Clinical, autoimmune, and psychiatric parameters correlate with sleep disturbance in patients with systemic sclerosis and rheumatoid arthritis

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ABSTRACT

Objective. *Sleep disturbance is an important contributor to poor quality of life in rheumatic disorders. This study aims to test whether clinical, autoimmune and psychological factors are associated with sleep disturbance in systemic sclerosis (SSc) compared to rheumatoid arthritis (RA) patients and controls.*

Methods. *101 female subjects (SSc=33, RA=34, healthy controls=34) participated in this observational, cross-sectional, parallel group study. Sleep disturbance was assessed with the Pittsburgh Sleep Quality Index (PSQI). Other assessments included the visual analogue scale (VAS) for pain, 36-item Short-Form Health Survey (SF-36), Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI). Clinical parameters, therapeutic regimen, and serologic status were recorded.*

Results. *In SSc patients, PSQI scores were higher than in RA patients and controls. Linear regression analysis showed that in SSc patients PSQI scores was associated with BDI, disease duration, modified Rodnan skin score and VAS, while DAS28 and BDI were associated with PSQI scores in RA patients. Anti-Scl70 and ANA positive SSc patients showed higher PSQI scores compared to those ANA positive only, while no differences were observed in RA patients classified according to rheumatoid factor positivity. SSc patients treated with immunosuppressants had lower PSQI scores compared to those not on therapy, whereas only corticosteroid treatment was significantly associated with higher PSQI scores in RA patients. RA patients with disease activity higher than moderate (DAS28≥3.2) had higher PSQI scores than those with lower than moderate (DAS28<3.2).*

Conclusion. *Longitudinal studies are needed to identify disease-specific patterns associated with sleep disturbances and the influence on sleep function induced by immunosuppressive therapy among rheumatic patients.*

Introduction

Patients affected by rheumatic diseases are prone to develop sleep disorders, and more than 75% of these patients report sleep disturbance (1). Pain and depression are well known factors influencing sleep efficiency and quality and this association has been explored in a wide range of rheumatic conditions (2). Previous work has suggested that pain is the main factor inducing sleep problems when compared to non-rheumatic patients (3). The scope of study into the psychosocial aspects of rheumatic diseases, including those known to be related to sleep disturbance, has expanded to include associations between circulating cytokines, central nervous system binding sites of cytokines, and the association of both of these with diagnostic and prognostic serologies used in the clinical arena (4).

The central nervous system and the immune system maintain bidirectional communication (8). Sleep disturbances, such as deprivation or chronic restriction, increase proinflammatory cyto-kine release (9). Likewise, neurons and glia are able to produce and release cytokines and neurons of the hypothalamus, hippocampus, brainstem, and neocortex, all involved in sleep/wake cycle regulation, show reactivity to IL-1 and TNF-α. Proinflammatory cytokines, such as IL-1, IL-2, IL-6, IL-18, and TNF-α promote non-rapid eye movement (REM) sleep, whereas IL-4, IL-10, IL-13, and TGF-β inhibit non-REM sleep (10).

Systemic sclerosis (SSc) is associated with increased disability and reduced quality of life due to the multi-organ involvement of the disease and the limited therapeutic options available (5). Additionally, difficulty sleeping is a frequent and potentially debilitating comorbidity in SSc (6) and sleep disruption scores in patients with SSc and rheumatoid arthritis (RA) are higher than in the general population (7).

In order to better characterise sleep disorders in SSc patients and to identify patient subtypes who may be particularly susceptible to poor sleep, we sought associations between sleep disorders and pain perception, anxiety, depression, and disease-specific clinical and autoimmune parameters in SSc patients compared to RA patients and healthy controls.

Materials and methods

This observational, cross-sectional, parallel group study was approved by the ethics committee of the Faculty of Medicine, University of Messina. All subjects provided written informed consent.

Study population

Thirty-three SSc patients, 34 RA patients, and 34 age-matched controls participated in this study. Patients with SSc and RA were diagnosed according to ACR/EULAR criteria (11-12). Cases were recruited between May 2014 and December 2014 from the rheumatology outpatient clinic of the University Hospital of Messina. We limited the study to women because SSc occurs overwhelmingly in females and we wished to minimise any effect of gender on sleep quality. Inclusion criteria otherwise included age ≥30 years. Sixteen RA patients (32%) and 1 SSc patient (3%) with a diagnosis of secondary fibromyalgia were excluded from the study. Controls were recruited to match patients in age from a sample of convenience recruited from medical personnel of the University Hospital of Messina. Exclusion criteria for controls were: systemic inflammatory or chronic disease of any kind.

