Determinants of Sleep Impairment in Psoriatic Arthritis: An Observational Study with 396 Patients from 14 Countries

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ORIGINAL ARTICLE

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Authors

1. Penélope Esther Palominos. Serviço de Reumatologia, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul. Ramiro Barcelos 2350, 90035-903, Porto Alegre, Brazil. E-mail: penelopepalominos@gmail.com
2. Laura Coates. Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, B4495, Oxford OX3 7LD, Oxford, United Kingdom. E-mail: laura.coates@ndorms.ox.ac.uk
3. Charles Lubianca Kohem. Serviço de Reumatologia, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul. Ramiro Barcelos 2350, 90035-903, Porto Alegre, Brazil. E-mail: charleskohem@gmail.com
4. Ana-Maria Orbai. Division of Rheumatology, Johns Hopkins University School of Medicine, Mason F Lord Bldg Center Tower, Suite 4100, 5200 Eastern Ave. Baltimore, MD 21224, Baltimore, Maryland, United States. E-mail: aorbai1@jhmi.edu, ORCiD iD: 0000-0001-8644-8567
5. Josef Smolen. Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Spitalgasse 23, 1090, Vienna, Austria. E-mail: josef.smolen@wienkav.at
6. Maarten de Wit. Patient Research Partner, The Netherlands.

7. Uta Kiltz. Rheumazentrum Ruhrgebiet, Herne and Ruhr-University Bochum, Claudiusstraße 45, 44649, Herne, Germany. uta.kiltz@elisabethgruppe.de
8. Ying-Ying Leung. Department of Rheumatology and Immunology, Singapore General Hospital, Outram Rd, Singapore 169608, Singapore. E-mail: katyccc@hotmail.com
9. Juan Cañete, Rheumatology Department, Hospital Clínic and IDIBAPS, Carrer del Rosselló, 149, 08036, Barcelona, Spain. E-mail: JCANETE@clinic.cat
10. Rossana Scrivo, Rheumatology Unit, Department of Internal Medicine and Medical Specialties, Sapienza Università di Roma, 00161 Rome, Italy. E-mail: rossana.scrivo@uniroma1.it
11. Andra Balanescu. Sf Maria Hospital, University of Medicine and Pharmacy Carol Davila, Bulevardul Eroii Sanitari 8, 050474, Bucharest, Romania. E-mail: balanescu.andra@gmail.com
12. Emmanuelle Dernis. Le Mans Central Hospital, 194 Avenue Rubillard, 72000, Le Mans, France. E-mail: edernis@ch-lemans.fr
13. Sandra Meisalu, East-Tallinn Central Hospital, Ravi 18, 10138, Tallin, Estonia. E-mail: sandra.talli@gmail.com
14. Martin Soubrier. Rheumatology Department, Gabriel Montpied Hospital, 58 Rue Montalembert, 63000, Clermont-Ferrand, France. E-mail: msoubrier@chu-clermontferrand.fr
15. Sibel Zehra Aydin. University of Ottawa, the Ottawa Hospital Research Institute, 1053 Carling Ave, ON K1Y 4E9, Ottawa, Canada. E-mail: drsibelaydin@gmail.com
16. Inna Gaydukova. Rheumatology Department, North-Western State Medical University, Nevsky avenue, 86, 191025, St Petersburg, Russia. E-mail: ubp1976@list.ru

17. Umut Kalyoncu, Hacettepe University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Hacettepe Merkez Öğrenci Yurtları Sıhhiye, 06100, Ankara, Turkey. E-mail: umut.kalyoncu@yahoo.com
18. Laure Gossec. Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, 56 Boulevard Vincent Auriol, 75646, Paris France. Pitié Salpêtrière Hospital, AP-HP, Rheumatology Department, 47-83 Boulevard de l'Hôpital, 75013, Paris, France. E-mail: laure.gossec@gmail.com

Corresponding author: Penélope Esther Palominos. Serviço de Reumatologia, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul. Ramiro Barcelos 2350, 90035-903, Porto Alegre, Brazil. Phone: 55 51 33597662 Fax: 55 51 33597553. E-mail: penelopepalominos@gmail.com

ABSTRACT

Objective: Sleep quality is diminished in patients with psoriatic arthritis (PsA) and close to 40% of PsA patients consider sleep difficulties a priority domain. This work analyzes determinants of impaired sleep in patients with PsA.

