Sleep quality in patients with primary Sjögren's syndrome

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Abstract

Objective

To assess the sleep quality in primary Sjögren's syndrome (pSS) patients and evaluate its relationship with the disease, quality of life and mood disorders.

Methods

The sleep quality of 29 pSS women and 29 matched controls was assessed by the Pittsburgh Sleep Quality Index (PSQI). Seven domains are grouped according to three factors: F1 perceived sleep quality (subjective sleep quality, sleep latency, use of sleeping medication), F2 sleep efficiency (sleep duration, habitual sleep efficiency) and F3 daily disturbances (sleep disturbances, daytime dysfunction). These domains are scored as a single factor of global sleep quality. The Short Form Health Survey (SF-36), Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale and Hospital Anxiety and Depression Scale (HADS) were also administered. Disease activity and damage were evaluated with the EULAR Sjögren's syndrome disease activity index (ESSDAI), the Sjögren's Syndrome Disease Activity and Damage Indexes (SSDAI, SSDDI).

Results

The mean PSQI global score had higher pathological values (8.6±4.6) compared with controls (5.6±2.2) (p=0.002). F1 and F3 were significantly worse in cases (p=0.01, p=0.009). A negative correlation was found between SF-36 subscales and the global PSQI, F2 and F3. The anxiety HADS correlated with F2 and F3, while depression only with F3. No correlation with FACIT and disease indexes emerged.

Conclusion

Using PSQI, an impaired sleep quality was demonstrated in pSS patients, especially with perceived quality and the daily disturbances. It is associated with a reduced quality of life but not with disease-related variables.

Key words

Sjögren's syndrome, sleep disorders, fatigue, Pittsburgh Sleep Quality Index

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Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune disease characterised by lacrimal and salivary gland involvement, resulting in a loss of their function. Even though sicca symptoms are the most frequent features of the disease, the inflammatory process can extend to several other organs and tissues and constitutional symptoms, including fatigue, weight loss, fever, and widespread pain, may impair quality of life. Sleep disturbances, excessive daytime sleepiness and fatigue have been described in patients with pSS (1-4) alongside a wide spectrum of reasons: the possible overlap between pSS and fibromyalgia (5-6), mood disorders (7, 8), muscle and joint pain, night sleep restriction linked to the necessity to awake to drink water for sicca symptoms (9), restless legs symptoms and a concomitant obstructive sleep apnea syndrome (OSAS), which have been reported with a higher prevalence in pSS patients (10). It is not clear whether sleep disturbances in pSS may be related to disease activity or to the damage linked to the disease itself. In fact, no standardised tool for measuring disease activity and damage was available for pSS until the recent publication of the SS Disease Activity Index (SSDAI), the SS disease damage index (SSDDI) (11) and the EULAR SS Disease Activity Index (ESSDAI) (12). On the contrary, measuring sleep quality is an area of intensive research and several patient reported outcome instruments are available to measure different aspects of sleep dysfunction (13). The Pittsburgh Sleep Quality Index (PSQI) has been widely used (14-22) and has robust reliability (23, 15, 16), validity (23, 15, 17), responsiveness and interpretability (23). This tool has been successfully used in several rheumatic disorders (24-28).

Given that many different variables seem to influence sleep quality, and the paucity of data regarding this topic in pSS, the objectives of this study were: 1) to characterise sleep quality using PSQI in pSS patients compared to the general population; and 2) to assess the possible correlation between sleep disturbances and disease activity and damage, constitutional symptoms and mood disorders.

Patients and methods

Patients and outcome measures

Thirty-one female out-patients, with an established diagnosis of pSS according to the American-European Consensus group criteria (29), were consecutively enrolled during routine follow-up visits at the Sjögren's Syndrome Clinic, at the Sapienza University of Rome with the approval of the local ethics committee and after informed written consent. At the time of enrollment, demographic, clinical and laboratory data were collected and disease activity and damage were scored using validated scales (SSDAI-Sjögren's Syndrome Disease Activity Index, SSDDI-Sjögren's Syndrome Disease Damage Index, ESSDAI-EULAR Sjögren's Syndrome Disease Activity Index) (11, 12). Schirmer's test and sialometry values were used for an objective evaluation of dryness symptoms; they were considered pathological when lower than 5 mm/5 min and 1.5 ml/15 min, respectively. Moreover, the Italian validated versions of the Short Form Health Survey (SF-36) (30), the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale (31), the Hospital Anxiety and Depression Scale (HADS) (32) were administered. Two of the initial 31 patients recruited were excluded from the study for a proved OSA syndrome. As controls 29 age and sex matched healthy controls (HC) were recruited as well. To both patients and controls, the Pittsburgh Sleep Quality Index (PSQI) validated in Italian language (33), was administered after proper explanation.

