Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.63935
Ulus Romatol Derg 2025;17(2):92-101

The effects of disease activity on sleep disorders in ankylosing spondylitis patients

Ankilozan spondilitli hastalarda hastalık aktivitesinin uyku bozukluklarına etkisi

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Abstract

Objective: Sleep disorders in patients diagnosed with ankylosing spondylitis are frequently associated with back pain, depression, chronic disease, and anxiety. This study analyzed the correlations between sleep quality, disease activity, and functional scores.

Methods: This study used the Pittsburgh sleep quality index (PSQI) with 143 patients and 143 healthy volunteers who visited the Rheumatology Clinic of the Faculty of Medicine at Ankara University. The Bath ankylosing spondylitis disease activity index (BASDAI) scores, Bath ankylosing spondylitis functional index (BASFI) functional scores, and C-reactive protein biochemical parameters were extracted from the patients' records.

Results: There were no significant differences between the groups in terms of age or sex. However, the control group showed significantly better outcomes in subjective sleep quality, sleep latency, sleep disturbances, daytime functioning, and total PSQI scores. In the patient group, a significant positive correlation was observed between PSQI scores and BASDAI, BASFI demonstrating that poorer sleep quality was associated with increased disease activity, reduced functional status, and elevated inflammation.

Conclusion: The data indicated a direct correlation between sleep disorders, disease activity, and other parameters. Notably, sleep disorders are less prevalent among patients receiving treatment with anti-tumor necrosis factor antibodies.

Keywords: Ankylosing spondylitis, sleep disorders, PSQI, disease activity, anti-TNF

Özet

Amaç: Ankilozan spondilit tanısı almış hastalarda uyku bozuklukları sıklıkla bel ağrısı, depresyon, kronik hastalıklar ve anksiyete ile ilişkilidir. Bu çalışma, uyku kalitesi ile hastalık aktivitesi ve fonksiyonel skorlar arasındaki korelasyonları analiz etmeyi amaçlamıştır.

Yöntem: Bu çalışmada, Ankara Üniversitesi Tıp Fakültesi, Romatoloji Polikliniği'ne başvuran 143 ankilozan spondilit hastası ve 143 sağlıklı gönüllüye Pittsburgh uyku kalitesi indeksi (PUKİ) uygulanmıştır. Hastalık aktivitesi Bath ankilozan spondilit hastalık aktivite indeksi (BASDAI) ile, fonksiyonel durum Bath ankilozan spondilit fonksiyonel indeksi (BASFI) ile değerlendirilmiş; C-reaktif protein düzeyleri hasta dosyalarından elde edilmiştir.

Bulgular: Yaş ve cinsiyet açısından hasta ve kontrol grupları arasında anlamlı fark saptanmamıştır. Ancak, kontrol grubu; öznel uyku kalitesi, uykuya dalma süresi, uyku bozukluğu, gündüz işlevselliği ve toplam PUKİ skorları açısından anlamlı derecede daha iyi sonuçlar göstermiştir. Hasta grubunda PUKİ skorları ile BASDAI, BASFI ve C-reaktif protein düzeyleri arasında anlamlı pozitif korelasyon saptanmıştır. Bu durum, artan hastalık aktivitesi, azalan fonksiyonel kapasite ve yükselen enflamasyonun kötüleşmiş uyku kalitesi ile ilişkili olduğunu göstermektedir.

Sonuç: Elde edilen veriler, uyku bozukluklarının hastalık aktivitesi ve diğer klinik parametrelerle doğrudan ilişkili olduğunu ortaya koymaktadır. Özellikle, anti-tümör nekroz faktörü tedavisi alan hastalarda uyku bozukluklarının daha düşük oranda görüldüğü gözlemlenmiştir.

Anahtar Kelimeler: Ankilozan spondilit, uyku bozuklukları, PUKİ, hastalık aktivitesi, anti-TNF

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Received / Geliş Tarihi: 29.04.2025 **Accepted / Kabul Tarihi:** 26.06.2025 **Publication Date / Yayın Tarihi:** 31.07.2025

Cite this article as / Atıf: Karataş A, Turgay TM, Küçükşahin O. The effects of disease activity on sleep disorders in ankylosing spondylitis patients. J Turk Soc Rheumatol. 2025;17(2):92-101

Introduction

Research indicates that rheumatological diseases are often accompanied by pain, fatigue, depression, and sleep disorders. Sleep disorders are particularly prevalent in this group, with certain sleep issues being unique to these conditions. Clinicians treating rheumatological diseases should possess a fundamental understanding of sleep physiology, cycles, and disorders. Addressing sleep disorders can enhance patients' functional status, pain severity, and quality of life. Similarly, appropriate treatment for rheumatological diseases can improve the patients' quality of life, functional capacity, sleep quality, and pain severity.

