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Is fatigue a cause of work disability in Systemic Lupus Erythematosus? Results from a systematic literature review

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Abstract. – OBJECTIVE: Fatigue affects the almost totality of Systemic Lupus Erythematous (SLE) patients impairing physical function and leading to a strong reduction of health-related quality of life (HRQoL). Similarly, SLE patients have an increased rate of work loss and work limitations. The aim of our paper was to systematically assess the relationship between fatigue and work disability in SLE.

MATERIALS AND METHODS: We performed a systematic review using the terms "fatigue" and "employment", "work disability", "work impairment", "presenteeism" and "absenteeism".

RESULTS: 19 studies were identified. Fatigue was involved in the development of work loss. In employed patients, fatigue led to impairment of work productivity and presenteeism with a parallel increase of both direct and indirect health costs. Fatigue also affected parenting and household productivity.

CONCLUSIONS: An adequate control of fatigue could improve physical and work performance in SLE patients thus reducing rates of work loss.

Key Words
Fatigue, Lupus, Systemic Lupus Erythematosus, SLE, Work disability.

Introduction

Despite a better understanding of Systemic Lupus Erythematosus (SLE) pathogenesis[1,2], followed by an improvement in clinical management and therapies[3,4], patients affected by SLE are still burdened by a severe morbidity and a remarkable reduction of health-related quality of life (HRQoL)[5,6]. According to treat to target strategy, the last European League Against Rheumatism (EULAR) recommendations on SLE management underline the crucial role of three components related to quality of life (QoL): fatigue, pain and mood disorders[7]. Fatigue is a disabling condition affecting a wide proportion of SLE patients with a prevalence and a severity at least comparable with other rheumatic diseases[8]. The association with psychosocial factors as depression, pain, physical inactivity[9] and sleep disorders is strong, whereas the relationship with scores of disease activity is uncertain[10]. The treatment of fatigue in SLE patients is challenging: best evidences of efficacy concern Belimumab, a recombinant human immunoglobulin monoclonal antibody inhibiting the biological activity of soluble B-lymphocyte stimulator (BLyS)[11]. Among non-pharmacological approaches, physical activity and psychosocial interventions had a positive impact on fatigue[12]. Moreover, SLE patients have an increased rate of work loss[13]. Even when still employed, they are burdened by high rates of productivity loss, mainly due to impairment of work productivity and absenteeism[14]. In the present review we analyze the relation between fatigue and work disability (WD) reported in the literature.

Materials and Methods

Literature Search

A systematic literature search was performed in PubMed (Medline) and EBSCO up to December 2017 using the following MeSH terms: ("lupus"[All Fields] and "work disability"[All Fields]) or "lupus"[All Fields] and "employment"[All Fields]) OR "lupus"[All Fields]) and ("fatigue"[MeSH Terms] or "fatigue"[All Fields]). We also performed the search using the follow-

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ing terms: ("lupus"[All Fields] AND "absenteeism"[All Fields]) OR "lupus"[All Fields] AND "presenteeism"[All Fields]).

Study Selection

Study selection was performed by two authors (FB and DM), working independently. Duplicates were removed and all titles and abstracts resulting from the search strategy were reviewed to identify eligible papers. Afterwards full texts of the remaining studies were assessed. All articles finally selected fulfilled the following eligibility criteria: original articles written in English, reported statistic measure of association between fatigue and employment variables in SLE, included validated questionnaires measuring fatigue. Articles do not meeting inclusion criteria were excluded. The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Results

A total of 1523 were reviewed and, after selection, 19 papers were included in the present review (Table I) (Figure 1).

Work Disability and Fatigue

Cross sectional studies

Utset et al[15] compared working SLE patients with formal WD to patients with self-reported WD (SRWD). Fatigue levels were significantly higher in patients with SRWD but not in those with formal WD. The same Author then performed a further study demonstrating the association with both formal WD and SRWD[16].

According to Bultink et al[17] unemployed patients presented an impairment of almost total Short Form-36 (SF-36) subdomains, including physical function, general health and vitality, if compared with employed patients.

Al Dhanhani et al[18] reported both subunities SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) to significantly predict WD.