The PSQI (34) is the most commonly used retrospective self-report questionnaire that measures sleep quality over the previous month. It consists of 19 questions grouped in 7 components (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction), each weighted on a 0–3 scale, that are summed in a global PSQI score that ranges from 0 to 21 with a higher score indicating worse sleep quality. A result equal to 5 or above is considered indicative of poor sleep quality. The seven components

above reported can be grouped according to 3 main factors that synthesise sleep quality: F1, perceived sleep quality; F2, sleep efficiency; F3 daily disturbances. Basically in both the global and components scales, higher scores reflect greater sleep complaints.

The SF-36 (35) is a generic health status measure with a global score range of 0–100; better health status achieves higher scores. It consists of 36 items assessing 8 domains: physical functioning, bodily pain, role limitations due to physical health problems, general health perceptions, mental health, role limitations due to emotional problems, vitality, social functioning. The eight scales can be clustered into a physical component and a mental component, and it should be taken into consideration that lower scores indicate higher disability in each specific domain.

The FACIT-Fatigue scale (36) is a self-administered questionnaire that evaluates fatigue and its influence on daily activities and function. It comprises 13 items, each with a categorical response scale (0 = not at all; 4 = very much). A total score is the sum of the individual items and ranges between 0 (maximum fatigue) and 52 (no fatigue) with scores ≤32 reflecting severe fatigue. This scale has already been used in primary SS patients (3).

The HADS (37) is a self-report questionnaire divided into 2 subscales, HADS-A (anxiety) and HADS-D (depression), both with 7 questions and a score range from 0 (no depression or anxiety) to 21 (maximal depression or anxiety). For each subscale, a score of 0-7 indicates normality, 8-10 a borderline case, ≥11 a probable clinically significant anxiety or depression (38).

Statistical analysis

PSQI scores (global, F1, F2 and F3) have been compared between pSS patients and HC by means of the Student *t*-test.

A subsequent analysis of correlation has been carried out on pSS between PSQI scores (global, F1, F2 and F3) and scores of ESSDAI, SSDAI, SSDDI, HADS-Anxiety, HADS-Depression, FACIT, SF36, measure of sialometry and of duration of disease.

Table I. clinical and laboratory features.

Disease characteristics	Total sample (n=29)
Age, mean (SD), years	55.89 (12.15)
Disease duration, mean (SD), months	43.14 (47.36)
Xerophtalmia, n (%)	26 (89.6 %)
Xerostomia, n (%)	25 (86.2%)
Pathological Schirmer's test[a], n (%)	20 (68.9 %)
Pathological non stimulated Sialometry[b], n (%)	16 (55.2%)
Joint pain[c], n (%)	26 (89.6%)
ESSDAI, mean (SD)	4.45 (4.35)
SSDAI, mean (SD)	2.14 (1.87)
SSDDI, mean (SD)	1.48 (0.95)
ANA, n (%)	25 (86.2%)
SSA and/or SSB, n (%)	17 (58.6%)
Pathological minor salivary glands biopsy[d], n (%)	12 (92.3%)
Fibromyalgia[e], n (%)	2 (6.9%)
Sleep disturbance (PSQI >5), n (%)	24 (82.7%)
Physical score^{SF36}, mean (SD)	47.88 (21.54)
Mental score ^{SF36}, mean (SD)	45.68 (20.51)
HADS anxiety score, mean (SD)	10.44 (5.77)
HADS depression score, mean (SD)	7.41 (4.09)
FACIT , mean (SD)	35.06 (7.13)

[a]less than 5 mm in 5 minutes; [b]less than 1.5 ml in 15 minutes; [c]With or without joint inflammation; [d]Number of focus (50 cells/4mm^2) ≥1; [e]ACR criteria (Wolfe F. *et al*. The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity. *Arthritis Care Res* 2010; 62: 600-10).

Table II. Sleep quality differences between pSS and HC.

