Ref: Ro J Rheumatol. 2023;32(3)
DOI: 10.37897/RJR.2023.3.2

Pain characteristics and sleep dysregulation in patients with rheumatoid arthritis and ankylosing spondylitis: relationships with pain intensity and disease activity

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ABSTRACT

Background. Pain is a prominent manifestation in chronic immune-inflammatory rheumatic disorders, encompassing both nociceptive and non-nociceptive elements, the latter potentially resulting from central sensitization. The connection between inadequate sleep quality and the onset of central sensitization in individuals with chronic rheumatic diseases has been documented.

Objectives. This study aimed to analyze the characteristics of pain, sleep quality, and their correlation with pain intensity and disease activity in adults with rheumatoid arthritis and ankylosing spondylitis.

Methods. A prospective observational study was conducted, involving patients with RA, AS, and osteoarthritis. We evaluated pain intensity, pain characteristics, and sleep quality.

Results. The study group included 152 patients. RA was primarily characterized by nociceptive pain, but AS exhibited a higher prevalence of neuropathic pain. Significant associations were found between PD-Q scores and disease activity in patients with RA, but no such correlations were identified in patients with AS. Individuals with AS showed a significant inverse correlation between PD-Q scores and pain intensity. The PSQI scores did not show any notable variations among the three groupings. The quality of sleep was found to be connected with disease activity in RA but not in AS. A substantial and noteworthy correlation was found between the overall PSQI score and the scores obtained from the PD-Q in both subgroups of RA and AS.

Conclusion. Notable connections can be found between disease activity, pain characteristics, and sleep quality in chronic immune-inflammatory rheumatic diseases.

Keywords: nociceptive pain, neurophatic pain, sleep quality, disease activity, ankylosing spondylitis, rheumatoid arthritis, osteoarthritis

INTRODUCTION

Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are characterized as chronic, systemic, immune-inflammatory conditions [1]. Despite the advancements in the management of rheumatic disorders, pain continues to be a prominent manifestation of chronic rheumatic conditions, encompassing both nociceptive and non-nociceptive (neuropathic, unclear or "nociplastic") elements [2,3]. Neuropathic pain arises as a consequence of damage to the neurological system, often resulting from compression or irritation of nerve roots or peripheral nerves. This particular form of pain is commonly accompanied by unpleasant sensory disruptions, referred to as dysesthesia, and is typically characterized as a burning sensation or akin to "electric shock" sensations [4]. The incidence of neuropathic pain is more pro-

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Article History:
Received: 11 September 2023
Accepted: 19 September 2023

nounced in Hispanic and African descendant populations compared to white populations, potentially attributable to variations in drug utilization patterns and restricted availability of healthcare resources. Furthermore, it has been shown that a considerable proportion of individuals diagnosed with osteoarthritis, approximately 30%, may manifest symptoms that bear resemblance to those associated with neuropathic pain [5].

In the context of illnesses such as AS or RA, the persistence of pain over an extended period of time leads to the sensitization of nociceptors. Pain hypersensitization can be conceptualized as an adaptive mechanism, wherein there is a reduction in the pain threshold and an augmentation in the magnitude of response to stimuli surpassing this threshold. In the event that this phenomenon continues, there is a possibility of the occurrence of nociplastic change. This change is distinguished by an alteration in the equilibrium of the excitation-inhibition mechanism, wherein the nervous system gradually heightens its responsiveness to stimuli that are not pain-induing under normal circumstances [6].

Based on patient testimonials, weariness and sleep disruption are identified as the primary health factors of utmost significance, alongside pain. Individuals diagnosed with chronic rheumatic diseases frequently experience sleep disturbances, as evidenced by challenges in initiating sleep, difficulties in awakening, nocturnal awakenings, and excessive drowsiness during the day [7]. The prevalence of impaired sleep quality in individuals with inflammatory rheumatic conditions is extensively recognized [8], since it can have a substantial detrimental effect on daily functioning. Inadequate sleep quality has been found to intensify feelings of weariness, pain, symptoms of diseases, and negatively impact psychological well-being. Consequently, it is imperative to prioritize the management of sleep quality when addressing these disorders. The reported incidence of sleep-related issues among patients with rheumatoid arthritis ranges from 54% to 70%. In contrast, the prevalence of sleep disturbances in individuals with AS falls within the range of 50% to 64.5% [7,9].

The primary objective of this study was to examine the pain characteristics and sleep quality among adult patients diagnosed with RA and AS.

