

Variability of fatigue during the day in patients with primary Sjögren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis

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Abstract

Objectives

Fatigue is a common complaint of patients with primary Sjögren's syndrome (pSS), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA). The aim of this study was to examine and compare in patients with these diseases the course of fatigue within the first hour after awakening and during the day, and to examine sleep disturbance as a potential determinant of fatigue.

Methods

Eight repeated measurements at 5 fatigue dimensions were assessed on 2 consecutive days in the natural environment of female patients with pSS (n=29), SLE (n=23), RA (n=19), and healthy women (n=52). Sleep disturbance of the previous night was assessed. Fatigue levels and the change of fatigue after awakening and during the day were analysed with analyses of variance (adjusted for age).

Results

The patients showed significantly elevated levels at all fatigue dimensions as compared to healthy participants. Fatigue levels decreased in the first hour after awakening in patients with SLE and RA, but increased or did not change in patients with pSS. Fatigue progressively increased during the remainder of the day for all patient groups. Sleep disturbance correlated with overall fatigue levels, but hardly with the change of fatigue within the first hour after awakening.

Conclusion

Our study confirms the presence of increased fatigue in patients with pSS, SLE, and RA. Patients with pSS failed to show a decrease in fatigue in the first hour after awakening. Future research should examine the causes of this difference in fatigue after awakening.

Key words

Fatigue, sleep disturbance, Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus.

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Introduction

Primary Sjögren's syndrome (pSS), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) are systemic autoimmune diseases with a female preponderance. In patients with pSS, lymphocyte infiltration of exocrine glands results in the hallmark symptoms dryness of the eyes (keratoconjunctivitis sicca) and mouth (xerostomia) (1). SLE is a classical systemic immune complex disease with a broad range of clinical presentations such as the inflammation of joints, skin, mucosal membranes, pleural and pericardial membranes, and kidneys (2). The core feature of RA is inflammation of the joints (3). Fatigue has been identified as a major and common complaint with clear consequences for health-related well-being and functioning, and work ability in patients with pSS (4-10), SLE (11-13) and RA (14-18).

Fatigue is a disease-related symptom that varies during the day (19-20). After awakening, fatigue usually decreases to its lowest level before noon and then increases (21). Deviations in fatigue levels and variability of fatigue across the day may be affected by sleep disturbance (22-24) due to symptoms such as pain and dryness (25) or by changes in the regular 24-hour (circadian) rhythms of the hypothalamus-pituitary-adrenal (HPA) axis and cytokine system (26). In rheumatic diseases, a dysfunctional, cyclical pattern of heightened nighttime pain, non-restful sleep, and increased chronic fatigue has been described (27-28). Whether sleep disturbance affects the variability of fatigue during the day in rheumatic diseases has not yet been investigated.

The current study involves an analysis of the combined samples of female patients with pSS, SLE, RA and a healthy control group from previous research (20, 28). Fatigue was measured at eight repeated time points across the day on two consecutive weekdays in the patient's natural environment. Our aim was to compare between these patient groups the change in fatigue after awakening and during the day at multiple dimensions of fatigue, and to examine sleep disturbance as a potential determinant of fatigue.

Materials and methods

Participants

The study involved 123 female participants (≥ 18 years): 29 patients with pSS, 23 patients with SLE, 19 patients with RA, and 52 healthy control participants. The participants came from two previous studies (20, 28) with five additional patients (1 with pSS and 4 with SLE) who enrolled after the report of the previous study. Patients with pSS met the European classification criteria for Sjögren's syndrome (1) and had a lymphocyte focus score of at least 1 on a salivary gland biopsy. Patients with SLE and RA fulfilled the revised American College of Rheumatology (ACR) criteria for SLE (29) and RA (3), respectively. The patients with pSS and SLE were enrolled from the outpatient clinic of the Department of Rheumatology and Clinical Immunology at the University Medical Centre (UMC) Utrecht and had agreed to participate in a study that compared effects of oral administration of dehydroepiandrosterone and placebo on fatigue and general well being (30). The data were collected before the start of this treatment. The patients with RA were recruited from an ongoing population-based study among outpatients with recent-onset RA (31). The healthy control group was comprised of age-matched healthy female participants from the two studies, mostly neighbours and family of the patients to match socioeconomic status (20, 28). The study protocols were approved by the Medical Ethics Committee of the UMC Utrecht, and all participants completed an informed consent form.

