Research Article / Araştırma Makalesi

The Relationship Between Chronic Fatigue, Sleep quality, and Melatonin Levels in Sjogren's Syndrome

Sjögren Sendromu Tanılı Hastalarda Kronik Yorgunluğun Uyku Durumu ve Melatonin Düzeyi ile İlişkisi

Oğur KARHAN [1], Ali Berkant AVCI [2], İkbal Özen KÜÇÜKÇETİN [3], Veli YAZISIZ [4]

[1]Department of Medical Oncology, Faculty of Medicine, University of Harran, Şanlıurfa, TÜRKİYE
[2]Department of Rheumatology, Antalya Medical Park Hospital , Antalya , TÜRKİYE
[3]Department of Medical Biochemistry , Faculty of Medicine, Akdeniz University, Antalya , TÜRKİYE
[4]Department of Medical Rheumatology , Faculty of Medicine, Akdeniz University, Antalya , TÜRKİYE

Abstract

Background: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease and majority of patients have fatigue and insomnia. Melatonin has many functions in addition to improving sleep quality and duration.The aim of this study was to explore the relationship between fatigue and insomnia, and the association of melatonin levels with fatigue and insomnia in patients with pSS.
Materials and Methods: This cross-sectional cohort study included 116 patients and 27 healthy controls. Epworth Sleepiness Scale (ESS), Fatigue Severity Scale (FSS) and SF-36 questionnaires were obtained from patients. Melatonin was measured by ELISA from the patients' serum.
Results: Patients with pSS exhibited greater fatigue compared to the control group, additionally, patients with somnolence exhibited higher levels of fatigue compared to those without somnolence. The median melatonin level was 239 ng/L (189-460) in patients with fatigue and 266 ng/L (219-552) in patients without fatigue (p=0.11). Patients with and without daytime sleepiness had similar melatonin levels, too. The median melatonin level was 429 ng/L (268-774) in healthy controls compared to 254 ng/L (197-491) in patients with PSS (p=0.0098) The quality of life, as measured by the SF-36, was significantly worse in patients with fatigue across all subgroups compared to those without fatigue. There was no correlation between melatonin levels and the subparameters of the SF-36.
Conclusions: Fatigue had a negative impact on both quality of life and sleepiness. Those who experienced sleepiness had a poorer quality of life. Early morning serum melatonin levels were lower in PSS patients. There was no significant difference in mean serum melatonin levels between patients with and without fatigue. No correlation was found between serum melatonin levels and quality of life.

Keywords: Sjogren's syndrome, Fatigue, Sleepiness, Melatonin, Quality of life

Öz

Amaç: Primer Sjögren sendromu (pSS), sistemik bir otoimmün hastalıktır ve hastaların çoğu yorgunluk ve uykusuzluk yaşamaktadır. Melatonin, uyku kalitesini ve süresini iyileştirmenin yanı sıra birçok farklı işlevi olan bir hormondur. Bu çalışmanın amacı, yorgunluk ve uykusuzluk arasındaki ilişkiyi ve melatonin seviyelerinin yorgunluk ve uykusuzluk ile olan bağlantısını pSS hastalarında araştırmaktır.
Materyal ve Metod: Bu kesitsel kohort çalışmasına 116 hasta ve 27 sağlıklı kontrol dahil edilmiştir. Epworth Uykululuk Ölçeği (ESS), Yorgunluk Şiddeti Ölçeği (FSS) ve SF-36 anketleri hastalardan elde edilmiştir. Hastaların serum melatonin seviyeleri ELISA yöntemiyle ölçülmüştür.
Bulgular: pSS hastaları kontrol grubuna kıyasla daha fazla yorgunluk göstermiştir. Ayrıca, gündüz aşırı uykululuğu olan hastalar, olmayanlara göre daha yüksek yorgunluk seviyelerine sahipti. Yorgunluğu olan hastalarda medyan melatonin seviyesi 239 ng/L (189-460) iken, yorgunluğu olmayan hastalarda 266 ng/L (219-552) olarak ölçülmüştür (p=0.11). Gündüz aşırı uykululuğu olan ve olmayan hastaların melatonin seviyeleri benzer bulunmuştur. Sağlıklı bireylerde medyan melatonin seviyesi 429 ng/L (268-774) iken, pSS hastalarında 254 ng/L (197-491) olarak ölçülmüştür (p=0.0098). SF-36 ile ölçülen yaşam kalitesi, yorgunluğu olan hastalarda tüm alt gruplarda yorgunluğu olmayanlara kıyasla anlamlı derecede daha kötüydü. Melatonin seviyeleri ile SF-36'nın alt parametreleri arasında bir korelasyon bulunmamıştır.
Sonuç: Yorgunluk, hem yaşam kalitesi hem de uyku hali üzerinde olumsuz etkiye sahiptir. Gündüz uykululuğu yaşayan hastalar daha düşük yaşam kalitesine sahiptir. pSS hastalarında sabah erken saatlerde ölçülen serum melatonin seviyeleri daha düşük bulunmuştur. Yorgunluğu olan ve olmayan hastalar arasında serum melatonin seviyeleri açısından anlamlı bir fark saptanmamıştır. Ayrıca, serum melatonin seviyeleri ile yaşam kalitesi arasında bir korelasyon bulunmamıştır.