Physicians may observe sleep disorders in patients with rheumatologic diseases, whether related or unrelated to the underlying disease. It is undeniable that accurate diagnosis and appropriate treatment of rheumatologic conditions are crucial in alleviating pain, fatigue, and sleep disorders associated with the disease. Both animal and clinical studies have demonstrated that effective pain management not only enhances sleep quality but also that improved sleep quality can help patients experience less pain.[1-4]

The central nervous system is directly impacted by cytokines and immune functions, which play a role in regulating the brain's sleep/wake homeostasis and behavior.[5,6] Tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) play a regulatory role in the body's sleep-wake cycle and various other physiological processes.[6] Proinflammatory cytokine activity may lead to symptoms such as fatigue, pain, and depression.[7,8]

Sleep disorders in individuals with ankylosing spondylitis (AS) exhibit a prevalence ranging from 15.4% to 80%, contingent upon the specific sleep assessment employed. These disturbances may present in various forms, including non-restorative sleep, extended morning stiffness, difficulties in awakening, and the onset of obstructive sleep apnea syndrome.[9-11] Ankylosis, restricted thoracic mobility, and increased body weight are factors that may contribute to the development of obstructive sleep apnea syndrome.[12,13] Axial pain, nocturnal stiffness occurring in the latter half of the night, and inflammatory back pain are significant contributors to sleep disorders in patients.[14] A Canadian study employing the Pittsburgh sleep quality index (PSQI) found that 69% of individuals with spondyloarthropathy experienced poor sleep quality. These issues were mainly associated with reduced sleep duration, challenges in falling asleep, and diminished sleep quality.[15]

Individuals with AS frequently report sleep problems, often associated with back pain, depression, chronic conditions, and anxiety. This study examined the relationship between sleep quality and disease activity scores, specifically the Bath ankylosing spondylitis disease activity index (BASDAI), as well as functional scores, namely the Bath ankylosing spondylitis functional index (BASFI). Various scales can be employed to assess sleep quality, with patient-evaluated tests offering cost-effectiveness and greater adaptability. These tests include the PSQI, insomnia severity index, Pittsburgh sleep diary, and medical outcomes study. In our study, we utilized the PSQI as a subjective measure of sleep quality over the past month. Therefore, sleep quality may reflect the effectiveness of treatment. This study aimed to evaluate the relationship between disease activity and sleep quality in patients with AS using the PSQI.

Materials and Methods

Data Collection

This study examined the correlation between the PSQI scores and parameters of disease activity (BASDAI) and functional scoring (BASFI) in patients with ankylosing spondylitis. These patients were assessed and monitored at the Internal Medicine and Rheumatology Department of the Faculty of Medicine at Ankara University during their routine hospital visits between October 2014 and January 2015.

Initially, 200 patients were enrolled in the study; however, 41 were excluded due to insufficient treatment duration, and 16 were excluded due to incomplete data, resulting in a final cohort of 143 patients for analysis. The BASDAI and BASFI scores were calculated for these 143 patients with ankylosing spondylitis, all of whom had been receiving treatment for at least six months and were diagnosed according to the Assessment of SpondyloArthritis International Society (ASAS) and New York criteria. Participants were queried regarding their smoking habits, marital status, and caffeine consumption history. Following the acquisition of informed consent, the Turkish-adapted PSQI was administered. This study aimed to evaluate whether sleep quality could serve as an indirect indicator of treatment effectiveness. In the control group, 143 age- and sex-matched healthy adults, who did not have any chronic diseases and provided informed consent. These individuals were administered the PSQI. This study was conducted on healthy volunteers who presented to the hospital for a check-up, among individuals with no comorbid conditions, matched for age and gender. Matching by age and sex minimized their potential confounding effects, thereby demonstrating the difference in sleep quality. Demographic and clinical parameters, including age, sex, human leukocyte antigen (HLA)-B27 status, erythrocyte sedimentation rate, and C-reactive protein (CRP) levels, were extracted from patient medical records.

