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Depressive symptoms are associated with impaired sleep, fatigue, and disease activity in women with rheumatoid arthritis

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Abstract

Objectives: To investigate the associations between sleep quality, fatigue, disease activity and depressive symptoms in women with rheumatoid arthritis (RA).

Methods: Female patients with previous diagnosis of RA from a Rheumatology Outpatient Clinic at a tertiary referral centre, in Fortaleza, Brazil, were consecutively recruited into the study. Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI); fatigue by the Fatigue Severity Scale (FSS); daytime sleepiness by the Epworth Sleepiness Scale (ESS); and depressive symptoms by the Beck Depression Inventory II (BDI-II). RA activity was measured by the disease activity score (DAS28).

Results: One hundred ten women (mean age ± SD = 51.1 ± 13.0 y) were included in the study. On average, patients with depressive symptoms (BDI-II > 13), as compared to those without, showed poorer sleep quality (PSQI: 10.09 ± 4.1 vs 7.33 ± 3.55; $p = 0.001$ respectively), more fatigue (FSS: 4.69 ± 1.89 vs 3.34 ± 1.8; $p = 0.001$) and higher disease activity level (DAS28: 4.36 ± 1.53 vs 3.7 ± 1.39; $p = 0,047$). The logistic regression analysis showed that sleep quality is an independent predictor of depressive symptom severity.

Conclusion: Depressive symptoms, impaired sleep and fatigue are common in women with RA. Poor sleep is associated with greater frequency and severity of depressive symptoms in these patients, suggesting that screening for sleep and mood problems may be relevant both in clinical research and routine patient care. Future studies investigating the impact of measures to promote healthy sleep on depressive symptom control in this patient population are warranted.

Keywords: Rheumatoid arthritis, Sleep, Fatigue, Sleepiness, Depression

Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune disease, with overall prevalence estimated at 0.24% [1]. Women are three times more affected than men and usually report more symptoms and greater disability [1, 2]. Although RA primarily involves the joints, it may also cause important systemic manifestations [3]. Approximately 20–30% of RA patients become unable to work within a period of 3 years after diagnosis [4].

Depressive symptoms are common in RA [5]. Frequency of major depression in these patients has been reported to be almost 17%, considerably higher than that of the general population [6]. In clinical practice, diagnosis of depression in patients with RA is usually complicated by the fact that somatic symptoms of depression can overlap with symptoms of RA [7]. Fatigue, a common feature of depression, can affect 41% of RA patients [8]. Depressive symptoms in RA have been associated with increased pain [9], physical disability [10] and

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comorbidities [11], reduced quality of life [12] and higher mortality levels [13]. Recently, it has been reported that baseline and persistent depressive symptoms are associated with worse response to treatment and poorer long-term health outcomes [14]. The mechanism for the relationship between mood problems and RA outcomes remains incompletely understood [15]. The association between quality of sleep and depressive symptoms has not been adequately investigated in patients with RA in Brazil.

More than half of RA patients report sleep problems, including difficulty falling asleep, nocturnal awakenings, nonrestorative sleep and fatigue, a frequency that is three times higher than that of the general population [16]. It has been previously suggested that impaired sleep in RA is mainly secondary to joint pain, disease activity and altered mood [17–19]. On the other hand, there is evidence that disturbed sleep can be involved in the genesis of inflammatory disorders [20] and poor sleep quality has been shown to exacerbate pain perception in RA patients [21]. Additionally, sleep problems are recognized as an important risk factor for depression. Individuals suffering from insomnia are twice as likely to develop depression compared to those who do not have difficulty in sleep [22].

Fatigue is major symptom in patients with RA and has been associated with sleep problems, pain and depression. There is evidence that fatigue, poor sleep quality, pain, depression may be associated with greater disability in these patients [23].

The main purpose of this study was to assess the presence of depressive symptoms and its associations with sleep quality, fatigue, and disease activity in patients with RA.

Methods

This was a cross-sectional study of women with established RA, regularly attending an outpatient clinic at Dr. César Cals General Hospital, a tertiary referral centre in Fortaleza, Brazil, between April 2014 and December 2015. Female patients older than 18 years, who met the internationally-set RA diagnosis criteria [24], and whose therapeutic regimen had not been changed in the previous 3 months, were asked to take part in the study.