Variable	pSS patients (mean±SD)	Controls (mean±SD)	t (df 56)	*p*-value
PSQI global[a]	8.62 ± 4.58	5.59 ± 2.24	3.21	0.002
F1[b]	2.69 ± 2.30	1.38 ± 1.35	2.65	0.01
F2[c]	3.17 ± 2.22	2.24 ± 1.24	1.97	0.05
F3[d]	2.76 ± 1.33	1.97 ± 0.87	2.69	0.009

[a]Pittsburgh Sleep Quality Index global score; [b]Factor F1: perceived sleep quality; [c]Factor F2: sleep efficiency; [d]Factor F3: daily disturbance.

Results

Patients' clinical and laboratory data are summarised in Table I. No statistically significant difference was found for age between cases (55.58±11.95) and HC (55.67±12.07).

Results on sleep quality differences between cases and HC are summarised in Table II. Patients with pSS had a significantly higher mean PSQI global score (8.62±4.58) compared to HC (5.59±2.24; t=3.21, *p*=0.002) (Fig. 1). In the patient's group, 24 out of 29 showed sleep complaints (82.76%) while the percentage appeared slightly reduced in the HC group (69%; 20 out of 29). All 3 factors of the PSQI- perceived sleep quality (F1), sleep efficiency (F2) and the daily disturbances (F3)- reached a higher value in cases than in HC (*p*=0.01, *p*=0.05 and *p*=0.009, respectively) (Fig. 2).

Sixteen (55.2%) and 9 patients (31%) could be considered anxious or depressed, respectively. The mean anxiety HADS score was borderline in pSS patients (10.4±5.7), while the mean depression HADS score was at the higher limit of normal values (7.4±4.1). No significant correlation between anxiety/depression HADS and PSQI global score was found.

The FACIT fatigue scale was altered (mean values of 35.06±7.14), but there was no significant correlation with PSQI global scores.

Significant negative correlations were found between global PSQI score and SF-36 subscales of both physical and mental domains, such as physical ac-

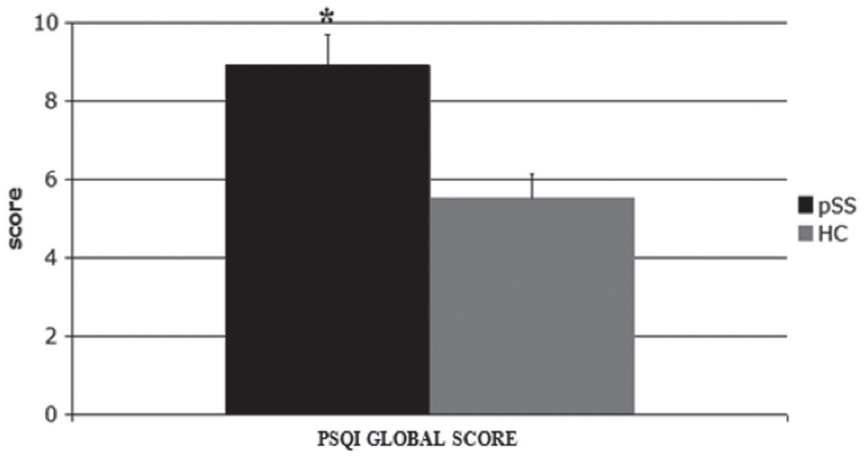

Fig. 1. PSQI global score differences between pSS and HC.
PSQI: Pittsburgh Sleep Quality Index global score (*p-value = 0.002).

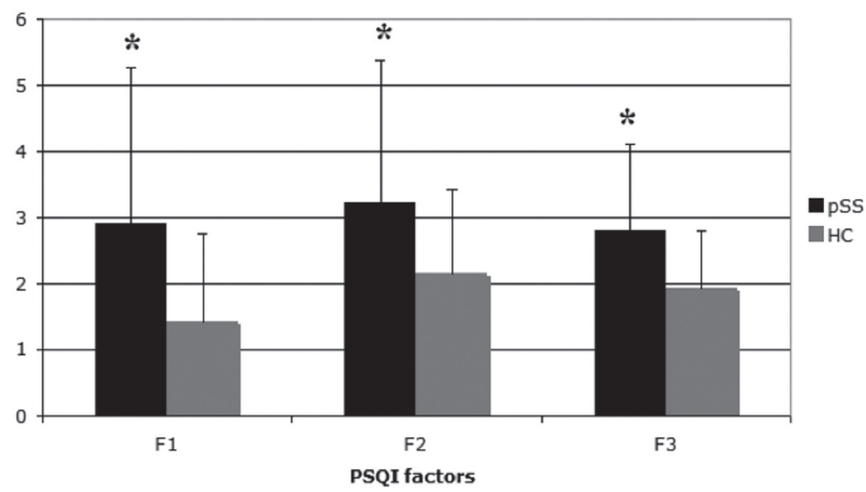

Fig. 2. PSQI Factors differences between pSS and HC.
Factor F1, perceived sleep quality (*p-value =0.01); Factor F2, sleep efficiency (*p-value =0.05); Factor F3, daily disturbance (*p-value =0.009).

