RESEARCH LETTER

Sleep quality and clinical and laboratory variables associated with sleep disturbances in patients with systemic sclerosis

Ewelina Machura-Porębska, Eugeniusz J. Kucharz, Robert Pieczyrak, Przemysław Kotyla

Department of Internal Medicine, Rheumatology and Clinical Immunology, Medical University of Silesia, Katowice, Poland

Introduction Systemic sclerosis (SSc) is a chronic autoimmune disease of unknown cause characterized by fibrosis of the skin and internal organs, vasculopathy, and immune disturbances. The disease is heterogeneous in clinical presentation and affects almost all organs and systems.[1,2] SSc significantly impairs quality of life and is associated with increased mortality.[3]

Sleep disturbances have been reported in patients with SSc, but only a few studies have been published. All reports indicated higher incidence of various sleep disturbances in patients with SSc, as compared with the general population. Using all-night polysomnography, Prado et al[4] revealed reduced sleep efficacy and increased arousal index. Poor sleep in SSc patients was associated with esophageal dyskinesia and dyspnea. These findings were confirmed in other studies, including larger groups of patients.[5] Most reports have suggested a leading role of gastrointestinal involvement and pain in generating sleep disturbances.[6,7] Other factors associated with poor sleep were also suggested, including depression, severe internal organ involvement, digital ulcers, and pruritis.[8] It became clear that patients with poor sleep quality had a worse quality of life in both mental and physical domains.[9] Less is known about an association between laboratory findings and poor sleep quality. In general, it is believed that sleep disturbances in SSc patients result from a number of factors that significantly affect their quality of life. On the other hand, sleep disturbances are commonly underdiagnosed or overlooked in clinical practice.

This study was designed to evaluate the characteristics of sleep in SSc patients and to establish a potential relationship between sleep disturbances and other factors detectable in the patients.

Patients and methods A total of 57 patients with SSc who fulfilled the classification criteria for the disease[10] were investigated. All patients were hospitalized in the Rheumatological Department of the University Hospital No. 7 in Katowice. Patients with unclear diagnoses, overlap syndromes, or other disorders known to affect sleep or taking medications directly affecting sleep or other psychotropic medications were excluded from the study. A control group consisted of 65 healthy individuals matched for age and sex.

Sleep quality was evaluated with the Pittsburgh Sleep Quality Index,[11] the Epworth Sleepiness Scale,[12] and the Berlin Questionnaire.[13] The Systemic Sclerosis Quality of Life Questionnaire,[14] Patient Health Questionnaire-9,[15] and Fatigue Assessment Scale[16] were also used. The patients' characteristics were based on the following demographic, clinical, and laboratory data: disease duration (from the occurrence of the first non-Raynaud symptom or sign), smoking history, coexisting chronic diseases, routine laboratory test results, and medications administered for all medical reasons. Cutaneous involvement was determined with the modified Rodnan skin score, and the measurements were performed by the same person in all the patients. Internal organ involvement was characterized with the Medsger Disease Severity Scale.[17] Body mass and body mass index (BMI) were determined. The following laboratory data were collected: serum antibodies, serum levels of C3 and C4 complement components, serum levels of creatinine, glucose, C-reactive protein (CRP), bilirubin, sodium, potassium, total calcium, total iron, uric acid, thyrotropin, free thyroxine, vitamin D, N-terminal pro–B-type natriuretic peptide, activity of creatine kinase, alanine aminotransferase, aspartate transaminase, and alkaline phosphatase. Blood hemoglobin, erythrocyte sedimentation rate, and prothrombin time (international normalized ratio) were also assayed. All tests were performed with standard methods routinely used in clinical practice. A detailed history of symptoms and signs was collected with

Correspondence to:
Eugeniusz J. Kucharz, MD, PhD, Department of Internal Medicine, Rheumatology and Clinical Immunology, Medical University of Silesia, ul. Ziołowa 45/47, 40-635 Katowice, Poland, phone: +48 32 359 83 91, email: ejkucharz@poczta.onet.pl
Received: September 21, 2023.
Revision accepted: January 30, 2024.
Published online: February 5, 2024.
Pol Arch Intern Med. 2024; 134 (2): 16676
doi:10.20452/pamw.16676