MATERIALS AND METHODS

We conducted a prospective observational study including patients with AS (fulfilling the modified 1984 New York diagnostic criteria), RA (fulfilling the ACR/EULAR 2010 classification criteria - American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR), or the ACR 1987 diagnosis criteria) and OA were recruited and evaluated in the Rheumatology Department of the Clinical Rehabilitation Hospital of Iasi from July 2022 to December 2022. We collected data covering demographics and disease-related variables such as C-reactive protein levels (CRP) as well as medication (nonsteroidal anti-inflammatory drugs, DMARDs - disease-modifying antirheumatic drugs). Disease activity measures such as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP), as well as Disease Activity Score (DAS28) were also noted. We excluded patients with comorbid neurological conditions. We evaluated pain intensity using the visual analog scale (VAS) and pain characteristics using the PainDETECT questionnaire (PD-Q). Sleep quality was assessed using the Pittsburg Sleep Quality Index (PSQI).

We performed the statistical analysis using IBM SPPS statistics version 23.0. The threshold for statistical significance was set at $p<0.05$.

RESULTS

The final study group included 152 patients (50 RA, 52 AS, and 50 OA) with a mean age of 57.62 years and a sex ratio (M/F) of 1:1. We used patients diagnosed with osteoarthritis as a control group. Table 1 summarizes the general characteristics of the study group.

TABLE 1. General characteristics of the study group (N=152)

Age (years)	57.62 ± 11.59	
Sex	Female	49%
	Male	51%
Residence	Urban	49.66%
	Rural	50.33%
VAS (0-10)	6.57 ± 1.19	
PD-Q	15.49 ± 7.11	
PSQI	9.36 ± 6.51	

Rheumatoid arthritis (RA)

In the subgroup of patients with RA, the mean age was 57.86 years with a standard deviation of 10.60 years and a F:M ratio 4.55:1. In this subgroup, we identified as the main type of pain nociceptive pain, followed by mixed pain and then neuropathic pain. Most patients with RA had poor sleep quality. Table 2 summarizes the general characteristics of RA patients (N=50).

We observed a correlation between nociceptive pain and increased usage of symptomatic medicine among patients with RA during their hospital stay ($p=0.033$).

TABLE 2. General characteristics of RA patients (N=50)

Age (years)	57.86 ± 10.60	
Sex	Female	82%
	Male	18%
Environment	Urban	48%
	Rural	52%
VAS (0-10)	6.34 ± 2.03	
PD-Q	13.31 ±6.68	
PSQI	8.91 ± 4.51	
Radiological stage	II - 44% III - 46% IV - 10%	
Rheumatoid factor	72%	
Anti-CCP antibodies	88%	
DAS28-CRP	3.84 ± 1.29	
Treatments	Conventional DMARDs	90%
	Biologic agents	38%
	Targeted synthetic DMARDs	14%

PD-Q in RA

We noticed that patients with RA exhibited a markedly higher incidence of nociceptive pain compared to individuals with OA (p=0.001). The remissive treatment, radiological stage or autoantibody positivity were not significantly associated with the type of pain according to PD-Q.

We found a significant correlation between PD-Q scores and DAS28-CRP in patients diagnosed with RA (p=0.007). The persistence of pain (Figure 1) was reported even in patients who were in remission according to DAS28-CRP. However, there was no significant correlation observed between PD-Q scores and pain intensity in individuals with RA (p=0.421).

PSQI in RA

There was a significant link between the overall score of the PSQI and RA disease activity as defined by DAS28-CRP (p=0.011). There was no significant connection between pain intensity and sleep quality in RA (p=0.093).

Correlations between PD-Q and PSQI in RA

Significant correlations were seen between PD-Q scores and total PSQI (p<0.001), as well as the individual domains of PSQI, within the RA subgroup. Furthermore, we found that among these individuals, VAS was associated with suboptimal subjective sleep quality, reduced sleep efficiency, and disrupted sleep patterns (p<0.05).

Ankylosing spondylitis (AS)

In the subgroup of patients with AS, the mean age was 57 years with a standard deviation of 12.90 years and a M:F ratio of 2:1. The majority of patients tested

TABLE 3. General characteristics of RA patients (N=50)

Age (years)	57 ± 12.90	
Sex	Female	33%
	Male	67%
Environment	Urban	49%
	Rural	51%
VAS	6.65 ± 2.07	
PD-Q	17.18 ± 5.81	
PSQI	9.96 ± 4.95	
Treatments	NSAIDs	54%
	DMARDs - Sulfasalazine	12%
	Biologics	23%
Radiological stage (sacroiliitis)	II	26.9%
	III	53.8%
	IV	19.2%
HLA-B27	Positive	96.2%
	Negative	3.8%
BASDAI	3.65 ± 2.37	
ASDAS-CRP	2.97 ± 1.20	