A board-certified rheumatologist (GLB) performed a physical examination of each patient. Demographic and clinical data including comorbidities, therapeutic regimen, and disease duration were collected. SSc patients underwent high-resolution computerised tomography (HRCT) of the chest to assess for the presence and extent of pulmonary fibrosis through the Warrick scoring method (13). Echocardiography with colour Doppler was performed to estimate pulmonary artery pressure and pulmonary function testing was done including measurement of the diffusing capacity of the lung for carbon monoxide (DlCO). Skin involvement was quantified using the modified Rodnan skin score (mRSS) (14). In RA patients disease activity was measured using the Disease Activity Score 28 with ESR (DAS) (15). Pain perception was measured in all patients by visual analogue scale (VAS) and Short-form 36 (SF36) was used to assess quality of life. Laboratory evaluation included erythrocyte sedimentation rate (ESR, rheumatoid factor, antinuclear antibody (ANA), anti-topoisomerase-1 antibody (Scl-70), and anti-centromere antibodies using commercially available ELISA kits.

Sleep disorders assessment

The Pittsburgh Sleep Quality Index (PSQI) measures the quality of patient sleep in the last month by means of a self-assessment questionnaire (16). The index evaluates seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of medication, and daytime dysfunction related to sleep disorders. The PSQI score is the sum of the individual components (total score 0–21). A global PSQI score greater than or equal to five correlates with a poor quality of sleep.

Psychiatric evaluation

Patient depression was measured using the Beck Depression Inventory (BDI), a validated Likert-type self-report questionnaire which has demonstrated the ability to identify depressed and non-depressed medical patients (17). Scores reflect the rate at which the disorder is manifested within the last two weeks (range 0–39; 0–9 = no depressive symptoms, 10–19 = mild depression, 20–29 = moderate depression, 30–39= severe depression). Patient anxiety was assessed using the State-Trait anxiety inventory (STAI), a validated questionnaire comprising two subscales used to assess the presence and severity of an existing anxiety disorder (STAI-Y1) as well as the propensity to develop a generalised anxiety disorder (STAI-Y2). Scores range from 20 to 80 and a score of 40 indicates the presence of anxiety (18).

Statistical analysis

Single linear regression analyses were used to assess the associations between sleep scores and other parameters. To ensure that the sample size was adequate in relation to the numbers of predictors (19) the model was limited to six variables. Kruskal-Wallis test followed by a Dunn multiple-comparison test or Mann-Whitney test were used to detect differences between groups. All statistical tests were two-tailed with a $p<0.05$ considered significant.

Results

Demographic and clinical data for cases and controls are shown in Table I. A PSQI value ≥5, considered the cut-off value for being a "poor sleeper", was present in 94% of SSc patients, 68% of RA patients, and 20% of controls. Depression, anxiety and PSQI scores are reported in Table II.

Distinct features of sleep dysfunction are present in systemic sclerosis and rheumatoid arthritis patients

Overall, sleep disorders were increased among SSc and RA patients. PSQI total score was higher in SSc and RA patients when compared with controls. Moreover, this score was significantly higher in SSc patients than in RA patients (Fig. 1A). PSQI subscale-analysis showed that SSc patients had significantly worse scores compared to controls in all subscales. There were significant differences between RA patients and controls in all subscales except "need for medications to sleep" and "daytime dysfunction due to sleepiness". When comparing SSc and RA patients directly, subscales analysis showed that sleep efficiency, duration, and "daytime dysfunction due to sleepiness" were all significantly worse in SSc patients (Fig. 1 A1-A7).

Association between sleep disorders and psychiatric symptoms, quality of life assessment and pain perception

Depression, anxiety, quality of life and pain perception scores were significantly worse when both SSc and RA patients were compared to controls but no significant differences were found between SSc and RA patients (Fig. 2A-F). In SSc patients, linear regression analyses showed a positive association between PSQI total score and depression, anxiety, and VAS and a reverse association with both mental and physical health. In RA patients, the trend was similar for depression, VAS, and quality of life assessment but not for anxiety scales. In controls, no significant associations were found between PSQI total score and VAS or physical health section of SF-36 questionnaire (Fig. 3A-F).

Clinical and autoimmune parameters define a subset of patients with sleep disorders

We sought next to identify clinical or autoimmune features which might predict a subset of patients with higher PSQI scores. Among SSc patients we found that skin involvement, as reflected by mRSS, and disease duration were associated with PSQI total score (Fig. 4A-B). Warrick scores and DLCO values did not correlate with PSQI score indicating that there were no significant differences in PSQI scores among patients with pulmonary fibrosis or pulmonary artery hypertension. When classified and analysed by serologic profile, those SSc patients with both anti-Scl-70 antibodies and ANA positivity had significantly higher PSQI total scores compared to those positive for ANA only (Fig. 4C). No significant differences were observed in patients with anti-centromere antibodies when compared to patients solely with positive ANA, solely with positive anti-Scl-70, or positive for both ANA and anti-Scl-70.