Next, Baker at al[13] collected employment data within a large population of more than a thousand SLE patients: by multivariate logistic regression analysis, physical function, assessed by SF-36 PCS, was identified as factors significantly related to onset of WD.

Work dynamics of Chinese SLE population were evaluated in two studies: in the first population sample even 85% patients reported fatigue as a factor related to job interruption, making it a strong independent predictor of WD[19]. Conversely, according to Zhu et al[20] SF-36 PCS predicted daily activity limitations but not labour productivity impairment.

Finally, Ekblom-Kullberg et al[21] reported significantly higher fatigue levels among WD SLE patients, when compared with not WD SLE patients.

Longitudinal studies

Bertoli et al[22] assessed risk factors for development of SRWD: baseline scores of SF-36 PCS were significantly different in patients who developed WD, whereas Fatigue Severity Scale (FSS) and SF-36 MCS scores were not. Thus, both SF-36 subscales were not loaded in the multivariable logistic regression analysis.

Two Authors have subsequently examined the potential predicting value of fatigue in the development of WD, largely disconfirming first data. Yelin et al[23] analyzed rates of work loss and work entry in a cohort of 957 SLE patients with a 4-year-follow up: baseline SF- 36 PCS scores were once again lower in patients who developed WD. In multivariate analysis lower physical functioning predicted work loss as better physical functioning predicted work entry.

Lawson et al[24] compared educational and vocational outcomes among adults with childhood-onset SLE (cSLE) in comparison with adult-onset SLE (aSLE): better physical function was a predictor of employment; similarly worse physical function at baseline was associated with fewer possibilities to be continuously employed.

Work Impairment and Fatigue

Cross sectional studies

Poole et al[25] firstly identified fatigue as a factor involved in employer restrictions and in difficulties related to interaction with physical and social environment, whereas did not find any correlation with employment status or job type. Almehed et al[26] reported a strong correlation between working ability and the SF-36 PCS, but not with the SF-36 MCS. According to Al Dhanhani et al[27], both subunities SF-36 PCS and MCS, together with The five-item Profile of Mood States (POMS)-Fatigue Subscale, significantly impaired different activities in employed patients: more severely crouching, bending, kneeling or working in awkward positions, but also lifting, carrying or moving objects, concentrating and/or keeping one's mind on work. Further, not employed patients reported high difficulties in lifting, carrying or moving objects, keeping up with the pace of work, meeting current job demands and scheduling.

Table I. Fatigue and work disability in SLE.

Author	Type of study	Population sample and rates of WD	Population characteristics	Measures of Fatigue	Measures of WD	Association with Employment
Utset et al[15], 2006	Cross-sectional	-50 SLE patients; 48% WD; 32% with Formal disability (FD); 16% with Self-reported work disability (SRWD)	-mean age 41; 46 women; 60% African-American; mean education years 13.5; mean disease duration (MDD) 8.6 yrs; median SDI 2	Multidimensional Fatigue Inventory (MFI)	FD e SRWD	Fatigue was significantly correlated with SRWD but not with FD
Poole et al[25], 2007	Cross-sectional	-15 SLE patients; 26.7% unemployed -15 healthy controls	-mean age 43; 93.4% women MDD 8 yrs; mean SLEDAI 7.9; mean education 12 years;	VAS	Not reported (NR)	Fatigue was significantly correlated with employer restrictions and physical and social environment of the workplace. Fatigue was not correlated to employment status or job type.
Bertoli et al[22], 2007	Longitudinal	-273 SLE patients; 19% WD	-women 90.5%; mean age 36.5; 30% Caucasian 28.9% African american; MDD 4.7	Fatigue Severity Scale (FSS)	SRWD	Baseline SF-36 PCS, but not FSS, were significantly different in patients who developed WD.
Bultnik et al[17], 2007	Cross-sectional	-147 SLE patients; 59 % unemployed	-mean age 38.4; 93% female; Caucasian 68%; MDD 6.3; mean SDI 1.2	SF-36	SRWD	Unemployed patients had significantly lower all SF-36 subunities scores (except for health change)
Panopalis et al[14], 2008	Longitudinal	-809 SLE patients; 48.7% employed	-mean age 48.2; women 92.6%; white 74%; MDD 13.7	Medical Outcomes Study Short Form 12 (SF-12)	Employment questionnaire derived by the Bureau of Labor Statistics	Worse physical and mental health status were significant predictors of higher costs due to changes in work productivity
Utset et al[16], 2008	Cross-sectional	-141 SLE patients; 42.7% WD	-women 92%; mean age 40.4; African- American 60.8%, Caucasian 26.6%; mean education level 14 years; mean SLEDAI 5.4; mean SDI 1.8	FSS	FD	Fatigue was significantly associated with FD also in multivariate analysis

