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Prevalence of Sleep Disorders Among Diabetic Patients with Systemic Lupus Erythematosus in Menoufia University Hospital

Asmaa Metwally Abdel Tawab[1], Doaa Salah Elgendy[2], Maha Mohamed Abd El Raof Salman*[3], Marwa Mohammad Sharaf[1]

Departments of [1]Chest Diseases, [2]Internal Medicine, Endocrinology Unit, and [3]Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Menoufia University, Menoufia, Egypt

***Corresponding author:** Doaa Salah Elgendy, **Mobile:** (+20) 01019965366,

Email: doaa.algendy@med.menofia.edu.eg, **ORCID Number:** 0000-0003-0954-6838

ABSTRACT

Background: Patients with diabetes and systemic lupus erythematosus (SLE) frequently have sleep disruption. Unfortunately, there is still a lack of knowledge about the relationship between the incidence of sleep disorders in SLE and the causes of these disorders.

Objectives: To study the sleep breathing disorders among diabetic patients with systemic lupus erythematosus (SLE) and associated relationship with both disease severity and activity.

Patients and Methods: Thirty diabetic patients with SLE and thirty apparent healthy control subjects were enrolled in this work. For all patients, full medical histories, in-depth clinical exams, Epworth sleepiness ratings (ESS), laboratory evaluations, and complete overnight polysomnography were done.

Results: Diabetic patients with SLE have a lower significant total sleep time (TST), sleep onset, sleep efficiency (%), percent of sleep in supine than controls ($p < 0.001$ for all). However, diabetic patients with SLE have a higher significant Spon Arousal index, number of awaking/hour, low limitation index and apnea/hypopnea index in supine than controls ($p < 0.001$ for all). Diabetic patients with SLE have a higher significant periodic leg movements during sleep (PLMS) sequence, apnea/hypopnea index (AHI), oxygen desaturation events (OD), percent of snoring time in TST, percent of rapid eye movement sleep (REM) in TST, total AHI in non-rapid eye movement sleep (NREM), total AHI in REM, ESR, CRP, uric acid and FBS, HBA1c% than controls ($p < 0.001$ for all). However, diabetic patients with SLE have a lower significant average oxygen saturation % and lowest oxygen saturation (%) than controls ($p < 0.001$ for all). **Conclusion**: Sleep breathing problems are frequently seen in people with systemic lupus erythematosus and diabetes. These patients' disease activity and poor glycemic management may be significant contributors to their sleep disruption.

Keywords: Sleep disorders, Systemic lupus erythematosus, Diabetes mellitus.

INTRODUCTION

Many rheumatic illnesses, such as SLE, rheumatoid arthritis, sarcoidosis, and Behcet's syndrome, have been linked to sleep difficulties [1].

Both Type 2 diabetes mellitus (T2DM) and sleep disorders are frequent health issues that are mutually destructive. Diabetes patients frequently experience sleep difficulties. Diabetes patients take more sleeping pills and report greater rates of insomnia, poor sleep quality, and excessive daytime drowsiness [2].

Due to restrictions in physiological gas exchange, SLE patients run the risk of developing sleep disordered breathing. Muscle weakness and weariness throughout the daytime may lead to hypoventilation. The assessment of SLE activity and responsiveness to treatment may be hampered by sleep apnea being present as a comorbidity [3].

It is still unclear how often sleep impairment is and what are the factors contributing to sleep quality in patients with SLE and diabetes.

We aimed to study the sleep breathing disorders among diabetic patients with SLE and associated relationship with both disease activity and severity.

PATIENTS AND METHODS

This comparative case-control study included 30 SLE diabetic patients admitted to Chest Department, Menoufia University Hospitals in the period from June 2018 to July 2021 to evaluate their sleep pattern changes and 30 healthy individuals as a control.

SLE was diagnosed according to the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria [4].

A through history and clinical examination including general and rheumatological examination were done. Laboratory investigations as fasting blood sugar and HBA1c for diagnosis of diabetes, erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA) and antidouble stranded antibodies (Anti-DNA) were done. Plain chest X-ray, ECG, echocardiography and high-resolution CT chest were done when needed.

Epworth sleepiness score (ESS) and SELDAI score for activity of SLE were calculated [5]**.** Also, resting arterial blood gases and post exercise arterial blood gases (After six minutes' walk) was measured. Pulmonary function tests were done using (Quark, PFT, Italy). The following measurements were done to all patients in the sitting position: Forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), FEV1/FVC ratio and maximum voluntary ventilation (MMV).