In RA patients, PSQI total score was associated with DAS-28. Specifically, patients with greater-than-moderate disease activity (DAS28 > 3.2) had significantly higher PSQI total scores than patients with less active disease (Fig. 5A-B). There was no correlation between PSQI total score and disease duration or between PSQI total score and rheumatoid factor positivity.

Concomitant immunosuppressive therapy is associated with higher PSQI in a disease-specific manner

In order to assess whether concomitant immunomodulatory therapy may have an impact on sleep function, we analysed PSQI total score according to immunosuppressive treatment regimen. SSc patients receiving non-corticosteroid immunosuppressive therapy (n=12) had significantly lower PSQI total score compared to those not on therapy (n=21) (Fig. 4D), while there was no difference in patients receiving corticosteroid therapy alone. In RA patients,

Table I. Clinical and demographic characteristics of patients with SSc, RA and healthy controls.

		SSc (n=33)	RA (n=34)	Controls (n=34)	*p*
Age (years)		56.1 ± 11.5	52 ± 12.6	53.2 ± 12.7	0.21
Female patient n (%)		33 (100)	34 (100)	34 (100)	/
PSQI		10.3 ± 4	7 ± 4.3	3.4 ± 3.4	<0.0001
PSQI subscales	Sleep Duration	1.7 ± 0.8	1.1 ± 1.1	0.6 ± 0.9	<0.0001
	Sleep Disturbances	1.6 ± 0.8	1.35 ± 0.8	0.9 ± 0.5	0.0003
	Sleep Latency	1.75 ± 0.9	1.2 ± 1.1	0.4 ± 0.7	<0.0001
	Day Dysfunction	1 ± 0.9	0.5 ± 0.8	0.3 ± 0.6	0.0004
	Sleep Efficiency	2.2 ± 1	1 ± 1.1	0.5 ± 0.9	<0.0001
	Sleep Quality	1.4 ± 0.65	1.35 ± 0.9	0.7 ± 0.6	0.0004
	Need medications to sleep	0.5 ± 1.1	0.3 ± 0.8	0, ± 0.5	0.08
BDI		9.5 ± 5.4	7.9 ± 6.3	4.2 ± 5.1	0.0001
STAI-Y1		51.6 ± 10.7	51.4 ± 12.6	42.5 ± 8.8	0.0008
STAI-Y2		50 ± 11	50.2 ± 11.4	41.5 ± 10.4	0.0011
Mental health (SF-36)		41.2 ± 11.1	41.7 ± 14.3	51.5 ± 7.8	0.0014
Physical Health (SF-36)		35.7 ± 10.3	38.3 ± 9.3	53.9 ± 5.1	<0.0001
VAS (pain)		41.2 ± 16.9	34.7 ± 21.5	3.5 ± 6	<0.0001
Disease duration (years)		7.1 ± 6.7	12 ± 8.7	/	0.0088
Diffuse SSc/limited SSc (%)		38/62	/	/	
Lung fibrosis, n (%)		20 (59)	/	/	
Modified Rodnan Skin score		17.9 ± 9	/	/	
PAP		31.9 ± 9.4	/	/	
DAS 28		/	3.5 ± 1.4	/	
Corticosteroid therapy n (%)		4 (12)	12 (35)	/	
DMARDs therapy n (%)		13 (40)	25 (73)	/	
Biologics n (%)		/	22 (64)	/	
DMARDs + Biologic therapy n (%)		/	13 (38)	/	

*Except where indicated otherwise, values are expressed as mean ± standard deviation.
SSc: Systemic Sclerosis; RA: Rheumatoid arthritis; PSQI: Pittsburgh Sleep Quality Index; BDI: Beck Depression Inventory; STAI: Anxiety State-Trait Inventory; SF-36: Short-form 36; VAS: Visual analogue scale; mRSS: Modified Rodnan Skin Score; PAP: pulmonary artery pressure; DAS28: disease activity score 28 joints. Statistical analysis was made using the Kruskal-Wallis test.

Table II. Sleep, depression and anxiety scores.

	SSc (n=33)	RA (n=34)	Controls (n=34)
"Poor sleepers" (PSQI ≥ 5)	31 (94)	23 (68)	7 (20)
No depressive symptoms (BDI < 9)	17 (51)	23 (68)	29 (85)
Mild depression (BDI 10 – 19)	15 (46)	9 (26)	5 (14)
Moderate depression (BDI 20 – 29)	1 (3)	2 (6)	0
Severe depression (BDI 30 – 39)	0 0	0	
Anxiety state (STAI-Y1 >40)	24 (72)	25 (73)	10 (29)
Anxiety trait (STAI-Y2 >40)	24 (72)	22 (73)	10 (29)

Table shows the number of subjects and the related percentage categorised by sleep, depression and anxiety scores. The percentage of poor sleepers, defined by a Pittsburgh Sleep Quality Index (PSQI) score higher or equal than 5, is higher in the systemic sclerosis group of patients than the other groups. More systemic sclerosis patients resulted to be affected by a mild depression compared to the other groups. Both anxiety state and trait percentages in disease groups (RA and SSc) were higher than controls.
SSc: Systemic Sclerosis; RA: Rheumatoid arthritis; PSQI: Pittsburgh Sleep Quality Index; BDI: Beck Depression Inventory; STAI: State-Trait Anxiety Inventory.