Procedure

Assessments were taken in the natural environment of the participants on two consecutive week days using an identical assessment procedure. On each day participants were alerted by a beep from a preprogrammed wristwatch at eight time points: 15, 30 and 45 minutes after awakening, and 10:00 am, 12:00 pm, 2:30 pm, 5:00 pm and 7:30 pm. At each time point, participants answered questions on fatigue in a booklet. On the evening prior to the start of the assessments, each participant was visited at

Competing interests: none declared.

her home by a research assistant, who explained the procedure. Participants were instructed to continue their usual sleeping, activities and working routines during the study. A short instruction manual was left at their homes during the time of the study.

Measures

At each beeped time point, fatigue was assessed with the five most characteristic items of the Multidimensional Fatigue Inventory (MFI) (32). The items are: ‘I feel tired’ (General Fatigue), ‘Physically, I feel able to do only a little’ (Physical Fatigue), ‘I feel very active’ (Reduced Activity, (reversed item)), ‘I am not up to much’ (Reduced Motivation), and ‘Thinking requires effort’ (Mental Fatigue). The response format was a five-point Likert scale that ranged from ‘0 = very much’ to ‘4 = not at all’ in the booklets of the patients with RA and from ‘1 = very much’ to ‘5 = not at all’ in the booklets for the patients with pSS and SLE. All scores were recorded from 0 (no fatigue) to 4 (severe fatigue). At 30 minutes after awakening, participants completed a 15-item Dutch questionnaire on sleep quality to assess quantitative and qualitative aspects of sleep of the past night (33). The response format was a dichotomous scale with ‘0 = no’ and ‘1 = yes’. Scale scores could range from 0 (‘high sleep quality’, *i.e.* ‘no sleep disturbance’) to 15 (‘low sleep quality’, *i.e.* ‘high sleep disturbance’).

Statistical analyses

The score distributions of fatigue and sleep disturbance scores were normal in the three patient groups: the skewness of the score distributions of individual mean scores across the sixteen repeated assessments of fatigue was between 0.004 for mental fatigue in the RA group and 0.90 for mental fatigue in the SLE group. The score distributions in the healthy group were not normal: the skewness varied from 1.66 for general fatigue to 2.82 for mental fatigue reflecting that most healthy participants reported no or hardly any fatigue. The internal consistency reliability of the repeated assessments of fatigue across the sixteen measurements was good:

Table I. Participant characteristics.

	pSS n=29	SLE n=24	RA n=19	Healthy n=52	Comparison
<i>Age (years)</i>					
Mean	53.3	43.6	54.8	51.2	$F=3.64$ $p=0.02$
SD	13.8	11.7	13.1	12.1	
<i>Marital status (%)</i>					
Unmarried	5 (17)	3 (13)	1 (5)	5 (10)	$\chi^2=3.33$ $p=0.75$
Married	19 (66)	16 (67)	16 (84)	41 (79)	
Widowed/divorced	4 (14)	4 (17)	2 (11)	5 (10)	
Unknown	1 (3)	1 (4)	0 (0)	1 (2)	
<i>Employment (%)</i>					
Employed	7 (24)	13 (54)	1 (5)	27 (53)	$\chi^2=19.39$ $p<0.001$
Unemployed	18 (62)	8 (33)	18 (95)	22 (42)	
Unknown	4 (14)	3 (13)	0 (0)	3 (6)	
<i>Education level (%)</i>					
Primary	5 (17)	3 (13)	11 (58)	12 (23)	$\chi^2=15.45$ $p=0.02$
Secondary	17 (59)	17 (71)	6 (32)	26 (40)	
Tertiary	7 (24)	4 (17)	2 (11)	13 (25)	
Unknown	0 (0)	0 (0)	0 (0)	1 (2)	
<i>Disease duration (years)</i>					
Mean	6.0	12.5	0.6	–	$F=28.37$ $p<0.001$
SD	5.6	6.5	0.4	–	

Cronbach’s alpha ranged from 0.95 to 0.99 in the three patient groups.

Three effects of fatigue were examined: 1) the group effect, examining differences between participant groups in overall fatigue levels across the time points, 2) the time point effect, examining whether fatigue varied between time points in the first hour after awakening and during the day, and 3) the group \times time point interaction effect, examining whether the three patient groups showed a different variability of fatigue in the first hour after awakening and during the day. The first effect was examined with Kruskal-Wallis one-way analysis of variance by ranks. The second and third effects were examined with repeated measures analyses of variance with day (2 levels) and time-of-day (3 levels in case of fatigue in the first hour after awakening, and 6 levels in case of variability of fatigue across the day) as within-subject factors and disease (SS, SLE, RA) as between-subject factor. In case of non-sphericity, the Greenhouse-Geisser correction was applied. The healthy control group was excluded in these repeated measures analyses because of the relatively small and insignificant shifts in fatigue in this group and the skewed score distribution. The repeated measures analyses of variance were adjusted for age

differences between groups by entering age as a covariate.