Methods: This was a cross-sectional analysis of an observational study (ReFlap, NCT NCT03119805), which included adult patients with definite PsA with ≥2 years disease duration from 14 countries. Sleep was assessed using the patient self-reported evaluation of sleep on a 0-10 numerical scale, included in the Psoriatic Arthritis Impact of Disease questionnaire (PSAID-12). A score ≥4 was considered as sleep impairment. Demographic and clinical variables associated to sleep impairment were assessed through univariate analysis and Poisson regression modeling leading to prevalence ratio (PR) [95% confidence interval].

Results: A total of 396 patients were analyzed: mean age 51.9±12.6 years, 51% were females, 59.7% were receiving biologic therapy, 53.3% had 1-5% of body surface area affected by psoriasis; 23.7% were in remission and 36.9% in low disease activity according to the Disease Activity in Psoriatic Arthritis (DAPSA) score. Median (25^{th}-75^{th}) patient's self-evaluation of sleep difficulties was 2 (0-6), 157 (39.6%) had sleep impairment. In the Poisson regression model, self-reported levels of anxiety (PR: 1.05 [1.02-1.08], p=0.003) and pain (PR: 1.06 [1.04-1.09], p<0.001) were independently associated to sleep impairment.

Conclusions: In this multicentric study, sleep impairment was present in 40% of PsA patients; pain and anxiety were associated to sleep impairment whereas inflammation was not. Impact on sleep appears multifactorial in PsA.

Keywords: psoriatic arthritis, sleep impairment, sleep quality, disease activity, quality of life, pain

1. INTRODUCTION

Patients with psoriatic arthritis (PsA) have an altered quality of life; in particular, they experience a diminished sleep quality compared to patients with psoriasis or healthy controls [1-4].

Furthermore, 36% of PsA patients consider sleep difficulties a priority and 56% rate this domain among the top 8 domains of importance out of 16 [5]. However, little is known regarding factors explaining sleep impairment in PsA.

Demographic factors such as age and gender, psychological distress such as anxiety and PsA disease activity were associated to sleep difficulties in previous studies [2-4]. However, these studies were usually conducted in a single center/country and most included a small sample size.

In the present work, the objective was to assess the frequency of sleep impairment and to explore determinants of impaired sleep, in PsA patients from 14 countries participating in an observational study [6] where PsA disease-specific measures were assessed concomitantly with patient reported outcomes.

2. METHODS

Study design and patients

This was a cross-sectional analysis of data from patients participating in the ReFlap observational study (NCT03119805) [6]. As previously published, ReFlap was a multicentric international study which included adult patients with definite PsA with ≥2 years disease duration. Patients were recruited in 21 centers from 14 countries from Europe, North and South America. In the present analysis, the baseline data from this study were used [6].

Data collection

To evaluate the impact of PsA on sleep, a self-reported question from the Psoriatic Arthritis Impact of Disease (PsAID-12), a questionnaire which evaluates the impact of PsA in 12 domains, was used [5, 7]. Sleep impairment was assessed through the question: “Choose the number that best describes the sleep difficulties (i.e. resting at night) you felt due to your psoriatic arthritis during the last week” and this variable was named PsAID-12 sleep numerical rating scale (NRS). Answers were provided by patients on a 0-10 scale, with zero representing no sleep difficulty and 10 representing extreme difficulty [5, 7]. A score ≥4 out of 10 was considered here as sleep impairment and a score below 4 was considered a patient acceptable status, based on previous work reporting this cutoff for other patient-reported questions [5].