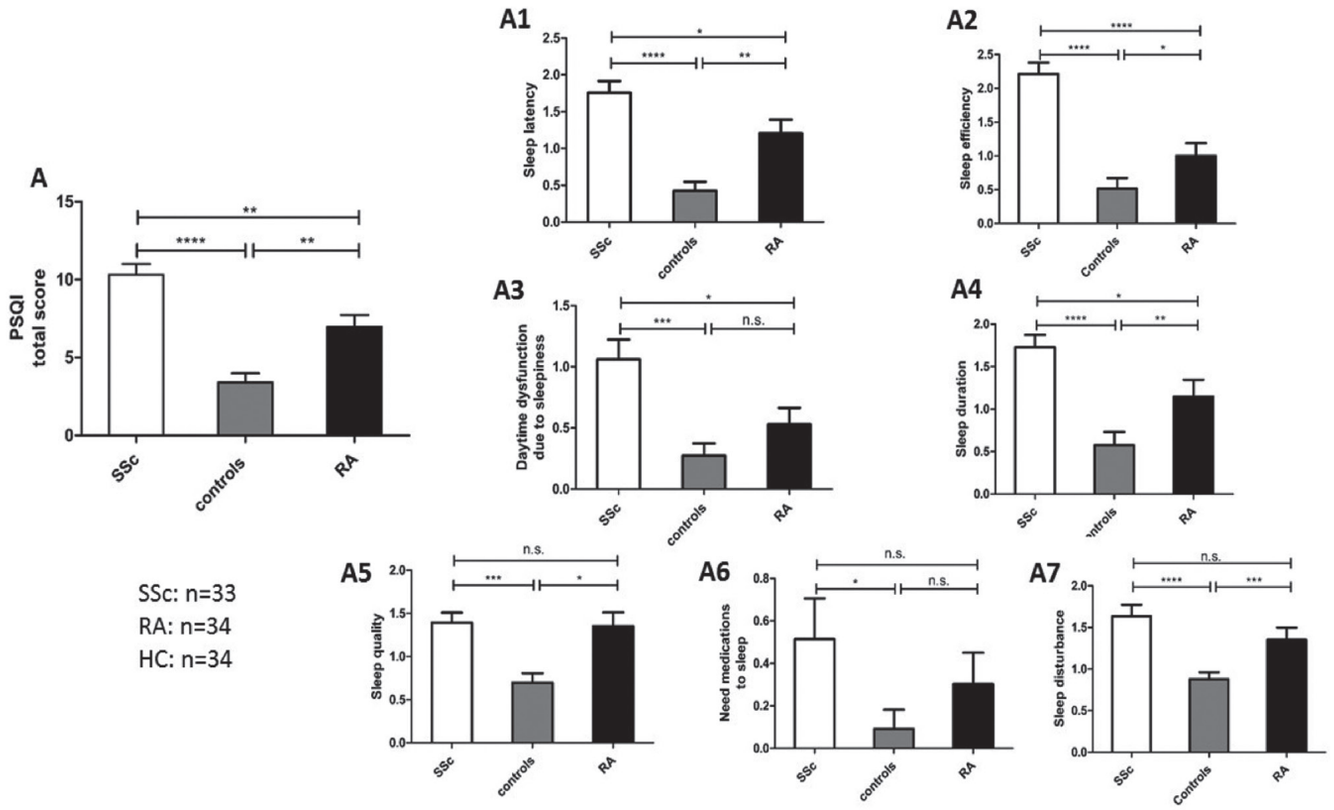

Fig. 1. A. Pittsburgh sleep quality index (PSQI) comparison, calculated using the Mann-Whitney test, between each group of subjects. PSQI total score is significantly worse for systemic sclerosis (SSc, n=33) compared to rheumatoid arthritis (RA, n=34)) patients and controls (n=34), and RA patients have worse PSQI total score compared to controls (n=34). **A1- A7**. SSc patients have significant worse scores in each subscale compared to controls (n=34), while significant differences have been observed, when compared to RA patients (n=34) in sleep duration, latency, efficiency and daytime dysfunction due to sleepiness. RA patients have significantly worse scores compared to controls in all subscales except daytime dysfunction due to sleepiness and sleep quality. * p between 0.05 and 0.02; ** p between 0.01 and 0.002; *** p between 0.001 and 0.0001; **** p<0.0001.