TABLE 1 Sleep quality and factors associated with sleep disturbances

Indices of sleep quality	Systemic sclerosis (n = 57)	Controls (n = 65)	*P* value
Sleep efficiency, %	83 (67–88)	100 (85–100)	<0.001
Sleep latency			
<15 min	18 (32)	40 (63)	0.002
16–30 min	25 (44)	18 (28)	
31–60 min	6 (11)	5 (8)	
>60 min	8 (14)	1 (2)	
General quality of sleep			
Good	18 (32)	42 (66)	<0.001
Poor	39 (68)	22 (34)	
Factors disturbing sleep			
Mild	1 (2)	5 (8)	<0.001
Moderate	13 (23)	41 (63)	
Severe	33 (58)	17 (26)	
Very severe	10 (18)	1 (2)	
Prevalence of moderate to very severe sleep disturbances in the systemic sclerosis patients with or without specific symptoms			
Variable	No symptom	Symptom present	*P* value
Early satiety	37 (73)	6 (100)	<0.001
Nausea, vomiting	39 (74)	4 (100)	<0.001
Constipation	31 (69)	12 (100)	<0.001
Articular pain	12 (57)	31 (86)	0.01
Bone lesions	37 (73)	6 (100)	<0.001
Serum anticentromere antibodies	37 (73)	6 (100)	<0.001
Sleep latency in patients with systemic sclerosis, min			
Variable	No symptom	Symptom present	*P* value
Nonarticular pain	7.5 (5–20)	20 (15.25–50)	0.04
Constipation	20 (5–25)	32.5 (18–50)	0.04
Sleep efficiency in patients with systemic sclerosis, %			
Variable	No symptom	Symptom present	*P* value
Constipation	85 (75–89)	72 (59.25–78)	0.01

Data are presented as number (percentage) or median (interquartile range).

questionnaires we developed for this study from all the patients.

Statistical analysis The calculations were performed using the R Project package (R Foundation for Statistical Computing, Vienna, Austria). The Shapiro–Wilk test was used to check if the variables follow normal distribution. Quantitative variables which did not follow normal distribution were displayed as median and interquartile range (IQR). Qualitative variables were expressed as numbers and percentages. The χ^2 test was used for comparison of qualitative variables. Comparison of the quantitative data between the 2 groups was carried out with the Mann–Whitney test. Comparison of the quantitative data between three and more groups (severity of internal organ involvement, ie, the Medsger Disease Severity Scale) was carried out using the Kruskal–Wallis test. The association between the parameters was investigated with the Spearman correlation test. The results were deemed significant for a *P* value below 0.05.

Ethics The Bioethical Committee of the Medical University of Silesia, Poland, endorsed the study protocol (KNW/0022/KB/71/19). All participants provided written informed consent to participation in the study and to publication of its results.

Results

Characteristics of the patients The SSc group consisted of 45 women and 12 men aged 26–62 years. Over half of them (34 patients; 60%), had normal BMI, while the remaining 23 patients (40%) had lowered BMI. Median (IQR) time from the occurrence of the first non-Raynaud symptom or sign was 4 (2–7) years. Forty-one patients (72%) suffered from a diffuse type of SSc, and 16 (28%) were diagnosed with limited SSc. Serum antitopoisomerase I antibodies were detected in 85%, and anticentromere antibodies in 15% of the patients.

Articular pain was reported by 36 patients (63%). The most common complaints were hand arthralgia (21 patients) and foot arthralgia (17 patients). Swollen joints were also common (28 patients; 49%) and with similar location (hand in 13 and feet in 11 patients). Nonarticular pain was reported by 28 patients (49%), and included mostly myalgia and nonspecific headaches. Interstitial lung disease was diagnosed in 42 patients (74%), and pulmonary hypertension in 10 patients (18%). Gastrointestinal manifestations were common, and included impaired swallowing, symptoms of reflux disorder, nausea and vomiting, loss of appetite, early feeling of satiety, and chronic constipation.

Most of the patients were treated with mycophenolate mofetil or cyclophosphamide. Some patients received corticosteroids in the early phase of the disease (terminated at least 8 months before the study). Symptomatic drugs, including phosphodiesterase-5 inhibitors and calcium channel antagonists, were also administered to the patients.

Sleep quality Several sleep disturbances were found in the SSc patients, some of which were associated with other symptoms or laboratory result alterations, as summarized in TABLE 1.