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Table I. Fatigue and work disability in SLE.

Author	Type of study	Population sample and rates of WD	Population characteristics	Measures of Fatigue	Measures of WD	Association with Employment
Mok et al[19], 2008	Cross-sectional	-105 SLE patients; 37% WD	-97% women; mean age 38.1; MDD 10; 12.6 years of education; mean SELENA SLEDAI 2.76; mean SDI 0.98	Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F)	SRWD	Fatigue was an independent predictor of WD
Al Dhanhani et al[18], 2008	Cross-sectional	-432 SLE patients; 23% WD	-88% women; mean age 35.9; MDD 7.3; 73% white; 44% completed high school education	SF-36	SRWD	Fatigue was an independent predictor of WD in the multivariate regression analysis
Baker et al[13], 2009	Cross-sectional	-1137 SLE patients; 19.09 % WD	-mean age 50 years; MDD 18 years	SF-36 PCS and Self-reported fatigue (Yes-No)	Not validated questionnaire	Fatigue was significantly associated with WD
Yelin et al[23], 2009	Longitudinal	-770 SLE patients; 23.4% WD	-90% women; 67% Caucasian; MDD 10.8	SF-36 PCS		Lower physical functioning predicted work loss and better physical functioning predicted work entry
Almehed et al[26], 2010	Cross-sectional	-163 SLE women; 37% WD	-mean age 48.5%; MDD 13.7; SLEDAI 2K 6.7; SDI 2.7	SF-36	Not reported self-administered questionnaires	Higher PCS was significantly associated with work ability
Zhu et al[20], 2012	Cross-sectional	-125 SLE patients; 16% WD	-women 95.2%; mean age 43.8; mean education level 11 yrs; MDD 12.1; mean SLEDAI 2; mean SDI 1	SF-36 PCS	Not validated questionnaire	Univariate analysis, but not multivariate logistic regression, showed a significant association between low PCS and WD and impaired non-labour
Gordon et al[28], 2013	Cross-sectional	-2058 SLE patients; 34.9% unemployed; presenteeism 43%; absenteeism 13%	-female 93.1%; MDD 8; 86.7% were aged <50 years basic education 28.2%; college education 36.6%; university education 35.1%	FSS and LupusQoL fatigue domain score	Work Productivity and Activity Impairment Questionnaire (WPAI)	Fatigue was significantly associated with presenteeism, overall work impairment and activity impairment in both univariate and multivariate analysis

Continued

Table I. Fatigue and work disability in SLE.