Anahtar Kelimeler: Sjögren sendromu, Yorgunluk, Uykululuk, Melatonin, Yaşam kalitesi

Corresponding Author / Sorumlu Yazar

Dr. Oğur KARHAN
Department of Medical Oncology, Faculty of Medicine, University of Harran, Şanlıurfa, TÜRKİYE

E-mail: dr_karhan@harran.edu.tr

Received / Geliş tarihi: 03.02.2025

Accepted / Kabul tarihi: 28.02.2025

DOI: 10.35440/hutfd.1631258

This study belongs to the year 2015 as an internal medicine specialty thesis with the number 10085970.

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by lymphocytic infiltration of the salivary and lacrimal glands (1). Besides sicca symptoms and arthralgia, nearly 70% of patients report fatigue, one of the most debilitating symptoms (2). Additionally, patients with pSS experience poorer sleep quality and insomnia (3, 4). Those with poor sleep quality exhibit higher levels of fatigue compared to those with good sleep quality (5). Quality of life (QoL) is significantly impaired in pSS patients compared to control groups (6). Fatigue is one of the primary predictors of poor QoL in pSS patients, regardless of other factors such as disease activity, age, and fibromyalgia (7) . Conflicting results have been reported regarding the relationship between serum cytokine levels and fatigue. While one study found no direct correlation between fatigue and serum cytokine levels (8), another study associated high levels of inflammatory cytokines with fatigue (9). A meta-analysis highlighted numerous discrepancies between fatigue and inflammatory markers in pSS patients (10).

Melatonin is the primary product of the pineal gland, secreted in a circadian manner, and has various physiological functions, including immune regulation, anti-infection, antioxidant, and anti-aging properties (11). External administration of melatonin regulates the immune response and ameliorates Sjögren's-like syndrome in rats (12). In a recent study, melatonin reduced lymphocytic infiltration, effectively prevented glandular damage, and maintained the functional integrity of the salivary glands in NOD mice by inhibiting IL-6/STAT3 (interleukin-6/signal transducer and activator of transcription 3 pathway) through receptor-dependent manner (13).

In addition, melatonin improves both the quality and duration of sleep (11). Melatonin levels are lower in patients with systemic lupus erythematosus (SLE) compared to controls, and this difference is related to disease activity (14). Similarly, serum melatonin levels are lower in pSS, which is associated with disease activity (15).

Unfortunately, there is still a lack of large-scale studies examining melatonin levels and their correlation with clinical features in patients with pSS. In this study, we aim to explore the relationship between fatigue and insomnia, and the association of melatonin levels with fatigue and insomnia in patients with pSS. Additionally, we seek to investigate the relationship between fatigue, sleep deprivation, and quality of life, as well as the correlation between serum melatonin levels and quality of life.

Materials and Methods

This is a cross-sectional cohort study was approved by the Ethics Committee of Akdeniz University (Approval no: 296; Date 18.06.2014). The study was conducted in accordance with the Declaration of Helsinki and informed consent forms were obtained from the patients whose data were used in the study, indicating their acceptance of the treatment. The study was conducted at the Department of Rheumatology, Akdeniz University Hospital. A total of 116 patients with PSS and 27 healthy controls were enrolled. Patients diagnosed with pSS over the age of 18 were included in the study. Individuals under the age of 18, those with pregnancy, and other rheumatological diseases, hepatitis C, sarcoidosis, malignancy, or a history of radiotherapy were excluded from the study.