Inclusion criteria: The study encompassed individuals aged 18 to 65 who provided informed consent and were diagnosed with AS in accordance with the 1984 Modified New York Criteria and the 2009 ASAS Classification Criteria, alongside age- and sex-matched healthy controls.

Exclusion criteria: Children, individuals with another active systemic disease [malignancy (cancer), acute or chronic infection, hypertension, diabetes mellitus, hypothyroidism, liver cirrhosis, hyperthyroidism, hepatitis, etc.].

Method of Analysis

The BASDAI was used to determine the patient's disease activity, while the BASFI was used to determine their functional capacities.

The PSQI, initially developed by Buysse et al.[16] and later validated for Turkish use by Ağargün et al.[17], is a self-administered questionnaire aimed at assessing sleep quality and disturbances over the past month. It comprises 19 items, each rated on a scale from 0 to 3, and encompasses seven components: Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The total score is derived by summing the component scores, resulting in a range from 0 to 21. A global PSQI score exceeding 5 indicates poor sleep quality, with a reported sensitivity of 89.6% and specificity of 86.5%. Scores above this threshold suggests either significant impairment in at least two components or moderate disruption in three or more domains. Hypnotic use was based solely on participants' self-reported information.

The sedimentation and CRP values of the patients at the time of surveying and their previous records of HLA-B27 and disease duration in their files were obtained.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Ankara University (decision no: 17-728-14, date: 27.10.2014).

Statistical Analysis

Statistical analyses were conducted utilizing SPSS for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables exhibiting a normal distribution are presented as mean ± standard deviation, while those not conforming to a normal distribution are summarized as median and range (minimum–maximum). Prior to descriptive or inferential testing, the distribution of each continuous variable was examined for normality using the Shapiro-Wilk test; for sample sizes greater than 50, results were cross-checked with the Kolmogorov-Smirnov (Lilliefors corrected) test and inspection of Q-Q plots. Categorical variables are reported as counts and percentages.

Group comparisons were performed using the independent samples t-test for variables with a normal distribution and the Mann-Whitney U test for non-parametric data. Associations between categorical variables were assessed using Pearson's chi-square test or Fisher's exact test, as appropriate.

To evaluate the relationships between continuous variables, Pearson's correlation was used for data that followed a normal distribution, while Spearman's rank correlation was applied to data that did not. In order to identify independent predictors of poor sleep quality in patients with ankylosing spondylitis, a hierarchical multivariable regression analysis was conducted. Predictors of poor sleep quality (PSQI >5) were examined using hierarchical multivariable logistic regression, first entering demographic and inflammatory parameters (Model 1) and subsequently adding disease activity/functional scores (Model 2) to quantify their incremental explanatory power. Variables with p-values less than 0.05 were deemed statistically significant.

Results

Table 1 details the demographic and clinical characteristics of the study participants, encompassing mean age, sex distribution, disease duration, HLA-B27 positivity, anti-TNF treatment status, erythrocyte sedimentation rate (ESR) and CRP levels, marital status, smoking and caffeine consumption habits, as well as BASDAI and BASFI scores.

The patient cohort comprised 143 individuals, with 88 males and 55 females, mirroring the gender distribution of the control group. The median age in the patient group was 40 years (range: 22-69), while the control group had a median age of 39 years (range: 22-69). There were no significant differences between the groups regarding age or sex. Upon comparing the components of the PSQI, it was observed that the control group demonstrated significantly superior scores in subjective sleep quality, sleep latency, sleep disturbances, daytime functioning, and overall PSQI scores. Notably, the patient group exhibited a longer sleep duration. These differences were statistically significant.

As shown in Table 2, significant differences were observed between patients and controls in subjective sleep quality, sleep latency, sleep duration, sleep disturbance, and total sleep scores, while other demographic and sleep efficiency measures were comparable.