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Complete overnight polysomnography was, using EMBLA S 4000 system (Iceland), was done over the course of a whole night in the Sleep Lab of the Chest Department (8 hours sleep). The system records the following parameters: Oxygen saturation, snoring, body position and the respiratory effort chart displays amplitude of respiratory effort over one second.

Results of polysomnography:

Apnea index (AI): is defined as the total stoppage of breathing via the lips and nostrils for a period of at least 10 seconds.

Hypopnea index (HI): is characterised as a 50% drop in breathing rate and depth that lasts for at least 10 seconds.

Apnea–hypopnea index (AHI): It is the typical quantity of apneas and hypopneas per sleeping hour. Those with an AHI 5 are not regarded as having Obstructive sleep apnea (OSA). On the other hand, an AHI > 5 and 15 is regarded as mild OSA, an AHI > 15 and 30 as moderate OSA, and an AHI > 30 as severe OSA [6].

Ethical approval:

This study was ethically approved by the Menoufia University's (IRB Approval number: 11/22 INTM5). After being fully informed, all participants provided written consent. The study was conducted out in line with the Helsinki Declaration.

Statistical analysis

For data entry and analysis, IBM SPSS software, version 20.0, was utilized (IBM Corporation, Armonk, New York). In order to present categorical data, numbers and percentages were used and Chi^2 was used to compare them.

The Shapiro-Wilk test was used to assess the normality of continuous data. Quantitative data were expressed using the terms range (minimum and maximum), mean, standard deviation, and median. The student t-test was used to compare two sets of quantitative data that were regularly distributed. In order to compare two groups for quantitative characteristics that were not normally distributed, the Mann Whitney test (U test) was used. The correlation between two quantitative variables was determined using the Pearson coefficient. The significance of the results was established at the 5% level.

RESULTS

With reference to gender, age, and neck circumference, there was no significant difference between the two groups. However, BMI and ESS showed a statistically significant difference between cases and control groups **(Table 1)**.

Table (1): Comparison of the two study groups based on demographic information

	Cases (n = 30)	**Control (n = 30)**	**Test of sig.**	**p**
	Mean ± SD.	Mean ± SD.		
Gender				
Male	6 (20%)	10 (33.3%)	χ^2= 1.364	0.243
Female	24 (80%)	20 (66.7%)		
Age (years)	45.9 ± 4.2	45.7 ± 4.2	t=0.245	0.807
BMI (kg/m^2)	28.4 ± 2.3	25.9 ± 2.2	t=4.302	**0.001***
Neck circumference (cm)	40.2 ± 2.1	39.1 ± 2.3	t=1.907	0.061
ESS	18.5 ± 1.4	5.8 ± 0.7	t=43.303*	**<0.001***

*: Statistically significant

Diabetic patients with SLE have a lower significant FVC %, FEV1/ FVC%, FEF25%-75% and MVV than controls **(Table 2).**

Table (2): Comparison of the outcomes of the lung function tests between the study groups

	Cases (n = 30)	**Control (n = 30)**	**t**	**p**
	Mean ± SD	Mean ± SD		
FVC %	50 ± 12.3	87.2 ± 1.9	16.296*	<0.001*
FEV1/FVC **%**	92.4 ± 2	96.7 ± 2	8.372*	<0.001*
FEF25%-75%	58.4 ± 5.3	93.4 ± 3.1	31.117*	<0.001*
MVV (L/min)	57.1 ± 2.7	81.8 ± 2.1	40.258*	<0.001*

*: Statistically significant

Regarding polysomnographic findings, diabetic patients with SLE have a lower significant total sleep time (TST), sleep onset, sleep efficiency (%), percent of sleep in supine than controls. However, diabetic patients with SLE have a higher significant Spon Arousal index, no of awaking/hour, low limitation index and apnea/hypopnea index in supine than controls. In the two groups, there was no significant change in REM latency/minute **(Table 3).**

Table (3): Comparison of the two examined groups based on the findings of the polysomnography

