Fatigue Predicts Future Reduced Social Participation, not Reduced Physical Function or Quality of Life in People with Systemic Sclerosis

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ABSTRACT

Objective. Although fatigue is one of the most problematic symptoms for people with systemic sclerosis, little is known about how fatigue impacts daily life over time. Such information is important when developing fatigue management interventions. This study was conducted to examine 1) if fatigue severity predicted outcomes of worse functioning (social participation, physical function), and quality of life and 2) if level of self-efficacy moderated significant relationships between fatigue and these outcomes.

Methods. Data were utilized from a clinical trial in which an online self-management intervention was tested (N = 267). Fatigue, social participation, and physical function were assessed by PROMIS measures. Quality of life was assessed by the EuroQol 5-domain instrument (EQ-5D-5L). Linear regressions were performed to examine how baseline fatigue related to functioning and quality of life outcomes 16 weeks later controlling for relevant covariates. PROMIS measures were used to measure self-efficacy in managing symptoms, daily activities, medications and treatments, emotions, and social interactions.

Results. Fatigue at baseline significantly predicted social participation 16 weeks later; but did not predict physical functioning or quality of life. Self-efficacy variables did not moderate the association between fatigue and social participation.

Conclusion. Fatigue severity predicted decreased social participation in people with systemic sclerosis. Interventions targeting fatigue should include support to maintain participation of social roles and activities. The level of reported self-efficacy did not vary the strength of the association between fatigue and decline in social participation indicating that there may be other targets to treat fatigue intervention beyond self-management.

Trial registration: NCT02494401

Keywords: fatigue, self-efficacy, systemic sclerosis, self-management

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by skin thickening in the extremities that may progress to internal organs and impair vascular, pulmonary, and gastrointestinal functioning[1, 2]. Although disease presentation and progression are heterogeneous, most individuals with SSc have high symptom burden, and fatigue is ranked as one of the most problematic symptoms[3-7]. Individuals with SSc have described fatigue's debilitating effects affecting the ability to perform daily living tasks[6, 10], work[11-13] and parent[14-16]. When assessed over time, fatigue was found to be high and relatively stable over 2-4 year periods, suggesting a missed opportunity to help individuals with SSc manage fatigue[8, 9]. Despite the unmet need, there are currently no established fatigue management interventions for this population.

The ability to create relevant fatigue management interventions is limited by the lack of longitudinal studies on fatigue's effect on functioning and quality of life. Such information will provide guidance on which elements should be integrated into new interventions. An earlier cross-sectional study showed that fatigue had a strong negative association with social participation, but not health-related quality of life or physical function[17]. However, one longitudinal study found that worsening fatigue was associated with worsening hand function[18].

There is also limited information on key moderators of the relationship between fatigue and outcomes over time which would not only help indicate who may be in most need of intervention, but may also provide support for which factors may be protective against fatigue's impact on outcomes. Self-efficacy, confidence in ability to manage symptoms (such as pain) has been identified as a potential moderator of a person's response to chronic pain interventions[19,20]. Because improvement in self-efficacy is a mechanism that leads to improved function[21], people with low self-efficacy may be at risk for having fatigue that is influential on outcomes over time.

To help plan a fatigue intervention, this study aimed to: 1) examine if baseline fatigue predicted social participation, physical function, and health-related quality of life from baseline to 16 weeks and 2) determine if baseline self-efficacy moderated any significant associations between fatigue and these outcomes. We utilized data from a previous randomized clinical trial (RCT) that compared an online self-management program versus a control arm to increase self-efficacy for managing symptoms[22]. In that RCT, there were no statistically significant differences between groups at 16 weeks and no significant mean changes within groups on self-efficacy or symptom measures over time. We hypothesized that fatigue at baseline would predict decreased social participation, reduced physical function, and worse health-related quality of life at 16 weeks. We also hypothesized that greater self-efficacy would diminish the association between fatigue and decline in these outcomes.