Disease activity was measured using the Disease Activity Score in 28 joints (DAS28), which comprises four scoring components, namely: number of swollen joints (0 to 28); number of painful joints (0 to 28); erythrocyte sedimentation rate (ESR); and general health visual analogue scale (VAS). DAS28 final score ranges from 0 to 10 and scores ≤ 2.6 were interpreted as remission; between 2.6 and 3.2, as low disease activity; between 3.2 and 5.1, as moderate activity; and > 5.1 as high activity [24].

Additionally, patients answered the following questionnaires, which have been previously translated and validated for use in Brazil: Beck Depression Inventory (BDI-II) [25]; Pittsburgh Sleep Quality Index (PSQI) [26]; Epworth Sleepiness Scale (ESS) [27]; Fatigue severity Scale (FSS) [28].

Depressive symptoms were assessed by the Beck Depression Inventory (BDI-II). This instrument consists of 21 sets of statements about the occurrence of depressive symptoms in the 15 days preceding the test application. Statements are classified in a Likert scale ranging from 0 to 3, to produce scores ranging from 0 to 63. Patients with BDI-II score > 13 were classified as positive for depressive symptoms [25, 29].

Sleep quality was assessed by the PSQI, a self-report questionnaire that consists of 19 items, creating seven components, each one dealing with a major aspect of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunctions. These components are weighted equally on a 0–3 scale, providing a global score ranging from 0 to 21 [26]. In the present study, scores higher than 5 were considered indicative of poor sleep quality. This cut-off point has shown satisfactory sensitivity (89.6%) and specificity (86.5%) to differentiate good from poor sleep quality [30].

Daytime sleepiness was evaluated by the Epworth Sleepiness Scale (ESS), a widely used instrument that infers the patient's likelihood of sleeping or dozing in eight daily life situations. This likelihood may range from zero (none) to three (high) for each situation. The final score corresponds to the sum of the values attributed to each individual question. Values higher than or equal to 10 were considered indicative of excessive daytime sleepiness [31].

Fatigue level was measured by the Fatigue Severity Scale (FSS), which consists of a sequence of 9 statements about the possible impact of fatigue on the responder's daily activities. For each statement, the subjects are asked to attribute a value from 1 to 7, depending on how appropriate they felt the statement applied to them over the previous 7 days. A low value indicates that the statement is not very appropriate whereas a high value indicates agreement. The final score represents the mean value calculated for the 9 items. Values higher than 4 indicate significant fatigue levels [32].

Additional socio-demographic and clinical data, including age, gender, time from diagnosis, and therapeutic regimen were gathered through interview and chart review.

Statistical analysis

Data are presented as mean ± standard deviation (SD) or frequency, as appropriate. Normality of the numerical data was assessed by the Kolmogorov-Smirnov test. Unpaired Student's t-test was used for variables with normal distribution. The Mann-Whitney test was used for non-normal variables. Categorical variables were analysed by the Fisher exact test. For comparative analysis, participants were allocated into two categories, according to the presence (BDI-II > 13) or absence of depressive symptoms. Spearman's correlation coefficients were calculated to examine possible correlations between BDI-II and other variables. Logistic regression analysis was performed to identify independent predictors for the occurrence of depressive symptoms using a forward stepwise approach. The Statistical Package for Social Science (SPSS) v22.0 (IBM CO., Armonk, NY, USA) was used for data analysis. A *p*-value < 0.05 was considered significant.

Results

One hundred and ten female patients, aged from 19 to 79 years, were included in the study. Depressive symptoms were present in 31.8% of the participants and were classified as mild (13 < BDI-II ≤ 19) in 14, moderate (19 < BDI-II ≤ 28) in 13 and severe (28 < BDI-II ≤ 63) in 6. Ten patients (9.1%) were on antidepressants (Amitriptyline: *n* = 05; Fluoxetine *n* = 02; Duloxetine: *n* = 1; Nortriptyline: *n* = 1; Amitriptyline + Fluoxetine: *n* = 1]. Poor quality sleep (PSQI > 5) was observed in 70.9% of the patients; fatigue (FSS > 4) in 41.8%; and excessive daytime sleepiness (ESS ≥ 10) in 39%. Disease activity level was calculated in 84 (76.4%) patients, for whom the

erythrocyte sedimentation rate was available at the time they were included in the study and was classified as moderate / high (DAS28 > 3.2) in 59.5%. There was no significant difference in age, time from diagnosis and questionnaire results between the 26 patients with missing DAS28 results and other study participants.