Other data collected

Variables studied were: gender, age at visit, age at PsA diagnosis, PsA disease duration, education (in years), work status (working full-time, working part-time, retired, disabled/unemployed), predominant type of PsA (peripheral, axial or enthesitic), current medication (conventional synthetic disease modifying antirheumatic drug - csDMARD-yes/no, biologic DMARD –bDMARD-yes/no, oral glucocorticoids yes/no), current smoking (yes/no), body mass index (BMI) category (underweight if BMI<18.5 kg/m^2, normal weight if BMI 18.5-24.9, overweight if BMI 25.0-29.9, obesity if BMI≥30), aerobic exercise (≥3 times a week, 1-2 times per week, 1-2 times per month, do not exercise regularly, cannot exercise due to disability/handicap), Leeds enthesitis index [8], number of tender joints out of 68 (TJC), number of swollen joints out of 66 (SJC), body surface area (BSA) with current psoriasis (no psoriasis, 1-5%, 6-20%, >20%), patient self-evaluation of psoriasis, pain and global disease activity in a 0-10 cm NRS, C reactive protein (in mg/dl) and disability according to the Health Assessment Questionnaire-HAQ (mild: 0 to ≤1, moderate: >1 to 2, severe: >2 to 3) [9].

To evaluate fatigue, the following question from PsAID-12 was used: “Circle the number that best describes the overall level of fatigue due to your psoriatic arthritis you have experienced during the last week” and answers were provided by patients on a 0-10 NRS [10].

Anxiety and depression were assessed through the respective questions from PsAID12: “Circle the number that best describes the level of anxiety, fear and uncertainty (for example about the future, treatments, fear of loneliness) due to your psoriatic arthritis you have experienced during the last week” and “Circle the number that best describes the level of depression due to your psoriatic arthritis you have experienced during the last week”, respectively; answers were provided by patients on a 0-10 NRS [5]. Previous diagnoses of anxiety and depression were recorded based on patients’ reporting during the visit and assessment of medical records.

Physicians were asked to evaluate on a 0-10 NRS if the patient current symptoms were caused by comorbidities i.e., other disease and not PsA (such as osteoarthritis, fibromyalgia, comorbidities); this variable was called “symptoms caused by other disease”. Physicians also evaluated on a 0-10 NRS if current symptoms were caused by severe disease, i.e. structural damage, deformed joints etc. and not active inflammation; this variable was called “symptoms caused by severe disease”.

Patients were classified according to the Disease Activity in Psoriatic Arthritis (DAPSA) score in remission (≤4), low disease activity/LDA (5-14), moderate disease activity/MDA (15-28) and high disease activity/HDA (>28) [11].

Work status and exercise were excluded since only some categories such as “cannot exercise due to handicap”, “working part time” an “unemployed/disabled” were associated to sleep impairment. These categories were probably associated to a more active PsA that prevented patients from working full-time and doing exercise. Since other variables representing PsA disease activity were included in the multivariate

model, the authors decided not to include “work” and “exercise” in the Poisson regression model.

Statistical analyses

All patients who attended the first visit of the ReFlap study and filled the self-evaluation of sleep in PsAID-12 as well as the following key variables: gender, age and elements necessary to calculate the DAPSA score were included [5, 11]. Patients with congestive heart failure and chronic obstructive pulmonary disease were excluded, since these comorbidities could affect sleep quality.

Sleep impairment was described as median and 25/75th percentiles.

The relationship between PsAID-12 sleep NRS and clinical variables was assessed through univariate analysis and the prevalence ratio (PR) with the 95% confidence interval (95% CI) reported for each variable.

In a second step, variables that were associated with sleep impairment (PsAID-12 sleep NRS≥4) in the univariate analysis with a p-value <0.20, were included in a Poisson regression model. Although cross-sectional studies with binary outcomes analyzed by logistic regression are frequent in rheumatology, the odds ratio obtained with this model can overestimate the prevalence ratio. In this work we used Poisson regression, an alternative for logistic regression, aiming to obtain more precise estimates of the prevalence ratio [12, 13].

Variables presenting multicollinearity effect were excluded from the Poisson model. Analysis was conducted using SPSS version 21.0 and a p-value <0.05 was considered statistically significant.

Ethical aspects

Ethics approval was obtained in each country and center. All patients gave written informed consent for their participation in the study. Four patient research partners participated in the ReFlap study [6].

3. RESULTS

A total of 396 patients were analyzed (Table 1): mean age 51.9±12.6 years, 202 (51%) were females, 221 (59.7%) were receiving biologic therapy, 201 (53.3%) participants had 1-5% of BSA affected by psoriasis, 293 (74%) had mild disability, 94 (23.7%) were in remission and 146 (36.9%) were in LDA according to the DAPSA score.