tivity (r=-0.63; p=0.0002), physical limitation (r=-0.49; p=0.007), physical pain (r=-0.43; p=0.02), vitality (r=-0.45; p=0.01), social activity (r=-0.47; p=0.01), emotional limitation (r=-0.40; p=0.03) and mental health (r=-0.42; p=0.02). No other significant correlation between PSQI global score and clinical variables emerged, in particular between PSQI and ESSDAI, SSDAI, SSDDI and disease duration. No difference was observed between SSA and/or SSB positive patients and negative ones, nor between untreated and treated patients independently from the drug (steroids, hydroxychloroquine or immunosuppressants).

A similar correlational analysis was carried out with PSQI factors. The factor of perceived sleep quality (F1) showed only a negative correlation with the mental health subscale of emotional limitation (r=-0.38; p=0.04). On the other hand, F2 (sleep efficiency) positively correlated with anxiety as assessed by HADS (r=0.46; p=0.01), and negatively correlated with SF-36 physical activity (r=-0.48; p=0.008) and pain (r=-0.40; p=0.03). Moreover, F2 also negatively correlated with social activity (r=-0.39; p=0.04), and mental health (r=-0.37; p=0.05). Finally, with respect to factor F3 (daily disturbances) a more complex picture emerged: the PSQI factor positively correlated with anxiety (r=0.50; p=0.005) and depression (r=0.44; p=0.01) as assessed by HADS, while a negative correlation was observed with fatigue scale of FACIT (r=0.46; p=0.01). A negative correlation was instead observed with some subscales of SF-36, such as physical activity (r=0.78; p=0.000001), physical limitation (r=-0.54; p=0.003), physical pain (r=-0.53; p=0.003), general health (r=-0.48; p=0.009), vitality (r=-0.75; p=0.000002), social activity (r=-0.62; p=0.0003), and mental health (r=-0.44; p=0.01).

No other significant correlation between PSQI factors and clinical variables resulted statistically significant.

Discussion

Patients with pSS present a higher probability of sleep troubles with respect to matched controls. They showed a significant decrease of global sleep quality (as assessed by global score) and this was reflected also by significant changes in perceived sleep quality, daily disturbances and, to less extent, in sleep efficiency. Correlational analysis showed that bad sleep quality is usually linked to low levels in both physical and mental health subscales, *i.e*. higher disability. This relationship is mainly explained by the amount and intensity of daily disturbances, a sleep quality factor that positively correlates also with mood disturbances of pSS patients.

People spend one third of their lifetime sleeping. A satisfying sleep quality is a requisite for a fine health status and vice versa a physical or mental disease may influence overall sleep quality. Sleep-wake disturbances have been described in patients with chronic disorders such as cancer (39), chronic fatigue syndromes (40) or generalised pain (41) and can affect the quality of life. However, the quality of sleep is generally neglected by both health care professionals, who do not routinely assess it in clinical practice (42), and patients themselves (43). This is particularly true in rheumatology, in fact, as far as we know, very few studies have evaluated the quality of sleep in patients with autoimmune diseases of rheumatological interest (24-28, 44, 45) and this topic has been the subject of an interesting review (46).

Using a standardised sleep questionnaire, Gudbjörnsson *et al*. (1) first registered a significantly higher sleep defi-

cit (difference between need of sleep and actual sleeping time) in patients with pSS compared to healthy matched controls and subjects with Rheumatoid Arthritis, possibly caused by muscular tension, restless legs syndrome, or nocturnal pain. Actually, joint pain has been linked to poorer quantity/quality of sleep in pSS patients (9) and human and animal experimental research studies show a bidirectional relationship of disordered sleep to pain and fatigue. Even if fatigue, occasionally linked to a concomitant fibromyalgia (6), is a very common feature in pSS with a great impact on the quality of life (47), we could not demonstrate any correlation between fatigue and sleep disorders. This negative observation has been previously reported by Usmani and colleagues (10) who did not find any significant link between measures of sleep disruption, sleep apnea severity, and FACIT-F scores in pSS patients. It is plausible that fatigue in pSS may arise from different factors including fibromyalgia (4-6, 40), cytokine disequilibrium (48, 49), autonomic nervous system disturbances (50), anxiety and depression (51-53), reduced aerobic capacity (54), and sub-clinical myositis (55). Sleep abnormalities as a possible cause of fatigue in pSS needs to be further evaluated, hopefully looking at both sleep micro- and macrostructure typical of these patients.