	Cases (n = 30)	**Control (n = 30)**	**Test of sig.**	**p**
	Mean ± SD	Mean ± SD		
Total sleep time (TST) (minute)	270.7 ± 5.4	294.0 ± 11.8	t= 9.804	<0.001*
Sleep onset (minute)	38.1 ± 6	45.2 ± 6.6	t= 4.346	<0.001*
Sleep efficiency (%)	63.4 ± 4.4	88.4 ± 2	t= 28.066	<0.001*
REM latency/min	239.4 ± 59.4	223.9 ± 49.8	t= 1.098	0.277
Spon Arousal index	76.4 ± 19.5	50.2 ± 7.2	t= 6.923	<0.001*
No of awaking/h	48.3 ± 9.1	1.7 ± 0.7	U= 23.50	<0.001*
Flow limitation index	34.1 ± 14.4	17.8 ± 9	U= 119.50	<0.001*
% of sleep in supine	63.5 ± 12.5	69.3 ± 12.4	U= 291.0	0.018*
A+H in supine	16 ± 4.9	8.1 ± 2.4	U= 38.50	<0.001*

*: Statistically significant

Diabetic patients with SLE have a higher significant periodic leg movements during sleep (PLMS) sequence, apnea/hypopnea index (AHI), oxygen desaturation events (OD), percent of snoring time in TST, percent of REM in TST, total AHI in non-rapid eye movement sleep (NREM), total AHI in rapid eye movement sleep (REM), ESR, CRP, uric acid and FBS than controls. However, they have a lower significant average oxygen saturation% and lowest oxygen saturation (%) than controls **(Table 4).**

Table (4): Comparison of the two research groups based on many criteria

	Cases (n = 30)	**Control (n = 30)**	**Test of Sig.**	**p**
	Mean ± SD	Mean ± SD		
PLMS sequence	2.9 ± 1.3	0 ± 0	t= 12.540*	<0.001*
Average Oxygen saturation%	87.7 ± 4.7	95.6 ± 1.1	t= 9.024*	<0.001*
Lowest Oxygen saturation%	80.1 ± 9.9	90.3 ± 4.7	t= 5.107*	<0.001*
AHI	24.7 ± 2.2	6.2 ± 0.9	t= 43.379*	<0.001*
OD	24.7 ± 2.2	3.7 ± 0.8	t= 50.493*	<0.001*
% of snoring time in TST	11.4 ± 2.2	2 ± 1	U= 0.000*	<0.001*
% of REM in TST	16.2 ± 1.3	12.5 ± 2.1	t= 8.10*	<0.001*
Total AHI in NREM	109.4 ± 8.5	6.2 ± 1.4	t= 65.938*	<0.001*
Total AHI in REM	36.6 ± 7.6	10.3 ± 1.1	U= 0.000*	<0.001*
ESR	64.8 ± 36.1	16.9 ± 8.4	t= 7.066*	<0.001*
CRP			χ^2= 32.308*	<0.001*
Negative	9 (30.0%)	30 (100.0%)		
Positive	21 (70.0%)	0 (0.0%)		
Uric acid	5.1 ± 1.1	3.8 ± 0.9	t= 4.729*	<0.001*
FBS	178.1 ± 47.4	92.9 ± 10.2	t= 9.625*	<0.001*

*: Statistically significant

Regarding arterial blood gases (ABG), there was a significant difference between (ABG) before and after exercise (6-minute walk), between cases and controls regarding pH, $PaCO_2$, PaO_2 and O_2 saturation **(Table 5).**

Table (5): Comparison of arterial blood gases in the studied groups, before and after exercise (6-minute walk)

	Before	After	t	p
	Mean ± SD.	Mean ± SD.		
PH				
Cases (n = 30)	7.4 ± 0	7.4 ± 0	3.321*	0.002*
Control (n = 30)	7.4 ± 0	7.4 ± 0	2.078*	0.047*
t_1 (p_1)	**0 (1)**	**0 (1)**		
$PaCO_2$				
Cases (n = 30)	41.3 ± 1.5	43.3 ± 1.1	6.927*	<0.001*
Control (n = 30)	38 ± 1	41.1 ± 0.8	12.102*	<0.001*
t_1 (p_1)	**10.053* (<0.001*)**	**8.637* (<0.001*)**		
PaO_2				
Cases (n = 30)	79.3 ± 2.3	63.1 ± 4.8	17.681*	<0.001*
Control (n = 30)	85.6 ± 1.5	93 ± 3	11.290*	<0.001*
t_1 (p_1)	**12.838* (<0.001*)**	**27.520* (<0.001*)**		
O_2 sat				
Cases (n = 30)	91.5 ± 0.9	87.6 ± 2.3	8.464*	<0.001*
Control (n = 30)	96.4 ± 0.9	92 ± 3.2	7.396*	<0.001*
t_1 (p_1)	**20.485* (<0.001*)**	**6.105* (<0.001*)**		