On average, patients with depressive symptoms (BDI-II > 13), as compared to those without, showed poorer sleep quality (PSQI: 10.09 ± 4.1 vs 7.33 ± 3.55; *p* = 0.001), more fatigue (FSS: 4.69 ± 1.89 vs 3.34 ± 1.8; *p* = 0.001) and higher disease activity level (DAS28: 4.36 ± 1.53 vs 3.7 ± 1.39; *p* = 0.047). Daytime sleepiness was not significantly different between the two groups (Table 1). Analysis of the seven PSQI components showed that patients with depressive symptoms had poorer subjective sleep quality and more sleep disturbances and use of sleep medication (Fig. 1). Patients with moderate/ high disease activity (DAS28 > 3.2) showed poorer sleep quality (PSQI global score: 9.91 ± 4.08 vs 7.0 ± 3.67; *p* < 0.01) than those in remission/ low disease activity.

Sixty-nine (62.7%) patients were on regular use of glucocorticoids, 90 (81.8%) on traditional disease-modifying antirheumatic drugs; and 23 (20.9%) on biologic disease-modifying antirheumatic drugs.

The occurrence of depressive symptoms (BDI-II > 13) was positively correlated with sleep impairment (*r* = 0.378; *p* < 0.001), fatigue (*r* = 0.307; *p* = 0.001) and disease activity (*r* = 0.333; *p* = 0.002). Stepwise multiple regression analysis, with age, disease duration, PSQI, DAS28, FSS, and ESS scores as independent variables, showed that the PSQI global score was an independent predictor for the occurrence of depressive symptoms (Table 2).

Table 1 Demographic and clinical characteristics, quality of sleep, fatigue, and daytime sleepiness in 110 RA female patients

|	Total *n* = 110	BDI-II ≤ 13 *n* = 74	BDI-II > 13 *n* = 36	*p*
Age, years (mean ± SD)	51.2 ± 8.1	52.3 ± 13.3	48.6 ± 12.15	0.054[b]
Disease duration, years (mean ± SD)	8.1 ± 7.8	8.9 ± 8.5	6.4 ± 5.7	0.147[b]
DAS28 score[a] (mean ± SD)	3.89 ± 1.45	3.7 ± 1.4	4.36 ± 1.53	0.047[b]
Moderate / high activity disease (DAS28 > 3,2), n (%)[a]	50(59.5)	31(53.4)	19(73.1)	0.100[c]
PSQI global score (mean ± SD)	8.21 ± 3.93	7.33 ± 3.55	10.09 ± 4.1	0.001[b]
Poor sleep, n (%)	78(70.9)	48(64)	30(85.7)	0.024[c]
FSS (mean ± SD)	3.77 ± 1.93	3.34 ± 1.8	4.69 ± 1.89	0.001[b]
Fatigue, n (%)	47(42.7)	26(34.7)	21(60)	0.014[c]
ESS (mean ± SD)	8.73 ± 5.41	8.39 ± 5.04	9.46 ± 6.15	0.450
EDS, n (%)	43(39.1)	28(37.3)	15(42.9)	0.676[c]
BDI-II (mean ± SD)	10.84 ± 9.11	5.55 ± 3.94	21.89 ± 6.65	< 0.01[b]

p values are for comparisons between groups of patients with (BDI-II > 13) and without depressive symptoms
Definition of abbreviations - *BDI-II* Beck Depression Inventory II, *DAS28* disease activity score in 28 joints, *PSQI* Pittsburgh Sleep Quality Index, *FSS* Fatigue Severity Scale, *ESS* Epworth Sleepiness Scale, *EDS* Excessive daytime sleepiness
[a]DAS28 values for 84 patients
[b]Mann-Whitney
[c]Fisher exact test