All patients signed an informed consent form. Demographic data such as age, sex, main symptoms at the time of diagnosis, anti-nuclear antibody (ANA), romatoid factor (RF), anti-SSA, anti-SSB positivity, erythrocyte sedimentation rate and CRP levels were collected from the medical records. Patient blood samples were collected between 9:00 am and 10:00 am and stored at -80 °C until analysis. Melatonin was measured by ELISA test from patients serum. The study obtained ethical approval from the institutional review board.

The Epworth Sleepiness Scale (ESS) was used to measure participants' sleepiness state (ESS) (16). The ESS consists of 8 items in which the rate of the tendency to sleepy state ranges from zero to three for each of the items. The activities listed include sitting and reading, watching television, passive sitting in a public area, being a passenger in a vehicle for at least an hour without interruption, reclining for rest in the afternoon when possible, engaging in seated conversation, sitting quietly post-lunch without alcohol, and remaining in a stationary car during traffic for a few minutes. A higher score reflects an increased propensity for daytime sleepiness. A cumulative score of 10 or more suggests insufficient sleep

The severity of fatigue and its effect on daily activities were evaluated using the Fatigue Severity Scale (FSS) (17). This scale comprises nine items designed to assess fatigue symptoms by considering their influence on motivation, physical activity, functional capacity, and daily tasks. The FSS is scored by computing the mean of all nine items, with elevated scores reflecting greater fatigue severity. A total score of 36 or above indicates the presence of significant fatigue.

The health-related quality of life of the patients was evaluated utilizing the SF-36 instrument (18). The SF-36 consists of 8 domains representing physical functioning, physical role, bodily pain, mental health, emotional role, social functioning, vitality, and general health. Each of these domains has values between 0 and 100, with lower values indicating a lower quality of life.

Descriptive statistics were presented using mean, standard deviation, median, and interquartile range values. To compare continuous variables between two groups, the Student's t-test and Mann-Whitney U test were used for normally distributed and non-normally distributed data, respectively. The chi-square test was utilized to assess cate-

gorical variables between the two groups. Correla tion analysis was conducted using the Spearman correlation test for nonparametric data. Normality assumptions were evaluated using the Kolmogorov-Smirnov test, and significance was set at a p-value ≤ 0.005.

Results

This cross-sectional study included 116 patients diagnosed with pSS and 27 healthy controls. The majority of participants in both groups (109 out of 116 patients and 26 out of 27 healthy individuals) were female. The mean age of the patients was 48 years, compared to 47 years in the control group. At the time of diagnosis, half of the patients experienced arthralgia, 85.3% had xerostomia, and 78% presented with xerophthalmia. The main characteristics of the patients are outlined in Table 1.

Table 1. Main characteristics of patients at the time of diagnosis

		N (%)
RF	**positive**	24 (20.6)
ANA	**positive**	74 (63.8)
Schirmer	**sağ (≤5 mm)**	51 (43.9)
Schirmer	**sol (≤5 mm)**	51 (43.9)
BUT	**sağ (≤10 sn)**	53 (45.6)
BUT	**sol (≤10 sn)**	52 (44.8)
Anti SSA	**positive**	41 (35.3)
Anti SSB	**positive**	26 (22.4)
ESR*		31 (26.7)
CRP*		25 (21.5)

**Values of at the time of melatonin measurement*
ANA: Antinuclear antibody; BUT: Breakup time; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; mm: Millimeter; N: Number; RF: Rheumatoid factor; sec: Second

The relationship between fatigue and sleepiness

Patients with pSS exhibited greater fatigue compared to the control group, with 59.1% (n=68) of patients and 0% (n=0) of controls reporting fatigue (p=0.000). Patients with PSS experienced significantly higher daytime sleepiness than the control group, with a prevalence of 36.9% compared to 0% in healthy individuals. Moreover, those experiencing somnolence reported greater fatigue levels than those without. Among patients with sleepiness, fatigue prevalence was 79.5%, whereas it was 45.8% in those without sleepiness (*p*=0.001), as detailed in Table 2.