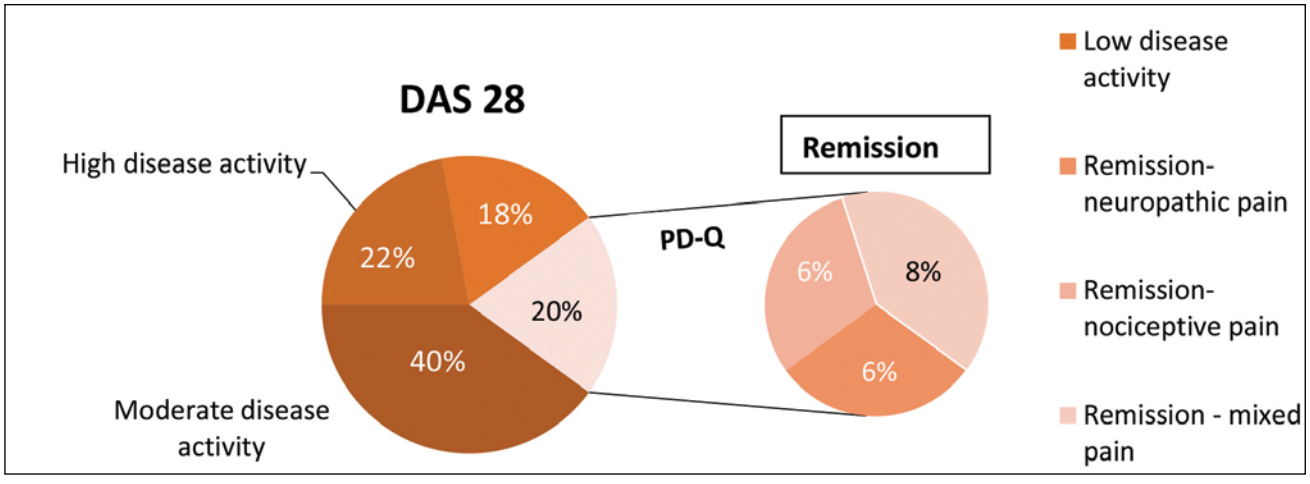

FIGURE 1. Pain characteristics in patients with RA in remission according to DAS28-CRP

positive for HLA-B27 (Human Leukocyte Antigen B27). Table 3 summarizes the general characteristics of patients with AS.

PD-Q in AS

The results of the study indicated that there was a significant inverse relationship between PD-Q scores and VAS in individuals with AS (p=0.037). No statistically significant links were seen between the PD-Q values and ASDAS-CRP scores or BASDAI (p>0.05).

PSQI in AS

Our findings indicated that there was no significant variation in sleep quality observed in individuals with AS based on disease activity. There was no observed improvement in sleep quality among patients in remission (ASDAS-CRP<2.1). The patients with high disease activity (ASDAS-CRP>3.5) also did not exhibit statistically significant differences in overall sleep quality compared to the rest of the AS group. Higher BASDAI scores were not associated with poorer sleep quality. No significant association was observed between the total PSQI and pain intensity in this subgroup.

Correlations between PD-Q and PSQI in AS

We found a significant association between the total PSQI and PD-Q scores (p<0.001) in individuals with AS. There was a strong association between PD-Q and various aspects of sleep quality in individuals with AS, including subjective sleep quality, sleep latency, sleep length, sleep efficiency, and sleep disturbance (p<0.001).

Comparison of PD-Q and PSQI scores between RA, AS and OA

In individuals with RA, the occurrence of nociceptive pain was shown to be higher compared to individuals with AS (p=0.009) and OA (p=0.049). The occurrence of neuropathic pain was significantly higher in the AS subgroup compared to the patients with RA and OA (p=0.001). PSQI values did not differ amongst the 3 subgroups (p=0.508).

DISCUSSIONS

Rheumatoid arthritis and ankylosing spondylitis are chronic inflammatory disorders characterized by pronounced physical impairment, pain, and stiffness, primarily affecting the joints. Both disorders have the potential to impact individuals across all age groups, however RA is frequently diagnosed in women of middle age, whilst AS seems to predominantly affect younger men [5,10].

Pain represents the prevailing symptom in rheumatic illnesses, serving as the primary impetus for patients to seek medical attention [11,12]. The PD-Q was utilized in our study to evaluate the nature of pain. The PD-Q instrument was developed in 2006 with the purpose of distinguishing between neuropathic and nociceptive pain in individuals experiencing persistent low back pain. The questionnaire has a total of nine inquiries pertaining to the precise location, perceived quality, level of intensity, and characteristic pattern of pain, with any potential sensory anomalies that may manifest.