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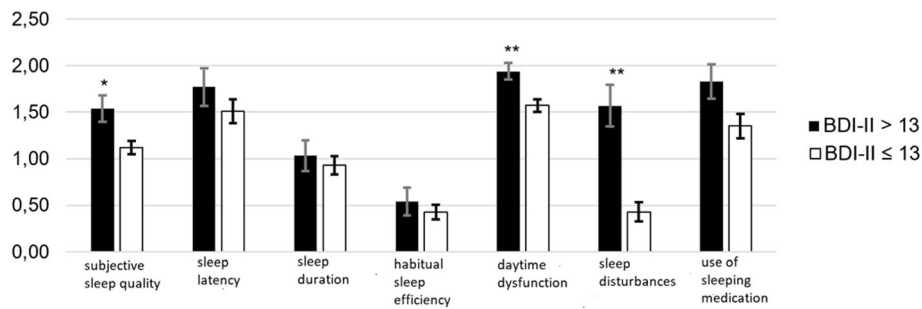
Fig. 1 Pittsburgh Sleep Quality Index components subjective sleep quality, sleep disturbances, use of sleep medication and daytime dysfunction were significantly impaired in RA patients with depressive symptoms as compared to those without depressive symptoms. Definition of abbreviations - BDI-II: Beck Depression Inventory. * $p < 0,05$; ** $p < 0,01$

Discussion

This study shows that depressive symptoms, sleep impairment and fatigue are very common in Brazilian women with RA. Importantly, poor sleep quality was found to be an independent predictor of depressive symptoms in these patients.

Almost one third of the study participants had depressive symptoms. Retrospective studies comprising large numbers of subjects also found a high prevalence of depressive symptoms in RA [5, 33]. A strong relationship between RA diagnosis and risk of depression was reported in 3698 newly diagnosed patients with RA. The incidence of depression in the RA cohort was 1.74-fold higher than in non-RA subjects [34]. In a retrospective study of a matched cohort of 18,285 participants it was found that RA patients were two times more likely to develop depression [35].

The present results show that the presence of depressive symptoms in patients with RA is associated with higher levels of disease activity, as previously reported [36]. In a study of 87 older women with RA, initially evaluated for depression and weekly assessed for 12 to 20 weeks for pain, depressive symptoms were found to

be related to elevations in pain [37]. The effects of depression on markers of immune activation were evaluated in another study of 45 women with RA and 106 controls with no autoimmune disease. A greater CD4 activation was found among RA patients who were depressed as compared to other groups. Depressed RA patients under stress showed the highest levels of IL-6. Those results suggest that depression plays a significant role in autoimmune processes associated with RA [38]. It has also been previously reported that baseline depression in patients with RA can predict disease activity and disability after a two-year follow-up period [14].

In this study, poor-quality sleep was found in more than two thirds of the participants and was related to disease activity. This finding is in agreement with previous reports of a high prevalence of disturbed sleep in RA, particularly, in the more active cases [17–19, 38, 39]. Cytokines, including TNF-α and IL-6, which also play a significant pathogenetic role in RA, could be involved in the genesis of the sleep problems observed in these patients [40]. It has been previously reported that sleep deprivation can increase the concentration of Toll-like receptor 4 (TLR-4) which, in turn, stimulates the production of interleukin-6 (IL-6) and tumour necrosis factor - alpha (TNF-α), two proinflammatory cytokines directly involved in RA [41]. Additionally, sleep deprivation can lead to greater expression of genes related to these cytokines through nuclear factor - kappa B (NF-κB) activation, which is the main gene-transcription regulatory pathway in the inflammatory signalling cascade [20].

This study confirms previous reports of a high frequency of fatigue in RA [8]. Although it is generally recognized that inflammation plays a significant role in the development of fatigue in RA, there is also evidence that non-inflammatory pathways could be involved [42]. It is likely that fatigue in patients with RA has a multifactorial origin, probably involving a wide range of factors, which may include obesity, sedentary lifestyle, sleep disturbances, loss of muscle mass and depression [43].