Differences between participant groups in sleep disturbance were examined with Kruskal-Wallis one-way analysis of variance by ranks. The association between sleep disturbance and overall fatigue levels and the change in fatigue in the first hour after awakening were examined within the total patient group through Pearson’s partial correlations for the two days separately while adjusting for age. The change in fatigue in the first hour after awakening was defined as the fatigue level 45 minutes after awakening minus the fatigue level 15 minutes after awakening.

In case of incidental missing values of fatigue scores (a maximum of 2 in pSS, 1 in SLE, and 2 in RA), analyses were conducted without these patients. A p -value <0.05 was considered to be significant.

Results

Table I describes the participant characteristics. The patients with SLE were significantly younger than the three other groups ($p=0.02$). The majority of patients with SLE and healthy control patients were employed, whereas relatively few patients with pSS and RA were employed ($p<0.001$). The patients with RA had more frequently primary edu-

cation as the highest educational level ($p=0.02$) compared to the other three groups. The patient groups differed in terms of disease duration ($p<0.001$) as a result of the different focuses of the two studies: the RA study focused on patients with a recent diagnosis, whereas the SLE and pSS study included patients with established disease.

Overall fatigue levels and sleep disturbance

Table II describes for each group the median levels of the five fatigue dimensions across the sixteen measurements at the two days and of sleep disturbance. As compared to the healthy control group, the three patient groups showed significantly elevated overall levels at all fatigue dimensions as well as significantly more sleep disturbance ($p<0.001$ for all variables). The disease groups did not significantly differ from each other on any of these variables (all p -values ≥ 0.13).

Fatigue variability

Figures 1 and 2 show the variability of fatigue in the first hour after awakening and the variability of fatigue during the day at the five fatigue dimensions in the three patient groups as well as in the healthy control group. The vertical axis represents the scores on a fatigue dimension and the horizontal axis represents the time across the day. The healthy control group always had the lowest levels and a low variability of scores across the day. For this reason, the healthy control group was not included in the repeated measures analyses of variance.

Fatigue after awakening

The fatigue levels of the three patient groups in the first hour after awakening are shown in Figure 1. A significant or almost significant decrease in fatigue in the first half hour after awakening was observed for three of the five fatigue dimensions: general fatigue ($p=0.053$), physical fatigue ($p=0.003$), and reduced activity ($p=0.049$). Significant interaction effects between the type of disease and the time after awakening indicate that the pattern of change in fatigue after awakening

Table II. Median levels and interquartile ranges of the five fatigue dimensions and sleep disturbance of the four groups.

	pSS n=27-29 Median (range)	SLE n=23-24 Median (range)	RA n=18-19 Median (range)	Healthy n=52 Median (range)	Comparison
General fatigue	2.3 (1.9–3.4)	1.9 (1.4–2.7)	2.3 (0.8–2.9)	0.2 (0.0–0.6)	$K=67.5^*$
Physical fatigue	1.9 (1.3–3.1)	1.3 (0.6–2.0)	1.6 (0.3–2.8)	0.0 (0.0–0.3)	$K=57.8^*$
Reduced activity	1.8 (1.0–2.9)	1.3 (0.3–1.8)	2.1 (0.2–2.6)	0.0 (0.0–0.4)	$K=54.0^*$
Reduced motivation	1.5 (0.8–2.6)	1.1 (0.3–1.9)	1.6 (0.2–2.8)	0.0 (0.0–0.3)	$K=44.5^*$
Mental fatigue	1.3 (0.5–2.6)	0.8 (0.0–1.7)	2.1 (0.1–2.8)	0.0 (0.0–0.3)	$K=35.6^*$
Sleep disturbance	6.0 (4.5–8.0)	5.5 (4.0–7.0)	5.0 (2.0–7.5)	2.3 (0.5–5.5)	$K=23.9^*$

* $p<0.001$

differs between the patient groups. Such a significant interaction was demonstrated for general fatigue ($p=0.006$), physical fatigue ($p=0.01$), reduced activity ($p=0.02$), and reduced motivation ($p=0.006$). With respect to general and physical fatigue, the patients with pSS differed significantly from both the patients with SLE ($p=0.001$ and $p=0.03$) and the patients with RA ($p=0.02$ and $p=0.01$). For these two variables, the patients with SLE and the patients with RA on average displayed a decrease in fatigue after awakening (45 min. level minus 15 min. level across two days), whereas the patients with pSS on average displayed an increase in fatigue. A decrease in general fatigue across the two days was observed in 58% and 47% of the patients with SLE and RA, and in 10% of the patients with pSS; an increase in general fatigue was shown by 4% (SLE), 21% (RA), and 38% (pSS) of the patients. A decrease in physical fatigue across the two days was observed in 38% (SLE), 42% (RA), and 18% (pSS); an increase in 13% (SLE), 11% (RA), and 36% (pSS). Also in case of reduced activity, the patients with pSS differed significantly from the patients with SLE ($p=0.03$) and the patients with RA ($p=0.006$). The patients with SLE and RA on average showed a decrease after awakening, whereas the patients with pSS on average did not change. A mean decrease in reduced activity across the two days was observed in 58% (SLE), 53% (RA), and 19% (pSS); an increase in 8% (SLE), 11% (RA), and 30% (pSS). For reduced motivation, the patients with RA on average showed a decrease after awakening, whereas the