The median melatonin level was 239 ng/L (189-460) in patients with fatigue and 266 ng/L (219-552) in patients without fatigue (p=0.11). Patients with and without daytime sleepiness had similar melatonin levels, with a median of 234 ng/L (191-363) in those with daytime sleepiness and 270 ng/L (202-603) in those without daytime sleepiness (p=0.11). Healthy controls exhibited higher melatonin levels than patients with PSS. The median melatonin level was 429 ng/L (268-774) in healthy controls compared to 254 ng/L (197-491) in patients with PSS (p=0.0098). The quality of life, as measured by the SF-36, was significantly worse in patients with fatigue across all subgroups compared to those without fatigue Table 3.

Similarly, patients with daytime sleepiness demonstrated a lower quality of life across all subdomains of the SF-36 compared to those without daytime sleepiness (Table 4). The affected quality of life parameters included physical functioning, physical role functioning, pain, general health, vitality, social functioning, emotional role functioning, and mental health.

The relationship between melatonin levels and the subparameters of the SF-36 was examined. There was no correlation between physical functioning and melatonin levels (r=0.02, p=0.787). Similarly, no correlation was observed between physical role functioning and melatonin levels (r=0.07, p=0.44). All other subparameters also showed no significant correlations Table 5.

Table 2. The Relationship Between Sleepiness and Fatigue

Sleepiness* Fatigue		Fatigue		Total	P
		No	Yes		
Without sleepiness	N	39	33	72	0,001
	%	54,2%	45,8%	100,0%	
Sleepiness	N	9	35	44	
	%	20,5%	79,5%	100,0%	
Total	N	48	68	116	
	%	41,4%	58,6%	100,0%	

Table 3. Comparison of Quality of Life Between PSS Patients With Fatigue and Those Without Fatigue

	Fatigue Median (IQR)	Not fatigue Median (IQR)	P value
Physical functioning	45 (25-57.5)	67 (50-80)	P<0.0001
Physical role functioning	0 (0-50)	100 (12.5-100)	P<0.001
Pain	32 (21-44)	44 (40-64)	P<0.0001
General health	33 (29-37)	50 (45-58)	P<0.0001
Vitality	30 (20-40)	45 (30-60)	P=0.0007
Social functioning	50 (25-62,5)	75 (62,5-87,5)	P<0.0001
Emotional role functioning	0.5 (0-66)	100 (33-100)	P<0.0001
Mental health	40 (32-54)	52(44-64)	P=0.0001

IQR: Interquartile range

Table 4. Comparison of Quality of Life Between pSS Patients With Daytime Sleepiness and Those Without Daytime Sleepiness

	Patients with daytime sleepiness Median (IQR)	Patients without daytime sleepiness Median (IQR)	P value
Physical functioning	37.5 (25-50)	60 (40-75)	P=0.0002
Physical role functioning	0 (0-25)	75 (0-100)	P=0.0001
Pain	22 (20-44)	43 (30-54)	P=0.0003
General health	29 (16-39)	45 (37-58)	P<0.0001
Vitality	25 (20-35)	35 (30-55)	P=0.0007
Social functioning	50 (25-62.5)	62 (50-87.5)	P<0.0001
Emotional role functioning	0 (0-33)	66 (33-100)	P<0.0001
Mental health	40 828-52)	48 (36-60)	P=0.0192

Table-5. SF-36 subparameters and melatonin level

	r value	P value
Physical functioning and melatonin	0.02	P=0.787
Physical role functioning and melatonin	0.07	P=0.44
Pain and melatonin	0.07	P=0.42
General health and melatonin	0.11	P=0.23
Vitality and melatonin	0.03	P=0.71
Social functioning and melatonin	-0.006	P=0.95
Emotional role functioning and melatonin	0.10	P=0.29
Mental health and melatonin	0.02	P=0.76

Discussion

Fatigue is commonly associated with numerous rheumatologic diseases, including primary Sjögren's Syndrome (pSS). Nearly two-thirds of individuals with pSS experience fatigue (2). In our study, we found that 59.1% of patients reported fatigue, while none of the control group did. This finding aligns with existing literature indicating that fatigue is more prevalent in pSS patients compared to controls. Additionally, our study revealed that patients with pSS experienced more daytime sleepiness than the control group (36.9% vs. 0%). In a previous study (4), 55% of pSS patients reported excessive daytime sleepiness, though it included only 32 patients compared to our 116 patients, which may account for the discrepancy. Consistent with our findings, a meta-analysis also indicated that patients with pSS experience more sleep disturbances than controls (19).