*: Statistically significant

In case group, mean of Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and of HBA1c are shown in table 6. 70% of the patients were active**.**

Table (6): Results of the studied patients regarding SLEDAI, activity, and HBA1c (n = 30)

SLEDAI	
Mean ± SD.	7.6 ± 3
Median (Min. – Max.)	7 (3 – 13)
Activity	
Non, **No. (%)**	9 (30.0%)
Active, **No. (%)**	21 (70.0%)
HBA1c	
Mean ± SD.	7.6 ± 1.1
Median (Min. – Max.)	7.5 (5.9 – 10)

There was a significant positive correlation between apnea hypopnea index with ESR, CRP, HBA1c (%) and Anti-ds DNA **(Table 7).** Also, there was a positive significant correlation between SLEDAI and HBA1c with FVC% **(Table 8).**

Table (7): The correlation between the apnea hypopnea index and patient investigations in the cases group (n = 30)

	AHI	
	r	**P**
ESR	0.74	**<0.001***
CRP	0.73	**<0.001***
HBA1C (%)	0.72	**<0.001***
ANA (MG/DL)	0.50	0.08
ANTI-DS DNA (MG/DL)	0.44	**0.02***

r: Pearson coefficient. *: Statistically significant

Table (8): The correlation between SLEDAI, HBA1c and FVC, ESS, fev1/FVC in cases group (n = 30)

	SLEDAI		HBA1c	
	r	**p**	**R**	**p**
FVC %	-0.735	**<0.001***	-0.523	**0.003***
ESS	-0.011	0.953	0.103	0.589
FEV1/FVC%	-0.024	0.898	-0.178	0.345

r: Pearson coefficient. *: Statistically significant

DISCUSSION

Due to gas exchange constraints, patients with SLE are more prone to experience sleep disordered breathing. Hypoxemia during the day produces muscular weakness and weariness, which can lead to hypoventilation [3]. Due to overlapping symptoms, sleep-related breathing disorders (SRBDs) are still under-diagnosed in individuals with SLE and diabetes. Although fatigue is a somewhat general symptom, sleep disorders usually manifest alongside fatigue, and accompanying symptoms, such as daytime sleepiness and overnight respiratory difficulties, may be typical manifestations of both conditions [7].

Sleep disturbance in patient with SLE may contribute to development of diabetes. Elevated cortisol levels due to steroid treatment in SLE patients have been connected to a greater distribution of body fat in the center, which is correlated with insulin resistance [8]. Swelling and sympathetic activity are both increased and may be involved in the relationship between sleep disturbance and diabetes risk. Both are triggered by sleep disturbance and have been related to insulin resistance and, ultimately, T2DM. In laboratory models, sleeplessness has also been shown to accelerate cell function loss and enhance cell apoptosis with increased cell mass loss [9]. Finally, sleep deprivation can produce weariness, which can lead to a decrease in the physical activity levels and intensity, which may have an impact on the development of T2DM [10].

Age, gender, and neck circumference did not significantly differ between patients and controls in this study, however there was a highly statistically significant difference in BMI and ESS. This is in line with **Peppard *et al.*** [11] earlier research, which demonstrated that regardless of age, gender, sleeping position, smoking history, baseline SaO_2, or event duration, BMI is a significant predictor of the severity of oxygen desaturation during apneic and hypopneic episodes of sleep disordered breathing.

Also in the current study, diabetic Patients with SLE have a lower significant FVC%, FEV1/FVC%, FEF25 %-75% and MVV than controls.

Diabetic patients with SLE have lower significant total sleep time (TST), sleep start, sleep efficiency (%), and percent of sleep in supine than controls, according to research on the characteristics and quality of sleep in SLE patients. The major Factors Arousal index, the number of awakened/hour, the low limitation index, and the apnea/hypopnea index in supine are all higher in diabetic patients with SLE than in controls. In the two groups, there was no significant change in REM latency/minute. These results agree with a study done by **Rogelio *et al.*** [12] on forty SLE patients and they found that sleep is lighter and more fragmented with decreased SE and increased apnea/hypopnea index in SLE patients.