patients with pSS on average showed a small increase ($p=0.006$). A decrease in reduced motivation across the two days was observed in 33% (SLE), 53% (RA), and 14% (pSS); an increase in 8% (SLE), 5% (RA), and 29% (pSS). There was neither a significant effect of time-of-day nor a significant interaction effect between disease group and time-of-day for mental fatigue. A decrease in mental fatigue across the two days was observed in 29% (SLE), 47% (RA), and 18% (pSS); an increase in 17% (SLE), 16% (RA), and 25% (pSS).

Variability of fatigue during the day

The fatigue scores of the three patient groups during the day are shown in Figure 2. A significant progressive increase in fatigue during the day in the three patient groups was observed for three of the five fatigue dimensions: general fatigue ($p<0.001$), physical fatigue ($p=0.009$), and mental fatigue ($p=0.01$).

Tests of the interaction between the patient group and fatigue levels during the day were not significant, with mental fatigue as the only exception ($p=0.048$). The patients with RA showed steady levels of mental fatigue during the day as compared to the slightly increasing levels of mental fatigue in the patients with pSS ($p=0.051$).

Sleep disturbance

To examine whether fatigue levels and fatigue variability were due to sleep disturbance, correlations were computed in the total patient group. Sleep disturbance was significantly associated with the overall levels of all fatigue

Fig. 1. The fatigue levels of the three patient groups at 15, 30, and 45 minutes after awakening.

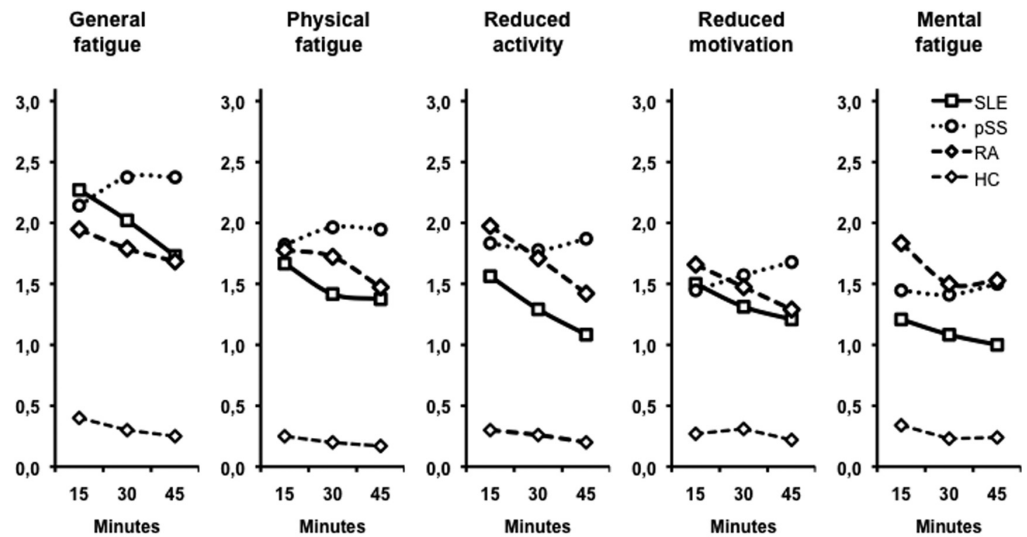
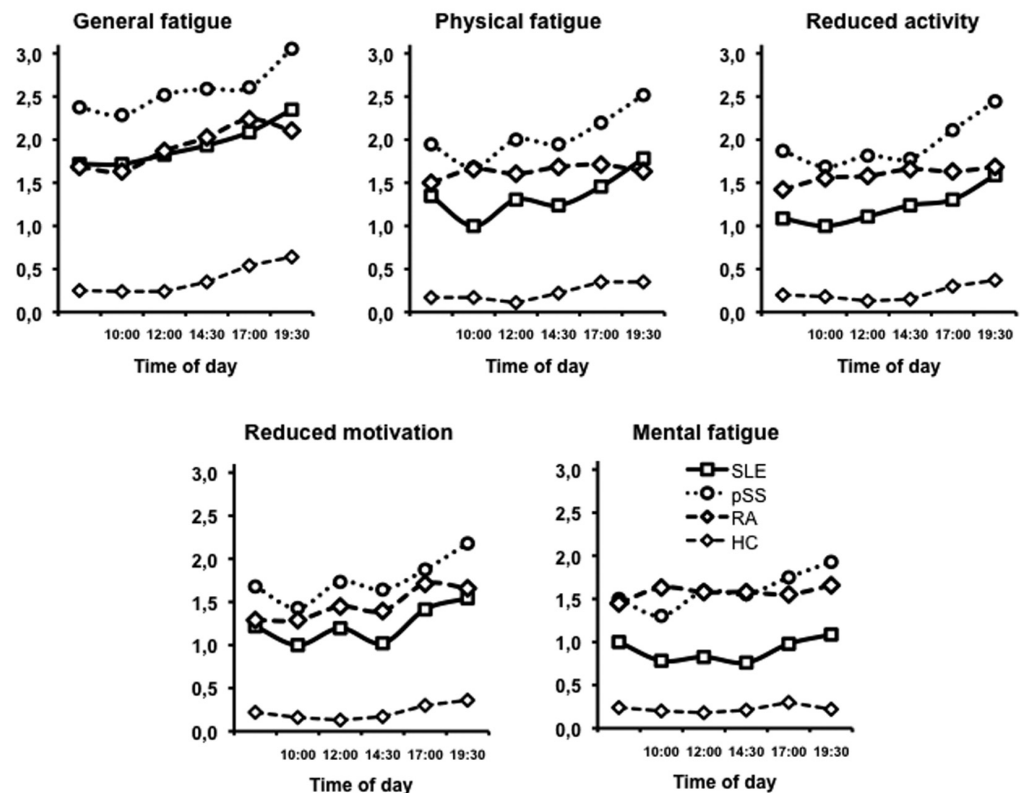