The relationship between sleep and pain is even more complex: sleep deprivation is suspected to play a role in the onset and flares of some rheumatologic diseases but, as far as we know, only animal models support this hypothesis (56). In humans, sleep abnormalities can induce a hyperalgesic state (57) and modulate pain, and vice versa pain may negatively affect sleep, so that a vicious cycle of perpetuation and augmentation could arise. Wide spread pain is very common in patients with pSS (58). The result of this study seems to confirm the link between pain and sleep troubles as the higher the pain as estimated by SF36, the lower the quality of sleep.

Dryness and the consequent necessity to frequently awake to sip water is another possible reason for sleep deprivation and daytime fatigue (9). Considering that strong relationships between mouth drying, increased surface tension of upper airway lining fluid, and increased airway collapsibility and obstructive sleep apneas have been demonstrated (59), the increased airway drying is a likely explanation for the increased prevalence of OSA in pSS (10). As a matter of fact, 2 out of 31 consecutive pSS patients (6.4%) consecutively recruited for this study have a demonstrated OSA syndrome, both of which are already using continuous positive airway pressure devices at night.

Mood disorders, frequently reported in pSS patients (60), have been also associated to sleep disturbances (61, 62). Anxiety disorders are associated with all PSQI subscales except use of medications for sleep (63) and in older subjects symptoms of short sleep duration, daytime sleepiness and sleep disturbances are independently related to anxiety (64). Several studies suggest that insomnia, chronic pain, and depression frequently overlap and are mutually interacting conditions with still unclear underlying mechanisms (65). Other epidemiological evidence suggests that the link between insomnia and depression is bidirectional. It is estimated that about 20% of patients with insomnia show some depressive symptoms whereas depression and depressive symptoms seem to be the most important risk factors for insomnia (66).

In the present study, a high percentage of cases exhibit a clinical significant anxiety and/or depression, both associated with daily disorders but not with abnormalities in the perceived quality of sleep. Actually, it's rather difficult to establish what comes first between mood disorders and sleep disturbances. A powerful and original aspect of our study is that it is the first one in which sleep quality in pSS was correlated with disease activity and damage demonstrating that sleep disturbances are independent from these variables. Moreover, neither correlation was found between reduced quality of sleep and immunological profile (*i.e* the presence of autoantibodies) and nor with treatment.

This study also has some limitations: the first is its relatively small sample size. Despite this, statistically significant differences were observed in the prevalence of sleep disturbances between patients and controls. Secondarily, an overall neuropsychological testing would have been strengthened the study by assessing possible cognitive and behavioural effects of sleep quality decrease in pSS patients.

Future studies will better clarify the strong relationship between pSS and sleep also from a quantitative point of view: in this vein, an overnight polisomnography could add interesting information about micro- and macrostructure of sleep, sleep temporal dynamics, as well as regarding possible differential effect on power spectra of slow-wave activity, the best marker of sleep homeostasis.

In summary, sleep disturbances, fatigue and mood disorders, are associated with pSS and more extensive research is needed to better evaluate their intertwined relationship and determine whether interventions addressing these co-morbidities will help the underlying disease process and improve patients' quality of life.

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References

1. GUDBJÖRNSSON B, BROMAN JE, HETTA J, HÄLLGREN R: Sleep disturbances in patients with primary Sjögren's syndrome. *Br J Rheumatol* 1993; 32: 1072-6.
2. GODAERT GL, HARTKAMP A, GEENEN R *et al*.: Fatigue in daily life in patients with primary Sjögren's syndrome and systemic lupus erythematosus. *Ann N Y Acad Sci* 2002; 966: 320-6.
3. WALKER J, GORDON T, LESTER S *et al*.: Increased severity of lower urinary tract symptoms and daytime somnolence in primary Sjögren's syndrome. *J Rheumatol* 2003; 30: 2406-12.
4. IANNUCCELLI C, SPINELLI FR, GUZZO MP *et al*.: Fatigue and widespread pain in systemic lupus erythematosus and Sjögren's syndrome: symptoms of the inflammatory disease or associated fibromyalgia? *Clin Exp Rheumatol* 2012; 30 (Suppl. 74): 117-21.
5. TISHLER M, BARAK Y, PARAN D, YARON M: Sleep disturbances, fibromyalgia and primary Sjögren's syndrome. *Clin Exp Rheumatol* 1997; 15: 71-4.
6. PRIORI R, IANNUCCELLI C, ALESSANDRI C *et al*.: Fatigue in Sjögren's syndrome: relationship with fibromyalgia, clinical and bio-