PSQI total score did not differ among those receiving disease-modifying antirheumatic drugs (DMARDs) only, biologic therapy only, or DMARDs plus biologic therapy. In contrast, significantly higher PSQI total score was observed in patients receiving corticosteroid treatment (n=14) compared to those who were not (n=20) (Fig. 5C).

Discussion

Recently there has been a greater appreciation for and a growing interest in the psychosocial aspects of SSc with increased attention focused on measures and interventions that may be clinically meaningful in improving patient quality of life (20). In this study we demonstrate that sleep disorders occur more frequently in patients with SSc than in patients with RA or in healthy controls (Table II). Our data, while confirming previous reports of this phenomenon in SSc, broaden the knowledge base in this area by comparing sleep pathology between SSc and RA patients and by examining clinical and serologic status in these patient groups.

In SSc patients sleep disorders have been previously associated with depressive symptoms, pain perception, and physical health as measured by SF-36 (21). Our data confirmed these associations (Fig. 2). It has also been shown that pain is an independent predictor of sleep disturbance in various arthritides (7) and our results confirm that, in SSc and RA patients (as previously demonstrated by Frech *et al*.) (22), pain perception represents an independent predictor of worse sleep outcome. While our study did not focus on the aetiology of patient pain, it is interesting that patients with SSc reported significantly higher pain scores than in patients with RA (with resultant significantly more impaired sleep). While patients with SSc may certainly develop painful comorbidites (*i.e*. Raynaud's phenomenon, inflammatory arthritis, gastrointestinal dysfunction), the most common manifestation of the disease, skin fibrosis, is in itself not painful. This may suggest a somatic element or difference in pain-processing between SSc and patients with other rheumatic disease such as RA.

Psychiatric symptoms are frequent among SSc patients and our data are in line with the results reported by previous investigators (23) although to a lesser degree. Depression is an important factor in other pathologic conditions prominently associated with disordered sleep (*i.e*. fibromyalgia) and may represent another independent predictor of poor sleep in SSc patients as well (5). Anxiety is an understudied aspect of SSc and, while it positively correlates with PSQI scores in SSc and it probably represents an important difference between RA and SSc patients in sleep outcome.