Fig. 2. The fatigue levels of the three patient groups during the day.



dimensions, except mental fatigue at day 1 ($r=0.20$, $p=0.10$). The significant Pearson's partial correlation coefficients (adjusted for age) ranged from $r=0.27$ ($p=0.02$) for mental fatigue at day 2 to $r=0.44$ ($p<0.001$) for physical fatigue at day 2: more sleep disturbance was associated with more severe fatigue during the day. Sleep disturbance did not significantly correlate with the change in fatigue in the first hour after awakening (r varied from -0.04 for re-

duced activity at day 2 to 0.16 for mental fatigue at day 2, $p\geq 0.19$).

Discussion

This study compared overall fatigue levels and the change in fatigue in the first hour after awakening and during the day in patients with primary Sjögren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis. Fatigue levels did not differ between the three patient groups, but fatigue levels

in all patient groups deviated a lot from the fatigue levels in the healthy control group. These results replicate previous observations of elevated fatigue levels in patients with pSS, SLE and RA (5, 11, 15). This confirms that fatigue is a major problem in patients with these rheumatic diseases.

As awakening is a rather uniform stressor for all participants, it offers an opportunity to examine the variability of fatigue. Fatigue usually decreases im-

mediately after awakening (21, 34). In the current study, during the first hour after awakening, fatigue decreased in the patients with SLE and RA, but it increased or did not change in the patients with pSS. Sleep might have been less refreshing for patients with pSS. Disturbed sleep in pSS patients may occur because they either drink so much during the day that they have to empty their bladder during the night, or because they awake due to oral dryness because of reduced submandibular and parotid flow (35-37). Abnormal electroencephalographic patterns have suggested problems in the sleep recovery phase of patients with pSS (38-39). However, in the current study, self-reported sleep disturbance did not differ between the three patient groups, and sleep disturbance was not associated with the change in fatigue in the first hour after awakening.

The HPA axis is activated in autoimmune diseases, and the HPA axis activity has been implicated in fatigue and sleep disturbances (40). Elevated cortisol levels in the afternoon and evening have been found in patients with RA (41-42), whereas in patients with pSS relatively low cortisol levels were observed in the afternoon (43). The increased cortisol secretory activity during the first 45 minutes following awakening, the cortisol awakening response, is an important feature of neuroendocrine rhythmicity and has been recognised as a potentially valuable biological marker of health status (44). A failure of this adaptive response in patients with pSS perhaps explains the absence of a decrease in fatigue in the first hour after awakening.