Table 2 Results of the stepwise multiple regression analyses using depressive symptoms as the dependent variable

Independent variables	B	SE	Wald	p	OR	95% CI for OR	
						Lower	Higher
Age	−0.007	0.023	0.102	0.749	0.993	0.949	1.039
Disease duration	−0.019	0.046	0.160	0.690	0.982	0.896	1.075
DAS28	0.271	0.201	1.819	0.177	1.312	0.884	1.945
PSQI	0.199	0.082	5.837	0.016	1.22	1.038	1.434
FSS	0.024	0.019	1.685	0.194	1.025	0.988	1.063
ESS	−0.013	0.049	0.072	0.789	0.987	0.897	1.086
Constant	−4.320	1.724	6.277	0.012	0.013		

Definition of Abbreviations: *BDI-II* Beck Depression Inventory, *DAS28* Disease activity score in 28 joint, *PSQI* Pittsburgh Sleep Quality Index, *FSS* Fatigue Severity Scale, *B* coefficients, *OR* Odds ratio, *CI* Confidence interval

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More than a third of the subjects in this study reported excessive daytime sleepiness, a frequency much higher than that found in the general adult population [44, 45]. No difference in daytime somnolence was observed between participants with and without depressive symptoms. A previous study in RA patients described a negative correlation between disease activity and subjective daytime sleepiness. Further studies are needed to clarify the relation between somnolence, disease activity, and depressive symptoms in RA [19].

The present results confirm that RA patients with depressive symptoms, on average, show higher disease activity than patients without these symptoms. Previously, an association between baseline depression symptom status and disease activity was found in a prospective study of 18,421 RA patients receiving biologic treatment. Depressive symptoms contributed to increased DAS28 over a 12-month follow-up period, and had an impact in changes in DAS28 in response to treatment. Interestingly, depression was associated with both subjective and objective aspects of disease activity, as assessed by specific components of the DAS28. It was suggested that these findings could be secondary to the negative impact of depression on health-related behaviours, particularly, medication adherence. They could also be related to biological factors, such as, systemic inflammation and elevated cytokines typically associated with disease severity in RA, which are also present in people with depressive disorder, or both [46].

An important finding of the present study is an independent association between poor-quality sleep and depressive symptoms. Disrupted sleep is generally recognized as a major feature of depression [47]. However, the relationship between poor sleep and depressive symptoms is probably bidirectional and may involve several factors [48]. Previous studies have shown a significant correlation between subjective sleep quality, as assessed by the global PSQI score, and measures of depression [49]. Additionally, depressed subjects present significantly higher PSQI scores than normal controls [30]. It has been suggested that the PSQI is better than objective measures of sleep for the detection of negative perceptions of sleep commonly found in patients with depression [50].

This study has limitations that must be considered. No male patients were included, so these results cannot be extrapolated to the entire RA population, mostly because of previously described effects of gender on disease activity measures as well as possible differences in cut-off values for some of the questionnaires that were used. Moreover, the presence of depressive symptoms assessed by the BDI-II is not sufficient for the diagnosis of depressive disorder, which requires a clinical structured interview. Besides, due to the cross-sectional design, causality cannot be implied, and prospective studies should be conducted to further investigate the associations between sleep quality, disease activity, fatigue, daytime sleepiness and depressive symptoms in RA patients.

Conclusions

This study shows a high frequency of impaired sleep, fatigue, and depressive symptoms in RA patients. Poor-quality sleep, found in the majority of cases, is associated with a higher frequency and severity of depressive symptoms. These findings highlight the importance of screening for sleep and mood disorders in RA patients both in clinical trials and in clinical practice. Future studies examining the impact of measures to promote healthy sleep on depressive symptom control in this patient population are warranted.

Authors' contributions
FHAL: acquisition of subjects and data, interpretation of data, preparation of manuscript. MVCF: Screening and clinical evaluation of the subjects. VMSB: critical review of manuscript. PFCB: study concept and design, analysis and interpretation of data, preparation of manuscript. The author(s) read and approved the final manuscript.

Authors' information
Not applicable.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol complied with the Declaration of Helsinki. All participants signed an Informed Consent Form, which was previously approved by the local Research Ethics Committee (no. 562.792, 2014).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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