We found that only one-third of the SSc patients had good general sleep quality, as compared with two-thirds in the control group (TABLE 1). SSc was associated with prolonged sleep latency and diminished sleep efficiency. Median (IQR) of total sleep time was similar to that of the controls (7 [6–8] h vs 6.75 [6–8] h). Men with SSc had shorter sleeping time than women ($P = 0.047$). Women and men also differed in their median sleep efficiency (83% [67–88]% vs 100% [85–100]%). SSc was associated with greater frequency of restless leg syndrome, as compared with the controls (17 patients, 30% vs 4 healthy individuals, 6%; $P < 0.001$).

The occurrence of gastrointestinal symptoms was shown to be associated with sleep disturbances. All patients with early satiety, nausea, vomiting, or constipation suffered from moderate to very severe sleep disturbances, while only some of the SSc patients without the symptoms had sleep problems (TABLE 1). Nausea and/or vomiting were also associated with an increase in the hypersomnolence index (according to the Epworth Sleepiness Scale). In the SSc patients suffering from nausea or vomiting, mean (SD) value of this index was 12.75 (2.22), while in those without the symptoms it was 6.98 (4.37) ($P = 0.009$). Constipation was associated with impaired sleep latency (TABLE 1) and median sleep efficiency (72% [59.25–78]% vs 85% [75–89]% in the patients with and without the symptom; $P = 0.01$).

Articular pain enhanced sleep disturbances (TABLE 1); 81% of the patients with this symptom had low sleep quality, while among those without articular pain this rate was 48%. Nonarticular pain affected median sleep latency (20 [15.25–50] min vs 7.5 [5–20] min in those with and without the symptom; $P = 0.042$).

Arterial hypertension was associated with longer median sleep duration (7 [7–7.88] h vs 6.5 [5.75–7.5] h in the patients with or without arterial hypertension; $P = 0.03$), and better median sleep efficiency (87% [78–91.25]% vs 80% [62–86.5]%).

The risk of sleep apnea was similar in the SSc patients and the control group. Pulmonary involvement (interstitial lung disease and/or pulmonary hypertension) was detected with chest high-resolution computed tomography and/or echocardiography, and was found to be in an early clinical stage. Median forced vital capacity in the SSc patients was 80% of predicted value (IQR, 70–96.75), and median diffusion lung capacity for carbon monoxide (DLCO) was found to be 74% (IQR, 59.25–86) of the predicted value. Low DLCO was associated with higher frequency of insomnia symptoms ($P = 0.03$), but there were no other associations between pulmonary manifestations and sleep disturbances.

A correlation was shown between the disease duration (any overt non-Raynaud symptom) and sleep latency ($R = 0.388$; $P = 0.003$). Interestingly, some laboratory data correlated with sleep disturbances. A C3 complement component level positively correlated with sleep duration ($R = 0.286$; $P = 0.04$), hypersomnolence correlated with CRP levels ($R = 0.337$, $P = 0.01$), and a negative correlation was found between hypersomnolence and serum potassium ($R = –0.333$; $P = 0.01$) and iron levels ($R = –0.594$; $P = 0.001$). A negative correlation was shown between sleep efficiency and serum potassium levels ($R = –0.287$; $P = 0.03$).

As expected, total quality of life decreased in the SSc patients with enhanced sleep disturbances. These patients also had a higher fatigue index.

Discussion Sleep problems are common in the patients with SSc; abnormal Pittsburgh Sleep Quality Index scores indicating poor sleep quality were shown in 68% of our SSc patients. This finding is consistent with other reports. Horsley-Silva et al[7] demonstrated poor sleep quality in 68%, Sariyildiz et al[8] in 69%, and Figueiredo et al[9] in 73% of their SSc patients. A higher percentage of SSc patients with impaired sleep quality (94%) was reported by Bagnato et al.[18]

Sleep disturbances in SSc individuals result from a number of factors. Complexity and common concurrence of these factors can explain a lack of association of such variables as skin involvement, the Medsger Disease Severity Scale, or BMI with sleep disturbances. Only disease duration was shown to be related to sleep latency. It is suggested that the indices reflecting the severity of systemic involvement tend to be associated with sleep quality indices. Figueiredo et al[9] found sleep disturbances to be associated with the Medsger index with higher disease severity.