METHODS

Recruitment was undertaken at two universities, on websites, and social media[22]. Inclusion criteria were US residency, SSc diagnosis, age $\geq$ 18 years, basic computer literacy, access to internet and email, and English speaking. After informed consent was obtained, participants were sent an online survey to complete baseline assessments. Participants were then randomized into the 16-week intervention or to the control arm; randomization was stratified by baseline depressive symptoms scores to ensure adequate distribution in each arm. Participants in the intervention were provided log-in information to the secure intervention website and provided a new learning module weekly. Participants in the control arm received a scleroderma book written for patients with SSc. Both groups were contacted every 4 weeks and provided gift card incentives throughout the study. Post-intervention, all participants were sent the same survey battery as provided at baseline. The study was approved by institutional human subjects review

boards at University of New Mexico, University of Michigan, and Medical University of South Carolina.

Measures

Fatigue was measured by the subscale of Patient Reported Outcomes Measurement Information System 29 version 2.0 (PROMIS v.2) at baseline and 16 weeks[23]. The PROMIS 29 v.2 instrument has been in validated in a large SSc sample[24]. Scores were converted to a T score metric where a mean of 50 and standard deviation of 10 represents the US population; higher scores indicates worse fatigue. Outcomes of social participation, physical function, and quality of life were assessed at baseline and 16 weeks. PROMIS 29 v.2 was also used to measure social participation (Ability to Participate in Social Roles and Activities) and physical function. Scores were converted to T scores; higher scores indicate better ability/function. Health-related quality of life was measured by the EuroQol 5-domain instrument (EQ-5D-5L), a commonly-used instrument in samples with chronic conditions[25]. Participants rate their health state in the areas of mobility, self-care, activity, pain, and anxiety on a scale of no problems, slight problems, moderate problems, severe problems and extreme problems. Responses are transformed to a health utility metric using a specific algorithm. The possible range of scores from 0 to 1.0 (full/optimal health)[26].

Five domains of self-efficacy were assessed as moderators from the PROMIS Self-Efficacy for Managing Chronic Conditions assessment[27]: self-efficacy for managing symptoms, performing daily activities, managing medications and treatments, managing emotions, and managing social interactions. Scores were transformed to a T metric with higher scores indicating greater self-efficacy.

Demographic, Clinical Characteristics, and Other Covariates

Demographics included age, race, ethnicity, sex, education level, marital status, and employment status. Clinical characteristics included scleroderma subtype (limited/CREST/sine, diffuse, or overlap) and disease duration (based on year diagnosed). Participants rated their overall health as excellent, very good, good, fair, or poor. Symptom covariates in the multivariable models included pain interference and depressive symptoms as assessed from the PROMIS 29 v.2. Higher scores indicated worse symptoms.

Data Analysis

Baseline characteristics were described by frequency and proportion for categorical data, mean and standard deviation for normally distributed continuous data, and median and interquartile range for non-normally distributed continuous data. Linear regression was used to assess the association between fatigue at baseline and outcomes 16 weeks later in separate analyses for social participation, physical function, and health-related quality of life. Models were adjusted for baseline level of the outcome and covariates: age, gender, ethnicity, scleroderma type, years since diagnosis, pain interference and depressive symptoms scores at baseline, treatment group, and, for social participation and quality of life outcomes, baseline level of physical function. Self-efficacy domains assessed at baseline were then investigated as possible moderators of the association between fatigue and the outcomes by inclusion of interaction terms in models.

RESULTS

The sample of 267 participants consisted of 91% women; the mean age was 53.7 (range 20 – 83 years)[22]. Seventeen percent of the sample was non-White and 64% were married. The sample

had a mean of 16 years of education, with 74% who reported having a degree or equivalent professional qualification. With regard to work status, 26% were on disability or sick leave. Subtypes of SSc most frequently reported were limited or sine (45%), followed by diffuse (43%); and SSc overlap with another rheumatic disease (12%). The median reported time since diagnosis was 9 years (interquartile range of 5 – 16 years). Self-rated health was reported to be fair or poor for 44% of the sample.