Author	Type of study	Population sample and rates of WD	Population characteristics	Measures of Fatigue	Measures of WD	Association with Employment
Drenkard et al[31], 2014	Longitudinal	-689 SLE patients; 49% WD;	-mean age 43.8%; women 93.9%; MDD 13.1; African-American 79.2%; high school or lower 34.7%	VAS 0-3	WPAI	Fatigue significantly impaired all WPAI domains
Lawson et al[24], 2014	Longitudinal	-115 childhood-onset SLE (cSLE) patients, 15% WD -814 adult-onset SLE (aSLE) patients, 36% WD	-mean age 29; female 82%; white 44%; MDD 15; SLAQ 9; low educational level 28% -mean age 44; female 94%; white 62%; SLAQ 13; MDD 11; low educational level 17%	SF-36 PF	SRWD	Higher physical function score was a predictor of employment; Subjects with worse physical function at baseline were also less likely to be continuously employed
Al Dhanani et al[27], 2014	Cross sectional	-180 employed SLE patients;	-mean age 43.3; -College education or above 75.4%; SDI>0 in 53.6% - mean SELENA SLEDAI 3.2 -MDD 16.4	five-item Profile of Mood States —Fatigue Subscale	workplace activity limitations scale (WALS)	Fatigue was significantly associated with workplace activity limitations
Ekblom-Kullberg et al[21], 2014	Cross-sectional	-181 SLE women; 47% WD	-mean age 44; MDD 12.7; years of education 13.4	VAS	FD	Fatigue levels were significantly higher in WD patients
Utset et al[29], 2015	Cross-sectional	-344 SLE patients; 31% WD -321 healthy subject	-WD SLE patients: mean age 43.8; MDD 10.7; SLICC/DI>143%; not African-American race 37%	FACIT-F	WHO Health and Work Performance Questionnaire (HPQ)	Fatigue was independently associated with WD and low presenteeism
Cosatti et al[30], 2017	Cross-sectional	-130 SLE patients; Absenteeism 8%, presenteeism 19%, overall work impairment (absenteeism plus presenteeism) 26%	-mean age 39; MDD 7; 91% women; 75% more than 12 years of formal education; mean SLEDAI 0; mean SDI 0	VAS	WPAI	Fatigue significantly correlated with presenteeism in the univariate analysis, but not in the multivariate analysis.

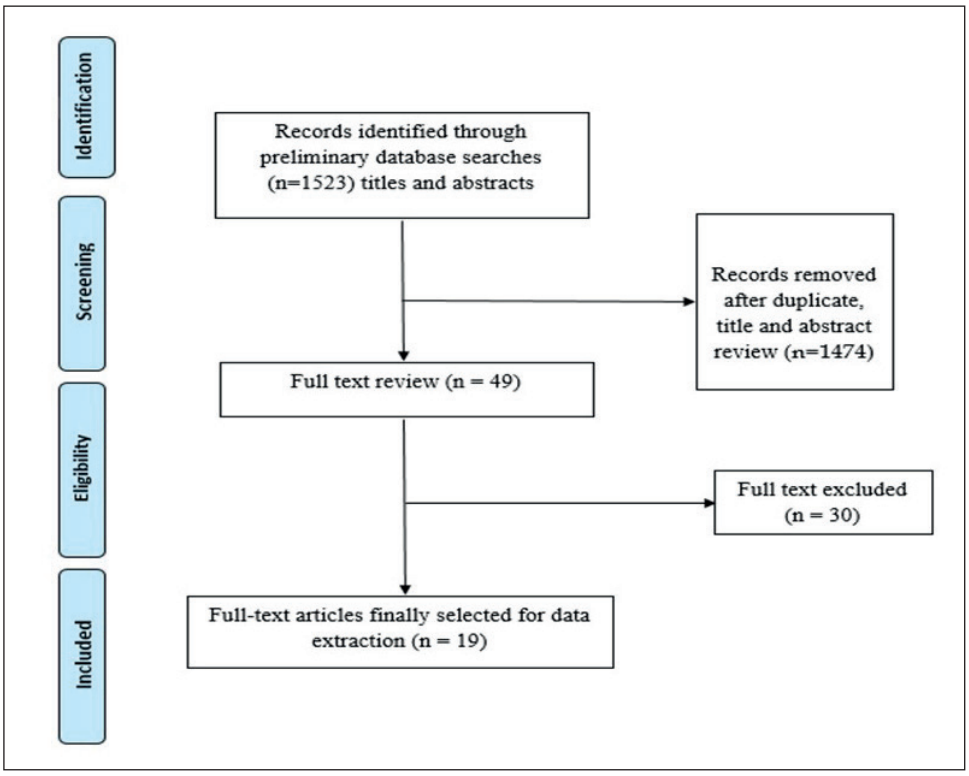

Figure 1. Identification of eligible studies.

Gordon et al[28] performed a multicentric research concerning the burden of SLE on the productivity and careers of patients on a population of 2070 European SLE patients: fatigue was the most affected domain and significantly impaired both household and work productivity.