Our results showed longer sleep latency and reduced sleep efficiency in the SSc patients than in the controls, which is consistent with the findings of Sariyildiz et al.[8] Prado et al[4] reported lower sleep efficiency in 70% of patients with SSc, which is similar to our study results. Moreover, polysomnography revealed reduced rapid eye movement sleep, increased arousal index, and increased slow-wave sleep in SSc patients.[4] Little is known about the factors that influence sleep latency and sleep efficiency in SSc patients. In our study, constipation and a tendency to hyperkalemia affected sleep efficiency. Constipation, nonarticular pain, and longer disease duration impaired sleep latency.

We reported for the first time an association between electrolyte imbalance and disordered sleep in SSc patients. The patients with lower serum potassium and iron levels had higher Epworth Sleepiness Scale scores, while elevated serum potassium levels were independent predictors of impaired sleep efficiency. Potassium supplementation markedly increased actigraphy-based sleep efficiency and decreased daytime sleepiness, while increased serum potassium levels improved polysomnographic homeostasis of the sleep architecture,[19] and hyperkalemia may contribute to poor sleep quality.[20] A potential link between the sleep-wake cycle and electrolyte balance may be clinically meaningful; however, its pathomechanism remains unknown.

A negative association between hypersomnolence and low serum iron level was shown. Decreased serum iron level was found in about one-third of the SSc patients, and it is believed to be a cumulative result of such factors as bleeding from the stomach telangiectasias (watermelon stomach) and diverticula of the colon as well as impaired iron absorption (bacterial colonization of the small intestine and fibrosis of the intestinal wall, impaired motility of the gastrointestinal system, and decreased appetite). Low tissue level of iron can be one of etiological factors of common occurrence of fatigue in the SSc patients.

Sleep disturbances occurred more frequently in the SSc patients with gastrointestinal manifestations. Diarrhea, bloating, fecal incontinence, and constipation were important correlates with sleep problems in SSc. We observed poor sleep quality in all patients who reported vomiting or nausea at night. Vomiting or nausea at night were also independent predictors of excessive daytime sleepiness in SSc patients. Other studies have also shown a negative association between gastrointestinal involvement and sleep patterns in SSc patients.[5,6,21] One of the mechanisms may be worsening gastrointestinal motor dysfunction, which interferes with the sleep structure. Moreover, gastroesophageal reflux can cause or increase the severity of SSc-associated interstitial lung disease.

Novel observations from our study involve associations between some laboratory data and sleep quality. We found an association between the serum C3 complement component level and sleep duration. The C3 complement component level is known to be altered in various autoimmunological diseases, including systemic lupus erythematosus. Additionally, Manzar et al[22] found a correlation between serum C4 complement levels and sleep duration and sleep quality in healthy men. Acute-phase reactants are also suggested to affect sleep quality. Our study revealed a correlation between CRP levels and hypersomnolence. Acute-phase reactants are also suggested to affect sleep quality. Our study revealed a correlation between CRP levels and hypersomnolence. In SSc, an impaired acute-phase response was revealed. The mechanism of this phenomenon and the correlation between the disease activity and inflammatory indices level remain unclear.[23] Given inconsistent evidence for the significance of various chronotypes in obstructive sleep apnea,[24] it would be of interest to assess them in SSc patients in association with polysomnography.

In summary, sleep disturbances in SSc are a very common and important but underrated clinical problem. They are caused by a set of factors of various nature and are probably related to several organ manifestations, but their pathomechanisms remain unclear. Moreover, sleep quality in SSc patients may have a significant impact on their physical and mental function, as well as treatment outcomes. It seems that the medical history of SSc patients should include details on sleep patterns. More research is needed to understand the role of sleep disturbances in the clinical course of SSc. They may result in development of clinical guidelines for the diagnosis and management of sleep abnormalities in patients with SSc.

ARTICLE INFORMATION

ACKNOWLEDGMENTS None.

FUNDING None.

CONFLICT OF INTEREST None declared.

HOW TO CITE Machura-Porębska E, Kucharz EJ, Pieczyrak R, Kotyla P. Sleep quality and clinical and laboratory variables associated with sleep disturbances in patients with systemic sclerosis. Pol Arch Intern Med. 2024; 134: 16676. doi:10.20452/pamw.16676

REFERENCES

1 Volkmann ER, Andréasson K, Smith V. Systemic sclerosis. Lancet. 2023; 401: 304-318.

2 Lescoat A. Very Early Diagnosis of Systemic Sclerosis (VEDOSS): deciphering the heterogeneity of systemic sclerosis in the very early stages of the disease. J Scleroderma Relat Disord. 2023; 8: 3-6.