The results of the current study demonstrated a relationship between the degree of restrictive pulmonary functions in SLE patients and data of polysomnography and it has been found that patients with SLE have a higher significant PLMS sequence, AHI, OD, percent of snoring time in TST, percent of REM in TST, total AHI in NREM, total AHI in REM, ESR, CRP, uric acid and FBS than controls. However, they have a lower significant average oxygen sat% and lowest oxygen saturation% than controls. Several studies have found lower sleep efficiency in SLE patients, which is consistent with our findings [13]. Previous investigations revealed that SLE patients had lower sleep efficiency compared to healthy controls and higher sleep latency, greater levels of sleep fragmentation, more arousals, more awake time at night [14-15]. **Meidan *et al.*** [16] investigated the sleep disturbance in SLE patients and healthy controls. They discovered that the AHI, ODI, and RDI scores in the SLE group were higher than those in the control group (9.2 ± 6.8 vs. 3.9 ± 3.5, $p = 0.004$, 2.5 ± 2.7 vs. 1.3 ± 1.4, $p = 0.04$ and 13.5 ± 6.5 vs. 9.7 ± 3.6, respectively).

The current study demonstrated that there was a significant positive correlation between apnea hypopnea index with ESR, CRP, HbA1c (%) and Anti-ds DNA. Also, there was a positive significant correlation between SLEDAI and HBA1c with FVC%. Case group showed significantly elevated mean of FBS (178.1 ± 47.4) and HBA1c (7.6 ± 1.1). This is consistent with the findings of **Magadmi *et al.*** [17], who found that SLE patients had considerably worsened insulin resistance compared to healthy controls. Also, **Gazareen *et al.*** [18] reported that, with respect to insulin sensitivity profile, SLE patients have significantly higher fasting insulin, HBA1c, HOMA IR, HOMA b-cell, and C-peptide than controls, and there is a positive correlation between IR and fasting glucose, HOMA b-cell, and C-peptide in SLE patients**.** This is in line with the findings of **Chandrasekhara *et al.*** [7], who hypothesized that the most significant cause of sleep disruption in SLE patients is disease activity, which may be partly attributed to patients' reduced levels of physical activity. Additionally, it has been discovered that abnormal periodic limb movements are very common in SLE, with one study in particular demonstrating a threefold increased prevalence of "restless leg syndrome".

The research by **Iaboni *et al.*** [19] had a tiny sample size of 35; the study by **Valencia-Flores *et al.*** [20] had a small sample size of 14. According to their research, SLE patients typically experience stage transitions, a high proportion of alpha intrusions into NREM sleep, an increase in stage 1 sleep, and a decrease in stage 3–4 slow-wave deep sleep.

In both the general population and individuals with chronic conditions like SLE and diabetes, sleep problems have been demonstrated to compromise health-related quality of life [21-22]. Few studies have looked at how sleep disruption affects SLE patients' health-related quality of life. So, this provides yet another crucial subject for further studies.

Bromley *et al.* [10] found that in patients with poorly controlled diabetes (HbA1C ≥ 7%), intermittent hypoxia, a consequence of sleep apnea, is prevalent (37.2%). In addition, It was closely related to having poor glycemic control (OR: 2.31, 95%CI: 1.06-5.04) **[23]**. Further research is required to determine whether OSA may eventually cause the development of DM, as it is yet unclear whether this is the case.

In contrast to our research, **Sahebari *et al.* [24]** study found that more than half of newly diagnosed lupus patients had sleep abnormalities, particularly sleep apnea. Although, there was no significant difference between the lupus patients and the healthy controls at least at the beginning of the illness, hence, it can be said that in the early stages of the disease, the lupus condition has no appreciable impact on the development of sleep disturbances. Sleep quality in those individuals appears to be more affected by the chronicity and complexities of the illness, as well as the use of glucocorticoid medication for the chronic illness that eventually results in diabetes.

Our sample size was rather limited, and research with bigger patient samples is needed for more accurate assessments given the numerous possible variables to sleep quality. This is one of the study's shortcomings. Second, we did not assess the impact of steroid and other SLE-related medications on sleep disorders.

CONCLUSION

Diabetic patients with SLE have changes in the sleep pattern in the form of increased AHI, the number of awakenings, arousals/night and decreased FVC%. Poor glycemic control and increased disease activity score (SELDAI) may predispose to the incidence of these changes. Therefore optimum treatment of the disease activity together with good glycemic control is required for management of those patients.

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