Values for symptom, functioning, and quality of life measures are shown in Table 1. As this was a non-significant trial, values from baseline and 16-week outcome periods are shown for the entire sample; specific values by arm have been reported elsewhere[22]. Symptoms remained relatively stable between baseline and 16 weeks. Fatigue and pain interference were rated as most severe of the symptoms; mean T scores were .87 and .80 SD above the US population. Depressive symptoms and the majority of self-efficacy measures were all within .5 standard deviations of the normative sample mean, except for self-efficacy to manage daily activities which was lower than the normative sample by .64 SD. Of outcomes of social participation and physical functioning, physical functioning was lower by comparison. Reported physical function was almost 1 SD below a normative population whereas social participation was within .5 SD. Health-related quality of life health utility score from the EQ-5D-5L of .78 was also rated below the population norms of adults in other countries which was approximately .91-.92[28, 29], but slightly higher than what was seen in other studies of SSc (median of .69 and .75)[30, 31].

Results from the three linear regression models in which baseline fatigue was examined as a predictor of social participation, physical function, and health-related quality of life respectively are presented in Table 2. Of these models, baseline fatigue only predicted social participation. Higher fatigue severity predicted lower social participation, with every one-point increase in

fatigue corresponding to a .13 decrease in social participation. Greater baseline social participation and physical function contributed to higher social participation. Participants in the control arm had increased participation compared to the treatment group, although this increase was minimal (less than a two-point difference). Moderator analyses were performed in which self-efficacy variables were tested in the model in which social participation was the outcome. Self-efficacy variables did not moderate the association between fatigue and social participation.

DISCUSSION

In this post-hoc analysis, we examined if and how baseline fatigue severity predicted measures of functioning (social participation and physical function) and health-related quality of life 16 weeks later. In SSc, there have been few studies in which fatigue and these outcomes are examined longitudinally [10, 16], and none have measured social participation. We found that baseline fatigue severity only predicted worse social participation, but had no significant impact on physical function and health-related quality of life. The effect of fatigue on social participation but not physical function may be reflecting how people adapt to living with SSc. In a disability framework, it has been proposed that daily life activities are obligatory, such as dressing or meal preparation; committed, such as work or caring for one's children; or discretionary, such as social activities, exercise, or hobbies[32]. Studies in people with rheumatic conditions other than SSc have shown that activities are intentionally limited or restricted, with discretionary activities being reduced to preserve time and energy for obligatory activities[33-35]. This pattern has also been shown in SSc in which people reported lower participation in social activities compared to domestic and household maintenance activities[36]. It may be that people with SSc and fatigue are reducing social participation to optimize basic physical functioning

necessary to their everyday living. In this study, social participation was measured in general categories of activities including work, leisure, and activities with family and friends by the PROMIS 29 without reflecting nuances of this framework. Despite this general measurement of social participation, the association of fatigue and social participation found in this study is concordant with SSc literature. There is an association between fatigue and work disability[9-11] and marked declines in ability to work over time[10]. Further, qualitative studies involving people with SSc have depicted how fatigue interferes with social and leisure activities and the ability to carry out life roles [8, 12-14]. This study established a longitudinal association between fatigue and social participation; however, further research is needed to examine processes by which people with SSc restrict their social participation and how fatigue influences the process.

Fatigue was not a significant predictor of health-related quality of life in SSc. Fatigue and health-related quality of life in SSc are associated in cross-sectional studies[30, 31], but it appears that factors other than fatigue may be more consequential. In one study, the association between fatigue and health-related quality of life was diminished when disability was added in the multivariate model[37]. In a cross-sectional analysis using baseline data from this study, we examined relative influence of fatigue, pain interference, and depression on health-related quality of life using hierarchical models. Fatigue only added 1% additional variance in health-related quality of life after pain interference and depression were added, which combined explained 53% of the variance[17].