3 Jaafar S, Lescoat A, Huang S, et al. Clinical characteristics, visceral involvement, and mortality in at-risk or early diffuse systemic sclerosis: a longitudinal analysis of an observational prospective multicenter US cohort. Arthritis Res Ther. 2021; 23: 170.

4 Prado GF, Allen RP, Trevisani VM, et al. Sleep disruption in systemic sclerosis (scleroderma) patients: clinical and polysomnographic findings. Sleep Med. 2002; 3: 341-345.

5 Frech T, Hays RD, Maranian P, et al. Prevalence and correlates of sleep disturbance in systemic sclerosis-results from the UCLA scleroderma quality of life study. Rheumatology (Oxford). 2011; 50: 1280-1287.

6 Milette K, Hudson M, Körner A, et al. Sleep disturbances in systemic sclerosis: evidence for the role of gastrointestinal symptoms, pain and pruritus. Rheumatology (Oxford). 2013; 52: 1715-1720.

7 Horsley-Silva JL, Umar SB, Vela MF, et al. The impact of gastroesophageal reflux disease symptoms in scleroderma: effects on sleep quality. Dis Esophagus. 2019; 32: 1-6.

8 Sariyildiz MA, Batmaz I, Bozkurt M, et al. Sleep quality in rheumatoid arthritis: relationship between the disease severity, depression, functional status and the quality of life. J Clin Med Res. 2014; 6: 44-52.

9 Figueiredo FP, Aires GD, Nisihara R, Skare TL. Sleep disturbance in scleroderma. J Clin Rheumatol. 2021; 27: S242-S245.

10 van den Hoogen F, Khanna D, Fransen J, et al. 2013 Classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013; 65: 2737-2747.

11 Buysse DJ, Reynolds CF 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28: 193-213.

12 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991; 14: 540-545.

13 Netzer NC, Stoohs RA, Netzer CM, et al. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. 1999; 131: 485-491.

14 Ndosi M, Alcacer-Pitarch B, Allanore Y. Common measure of quality of life for people with systemic sclerosis across seven European countries: a cross-sectional study. Ann Rheum Dis. 2018; 77:1032-1038.

15 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001; 16: 606-613.

16 Michielsen, HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief selfrated fatigue measure the fatigue assessment scale. J Psychosom Res. 2003; 54: 345-352.

17 Medsger TA Jr, Silman AJ, Steen VD, et al. A disease severity scale for systemic sclerosis: development and testing. J Rheumatol. 1999; 26: 2159-2167.

18 Bagnato GL, Fiorenza A, Cordova F, et al. Clinical, autoimmune, and psychiatric parameters correlate with sleep disturbance in patients with systemic sclerosis and rheumatoid arthritis. Clin Exp Rheumatol. 2016; 100: 49-55.

19 Drennan MD, Kripke DF, Klemfuss HA, Moore JD. Potassium affects actigraph-identified sleep. Sleep. 1991; 14: 357-360.

20 Ling LL, Chan YM, Mat Daud Z. Serum potassium and handgrip strength as predictors of sleep quality among hemodialysis patients in Malaysia. Asia Pac J Clin Nutr. 2019; 28: 401-410.

21 Wongthawa N, So-Gnern A, Mahakkanukrauh A, et al. Sleep quality and clinical association with sleep disturbance in systemic sclerosis. BMC Rheumatol. 2023; 7: 21.

22 Manzar MD, Rajput MM, Zannat W, et al. Association between sleep quality and inflammatory complement components in collegiate males. Sleep Breath. 2016; 20: 867-872.

23 Kucharz EJ, Grucka-Mamczar E, Mamczar A, Brzezinska-Wcisło L. Acute-phase proteins in patients with systemic sclerosis. Clin Rheumatol. 2000; 19: 165-166.

24 Sochal M, Binienda A, Ditmer M, et al. Correlations between the symptoms of insomnia, depression, sleep quality, antitumor necrosis factor therapy, and disrupted circadian clock gene expression in inflammatory bowel disease. Pol Arch Intern Med. 2023; 133: 16487.