Cytokines play a key pathological role in chronic rheumatic diseases. Both cytokines and disease-related symptoms such as fatigue and stiffness exhibit circadian rhythms (19), and cytokines, sleep disturbance, and fatigue are known to be mutually related (45). We found that the overall fatigue levels were high in patients with pSS, SLE and RA, and that fatigue levels progressively increased during the day. However, except for the change in fatigue in the first hour after awakening in patients with pSS, the pattern of change

in fatigue throughout the day seemed not to be influenced in these auto-immune diseases.

Although fatigue is indisputably an adverse consequence of the disease process, psychological factors, such as physical activity avoidance (46) and helpless cognitions (5), also impact on fatigue. Moreover, positive effects on fatigue have been found for physical exercise therapy in patients with pSS and SLE (47-48) and RA (49), for cognitive-behavioural therapy in patients with RA (50), and for sleep hygiene training (51). This suggests that the most promising venue to manage fatigue at this moment appears to be by cognitive and behavioural means.

A strength of this study is the use of momentary assessments, which have high validity for daily life and minimise recall bias compared to retrospective questionnaires (52). We statistically adjusted the results for the age differences between groups, but a weakness of the study which hampers the comparison between groups is that selected patients with pSS or SLE who had agreed to participate in a study aimed at a reduction of fatigue were compared to unselected patients with RA. Moreover, the patients with RA had shorter disease duration than the patients with pSS and SLE, and only pSS patients with a lymphocyte focus score of at least 1 on a salivary gland biopsy were included, which hampers generalisation to the total population of pSS patients. A further drawback is the small sample size. Using power analysis calculations with an α -level of 0.05 and a power (1- β) of 0.80, the sample size was just not large enough to discover large differences between groups in univariate analysis of variance and thus prohibits the generalisation of these results to the findings of small or medium differences between groups. However, in repeated measures analyses of variance with an auto-correlation of 0.60 between repeated fatigue assessments, with our sample size we were able to examine differences that are in between a small and medium effect size (53).

In conclusion, our study confirmed the presence of elevated fatigue levels during the day in patients with pSS, SLE

and RA and demonstrated an influence of sleep disturbance on overall fatigue levels. For some patients, fatigue during the day may be such a major problem that education and cognitive-behavioural, physical exercise, or sleep hygiene interventions could be tried to help patients to deal with fatigue. Patients with pSS failed to show a decrease in fatigue in the first hour after awakening. Future research should examine the causes of this difference in the course of fatigue after awakening.

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References

- VITALI C, BOMBARDIERI S, JONSSON R *et al.*: 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.
- D'CRUZ DP, KHAMASHTA MA, HUGHES GRV: Systemic lupus erythematosus. *Lancet* 2007; 369: 587-96.
- ARNETT FC, EDWORTHY SM, BLOCH DA *et al.*: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
- CHAMPEY J, CORRUBLE E, GOTTENBERG JE *et al.*: Quality of life and psychological status in patients with primary Sjögren's syndrome and sicca symptoms without autoimmune features. *Arthritis Rheum* 2006; 55: 451-7.
- SEGAL B, THOMAS W, ROGERS T *et al.*: Prevalence, severity, and predictors of fatigue in subjects with primary Sjögren's syndrome. *Arthritis Rheum* 2008; 59: 1780-7.
- TENSING EK, SOLOVIEVA SA, TERVAHARTIALA T *et al.*: Fatigue and health profile in sicca syndrome of Sjögren's and non-Sjögren's syndrome origin. *Clin Exp Rheumatol* 2001; 19: 313-6.
- BJERRUM K, PRAUSE JU: Primary Sjögren's syndrome. A subjective description of the disease. *Clin Exp Rheumatol* 1990; 8: 283-8.
- BARENDREGT PJ, VISSER MRM, SMETS EMA *et al.*: Fatigue in primary Sjögren's syndrome. *Ann Rheum Dis* 1998; 57: 291-5.
- MEIJER JM, MEINERS PM, SLATER J *et al.*: Health-related quality of life, employment and disability in patients with Sjögren's syndrome. *Rheumatology* 2009; 48: 1077-82.
- BELENGUER R, RAMOS-CASALS M, BRITTOZON P *et al.*: Influence of clinical and immunological parameters on the health-related quality of life of patients with primary Sjögren's syndrome. *Clin Exp Rheumatol* 2005; 23: 351-6.