In order to explore the differences in sleep outcome between subsets of RA

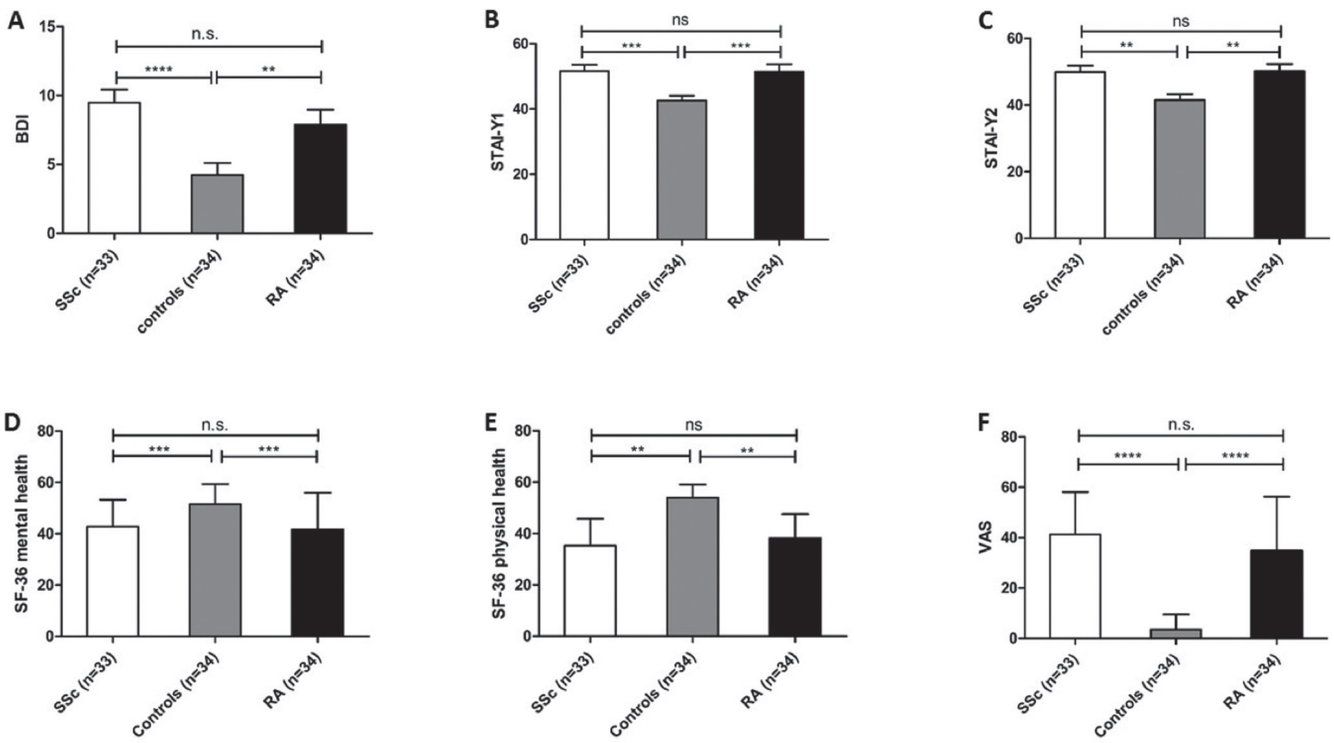

Fig. 2. Beck Depression Index (BDI, **A**), State and Trait Anxiety Index (STAI-Y1: state anxiety, **B**; STAI-Y2: trait anxiety, **C**), mental (**D**) and physical (**E**) SF-36 and VAS (**F**) scores were significantly higher both in systemic sclerosis (SSc, n=33) and rheumatoid arthritis (RA, n=34) when compared to controls (n=34), while no significant differences were observed when SSc and RA patients scores were compared to each other.
* *p* between 0.05 and 0.02; ** *p* between 0.01 and 0.002; *** *p* between 0.001 and 0.0001; **** *p*<0.0001.