In our study, we observed that patients with daytime sleepiness exhibited higher levels of fatigue compared to those without sleepiness. A study conducted in Brazil also identified a positive correlation between sleep disorders and fatigue (5). Additionally, another study found that patients with pSS experienced more sleep disturbances than the control group, and these disturbances may contribute to fatigue (20). These findings collectively suggest a strong relationship between sleepiness and fatigue.

Melatonin is a hormone secreted in a circadian rhythm, known for its diverse functions including antioxidant promotion, neural survival, circadian rhythm regulation, and sleep regulation (21). In the context of rheumatologic diseases, melatonin supplementation has shown positive effects in conditions such as fibromyalgia, osteoarthritis, and osteoporosis, but not in rheumatoid arthritis and lupus (22). Melatonin is thought to modulate T and B lymphocyte functions, inhibit inflammatory signals, downregulate apoptosis, and improve sleep, which has led to the hypothesis that melatonin could ameliorate symptoms of primary Sjögren's Syndrome (11).). For instance, melatonin administration has been found to alleviate Sjögren's-like symptoms in mice (12). In our study, we discovered that morning melatonin levels were significantly lower in patients with pSS compared to the control group. This result suggests that melatonin dysregulation may play a role in the etiology of pSS.

Interestingly, in our study, we found no statistically significant difference in melatonin levels between patients with and without sleep disturbance. The melatonin level was 234 ng/L (191-363) in patients with sleepiness and 270 ng/L (202-603) in patients without sleepiness. Similarly, in a study involving idiopathic Parkinson's disease, no correlation was observed between sleep quality and morning melatonin levels (23).). Since melatonin follows a circadian rhythm, serial measurements may be more appropriate than early morning measurements. Moreover, factors such as age, depression and anxiety, pain, and sicca symptoms may influence sleep quality in PSS (24).

Having established that patients with sleep disorders experience heightened fatigue, we aimed to investigate the correlation between fatigue and melatonin levels in patients with pSS. The etiology of fatigue in pSS has been extensively explored, with studies focusing on serum cytokine levels. For instance, one study revealed elevated levels of tumor necrosis factor-α (TNFα), interferon-α (IFNα), interferon-γ (IFN-γ), and lymphotoxin-α (LT-α) in patients with pSS compared to non-fatigued controls (9). Additionally, interleukin-6 levels were found to be higher in PSS patients with fatigue (25). In our study, we observed no disparity in melatonin levels between patients with and without fatigue.

Similarly, in another study, there was no significant variation in melatonin levels between patients with chronic fatigue syndrome and controls (26).

As expected, fatigue is one of the main predictors of poor quality of life in PSS (7, 27). In our investigation, patients experiencing fatigue exhibited lower quality of life across all domains assessed by the SF-36. This observation aligns with existing literature. Furthermore, our findings indicate that patients with daytime sleepiness also experience reduced quality of life across all aspects evaluated by the SF-36 test. Previous research has demonstrated a link between poor sleep quality and diminished quality of life (28), with another study among Chinese PSS patients highlighting a significant correlation between poor sleep quality and declining quality of life (29). In addition to the association between fatigue and sleepiness in PSS patients, our study reveals that both fatigue and sleepiness exert a negative impact on the quality of life among individuals with PSS.

Finally, our analysis revealed no significant correlation between melatonin levels and quality of life across all SF-36 domains, including physical functioning, physical role functioning, pain, general health, vitality, social functioning, emotional role functioning, and mental health**.** While melatonin administration has been shown to improve quality of life in patients with fibromyalgia (30), it did not have the same effect in cancer patients (31). Given melatonin's diverse functions, further research is warranted to explore the relationship between melatonin and quality of life.

Our study has some limitations. First, being a cross-sectional study, we measured melatonin levels at a single point in time. Considering melatonin's circadian rhythm, serial measurements may provide more accurate data. Second, we only measured serum melatonin levels, whereas salivary and urinary melatonin levels could also be informative. Finally, the potential effects of melatonin supplementation on sleep, fatigue, and quality of life were not assessed in our study, and our results did not include information on melatonin supplementation.