11. TENCH CM, MCCURDIE I, WHITE PD, D'CRUZ DP: The prevalence and associations of fatigue in systemic lupus erythematosus. *Rheumatology* 2000; 39: 1249-54.
12. GROOTSCHOLTEN C, LIGTENBERG G, DERKSEN R *et al.*: Health-related quality of life in patients with systemic lupus erythematosus: Development and validation of a lupus specific symptom checklist. *Qual Life Res* 2003; 12: 635-44.
13. BAKER K, POPE J, FORTIN P, SILVERMAN E, PESCHKEN C; 1000 FACES OF LUPUS INVESTIGATORS; CaNIOS: Work disability in systemic lupus erythematosus is prevalent and associated with socio-demographic and disease related factors. *Lupus* 2009; 18: 1281-8.
14. HEWLETT S, COCKSHOTT Z, BYRON M *et al.*: Patients' perceptions of fatigue in rheumatoid arthritis: Overwhelming, uncontrollable, ignored. *Arthritis Rheum* 2005; 53: 697-702.
15. MANCUSO CA, RINCON M, SAYLES W, PAGET SA: Psychosocial variables and fatigue: A longitudinal study comparing individuals with rheumatoid arthritis and healthy controls. *J Rheumatol* 2006; 33: 1496-502.
16. KILTZ U, VAN DER HEIJDEN D: Health-related quality of life in patients with rheumatoid arthritis and in patients with ankylosing spondylitis. *Clin Exp Rheumatol* 2009; 27 (Suppl. 55): S108-S11.
17. LACAILLE D, WHITE MA, ROGERS PA, BACKMAN CL, GIGNAC MAM, ESDAILE JM: A Proof-of-Concept Study of the "Employment and Arthritis: Making it Work" Program. *Arthritis Rheum* 2008; 59: 1647-55.
18. MINNOCK P, KIRWAN J, BRESNIHAN B: Fatigue is a reliable, sensitive and unique outcome measure in rheumatoid arthritis. *Rheumatology* 2009; 48: 1533-6.
19. STRAUB RH, CUTOLO M: Circadian rhythms in rheumatoid arthritis - Implications for pathophysiology and therapeutic management. *Arthritis Rheum* 2007; 56: 399-408.
20. DEKKERS JC, GEENEN R, GODAERT GLR, VAN DOORNEN LJP, BIJLSMA JWJ: Diurnal courses of cortisol, pain, fatigue, negative mood, and stiffness in patients with recently diagnosed rheumatoid arthritis. *Int J Behav Med* 2000; 7: 353-71.
21. STONE AA, BRODERICK JE, PORTER LS, KAELL AT: The experience of rheumatoid arthritis pain and fatigue: Examining momentary reports and correlates over one week. *Arthritis Care Res* 1997; 10: 185-93.
22. DREWES AM: Pain and sleep disturbances with special reference to fibromyalgia and rheumatoid arthritis. *Rheumatology* 1999; 38: 1035-8.
23. BELT NK, KRONHOLM E, KAUPPI MJ: Sleep problems in fibromyalgia and rheumatoid arthritis compared with the general population. *Clin Exp Rheumatol* 2009; 27: 35-41.
24. GUDBJORNSSON B, HETTA J: Sleep disturbances in patients with systemic lupus erythematosus: A questionnaire-based study. *Clin Exp Rheumatol* 2001; 19: 509-14.
25. NICASSIO PM, MOXHAM EG, SCHUMAN CE, GEVIRTZ RN: The contribution of pain, reported sleep quality, and depressive symptoms to fatigue in fibromyalgia. *Pain* 2002; 100: 271-9.
26. GAITANIS P, TOOLEY G, EDWARDS B: Physical activity, emotional stress, sleep disturbances, and daily fluctuations in chronic fatigue symptomatology. *J Appl Biobehav Res* 2005; 10: 69-82.
27. MAHOWALD ML, MAHOWALD MW: Night-time sleep and daytime functioning (sleepiness and fatigue) in less well-defined chronic rheumatic diseases with particular reference to the 'alpha-delta NREM sleep anomaly'. *Sleep Med* 2000; 1: 195-207.
28. GODAERT GLR, HARTKAMP A, GEENEN R *et al.*: Fatigue in daily life in patients with primary Sjögren's syndrome and systemic lupus erythematosus. *Ann NY Acad Sci* 2002; 966: 320-6.
29. TAN EM, COHEN AS, FRIES JF *et al.*: The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-7.
30. HARTKAMP A, GEENEN R, GODAERT GLR *et al.*: Effect of dehydroepiandrosterone administration on fatigue, well-being, and functioning in women with primary Sjögren syndrome: a randomised controlled trial. *Ann Rheum Dis* 2008; 67: 91-7.