As shown by Utset et al[29] in many reports, fatigue was significantly associated with WD. The same authors also explored absenteeism, presenteeism and work productivity. Fatigue levels were found to be significantly worse in patients with low presenteeism and WD. An inverse correlation involving fatigue and absenteeism was finally found, though not reaching the statistical significance.

Cosatti et al[30] recently performed a multicenter study including 130 SLE patients from Argentina. Fatigue significantly correlated with presenteeism in the univariate analysis, but not in the multivariate analysis. Noteworthy, all patients had absent disease activity and no organ damage.

Longitudinal Investigations

Panopalis et al[13] showed that both SF-36 MCS and PCS were significant predictor of higher direct healthcare costs and productivity costs due to changes in work productivity in a cohort of 812 SLE patients.

Last, Drenkard et al[31] assessed rates and predictors of work loss in a large group of SLE patients excluding fatigue from factors potentially involved in. Nevertheless, among patients still employed fatigue was associated with higher impairment of work productivity.

Discussion

LES has a significantly negative impact on work participation, including loss of employment, as can put up numerous barriers to job retention. Functional limitations are due to its multiple organ involvement, with variable activity, severity and damage. Even not representing a life-threatening involvement, fatigue is a common and disabling symptom leading to a strong impairment of physical function with functional limitations. In our review we tried to establish whether these limitations may interfere with individual's ability to work, even leading to unemployment. Therefore, we decided to separate work disability, defined as inability to do paid work due to illness[13], from work impairment, which included absenteeism, presenteeism and work productivity.

A primary goal of our review was therefore to assess the relationship between fatigue and work

loss. Among cross-sectional studies analyzed, the majority of Authors reported fatigue as a factor involved with WD[13,15-19,21,29]. More conflicting data concerned longitudinal studies: Yelin et al[23] and Lawson et al[24] reported fatigue as a predictor of WD, whereas Bertoli et al[22] did not.

Moreover, we tried to investigate, among employed patients, whether fatigue influenced work performance. In cross-sectional studies, Authors reported fatigue as a factor involved in work ability[26,27] and work productivity[28,29]. Moreover, both longitudinal SLE cohorts showed that fatigue led to significant impairment of work productivity[14,31]. Remarkably, fatigue was also found to significantly affect household productivity[20,28]. The impairment of work and home productivity was finally responsible of the increase of both direct and indirect health costs related to the disease[14].

Scholars analyzed the mechanisms underlying this phenomenon: first of all, fatigue was found to significantly affect presenteeism[28-31]. Moreover, exploring specific working tasks affected by the disease, higher fatigue levels were found to cause less endurance in temperature, lighting and equipment, and less interactions with employees and coworkers[25]. Other workplace activity limitations attributed to fatigue consisted in difficulties related to mobility, concentration and the pace and scheduling of work[27].

The studies included in this review reported validated questionnaires measuring fatigue. Nevertheless, some Authors quantified fatigue using SF-36 PCS. Even if PCS is also influenced by other physical sphere components such as pain, global health and physical role, we decided to include in the review also papers presenting only SF-36 PCS as surrogate measure of fatigue. Overall, in studies reporting only SF36 components summary, a relationship with work ability was described both for the physical and mental components[14,18,23,24,26].

Conclusions

We observed that fatigued SLE patients had a higher risk to experience work loss[14-24]. Not only, SLE patients who were employed commonly reported higher presenteeism and reduced work productivity[14,28-31]. Moreover, work impairment provoked by fatigue also concerned household activities and activities of daily living in general[20,28].

Conditions related to fatigue should be assessed routinely in every patient with SLE. Greater efforts are therefore required to understand pathophysiological mechanisms of fatigue especially considering conflicting data regarding the role of proinflammatory cytokines. Fatigue should be managed with the application of the appropriate diagnostic algorithms and the adoption and monitoring of effective therapies. An adequate control of fatigue is therefore essential to ensure an improvement of physical and psychological functions with a consequent increase of autonomy, self-esteem and work performance. Finally, it may contribute to the reduction of SLE indirect cost with unquestionable positive socio-economic consequences.

Ethical Approval:

This article does not contain any studies with participants or animals performed by any of the authors

Conflict of interest

The authors declare they have no conflict of interests.

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