SSc, and fibromyalgia (19). It significantly affects quality of life and often persists even when the underlying disease is controlled. The MAF is a revision of the original Piper fatigue scale, which was developed in the field of oncology but revised specifically for rheumatoid arthritis (20,21). The MAF scale has been used since then to assess fatigue in various rheumatological patient populations, such as SSc, ankylosing spondylitis, and chronic musculoskeletal physical therapy subjects, in many languages (22-24). In our study, subjects with VDD had higher MAF scale scores, indicating that these subjects experienced more advanced levels of fatigue. Yadav et al. (25) demonstrated that VDD is the strongest predictor of fatigue in subjects with rheumatoid arthritis. Another study has shown that VitD treatment helps alleviate fatigue even in healthy individuals (26). When the data are evaluated holistically, it becomes apparent that the results of our study are compatible with the results of other studies. Although the exact mechanism between VitD and fatigue is not yet fully understood, potential pathophysiological factors include oxidative stress, inflammation, cytokines, and neurotransmitters, as well as ion channel abnormalities (27).

In addition, a significant relationship was found between VDD and the PSQI. Higher PSQI scores were observed in subjects with VDD, which indicates poorer sleep quality.

VitD has significant effects on sleep metabolism. For example, the activation or degradation of enzymes in brain regions involved in sleep regulation, the metabolism of melatonin, and the influence on non-specific pain disorders are some of the underlying mechanisms by which VitD affects sleep (28). The positive effect of VitD on sleep has also been demonstrated that subjects receiving VitD supplementation have better sleep quality compared to the control group (29). These findings support the results of our study. It suggests that correcting VDD may improve both sleep and fatigue in SSc subjects.

Another finding of our study was that the ESR was significantly increased in the group with VDD. This can be explained by an inverse relationship between VitD and the inflammatory state (30). In addition, VitD regulates the expression of genes involved in immune reactions and encoding cytokines, promoting the synthesis of anti-inflammatory cytokines while regulating the production of pro-inflammatory cytokines. Both of these proven effects lead to a reduction in inflammation (31). MAF and symptom duration were identified as independent predictors of VDD. The independent relationship between the duration of symptoms, MAF, and VitD, may be explained by the contribution of VDD to the pro-inflammatory process. Besides, prolonged disease duration, limited mobility, reduced exposure to sunlight, or altered metabolism may also worsen the deficiency and exacerbate fatigue. As a result, the prolongation of the disease symptom duration and the more pronounced physical fatigue, which ultimately corresponds to higher MAF scale scores, may occur. The independent relationships identified between symptom duration, VitD levels, and fatigue severity suggest that VDD could act as both a consequence and a driver of disease burden in SSc.

Study Limitations

Limitations of this study include its cross-sectional design, which prevents drawing conclusions about causation and limits the ability to infer temporal relationships between VitD levels and fatigue. Additionally, small sample sizes may limit the generalisability of findings and reduce statistical power. The reliance on a single measurement of VitD levels and fatigue may not fully capture their dynamic relationship over time. Furthermore, potential confounding factors such as dietary intake of vitamin D, seasonal variations, and unmeasured comorbidities may have influenced the results. Future studies should address these limitations through longitudinal designs with larger and more diverse cohorts. Longitudinal studies are warranted to confirm these findings and explore the long-term effects of VitD supplementation on fatigue and overall quality of life in SSc subjects.

Conclusion

In conclusion, this study highlights a significant association between VDD and increased fatigue and sleep disturbances in subjects with SSc. These findings underscore the potential role of VitD in the multifactorial pathophysiology of fatigue and its impact on sleep quality in SSc. Addressing VDD through routine screening and targeted supplementation could offer a feasible strategy to alleviate fatigue, improve sleep quality, and enhance overall quality of life in this challenging disease.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Research Ethics Committee of Marmara University Faculty of Medicine (approval no: 09.2024.1166, dated 18/10/2024). The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained.

Information: This work has been submitted to the EULAR 2025 Congress.

Footnotes

Authorship Contributions

Concept: N.Ö., M.T.D., Design: N.Ö., M.T.D., Data Collection or Processing: N.Ö., M.T.D., Analysis or Interpretation: N.Ö., M.T.D., Literature Search: N.Ö., Writing: N.Ö., M.T.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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