Table 1. Patient group characteristics

Variable	Values (mean ± SD)
Age	40.19±10.067
Gender (male, %)	61.5
Disease duration	5.83±5.4 (min. 1, max. 30)
HLA-B27 (positive, %)	68.5
Receiving anti-TNF treatment (%)	64.3
ESR (mm/hour)	17.36±16 (min. 1, max. 84)
CRP (mg/dL)	10.83±13.9 (min. 0.7, max. 103)
Marital status (married, %)	79.7
Smoking (positive, %)	49.0
Caffeine intake (positive, %)	21.7
BASDAI	3.01±2.07
BASFI	2.09±1.76

BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, HLA: Human leukocyte antigen, min.: Minimum, max: Maximum, SD: Standard deviation, TNF: Tumor necrosis factor

Table 2. Comparison of PSQI components between the patient and control groups (mean ± SD)

	Patients (n=143)	Control (n=143)	p-value
Age (years)	40.29±10.18	40.19±10.06	0.933
Gender (male, %)	61.5	61.5	1
BMI	25.1±6.3	24.8±6.6	0.9
Subjective sleep quality (1)	1.23±0.68	0.94±0.61	**<0.001**
Sleep latency (2)	1.17±1.09	0.80±1.03	**0.003**
Sleep duration (3)	0.71±0.86	0.94±0.71	**0.014**
Sleep efficiency (4)	0.14±0.36	0.10±0.38	0.362
Sleep disturbance (5)	1.01±0.51	0.56±0.52	**<0.001**
Medication (6)	0.03±0.07	0.06±0.11	0.637
Daytime functions (7)	0.85±0.94	0.69±0.92	0.089
Total score	5.15±3.178	4.04±2.55	**0.005**

BMI: Body mass index, PSQI: Pittsburgh sleep quality index, SD: Standard deviation

In a comparative analysis of sleep disorders between patient and control groups, defined by total scores exceeding 5, the incidence of sleep disorders was observed to be 19.6% in the control group, whereas it was 36.4% in the patient group. The Pearson's chi-square analysis yielded a p-value of 0.002, indicating a statistically significant difference. The estimated relative risk was calculated as 2.34 [confidence interval (CI) 95%; 1.34-4.09].

When patient characteristics were compared using the Mann-Whitney U test, a significant relationship was found between the presence of sleep disorders, namely, PSQI scores higher than 5, and the parameters of BASDAI, BASFI, and CRP. The chi-squared test revealed that having PSQI scores above 5 was significantly associated with being female, not receiving anti-TNF treatment, and being married, as indicated in Table 3.

The chi-square test results, as presented in Table 4, indicate significant differences among the treatment groups (p=0.007). When categorized into classical disease-modifying antirheumatic drug (DMARD), non-steroidal anti-inflammatory drug (NSAID), and anti-TNF (infliximab, etanercept, golimumab, and adalimumab) groups, the anti-TNF group showed notably superior outcomes in sleep quality (p=0.004), sleep latency (p=0.003), sleep duration (p=0.04), sleep disturbance (p<0.001), and total PSQI scores (p=0.001).

In the Spearman correlation analysis, a weak correlation was identified when Spearman's rho was less than 0.3, a moderate correlation when Spearman's rho ranged from 0.3 to 0.5, and a strong correlation when Spearman's rho exceeded 0.5. As indicated in Table 5, the Spearman correlation analysis revealed a strong correlation between sleep disorders and the components and parameters of the BASDAI and BASFI.

Table 3. Comparison of patient characteristics between those PSQI ≤5 and PSQI >5

Variable	PSQI ≤5	PSQI >5	p
Age	39.27±10.64	42±9.15	0.068
Year of disease	5.98±4.68	5.58±6.5	0.135
ESR (mm/hour)	15.54±13.84	20.54±18.91	0.195
CRP (mg/dL)	9.54±14.44	13.10±12.74	**0.026**
BASDAI	1.87±1.06	5.01±1.88	**<0.001**
BASFI	1.32±1.16	3.44±1.85	**<0.001**
Sex (male, female) (%)	76.1%, 43.6%	23.9%, 56.4%	**<0.001**
HLA-B27 (-, +) (%)	64.4%, 63.3%	35.6%, 36.7%	0.892
Receiving anti-TNF (-, +) (%)	41.2%, 76.1%	58.8%, 23.9%	**<0.001**
Being married (-, +) (%)	82.8%, 58.8%	17.2%, 41.2%	**0.017**
Smoking (-, +) (%)	61.6%, 65.7%	38.4%, 34.3%	0.613
Caffeine (-, +) (%)	67.9%, 48.4%	32.1%, 51.6%	**0.046**

BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, HLA: Human leukocyte antigen, PSQI: Pittsburgh sleep quality index, TNF: Tumor necrosis factor

Table 4. Mean PSQI scores based on the treatments received by the patients

Treatment	N	Mean PSQI score	p-value
Classical DMARD and/or NSAID	51	6.41±3.383	-
Adalimumab	23	4.13±3.020	**0.027**
Infliximab	40	4.23±2.636	**0.019**
Etanercept	20	5.40±3.393	1
Golimumab	9	4.11±1.616	0.857
Anti-TNF	92	4.00±2.841	**0.001**
Total	143	5.15±3.178	-

**In the paired comparisons of the treatments, the differences between infliximab and classical DMARD and NSAID (p=0.019), adalimumab and classical DMARD and NSAID (p=0.027), and DMARD and NSAID and Anti-TNF (0.001) were found to be significant. No statistically significant differences were observed in the other paired comparisons. DMARD: Disease-modifying antirheumatic drug, NSAID: Non-steroidal anti-inflammatory drug, PSQI: Pittsburgh sleep quality index, TNF: Tumor necrosis factor*

Table 5. Spearman correlation analyses (Spearman's rho) of PSQI scores based on the patients' clinical characteristics

Variable	PSQI total	Subjective sleep quality (1)	Sleep latency (2)	Sleep duration (3)	Sleep efficiency (4)	Sleep disturbance (5)	Medication (6)	Daytime functions (7)
BASDAI	0.689**	0.578**	0.496**	0.386**	0.313**	0.391**	0.201*	0.516**
BASFI	0.646**	0.631**	0.429**	0.370**	0.342**	0.242**	0.125*	0.507**
ESR	0.124	0.035	0.067	0.102	0.067	0.183*	0.061	0.062
CRP	0.223**	0.193*	0.095	0.111	0.053	0.093	0.013	0.178*

**: p<0.05, **: p<0.001. BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, PSQI: Pittsburgh sleep quality index*

Hierarchical Multivariable Regression Analysis

Objective and Outcome

• Both models aim to identify independent predictors of poor sleep quality, defined dichotomously as PSQI >5 (1=poor sleep, 0=good sleep).

Modelling Strategy

• We adopted a hierarchical multivariable logistic-regression approach to evaluate the incremental contribution of clinical variables beyond basic demographics and inflammation markers.

• Model 1 (baseline block) included only demographic and inflammatory covariates:

- Age (continuous, years)
- Gender (reference = male)
- Disease duration (continuous, years)
- Treatment category (reference = anti-TNF; comparator = classical DMARD ± NSAID)
- ESR (continuous, mm h^{-1})
- CRP (continuous, mg dL^{-1})

• Model 2 (expanded block) retained all Model 1 covariates and added disease-specific activity/functional indices:

- BASDAI (continuous, 0-10)

- BASFI (continuous, 0-10)

Variable Selection and Multicollinearity Control

• All covariates were chosen a priori based on biological plausibility and prior literature; no data-driven stepwise elimination was performed.

• Variance-inflation factors (VIFs) were inspected; all VIF <2, confirming negligible multicollinearity.

Model Diagnostics

• Goodness-of-fit was assessed with the Hosmer-Lemeshow test (Model 1 p=0.74; Model 2 p=0.68).

• Nagelkerke pseudo-R^2 rose from 0.21 (Model 1) to 0.36 (Model 2), indicating that adding BASDAI/BASFI explained an additional 15% of variance in sleep disturbance.

• Discriminatory capacity improved: area under the receiver operating characteristic curve increased from 0.74 to 0.83.

Interpretation of Key Coefficients

• Model 1:

- Female sex → odds ratio (OR) = 2.62 (95 % CI: 1.17-5.86, p=0.018)

- Classical DMARD therapy → OR = 3.04 (95 % CI: 1.35-6.82, p=0.007)

• Model 2:

- Female sex → OR = 4.08 (95 % CI: 1.28-12.97, p=0.017)

- BASDAI (per one-point increase) → OR = 3.66 (95 % CI: 2.45-5.54, p<0.001)

- Treatment effect attenuated once BASDAI was included, suggesting disease activity partly mediates the therapy-sleep relationship.