logic features. *Clin Exp Rheumatol* 2010; 28 (Suppl. 63): S82-6.
7. WESTHOFF G, DÖRNER T, ZINK A: Fatigue and depression predict physician visits and work disability in women with primary Sjögren's syndrome: results from a cohort study. *Rheumatology* 2012; 51: 262-9.
8. SEGAL BM, POGATCHNIK B, HOLKER E *et al*.: Primary Sjögren's syndrome: cognitive symptoms, mood, and cognitive performance. *Acta Neurol Scand* 2012; 125: 272-8.
9. GOODCHILD CE, TREHARNE GJ, BOOTH DA, BOWMAN SJ: Daytime patterning of fatigue and its associations with the previous nights discomfort and poor sleep among women with primary Sjögren's Syndrome or Rheumatoid Arthritis. *Musculoskeletal care* 2010; 8: 107-17.
10. USMANI ZA, HLAVAC M, RISCHMUELLER M *et al*.: Sleep disordered breathing in patients with primary Sjögren's syndrome: a group controlled study. *Sleep Med* 2012; 13: 1066-70.
11. VITALI C, PALOMBI G, BALDINI C *et al*.: Sjögren's Syndrome Disease Damage Index and disease activity index: scoring systems for the assessment of disease damage and disease activity in Sjögren's syndrome, derived from an analysis of a cohort of Italian patients. *Arthritis Rheum* 2007; 56: 2223-31.
12. SEROR R, RAVAUD P, BOWMAN SJ *et al*.: EULAR Sjögren's Task Force. EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. *Ann Rheum Dis* 2010; 69: 1103-9.
13. DEVINE EB, HAKIM Z, GREEN J: A systematic review of patient-reported outcome instruments measuring sleep dysfunction in adults. *Pharmacoeconomics* 2005; 23: 889-912.
14. FICTENBERG NL, PUTMAN SH, MANN NR *et al*.: Insomnia screening in postacute traumatic brain injury: utility and validity of the Pittsburgh Sleep Quality Index. *Am J Phys Med Rehabil* 2001; 80: 339-45.
15. CARPENTER JS, ANDRYKOWSKI MA: Psychometric evaluation of the Pittsburgh Sleep Quality Index. *J Psychosom Res* 1998; (1): 5-13.
16. GENTILI A, WEINER D, KUCHIBHATLA M *et al*.: Test-retest reliability of the Pittsburgh Sleep Quality Index in nursing home residents [letter]. *J Am Geriatr Soc* 1995; 43: 1317-8.
17. BUYSSE DJ, REYNOLDS CF, MONK TH *et al*.: Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). *Sleep* 1991; 14: 331-8.
18. STEIN MB, CHARTIER M, WALTER JR: Sleep in nondepressed patients with panic disorder: I. Systematic assessment of subjective sleep quality and sleep disturbance. *Sleep* 1993; 16: 724-6.
19. MOELLER AA, OECHSNER M, BACKMUND HC *et al*.: Self-reported sleep quality in HIV infection: correlation to the stage of infection and zidovudine therapy. *J Acquir Immune Defic Syndr* 1991; 4: 1000-3.
20. SAYAR K, ARIKAN M, YONTEM T: Sleep quality in chronic pain patients. *Can J Psychiatry* 2002; 47: 844-8.
21. BACKHAUS J, JUNGHANNS K, BROOCKS A *et al*.: Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. *J Psychosom Res* 2002; 53: 737-40.
22. TSAY SL, RONG JR, LIN PF: Acupoints massage in improving the quality of sleep and quality of life in patients with end-stage renal disease. *J Adv Nurs* 2003; 42: 134-42.
23. BUYSSE DJ, REYNOLDS CF: The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; 28: 193-213.
24. SARIYILDIZ MA, BATMAZ I, BOZKURT M *et al*.: Sleep quality in rheumatoid arthritis: relationship between the disease severity, depression, functional status and the quality of life. *J Clin Med Res* 2014; 6: 44-52.
25. SARIYILDIZ MA, BATMAZ I, BUDULGAN M *et al*.: Sleep quality in patients with systemic sclerosis: relationship between the clinical variables, depressive symptoms, functional status, and the quality of life. *Rheumatol Int* 2013; 33: 1973-9.
26. BATMAZ I, SARIYILDIZ MA, DILEK B, BEZ Y, KARAKOÇ M, ÇEVIK R: Sleep quality and associated factors in ankylosing spondylitis: relationship with disease parameters, psychological status and quality of life. *Rheumatol Int* 2013; 33: 1039-45.
27. NICASSIO PM, ORMSETH SR, KAY M *et al*.: The contribution of pain and depression to self-reported sleep disturbance in patients with rheumatoid arthritis. *Pain* 2012; 153: 107-12.