Rheumatoid disorders are commonly characterized as an inflammatory condition affecting the joints, resulting in pain that is either inflammatory or nociceptive in nature. This pain can be triggered by various stimuli, including thermal, mechanical, or chemical factors. Notably, some inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-17, have been implicated in the pathogenesis of these diseases. The transmission of pain signals is facilitated through peripheral, spinal, and supraspinal pain pathways [5,10,13-15]. The results of our study suggest that the chronic pain experienced by the patients in our sample cannot be only attributable to inflammatory pain, as it also encompasses neuropathic pain. Additionally, it was noted that those diagnosed with AS exhibited a greater prevalence of non-nociceptive pain in comparison to those diagnosed with RA. According to the research conducted by Zhou [16], it was noted that approximately 33% of the 182 persons diagnosed with AS displayed signs of neuropathic pain.

RA can be managed through the utilization of conventional or biologic DMARDs. According to Ifesemen et al. [17], despite the ability of contemporary drugs to induce and sustain remission of inflammatory disease, a significant proportion of patients (80%) continue to endure ongoing pain, despite seeing their disease as being effectively managed. In a separate investigation conducted by Radawski et al. (2019), findings indicated that a mere 26% of individuals diagnosed with RA expressed contentment with their therapy, while a significant 76% reported experiencing constant pain [18, 19]. In the present study, we observed a correlation between nociceptive discomfort and increased usage of symptomatic medicine among patients with RA during their hospital stay.

The present study observed a significant inverse relationship between the severity of pain and PD-Q scores in persons diagnosed with AS. This conclusion is not consistent with the results reported by S. Lee et al., who revealed a positive correlation between PD-Q scores and pain levels as measured by the VAS. In addition, the study conducted by S. Lee demonstrated that individuals suffering from neuropathic pain and mixed pain exhibited more pronounced scores on the BASDAI and a greater incidence of enthesitis and peripheral arthritis [20].

Sleep disruption is a prevalent concern among these individuals and is recognized as a complex issue with multiple contributing factors. Potential factors that may contribute to the observed phenomenon encompass pain and the level of disease activity. The significance of sleep in immune system regulation is significant, as sleep disruptions and deprivation have been found to result in immunological dysregulation and heightened inflammation. A further factor that may contribute to disruptions in sleep patterns is the modification of pain perception, commonly referred to as "secondary fibromyalgia", as opposed to the influence of disease activity or inflammation. Consequently, this can worsen a range of health disorders, such as RA, AS, or OA [21-23].

In the present research, among the subgroup of individuals with RA, we observed a strong correlation between PD-Q scores and PSQI. Several studies have established a link between chronic pain and disruptions in sleep, indicating that 44% of individuals with chronic pain encounter poor sleep quality. Studies have also revealed that nociceptive stimuli can disrupt sleep, leading to significantly more arousals compared to non- nociceptive stimuli [24]. There was a significant correlation observed between the total scores of PSQI and disease activity in RA, being in line with Kontodimopoulos N et al.'s study. According to this research, the mean PSQI score was 10.2, suggesting poor sleep quality among RA patients. Additionally, the study noted an association between sleep quality and disease activity, indicating that patients with poor sleep quality also exhibited significantly higher levels of disease activity compared to good sleepers (with a mean DAS28 score of 3.8) [25].

Bayram et al. conducted a study that revealed a link between PD-Q scores and several sleep-related parameters in patients diagnosed with AS. These characteristics included total PSQI, sleep quality, sleep disturbance, and daytime dysfunction scores [26]. Our study revealed a noteworthy correlation between PD-Q scores and subjective sleep quality, sleep latency, sleep length, sleep efficiency, and sleep disturbance among persons with AS. Demirhan conducted a study to examine the potential impact of neuropathic pain on sleep quality among individuals diagnosed with axial spondyloarthritis. The findings of the study indicated that a significant proportion of patients reported experiencing sleep disturbances, irrespective of the existence of neuropathic pain [27]. Moreover, Deodhar et al. [28] proposed that sleep disturbances exhibited a substantial correlation with diminished quality of life, heightened pain levels, and increased disease activity among individuals diagnosed with AS. Nevertheless, our investigation did not yield a statistically significant association between the overall PSQI score and pain intensity (VAS).

CONCLUSION

The persistence of pain remains a major symptom in rheumatic illnesses, presenting a substantial challenge for healthcare practitioners, particularly within the framework of central sensitization. In our study group, the prevalence of non-nociceptive pain was shown to be greater in patients diagnosed with AS compared to those with AR and OA, while the occurrence of nociceptive pain was higher in cases of RA. Furthermore, it is important to acknowledge that pain levels may impact activity score values among individuals diagnosed with RA and AS. We found a significant link with disease activity in the RA subgroup, but not in AS. Moreover, poor sleep quality was associated with disease activity in RA, while this relationship was not seen in the AS subgroup. More research is necessary to elucidate the bidirectional connections between sleep quality and pain in chronic immune-inflammatory rheumatic diseases.

Conflict of interest: none declared
Financial support: none declared

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