Conclusions

In patients with pSS, fatigue negatively impacted both quality of life and sleepiness, with those experiencing sleepiness having a poorer quality of life. Early morning serum melatonin levels were lower in pSS patients compared to controls. There was no significant difference in median serum melatonin levels between patients with and without fatigue, and no correlation was found between serum melatonin levels and quality of life. There is a need for both basic research and large-scale clinical trials with a larger patient cohort to explore the effects of melatonin on pSS-related chronic fatigue and sleep disorders, its influence on the consequent decline in quality of life, and its potential role in the treatment of primary sjögren's syndrome.

Ethical Approval: *This is a cross-sectional cohort study was approved by the Ethics Committee of Akdeniz University (Approval no: 296; Date 18.06.2014). The study was conducted in accordance with the Declaration of Helsinki and informed consent forms were obtained from the patients whose data were used in the study, indicating their acceptance of the treatment.*

Author Contributions:
Concept: A.B.A, O.K, V.Y
Literature Review: O.K, İ.Ö.K, V.Y.
Design : A.B.A, O.K.
Data acquisition: O.K.
Analysis and interpretation: A.B.A, O.K, V.Y, İ.Ö.K.
Writing manuscript: A.B.A, O.K.
Critical revision of manuscript: A.B.A, O.K, V.Y, İ.Ö.K.

Conflict of Interest: *The authors have no conflicts of interest to declare.*

Financial Disclosure: *Authors declared no financial support.*

References

1. Stefanski AL, Tomiak C, Pleyer U, Dietrich T, Burmester GR, Dörner T. The Diagnosis and Treatment of Sjögren's Syndrome. Dtsch Arztebl Int. 2017;114(20):354-61.
2. Mæland E, Miyamoto ST, Hammenfors D, Valim V, Jonsson MV. Understanding Fatigue in Sjögren's Syndrome: Outcome Measures, Biomarkers and Possible Interventions. Front Immunol. 2021;12:703079.
3. Lewis I, Hackett KL, Ng WF, Ellis J, Newton JL. A two-phase cohort study of the sleep phenotype within primary Sjögren's syndrome and its clinical correlates. Clin Exp Rheumatol. 2019;37 Suppl 118(3):78-82.
4. Goulabchand R, Castille E, Navucet S, Etchecopar-Etchart D, Matos A, Maria A, et al. The interplay between cognition, depression, anxiety, and sleep in primary Sjogren's syndrome patients. Sci Rep. 2022;12(1):13176.
5. Dardin LP, Garcia ABA, Gazoni FM, Santos FCD, Mello MT, Trevisani VFM. Correlation of sleep quality with fatigue and disease activity among patients with primary Sjögren's syndrome: a cross-sectional study. Sao Paulo Med J. 2020;138(2):146-51.
6. Belenguer R, Ramos-Casals M, Brito-Zerón P, del Pino J, Sentís J, Aguiló S, et al. Influence of clinical and immunological parameters on the health-related quality of life of patients with primary Sjögren's syndrome. Clin Exp Rheumatol. 2005;23(3):351-6.
7. Dias LH, Miyamoto ST, Giovelli RA, de Magalhães CIM, Valim V. Pain and fatigue are predictors of quality of life in primary Sjögren's syndrome. Adv Rheumatol. 2021;61(1):28.
8. Hartkamp A, Geenen R, Bijl M, Kruize AA, Godaert GL, Derksen RH. Serum cytokine levels related to multiple dimensions of fatigue in patients with primary Sjogren's syndrome. Ann Rheum Dis. 2004;63(10):1335-7.
9. Davies K, Mirza K, Tarn J, Howard-Tripp N, Bowman SJ, Lendrem D, et al. Fatigue in primary Sjögren's syndrome (pSS) is associated with lower levels of proinflammatory cytokines: a validation study. Rheumatol Int. 2019;39(11):1867-73.
10. Miglianico L, Cornec D, Devauchelle-Pensec V, Berrouiguet S, Walter M, Stéphan F. Inflammatory biomarkers associated with depression, anxiety, and/or fatigue in primary Sjögren's syndrome–a systematic review. The European Journal of Psychiatry. 2022;36(3):143-51.
11. Liu Y, Tan YQ, Zhou G. Melatonin: a potential therapeutic approach for the management of primary Sjögren's syndrome. Immunol Res. 2023;71(3):373-87.
12. Liu Y, Weng X, Wei M, Yu S, Ding Y, Cheng B. Melatonin regulates the immune response and improves Sjögren's syndrome-like symptoms in NOD/Ltj Mice. Biochem Pharmacol. 2022;201:115073.
13. Liu Y, Wang F, Cheng B, Zhou G. Melatonin improves salivary gland damage and hypofunction in pSS by inhibiting IL-6/STAT3 signaling through its receptor-dependent manner. Mol Immunol.