28. ABBASI M, YAZDI Z, REZAIE N: Sleep disturbances in patients with rheumatoid arthritis. *Niger J Med* 2013; 22: 181-6.
29. VITALI C, BOMBARDIERI S, JONSSON R *et al*.; EUROPEAN STUDY GROUP ON CLASSIFICATION CRITERIA FOR SJÖGREN'S SYNDROME: Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61: 554-8.
30. APOLONE G, MOSCONI P: The Italian SF-36 Health Survey: translation, validation and norming. *J Clin Epidemiol* 1998; 51: 1025-36.
31. Italian version of FACIT obtained by http://www.facit.org/FACITOrg
32. COSTANTINI M, MUSSO M, VITERBORI P *et al*.: Detecting psychological distress in cancer patients: validity of the Italian version of the Hospital Anxiety and Depression Scale. *Support Care Cancer* 1999; 7: 121-7.
33. CURCIO G, TEMPESTA D, SCARLATA S *et al*.: Validity of the Italian version of the Pittsburgh Sleep Quality Index (PSQI). *Neurol Sci* 2013; 34: 511-9.
34. BUYSSE DJ, REYNOLDS CF 3RD, MONK TH, BERMAN SR, KUPFER DJ: The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; 28: 193-213.
35. BRAZIER JE, HARPER R, JONES NM *et al*.: Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992; 305: 160-4.
36. YELLEN SB, CELLA DF, WEBSTER K, BLENDOWSKI C, KAPLAN E: Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage* 1997; 13: 63-74.
37. ZIGMOND AS, SNAITH RP: The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67: 361-70.
38. SNAITH RP, ZIGMOND AS: The hospital anxiety and depression scale manual. Windsor, Ontario: NFER-Nelson; 1994.
39. ANCOLI-ISRAEL S, SAVARD J: Sleep and fatigue in cancer patients. *In:* KRYGER MR, ROTH T, DEMENT WC (Eds.) *Principles and Practice of Sleep Medicine*. Elsevier Saunders, San Louis, USA 2011; 1416-21.
40. MACFARLANE JG, MOLDOFSKY H: Fibromalgya and chronic fatigue syndromes. *In: Principles and Practice of Sleep Medicine* (KRYGER MR, ROTH T, DEMENT WC, Eds). Elsevier Saunders, San Louis, USA 2011; 1422-34.
41. LAVIGNE G, SMITH MT, DENIS R, ZUCCONI M: Pain and sleep. *In:* KRYGER MR, ROTH T, DEMENT WC (Eds.) *Principles and Practice of Sleep Medicine*. Elsevier Saunders, San Louis, USA 2011; 1442-51.
42. SAVARD J, MORIN C: Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol* 2001; 19: 895-908.
43. ENGSTROM C, STROHL R, ROSE L, LEWANDOWSKI L, STEFANEK M: Sleep alterations in cancer patients. *Cancer Nurs* 1999; 22: 143-8.
44. VINA ER, GREEN SL, TRIVEDI T, KWOH CK, UTSET TO: Correlates of sleep abnormalities in systemic lupus: a cross-sectional survey in an urban, academic center *J Clin Rheumatol* 2013; 19: 7-13.
45. MILETTE K, HUDSON M, KÖRNER A, BARON M, THOMBS BD: Sleep disturbances in systemic sclerosis: evidence for the role of gastrointestinal symptoms, pain and pruritus. *Rheumatology* 2013; 52: 1715-20.
46. ABAD VC, SARINAS PS, GUILLEMINAULT C: Sleep and rheumatologic disorders. *Sleep Med Rev* 2008; 12: 211-28.
47. HACKETT KL, NEWTON JL, FRITH J *et al*.: Impaired functional status in primary Sjögren's syndrome. *Arthritis Care Res* 2012; 64: 1760-4.
48. ROHLEDER N, ARINGER M, BOENTERT M: Role of interleukin-6 in stress, sleep, and fatigue. *Ann N Y Acad Sci* 2012; 1261: 88-96.
49. YOUINOU P, JAMIN C: The weight of interleukin-6 in B cell-related autoimmune disorders. *J Autoimmun* 2009; 32: 206-10.
50. TZIOUFAS AG, TSONIS J, MOUTSOPOULOS HM: Neuroendocrine dysfunction in Sjögren's syndrome. *Neuroimmunomodulation* 2008; 15: 37-45.
51. THEANDER L, STRÖMBECK B, MANDL T, THEANDER E: Sleepiness or fatigue? Can we detect treatable causes of tiredness in primary Sjögren's syndrome? *Rheumatology* 2010; 49: 1177-83.
52. SEGAL B, THOMAS W, ROGERS T *et al*.: Prevalence, severity, and predictors of fatigue in subjects with primary Sjögren's syndrome. *Arthritis Rheum* 2008; 15; 59:1780-7.
53. SPIEGELHALDER K, REGEN W, NANOVSKA S, BAGLIONI C, RIEMANN D: Comorbid sleep disorders in neuropsychiatric disorders