Median (25^{th}-75^{th}) PsAID-12 sleep NRS was 2 (0-6) and the highest tertile of data (4.0) coincided with the cut-off of PsAID-12 representing impact on sleep (≥4 on the 0-10 NRS); thus, 157 (39.6%) had sleep impairment. There was no difference in the reporting of sleep impact among the 14 countries (p=0.081) nor when countries were grouped by continent (Latin America x North America x Europe x Asia) (p= 0.492).

The distribution of the self-assessment of sleep impact in the sample is shown in Figure 1. A comparison of patients with and without sleep impairment is reported in Table 1.

After analyzing the results obtained in the univariate model (table 1), BSA was excluded due to multicollinearity but patient evaluation of psoriasis on a 0-10 NRS could be retained in the multivariate model representing the skin domain. Work status and exercise were excluded since only some categories such as “cannot exercise due to handicap”, “working part time” an “unemployed/disabled” were associated to sleep impairment. These categories were probably associated to a more active PsA that

prevented patients from working full-time and doing exercise. Since other variables representing PsA disease activity were included in the multivariate model, the authors decided not to include “work” and “exercise” in the Poisson regression model.

The variables statistically associated to sleep disturbance in the univariate analysis which were included in the Poisson regression model were: gender, DAPSA, Leeds enthesitis index, HAQ, patient evaluation of anxiety and depression, current medication, obesity and “symptoms caused by comorbidities”; the prevalence ratio (PR), 95%CI and p-value of each variable are described in Table 1.

In the first multivariable model (table 2), only DAPSA score (PR: 1.20 [95% CI 1.07-1.35] p=0.002 , 1.40 [95% CI 1.21-1.63] p<0.001 and 1.47 [95% CI 1.21-1.78] p< 0.001, respectively for LDA, MDA and HDA), anxiety (PR: 1.05 [95% CI 1.02-1.08] p=0.001) and severe disability (PR: 1.42 [95% CI 1.18-1.72] p<0.001) contributed to explain PsA impact on sleep. The inclusion of fatigue in the model did not change these results (data not shown).

Aiming to analyze the role of each component of the DAPSA score on sleep impairment, a second model including its components (TJC, SJC, pain and CRP) was implemented (Table 3). Patient global evaluation had to be excluded due to multicollinearity with the pain component. In this second model, anxiety remained a variable important to explain sleep impairment (PR: 1.05 [95% CI 1.02-1.08] p=0.003), but only the pain component of DAPSA remained significant (PR: 1.06 [95% CI 1.04-1.09] p<0.001). A 3-point increment in pain and anxiety score increased the chance of the subject reporting sleep impairment by 16% and 15%, respectively”. In this second model, severe disability showed only a trend (p=0.072) but it was not statistically significant (Table 3). The substitution of the variable “pain” for the variable “patient

global evaluation" demonstrated that global evaluation was also associated to sleep impairment (PR 1.04 [95% CI 1.01-1.07] p=0.006).

The substitution of the variables "patient self-assessment of anxiety and depression in PsAID-12" by previous history of anxiety (yes/no) and previous history of depression (yes/no), as collected in the comorbidity index completed by the physician, did not change the results (data not shown).

Physicians' opinion of patients' current symptoms being caused by other disease such as fibromyalgia and comorbidities (a score ≥6 in a 0-10 NRS) was also included but not associated with higher sleep impairment (PR 1.03 [95% CI 0.90-1.19] p=0.650).

The inclusion of the variable "work status" in the Poisson regression model did not change the results: pain and anxiety remained the variables associated to sleep impairment and work status was not associated to sleep impairment (working part time PR 1.32, 95%CI 0.94-1.84, p=0.111; retired PR 0.83, 95%CI 0.57-1.21, p=0.343; unemployed/disabled PR 1.26, 95%CI 0.90-1.77, p=0.171).

4. DISCUSSION

Quality of sleep is an aspect not frequently taken into account in PsA; however it may profoundly impact the patient's well-being [1, 14]. The present study brings to light important findings regarding sleep in PsA: in this population with mostly well-controlled PsA, 40% of participants reported sleep impairment; furthermore and contrary to expectations, the main factors independently associated to impaired sleep were pain and anxiety rather than inflammatory elements, indicating the complex nature of sleep impairment in PsA.