This study provides support for assessing fatigue in clinical practice as it may have profound effects on the daily lives of individuals with SSc affecting their participation in activities,

routines, and life roles. Fatigue in rheumatic diseases is under-studied[6, 38] and perceived by individuals with SSc as under-addressed in clinical care[39], but one of the challenges to intervening on fatigue is that it is multi-factorial in nature. Thombs et al. conceptualized fatigue in SSc as a combination of etiological factors (such as inflammatory cytokines), disease-specific manifestations (such as connective tissue changes), comorbidities, psychosocial factors, lifestyle habits, and contributors such as pain and sleep issues[38]. Basta developed a conceptual model with similar domains but also highlights the potential importance of work disability and sociodemographic contributors[4]. Longitudinal studies in SSc in which predictors of fatigue severity are examined support this multifactorial model. For instance, in a study where people were followed for a mean of 3.8 years, predictors of fatigue severity included baseline measures of ineffective coping skills (as reported on an illness behavior questionnaire), pain, and gastrointestinal symptom severity[15]. Further, decreased lung function was a predictor of change in fatigue during that period. Another study in which 215 patients with SSc were followed over a 3-year period, again found that symptoms of lung involvement and coping skills (in this case, less acceptance of one's condition) were independent predictors of higher fatigue, in addition to being female[16]. Addressing potentially modifiable factors would require a multi-modal approach and likely need to utilize a variety of care providers in fatigue management, including physicians, occupational and physical therapists, and psychologists. A better characterization of fatigue and its impact in future studies is warranted to identify optimal intervention strategies to target specific aspects of fatigue.

One potential clinical implication is the support for interventions targeting the relationship between fatigue and social participation. Because fatigue seems to affect participation in social

roles and activities, occupational therapists are particularly well-suited to work with these individuals as their main practice domain involves identification, resolution of, or adaptation to problems with participation in daily life roles and activities[40]. Despite this potential avenue for intervention, a recent review showed that rehabilitation services including occupational therapy and physical therapy are not well-utilized among people with SSc[41]. Thus, more education to providers regarding these services may be needed to promote referrals.

Interestingly, in this study, level of self-efficacy for managing different aspects of chronic disease did not moderate the association between baseline fatigue and decline in social participation. In essence, a person's higher self-efficacy at baseline was not protective against fatigue's effect on social participation. This finding may have potentially important implications for development of fatigue management interventions. While increasing self-efficacy can be useful in many aspects of disease management, a fatigue intervention that focuses only increasing self-efficacy in managing fatigue may not have the desired outcome of reducing effects on social participation.

Our study has strengths. First, it utilized a well-conducted RCT that captured data in subjects with SSc over a period of 16 weeks. Second, we were able to assess the prospective relationship between baseline fatigue and outcome measures of interest due to longitudinal nature of the data. Limitations of this study include utilization of self-report of participants who voluntarily participated in a RCT on an online self-management program. In addition, findings may be generalized only to people who use computers and have internet access and who were not newly diagnosed, as the median disease duration was 9 years. The report of disease characterization

such as subtype and duration of disease could not be verified by medical record. A 16-week duration to look at longitudinal effects is relatively short, and a longer follow-up period may provide more insight on the nature and persistence of effects (and may explain a lack of effect on physical functioning and health-related quality of life). Longitudinal data was gathered from people in a RCT, although there were no meaningful changes in the intervention and control groups. Future studies could provide a more nuanced measurement of social participation and should consider mixed methods approaches to understand how much the fatigue-social participation association has a perceived impact on individual's lives. Lastly, our study was limited by having only 2 assessment periods involving recall-based measures. A more intensive measurement protocol using ecological momentary assessment that would ascertain trajectories of fatigue and social participation over time would better characterize temporal patterns.

Conclusion

Fatigue severity predicted decreased social participation in people with SSc. Level of reported self-efficacy did not vary the strength of the association between fatigue and decline in social participation. Interventions targeting fatigue should include support to maintain participation of social roles and activities. A better understanding of the outcomes that fatigue most impacts can enable the design of an optimal fatigue management intervention that may include medical and behavioral-based targets. More research will be needed to characterize fatigue and its impact on individuals with SSc to inform this intervention development.