across the life cycle. *Curr Psychiatry Rep* 2013; 15: 364.
54. STRÖMBECK B, JACOBSSON LT: The role of exercise in the rehabilitation of patients with systemic lupus erythematosus and patients with primary Sjögren's syndrome. *Curr Opin Rheumatol* 2007; 19: 197-203.
55. LINDVALL B, BENGTSSON A, ERNERUDH J, ERIKSSON P: Subclinical myositis is common in primary Sjögren's syndrome and is not related to muscle pain. *J Rheumatol* 2002; 29: 717-25.
56. PALMA BD, GABRIEL JR A, COLUGNATI FA, TUFIK S: Effects of sleep deprivation on the development of autoimmune disease in an experimental model of systemic lupus erythematosus. *Am J Physiol Regul Integr Comp Physiol* 2006; 291: R1527-32.
57. LAUTENBACHER S, KUNDERMANN B, KRIEG JC: Sleep deprivation and pain perception. *Sleep Med Rev* 2006.
58. TER BORG EJ, KELDER JC: Lower prevalence of extra-glandular manifestations and anti-SSB antibodies in patients with primary Sjögren's syndrome and widespread pain: evidence for a relatively benign subset. *Clin Exp Rheumatol* 2014; 32: 349-53.
59. KIRKNESS JP, MADRONIO WHEATLEY JR, AMIS TC: Relationship between surface tension of upper airway lining liquid and upper airway collapsibility during sleep in obstructive sleep apnea hypopnea syndrome. *J Appl Physiol* 2003; 95: 1761-6.
60. VALTYSDOTTIR ST, GUDBJORNSSON B, LINDQVIST U *et al*.: Anxiety and depression in patients with primary Sjögren's syndrome. *J Rheumatol* 2000; 27: 165-9.
61. BERSANI FS, IANNITELLI A, PACITTI F, BERSANI G: Sleep and biorhythm disturbances in schizophrenia, mood and anxiety disorders: a review. *Riv Psichiatr* 2012; 47: 365-75.
62. PETERSON MJ, BENCA R: Mood disorders. *In:* KRYGER MR, ROTH T, DEMENT WC (Eds.) *Principles and Practice of Sleep Medicine*. Elsevier Saunders, San Louis, USA 2011; 1488-500.
63. RAMSAWH HJ, STEIN MB, BELIK SL, JACOBI F, SAREEN J: Relationship of anxiety disorders, sleep quality, and functional impairment in a community sample. *J Psychiatr Res* 2009; 43: 926-33.
64. POTVIN O, LORRAIN D, BELLEVILLE G, GRENIER S, PRÉVILLE M: Subjective sleep characteristics associated with anxiety and depression in older adults: a population-based study. *Int J Geriatr Psychiatry* 2014; 29: 1262-70.
65. FINAN PH, SMITH MT: The comorbidity of insomnia, chronic pain, and depression: dopamine as a putative mechanism. *Sleep Med Rev* 2013; 17: 173-83.
66. BENCA RM, PETERSON MJ: Insonnia and depression. *Sleep Medicine* 2008; 9 (Suppl. 1): s3-s9.