This study has strengths and limitations. A first element to discuss is the assessment of sleep. In previous studies, quality of sleep was usually evaluated through the Pittsburgh Sleep Quality Index (PSQI) [15], a 19-items self-reported instrument. Variables assessing sleep continuity and polysomnography were not conducted [16]. In the present study, a sleep-specific item (single question) taken from PsAID-12 was used [5]. However, single questions have often demonstrated good construct validity and the PsAID questions have been carefully constructed with patient research partners and each question has been validated [5, 17].

Another potential weakness is the use of questions assessing the outcomes “in the last week” and the cross-sectional design of the study which allows the description of sleep impairment in a limited amount of time and does not give insights into the evolution of the sleep domain over time in a chronic disease.

It appears that sleep impairment was less frequent in our study (40%) compared to previous studies on PsA (which found a prevalence of 68% and 84%) but also studies on other rheumatic diseases such as primary antiphospholipid syndrome and ankylosing spondylitis (which found a 70% prevalence of sleep disturbances) [3, 4, 18, 19]. The higher prevalence in those studies might be attributed to the small number of patients and the possible higher sensitivity of PSQI compared to our single question instrument to assess sleep. In the general population, the prevalence of dissatisfaction with sleep quality or quantity ranges from 10% to 50% [4, 20]. We cannot make a comparison with healthy subjects since our data set did not include healthy controls.

In our study, symptoms caused by psoriasis lesions did not contribute to sleep impairment. Although only 9.8% of our patients had more than 5% of BSA affected by psoriasis, this result is in agreement with the finding of Callis Duffin et al. that PsA leads to interference in sleep among patients with psoriasis [21]. Moreover, two other studies found a higher prevalence of sleep disorders in PsA patients compared to

those with psoriasis, leading to the hypothesis that pain caused by arthritis is a stronger predictor of the negative impact of PsA on sleep compared to the symptoms caused by psoriasis [3, 4]. A patient survey conducted by the National Psoriasis Foundation in the USA found that sleep impairment was associated with PsA and female gender; however disease activity and mood were not assessed [22]. Given the high prevalence of anxiety and pain in women with PsA [23], the true associations with sleep impairment may be anxiety and pain, as shown in our study.

In the present study, the strongest drivers of sleep impairment were pain and anxiety. The impact of anxiety on sleep was also evidenced in previous studies [2, 4]. Only the pain component of DAPSA score was independently associated with sleep disturbance whereas other “objective” variables more associated to “inflammation” such as swollen joints and CRP were not. This raises the hypothesis that the subjective experience of patients and the psychosocial and emotional burden of pain and anxiety are more important to explain the negative impact of PsA on sleep compared to inflammation. The result on inflammatory markers differs from that reported by previous studies in PsA: Krajewska-Włodarczyk et al. found that an increase in CRP was associated to worse sleep quality and Gezer et al. found a weak correlation between CRP and sleep disturbance [2, 3]. Patients included in the work from Krajewska-Włodarczyk et al. had much higher levels of CRP at baseline compared to our work and Gezer et al. did not perform multiple regression analysis but correlation tests [2, 3]. Differences in baseline characteristics of patients and statistical analysis could have contributed to different results regarding CRP. However, both authors did not find association between the swollen joint count and sleep disturbance, similar to our result.

Fibromyalgia causes widespread pain and altered sleep and is not rare (12-18%) in PsA patients [24, 25]. Coexisting fibromyalgia was related to worse disease activity scores in PsA and other spondyloarthritis and the presence of coexisting fibromyalgia is relevant to the PsAID-12 questionnaire [7, 24, 26]. We could

hypothesize that some of the negative impact of PsA on sleep was explained by concomitant fibromyalgia, not formally assessed in the present study. However, we analyzed the variable “symptoms caused by other disease”, where physicians graded from 0 to 10 their impression of the patient’s symptoms being caused by other disease including fibromyalgia and this variable was not associated to sleep impairment.

In summary, quality of sleep is a domain not frequently taken into account though it was impaired in 40% of PsA patients. The impact of PsA on sleep seemed to be mainly mediated by pain and anxiety rather than inflammation. We suggest that routinely assessing the quality of sleep is important. Future studies should focus on designing therapeutic strategies to improve sleep in order to improve patients’ quality of life in PsA.

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