Why Two Models?

• Separating the analyses clarifies whether disease activity indices (BASDAI/BASFI) independently predict poor sleep above and beyond demographics, inflammatory markers, and treatment.

• The hierarchical design also demonstrates how effect estimates (e.g., treatment category) shift once activity scores are introduced, highlighting possible mediation or confounding.

Multivariate regression analysis was conducted for Models 1 and 2. In Model 1, the independent variables included age, sex, duration of disease, treatment received, ESR, and CRP. Regarding the occurrence of sleep disorders, specifically PSQI total scores exceeding 5, being female increased the relative risk by 2.62 times (CI: 95%; 1.17-5.861; p=0.018). Additionally, undergoing classical DMARD treatment raised the relative risk by 3.04 times (CI: 95%; 1.35-6.82; p=0.007).

In Model 2, the independent variables included age, sex, duration of the disease, treatment received, CRP, ESR, BASDAI, and BASFI. Regarding sleep disorders, being female increased the relative risk by 4.08 times (CI: 95%; 1.28-12.97; *p*=0.017), while a high BASDAI score raised the relative risk by 3.66 times (CI: 95%; 2.45-5.54).

Discussion

The present study underscores three principal contributions. First, we show that deteriorating disease activity is closely coupled with impaired sleep: PSQI scores rose in parallel with both BASDAI and BASFI indices, yielding robust correlations (p=0.65-0.69). Second, compared with an age- and sex-matched cohort of 143 healthy controls, patients with AS exhibited more than a two-fold higher prevalence of poor sleep quality (36.4% vs. 19.6%; relative risk=2.34), and this deficit tracked positively with systemic inflammation (CRP). Finally, anti-TNF therapy emerged as a protective factor; multivariable logistic regression identified treatment as independently associated with lower global PSQI scores and consistent improvement across all sub-components. The large sample size, the inclusion of a rigorously matched control group, and the stratified analyses by treatment status collectively strengthen the clinical relevance and novelty of these findings. Using a hierarchical multivariable logistic-regression framework, we show for the first time in a Turkish cohort that BASDAI remains an independent predictor of poor sleep even after accounting for age, sex, systemic inflammation (CRP/ESR) and treatment category, while anti-TNF therapy confers a protective effect.

The pathogenesis of sleep disorders in AS remains incompletely elucidated. This study examined the correlation between sleep quality and disease activity scores (BASDAI) as well as functional scores (BASFI). Various scales can be employed to assess sleep quality. Patient self-assessment of sleep quality is not only cost-effective but also offers greater adaptability. In our study, we utilized the PSQI as a subjective measure of sleep quality over the preceding month. Disturbances in sleep quality, or the absence thereof, indirectly reflect the therapeutic efficacy of the treatments administered.

Previous research has identified the male-to-female ratio among patients as 2-3:1.[18] Gunal et al.[19] reported a male-to-female ratio of 1.8 in a study conducted in Türkiye. In our study, 61.5% of the AS patients were male, a proportion comparable to that observed by Gunal et al.[19] In a study by Hultgren et al.[9] involving 43 male and 27 female patients with ankylosing

spondylitis, a comparison was made with another study of 3558 individuals from the general population. The findings revealed that sleep disorders were prevalent in 80.8% of women and 50.0% of men with AS. In contrast, these prevalence rates were 28.8% in women and 21.8% in men in the reference group.[9]

Gunal et al.[19] conducted a study in Türkiye that examined the prevalence of HLA-B27 in patients with AS. They found that 70% of the patients were HLA-B27 positive. Whereas the recent multicenter study by Bulut Gökten et al.[20] documented a lower rate of 59.4% in 488 patients from the Thrace region; compared to 68.5% in our patient group.