2024;169:10-27.
14. Rasheed AB, Daoud MS, Gorial FI. Diagnostic utility of serum melatonin levels in systemic lupus erythematosus: a case-control study. Reumatismo. 2017;69(4):170-4.
15. Liu Y, Chen XQ, Wang F, Cheng B, Zhou G. Melatonin relieves Th17/CD4(-)CD8(-) T cells inflammatory responses via nuclear-receptor dependent manner in peripheral blood of primary Sjögren's syndrome. Int Immunopharmacol. 2022;109:108778.
16. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5.
17. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46(10):1121-3.
18. Saris-Baglama RN, Dewey CJ, Chisholm GB, Plumb E, King J, Kosinski M, et al. QualityMetric health outcomes™ scoring software 4.0: installation guide. Lincoln (RI): QualityMetric Incorporated. 2010.
19. Hackett KL, Gotts ZM, Ellis J, Deary V, Rapley T, Ng WF, et al. An investigation into the prevalence of sleep disturbances in primary Sjögren's syndrome: a systematic review of the literature. Rheumatology (Oxford). 2017;56(4):570-80.
20. Gudbjörnsson B, Broman JE, Hetta J, Hällgren R. Sleep disturbances in patients with primary Sjögren's syndrome. Br J Rheumatol. 1993;32(12):1072-6.
21. Xie Z, Chen F, Li WA, Geng X, Li C, Meng X, et al. A review of sleep disorders and melatonin. Neurol Res. 2017;39(6):559-65.
22. de Carvalho JF, Skare TL. Melatonin supplementation improves rheumatological disease activity: A systematic review. Clin Nutr ESPEN. 2023;55:414-9.
23. Uysal HA, Tıftıkcıoğlu BI, Öcek L, Zorlu Y. Serum Levels of Melatonin and Sleep Evaluation Scales in the Diagnosis of Sleep Disorders in Patients with Idiopathic Parkinson's Disease. Noro Psikiyatr Ars. 2019;56(4):264-8.
24. Tcholakov B, Qasim H. The Relationship Between Sjogren's Syndrome and Sleep Disturbance: A Case Report. Cureus. 2022;14(10):e30321.
25. Ng WF, Bowman SJ. Primary Sjogren's syndrome: too dry and too tired. Rheumatology (Oxford). 2010;49(5):844-53.
26. Korszun A, Sackett-Lundeen L, Papadopoulos E, Brucksch C, Masterson L, Engelberg NC, et al. Melatonin levels in women with fibromyalgia and chronic fatigue syndrome. J Rheumatol. 1999;26(12):2675-80.
27. Ibn Yacoub Y, Rostom S, Laatiris A, Hajjaj-Hassouni N. Primary Sjögren's syndrome in Moroccan patients: characteristics, fatigue and quality of life. Rheumatol Int. 2012;32(9):2637-43.
28. Priori R, Minniti A, Antonazzo B, Fusconi M, Valesini G, Curcio G. Sleep quality in patients with primary Sjögren's syndrome. Clin Exp Rheumatol. 2016;34(3):373-9.
29. Cui Y, Li J, Li L, Zhao Q, Chen S, Xia L, et al. Prevalence, correlates, and impact of sleep disturbance in Chinese patients with primary Sjögren's syndrome. Int J Rheum Dis. 2020;23(3):367-73.
30. Castaño MY, Garrido M, Rodríguez AB, Gómez M. Melatonin Improves Mood Status and Quality of Life and Decreases Cortisol Levels in Fibromyalgia. Biol Res Nurs. 2019;21(1):22-9.
31. Fan R, Bu X, Yang S, Tan Y, Wang T, Chen H, et al. Effect of melatonin on quality of life and symptoms in patients with cancer: a systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2022;12(9):e060912.