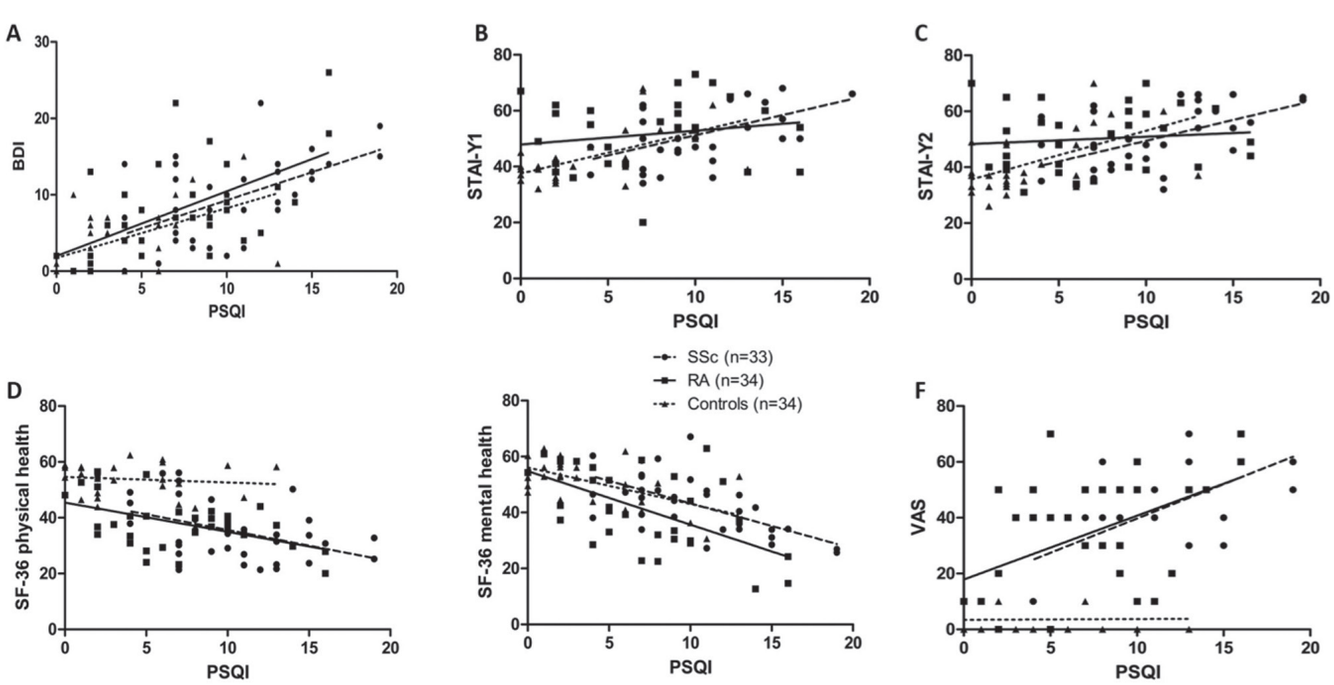

Fig. 3. A-E. Linear regression analyses between Pittsburgh Quality Sleep Index (PSQI) total score and depression (BDI, **A**), State and Trait Anxiety Index (STAI-Y1= state anxiety, B; STAI-Y2= trait anxiety, **C**), mental (**D**) and physical (**E**) SF-36 and VAS (**F**) scores in systemic sclerosis (SSc, n=33), rheumatoid arthritis (RA, n=34) patients and healthy controls (n=34). BDI is positively associated with PSQI total score in all groups (for SSc: p=0.001, r^2=0.30; for RA: p=0.0005, r^2=0.32; for controls: p=0.0004, r^2=0.34), while anxiety scores were positively associated with PSQI in SSc (STAI-Y1: p=0.001, r^2=0.29; STAI-Y2: p=0.0009, r^2=0.30) and in controls (STAI-Y1: p=0.003, r^2=0.33; STAI-Y2). VAS values were significantly associated with PSQI total scores in SSc (p=0.0008, r^2=0.39) and in RA (p=0.022, r^2=0.22).Mental health SF-36 were inversely associated with PSQI total score in all subjects (for SSc: p<0.0001, r^2=0.39; for RA: p=0.0005, r^2=0.33; for controls: p<0.0006, r^2=0.31), while a similar trend was found for physical health SF-36 and PSQI total score in SSc patients (p=0.01, r^2=0.19) and in RA patients only (p=0.005, r^2=0.24).

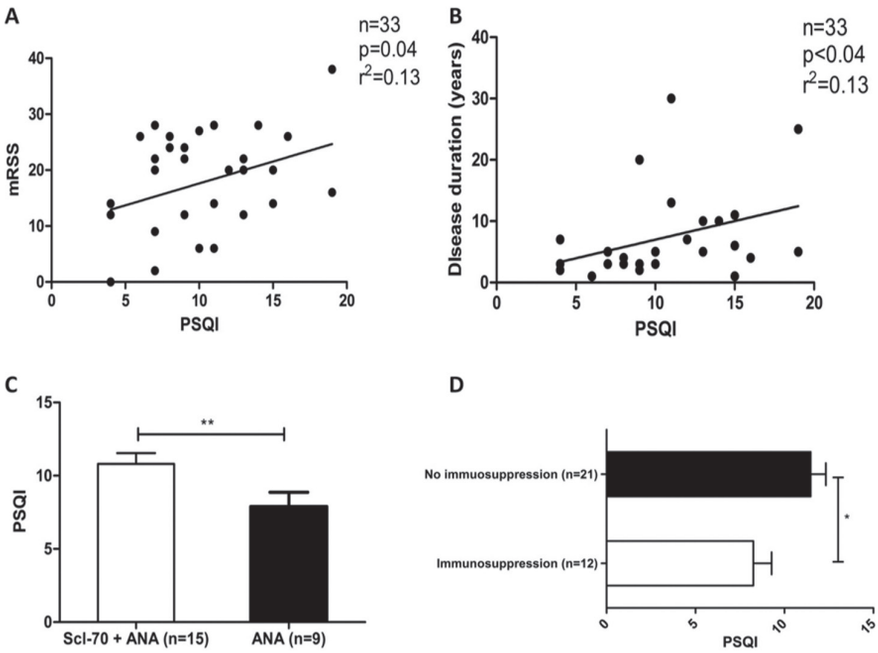

Fig. 4. Among SSc patients (n=34) the modified Rodnan skin score (mRSS, **A**) and disease duration (**B**) are positively associated with Pittsburgh Quality Sleep Index (PSQI) scores. Double positivity for ANA and anti-Scl-70 is associated with higher PSQI scores compared to patients with ANA positivity only (**C**). Patients receiving immunosuppressant therapy have significant lower PSQI values (**D**). *p between 0.05 and 0.02; ** p between 0.01 and 0.002; *** p between 0.001 and 0.0001; **** p<0.0001.