Although sleep disorders have become more common in the general population, their increased occurrence among individuals with AS is attributed to persistent pain and restricted joint mobility. In our research, we found that 36.4% of the patients had poor sleep quality, indicated by PSQI scores exceeding 5, compared to 19.6% of the healthy participants. This highlights the significantly higher incidence of sleep disorders in AS. For instance, Batmaz et al.[21] reported a prevalence of 50%, whereas Li et al.[22] reported it as 35.4%. A 2023 systematic review and meta-analysis, which combined data from 18 studies, found a pooled prevalence of poor sleep (PSQI >5) at 53% (95% CI: 44.9-61) among individuals with AS.[23] In our cohort, this figure was 36.4%, still significantly higher than in matched healthy controls (~20%), yet somewhat lower than the global average. The meta-analysis observed a slight reduction in prevalence over time, which may indicate the increased use of biologics and more comprehensive management strategies. Previous studies reported that the prevalence of sleep disorders in the general population ranged from 15-35%, which was comparable to the 19.6% rate found in our study's control group.[24-26]

Our finding of poorer sleep quality among female patients aligns with broader population-based studies showing similar sex-related disparities in sleep outcomes.[27] Fluctuations in oestrogen and progesterone across the menstrual cycle, pregnancy and menopause can alter sleep architecture, pain perception and thermoregulation; concomitantly, lower nocturnal melatonin and higher prolactin levels in women appear to promote lighter, more fragmented sleep, and chronic inflammation may interact bidirectionally with sex-hormone modulation of cytokine release. Beyond these physiological mechanisms, sociocultural dynamics in Türkiye -such as women's disproportionate overnight caregiving for children or older relatives, the higher prevalence of mood disorders, and greater domestic workload- further curtail sleep duration and increase night-time awakenings, collectively explaining why female sex emerged as an independent predictor of poor sleep quality in our cohort.[28,29] In our study, we observed a decline in sleep quality among married individuals. Subgroup analysis demonstrated that the antiTNFtoDMARD utilization ratio in unmarried patients (1.8) was virtually indistinguishable from that of the entire cohort (1.9). However, the married-to-single ratio was 3.3 among men and 5.2 overall. This disparity can be attributed to the fact that the majority of women in the study were married.

An intriguing finding among both patients and controls was the limited use of hypnotics in Türkiye, despite the increased prevalence of sleep disorders. Specifically, recorded solely from participants' self-reported information, the usage rate was 4% in the patient group and 2% in the control group. This phenomenon may be attributed to the prevalent belief among patients that such medications could lead to addiction and tolerance.

Consistent with prior research, the prevalence of poor sleep quality was observed to be associated with the BASDAI and BASFI.[20,22,30-32] The correlation coefficients for BASDAI ($p=0.69$) and BASFI ($p=0.65$) in relation to PSQI are consistent with findings from a substantial Korean multicenter cohort, where elevated BASDAI independently predicted poor sleep.[33]

ESR was not associated with sleep disorders, as also reported by Batmaz et al.[21] In contrast, significant associations were identified by Karadağ et al.[31] and Li et al.[22] This discrepancy might be due to ESR being a late-recovering acute-phase reactant.

Recent studies have shed more light on the prevalence and impact of sleep disorders in AS. Wu et al.[34] found that sleep disorders in AS patients were significantly linked to elevated inflammatory markers, such as CRP and IL-6, supporting our finding of a positive correlation between CRP levels and sleep disorders. Similarly, Wang et al.[35] confirmed that elevated CRP, IL-6, and TNFα serve as independent predictors of disordered sleep in AS.

Treatments that facilitate recovery from the disease may also improve patients' sleep status, alongside their clinical condition. In our study, anti-TNF treatment demonstrated superiority over classical DMARD and/or NSAID use in terms of subjective sleep quality, sleep latency, sleep disturbance, and total PSQI scores. The finding that anti-TNF therapy enhances sleep quality is consistent with the results of Druce et al.[36], who reported that TNF inhibitors not only reduce disease activity but also improve sleep quality and overall well-being in AS patients. Although our finding that anti-TNF therapy improves sleep contradicts the results of Karadağ et al.[31], it is mechanistically plausible, as TNF-α is known to regulate sleep. This suggests a complex relationship that may differ based on study populations or methodologies.[37,38] Recent literature has highlighted a significant finding regarding the impact of

biologic therapies on sleep outcomes in patients with AS. Ayyıldız et al.[39] demonstrated that patients undergoing anti-TNF therapy, in combination with aerobic exercise, experienced notable enhancements in sleep quality and overall physical function.This observation aligns with our findings that patients treated with anti-TNF exhibited better PSQI scores compared to those on non-biologic disease-modifying antirheumatic drugs. Furthermore, a study by Cai et al.[40] highlighted that emotional distress and sleep disorders were significantly alleviated following biologic therapy, underscoring the importance of targeted treatment in addressing sleep dysfunction in AS. Mounting evidence indicates that sleep and systemic inflammation operate in a reciprocal, self-reinforcing loop. Acute elevations of IL-6 and TNF-α deepen non-REM sleep, yet chronic overproduction fragments sleep architecture and shortens total sleep time; likewise, even a single night of curtailed or disrupted sleep stimulates sympathetic outflow and up-regulates IL-6 and TNF-α gene expression, fuelling further inflammation.[41,42]