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Table 1. Baseline and 16 Week Symptoms, Function, and Quality of Life Variables

Measures	Baseline (N=267)	16 weeks[a]
Fatigue*	58.7 (10.4)	58.7 (10.8)
Pain interference	58.0 (9.3)	57.2 (9.4)
Pain intensity (0–10 NRS)	4.2 (2.2)	4.1 (2.3)
Depressive symptoms	51.3 (9.8)	51.2 (9.6)
Self-efficacy for managing social interactions[b]	45.1 (39.4– 52.9)	46.7 (40–59.8)
Self-efficacy for managing daily activities[b]	43.6 (40.1–48)	43.4 (39.7–48.8)
Self-efficacy for managing medications/ treatments[b]	50.4 (42.7–55.5)	50.9 (42–60.6)
Self-efficacy for managing symptoms[b]	46.8 (41.9–53.1)	46.9 (42.3–53.6)
Self-efficacy for managing emotions[b]	46.4 (41.6–51.3)	46.7 (40.4–52)
Social Participation	45.0 (8.2)	46.3 (9.2)
Physical Function	40.4 (7.1)	40.9 (7.8)
Quality of Life (EQ-5D-5L)	0.78 (0.08)	0.71 (0.17)

Note. The PROMIS 29 v.2 was used which comprised scales of Fatigue, Pain Interference, Pain Intensity, Depressive symptoms, Self-efficacy variables, Ability to Participate in Social Roles (Social Participation), and Physical Function. NRS: numerical rating scale; EQ-5D-5L: EuroQol 5-domain instrument[a]. In all, 92% follow-up data (N = 246) for fatigue, pain interference, pain

intensity, depressive symptoms, self-efficacy for managing emotions, and social participation; 93% follow-up data (N = 247) for Self-efficacy for managing social interactions, Self-efficacy for managing daily activities, Self-efficacy for managing medications/treatments, Self-efficacy for managing symptoms, and Quality of Life EQ-5D-5L.

[b] Median (IQR)

Table 2. Baseline fatigue as a predictor of social participation, physical function and quality of life at 16 weeks

Baseline Variables	Social participation (N=245)			Physical function (N=245)			Quality of life (N=244)		
	B	95% CI	P	B	95% CI	P	B	95% CI	P
Fatigue	-0.13	-0.24, -0.02	0.02	-0.04	-0.12, 0.05	0.39	-0.002	-0.004, 0.0006	0.16
Age	-0.003	-0.07, 0.06	0.92	-0.03	-0.08, 0.03	0.36	0.002	0.0005, 0.004	0.008
Female	-0.98	-3.54, 1.58	0.45	-0.38	-2.54, 1.79	0.73	0.006	-0.05, 0.06	0.84
Minority	-0.43	-2.40, 1.53	0.67	0.03	-1.63, 1.70	0.97	0.05	0.002, 0.09	0.04
SSc type[a]									
Diffuse	0.54	-1.02, 2.09	0.50	-0.34	-1.66, 0.98	0.61	0.007	-0.03, 0.04	0.70
Overlap	-0.21	-2.65, 2.24	0.87	-1.68	-3.76, 0.40	0.11	-0.005	-0.06, 0.05	0.86
Years since dx	-0.03	-0.12, 0.05	0.42	0.004	-0.07, 0.08	0.91	-0.001	-0.003, 0.0008	0.26

Pain interference	0.01	-0.10, 0.13	0.80	-0.02	-0.11, 0.08	0.74	-0.001	-0.004, 0.002	0.46
Depressive symptoms	-0.02	-0.11, 0.07	0.65	-0.02	-0.10, 0.05	0.57	-0.002	-0,004, 0.0002	0.08
Treatment arm[b]									
Control	1.76	0.33, 3.19	0.02	0.54	-0.67, 1.75	0.38	0.01	-0.02, 0.04	0.50
Social part.	0.65	0.50, 0.80	<0.001	–			–		
Physical function	0.19	0.04, 0.33	0.01	0.82	0.71, 0.93	<0.01	0.003	-0.0001, 0.006	0.06
Quality of life	–			–			0.83	0.52, 1.15	<0.001

CI: confidence interval; SSc: systemic sclerosis; dx: diagnosis; Social Part: Social Participation

[a]Limited SSc is the reference group

[b]Intervention arm is the reference group

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