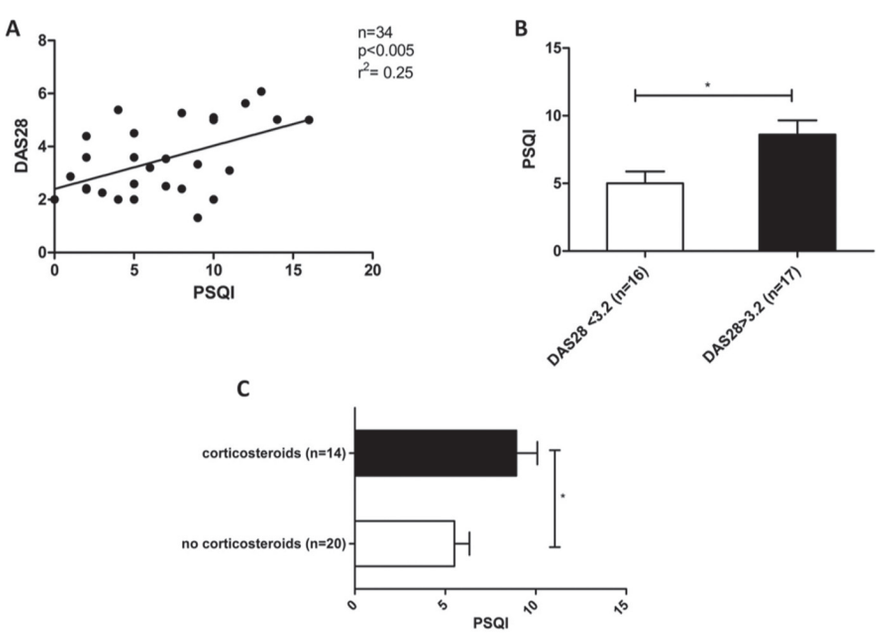

Fig. 5. In Rheumatoid arthritis patients disease activity score (DAS28, **A**) positively correlates with Pittsburgh Quality Sleep Index (PSQI) values and patients with disease activity lower than moderate (DAS28<3.2) have lower PSQI scores than patients with higher than moderate activity (DAS28>3.2, **B**) Corticosteroid administration is associated with worse sleep outcome (**C**). *: p between 0.05 and 0.02; ** p between 0.01 and 0.002; *** p between 0.001 and 0.0001; **** p<0.0001.

and SSc patients, we analysed specific features of each autoimmune disorder. We found that there are disease- and treatment-specific associations with worse sleep outcome in both groups: in SSc a higher mRSS and double-positivity for both anti-Scl-70 and ANA were associated with higher PSQI scores while no differences were found in PSQI scores among SSc patients with fibrotic or hypertensive pulmonary complications, indicating that it probably is not the lung comorbidity *per se* inducing sleep dysfunction. In RA patients higher disease activity was positively associated with worse PSQI values. In contrast with the results found in SSc patients, serology (as assessed by rheumatoid factor positivity) was not able to distinguish PSQI outcomes in RA patients.

In addition, we found that the use or absence of immunosuppressive therapy was associated with differing sleep outcomes. Among SSc patients, those receiving immunosuppressive agents showed better sleep outcomes. Conversely, we did not find any differences in sleep disturbances when RA patients were classified according to biologic or DMARD treatment. We did find that corticosteroid use defined a subset of patients with higher PSQI scores in this latter group. Immunosuppressant therapy is usually undertaken in SSc patients in an effort to address skin or lung fibrosis, clinical manifestations which are, in themselves, usually not painful. One could speculate that immunotherapy in these patients may have led to an improvement in sleep function unrelated to its effect on other disease manifestations.

These differences in outcomes related to antibody status and treatment with immunosuppressant agents raises the possibility that disease-specific cytokine or antibody profiles may impact quality of sleep. This could occur indirectly via pain-mediated worsening of sleep or directly via some alteration in central sleep mechanisms. Cytokines have been recognised as playing a role in the physiological regulation of sleep (24), and, in particular, interleukin-1β (IL-1) and tumour necrosis factor-α (TNF-α) have been well-characterised as regulators of sleep (25) both through similar mechanisms (26). Although TNF-α from peripheral blood mononuclear cells in RA patients has been reported to be a relevant factor in daytime sleepiness (27), anti-TNF therapies failed to reduce sleep disturbance scores in these patients (28-29). Conversely, recent data on abatacept in RA patients who failed anti-TNF therapy suggested a positive effect on sleep scores (30). In SSc there are no

specific studies addressing the effect of immunosuppressive therapy on sleep outcomes. It remains to be determined whether the differences in the incidence of sleep disturbances between SSc and RA could be due to different autoantibody patterns, cytokine milieu, or disease-specific approaches in immunosuppressive treatment (Fig. 3-4). Brain-immune interactions remain an essential component in psychiatric and medical comorbidities that significantly impact health and sleep (31).

This study has some limitations: the number of subjects in each group is low, limiting multivariate analysis. The assessment of sleep disorders, pain level, quality of life, depression, and anxiety were assessed using tools based on patient-reported measures, thus not allowing objective confirmation. However, as mentioned above, these tools have shown good reliability and efficacy in suggesting the presence or absence of these phenomena. As suggested previously, complexities in pain processing may differ across different diseases and the prevalence of somatisation leading to poor sleep may differ in a disease-specific manner, complicating efforts to compare possible cytokine or antibody effects among different diseases.

Conclusions

In conclusion, sleep disorders represent an important psychosocial factor impacting health and normal function in patients affected by chronic rheumatic diseases. More detailed descriptions of specific clinical subsets which may be at higher risk of developing sleep disturbance could allow the clinician to target disease-specific aspects that might affect sleep outcome. In particular, the role of cytokines as sleep regulatory factors, the presence and activity of specific antibody subsets, and the changes induced by immunosuppressive therapy need to be characterised in longitudinal observational and clinical trials.

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