31. VAN DER HEIDE A, JACOBS JWJ, VANALBADAKUIPERS GA, KRAAIMAAT FW, GEENEN R, BIJLSMA JWJ: Physical disability and psychological well-being in recent-onset rheumatoid arthritis. *J Rheumatol* 1994; 21: 28-32.
32. SMETS EMA, GARSSEN B, BONKE B, DE HAES JCJM: The multidimensional fatigue inventory (MFI). Psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995; 39: 315-25.
33. MEIJMAN TF, THUNNISSEN MJ, DEVRIES-GRIEVER AGH: The after-effects of a prolonged period of day-sleep on subjective sleep quality. *Work Stress* 1990; 4: 65-70.
34. CUTOLO M, SERIOLO B, CRAVIOTTO C, PIZZORNI C, SULLI A: Circadian rhythms in RA. *Ann Rheum Dis* 2003; 62: 593-6.
35. VAN DEN BERG I, PIJPE J, VISSINK A: Salivary gland parameters and clinical data related to the underlying disorder in patients with persisting xerostomia. *Eur J Oral Sci* 2007; 115: 97-102.
36. PIJPE J, KALK WWI, BOOTSMA H, SPIJKERFVET FKL, KALLENBERG CGM, VISSINK A: Progression of salivary gland dysfunction in patients with Sjögren's syndrome. *Ann Rheum Dis* 2007; 66: 107-12.
37. ATKINSON JC, TRAVIS WD, PILLEMER SR, BERMUDEZ D, WOLFF A, FOX PC: Major salivary gland function in primary Sjögren's syndrome and its relationship to clinical features. *J Rheumatol* 1990; 17: 318-22.
38. NIEMELÄ RK, HAKALA M: Primary Sjögren's syndrome with severe central nervous system disease. *Semin Arthritis Rheum* 1999; 29: 4-13.
39. WANG B, GLADMAN DD, UROWITZ MB: Fatigue in lupus is not correlated with disease activity. *J Rheumatol* 1998; 25: 892-5.
40. ADLER GK, GEENEN R: Hypothalamic-pituitary-adrenal and autonomic nervous system functioning in fibromyalgia. *Rheum Dis Clin North Am* 2005; 31: 187-202.
41. DEKKERS JC, GEENEN R, GODAERT GLR, VAN DOORNEN LJP, BIJLSMA JWJ: Diurnal rhythm of salivary cortisol levels in patients with recent-onset rheumatoid arthritis. *Arthritis Rheum* 2000; 43: 465-7.
42. CATLEY D, KAELL AT, KIRSCHBAUM C, STONE AA: A naturalistic evaluation of cortisol secretion in persons with fibromyalgia and rheumatoid arthritis. *Arthritis Care Res* 2000; 13: 51-61.
43. JOHNSON EO, VLACHOYIANNPOULOS PG, SKOPOULI FN, TZIOUFAS AG, MOUTSOPOULOS HM: Hypofunction of the stress axis in Sjögren's syndrome. *J Rheumatol* 1998; 25: 1508-14.
44. THORN L, HUCKLEBRIDGE F, EVANS P, CLOW A: The cortisol awakening response, seasonality, stress and arousal: A study of trait and state influences. *Psychoneuroendocrinology* 2009; 34: 299-306.
45. VGONTZAS AN, PAPANICOLAOU DA, BIXLER EO *et al.*: Circadian interleukin-6 secretion and quantity and depth of sleep. *J Clin Endocrinol Metab* 1999; 84: 2603-7.
46. SOKKA T, HAKKINEN A, KAUTIAINEN H *et al.*: Physical inactivity in patients with rheumatoid arthritis: Data from twenty-one countries in a cross-sectional, international study. *Arthritis Rheum* 2008; 59: 42-50.
47. STROMBECK B, JACOBSSON LTH: 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.
48. TENCH CM, MCCARTHY J, MCCURDIE I, WHITE PD, D'CRUZ DP: Fatigue in systemic lupus erythematosus: a randomized controlled trial of exercise. *Rheumatology* 2003; 42: 1050-4.
49. CUP EH, PIETERSE AJ, TEN BROEK-PASTOOR JM *et al.*: Exercise therapy and other types of physical therapy for patients with neuromuscular diseases: A systematic review. *Arch Phys Med Rehabil* 2007; 88: 1452-64.
50. EVERS AWM, KRAAIMAAT FW, VAN RIEL P, DE JONG AJL: Tailored cognitive-behavioral therapy in early rheumatoid arthritis for patients at risk: a randomized controlled trial. *Pain* 2002; 100: 141-53.
51. MORIN AK, JARVIS CI, LYNCH AM: Therapeutic options for sleep-maintenance and sleep-onset insomnia. *Pharmacotherapy* 2007; 27: 89-110.
52. BOLGER N, DAVIS A, RAFAELI E: Diary methods: Capturing life as it is lived. *Annu Rev Psychol* 2003; 54: 579-616.
53. FAUL F, ERDFELDER E, LANG AG, BUCHNER A: G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007; 39: 175-91.