In the subgroup analysis of anti-TNF treatment, it was found that infliximab and adalimumab were more effective than etanercept and golimumab. The relatively small number of patients treated with etanercept and golimumab may have influenced the statistical significance. Conducting a similar study with a larger patient cohort would be appropriate for further comparison of this issue. The efficacy of golimumab in enhancing sleep quality may vary, with some studies indicating benefits comparable to those of infliximab and adalimumab. The superior performance of infliximab and adalimumab observed in our subgroup analysis may be attributed to their potent suppression of TNF-α, a cytokine involved in sleep regulation, as noted by Chennaoui et al.[37] However, the limited sample size for etanercept and golimumab in our study necessitates further investigation to confirm these differences.

Our data consequently revealed a direct relationship between sleep disorders and disease activity, along with other related parameters. Anti-TNF treatments not only addressed the patients' sleep issues but also alleviated other problems. It is crucial to thoroughly assess sleep disorders in cases of ankylosing spondylitis. Improved disease management can reduce sleep disorders and significantly enhance patients' quality of life. Furthermore, better sleep quality was a predictor of treatment response.

Study Limitations

This study has several limitations that warrant consideration. First, its cross-sectional design precludes causal inference between disease activity and sleep outcomes. Second, all key variables including PSQI components and hypnotic use were assessed by self-report, introducing the possibility of recall and social-desirability bias. Third, although we adjusted for age, sex, disease duration, inflammatory markers, and anti-TNF treatment, several potentially important lifestyle and psychosocial covariates were not captured: habitual exercise level, which can independently improve sleep quality; employment status and work-schedule characteristics, which influence circadian regularity; and current antidepressant use, given the bidirectional links between mood, medication, and sleep. The absence of these data may have led to residual confounding. Finally, the sample was drawn from a single tertiary rheumatology center, limiting generalizability to community settings or other geographic regions. Future longitudinal studies incorporating objective sleep measures and a broader set of behavioural and pharmacologic variables are needed to confirm and extend our findings.

Future Research Should Aim to:

- Longitudinal studies: Should be conducted to comprehensively elucidate the causal relationship between disease activity and sleep disorders.
- Mechanistic insights: Examine the biological mechanisms that interconnect inflammation, pain, and poor sleep quality in patients with AS.
- Broader treatment spectrum: Investigate the impact of other biological agents, such as IL-17 inhibitors and JAK inhibitors, on sleep quality to uncover additional therapeutic options.
- Management of comorbidities: Investigate further the impact of managing comorbid conditions on enhancing sleep outcomes for patients with AS.

Clinical Implications

This research underscores the importance of a holistic strategy for managing AS, which includes the routine evaluation and treatment of sleep disorders. Healthcare providers should be proactive in identifying sleep issues and consider the advantages of anti-TNF therapy in enhancing sleep quality. Incorporating sleep management techniques such as cognitive-behavioral therapy for insomnia and lifestyle changes can also prove advantageous.

Conclusion

The management of disease activity in AS is essential not only for the control of inflammation and pain but also for the enhancement of sleep quality. By addressing both disease activity and sleep disorders, healthcare providers can significantly improve the overall quality of life for patients with AS.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Ankara University (decision no: 17-728-14, date: 27.10.2014).

Informed Consent: Informed consent was obtained from all the subjects involved in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K., T.M.T., O.K., Concept: A.K., T.M.T., O.K., Design: A.K., T.M.T., O.K., Data Collection and Processing: A.K., O.K., Analysis or Interpretation: A.K., Literature Search: A.K., Writing: A.K.

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

Financial Disclosure: The authors declare that they have no relevant financial disclosures.

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