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Fatigue: an overlooked determinant of physical function in scleroderma

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Objectives. To examine the frequency and correlates of fatigue and its impact on physical and social functioning in patients with scleroderma, and to investigate whether fatigue mediates an association between pain and physical function.
Methods. One hundred and seven scleroderma patients attending an academic scleroderma specialty centre completed measures of fatigue, sleep, pain, depressive symptoms, and physical and social functioning. Patients had received a comprehensive clinical assessment with a diagnosis of limited or diffuse scleroderma from their attending rheumatologist.
Results. In this sample of scleroderma patients, 76% reported experiencing fatigue and 61% of these patients reported fatigue as one of their three most distressing symptoms. Patients endorsing greater pain had higher levels of self-reported fatigue, as did those reporting greater depression and poorer functioning. Multiple regression analyses indicated that global fatigue was a significant cross-sectional correlate of physical, but not social, functioning after controlling for depressive symptoms, level of education, poor sleep quality and disease subtype. However, global fatigue did not predict physical function when pain was included in the analyses.
Conclusions. Our findings indicate that fatigue is common in scleroderma and that pain and fatigue are significant determinants of physical functioning for patients with limited and diffuse disease subtypes. Future research should investigate whether effective pain treatments reduce symptoms of fatigue, as well as identify other possible causes of fatigue in order to improve quality of life for scleroderma patients.

Key words: Scleroderma, Fatigue, Quality of life, Pain, Sleep, Mood.

Introduction

SSc (scleroderma) is a rare and chronic autoimmune disease that affects the skin and can damage multiple organ systems, including the respiratory, digestive, circulatory and cardiovascular systems. The clinical presentation, course of the disease and degree of severity of scleroderma are heterogeneous [1]. Scleroderma is four times more likely to affect women than men [2], has an estimated population prevalence of 240 per million and is characterized by hardening of the skin, inflammation, vascular injury and visceral fibrosis [3, 4]. This disorder can cause acute and chronic pain from several clinical problems, such as RP, ischaemic digital ulcers, thickening inflexible skin with tissue breakdown and joint contractures [5]. Scleroderma is classified into two main subtypes, limited and diffuse, based on the degree and location of skin involvement [6].

The limited psychosocial studies of scleroderma have focused on the incidence and correlates of pain, depression and body image dissatisfaction [7]. Studies demonstrate that pain is common in scleroderma patients and has a particularly strong influence on patients' physical functioning and social adjustment [8]. Several studies have also confirmed that depressive symptoms are common sequelae [8–10]. Although not as well studied, fatigue may be a significant source of distress and disability in patients with scleroderma. Scleroderma patients frequently report fatigue [11, 12] but there has been limited empirical research investigating its frequency, characteristics and correlates [13]. Fatigue has multiple dimensions (e.g. physiological, psychological, social) and is a common complaint among patients with various rheumatological conditions, including RA (80–93%) [14], AS (65%) [15, 16] and SLE (81%) [17]. Correlates of fatigue in RA include pain, female sex, poorer quality of sleep, longer disease duration and greater functional limitations, with pain being the strongest correlate of fatigue [14]. Psychosocial correlates include depressive symptoms and self-efficacy [18], and problematic social support and social mobilization [19].

Due to the limited empirical studies examining fatigue in scleroderma, the first objective of the current study was to determine the frequency and correlates of fatigue in scleroderma patients, and to examine whether patients with limited and diffuse subtypes differed in report of fatigue. The second aim was to evaluate whether fatigue affected scleroderma patients' physical and social function. The third goal was to determine whether global fatigue mediated the previously established relationship between pain and physical functioning [8] in scleroderma patients.

Patients and methods

Patients and procedure

Study participants were recruited by mail through the Johns Hopkins Scleroderma Center from a list of patients seen in the clinic from 1998 to 2000. The diagnosis of scleroderma was confirmed and each patient was classified with either limited or diffuse scleroderma by a rheumatologist at the centre according to established guidelines [6, 20]. Questionnaire packets containing the consent form and measures described below were mailed with a cover letter inviting participation in the study. The cover letter explained informed consent and confidentiality. A stamped return envelope was included in the packet. Patients were instructed to sign the consent form and return it along with the completed packet. Scleroderma patients received a follow-up phone call 10 days after the mailing to make sure they had received the questionnaire packet and to ask whether they had any questions about the study. All study procedures were approved by the Johns Hopkins Medicine Institutional Review Board, and informed consent was obtained prior to the initiation of study procedures. Patients were not compensated for participation in the study.

Physical functioning. The HAQ-disability index (HAQ-DI) [21] is a self-report measure with demonstrated reliability and validity for the assessment of physical functioning in scleroderma patients [22]. It yields a 20-item disability index that assesses patients' ability to carry out normal daily activities in eight categories (dressing and grooming, arising, eating, hygiene, walking, reach,

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grip and other common daily activities, such as doing chores and running errands) over the past week. A total disability score is calculated by summing the individual scores for each of the eight categories and dividing by the number of categories answered. Possible item scores range from 0 (without any difficulty) to 3 (unable to do) with higher scores representing greater disability. In the current study, the HAQ-DI demonstrated excellent internal consistency ($\alpha = 0.95$).

Social network characteristics. The Social Network Index (SNI) [23] was used to assess participation during the past 2 weeks in each of the 12 types of social relationships, including spouse, parents, children, parents-in-law, other close relatives, close neighbours, friends, coworkers, schoolmates, fellow volunteers, members of religious groups and members of groups without religious affiliations. The SNI consists of two scales that sum the total number of contacts across all types of relationships (network size) and sum the total number of different social groups in an individual's social network (network diversity). Social network diversity scores range from 0 to 12.

Fatigue. The Multidimensional Assessment of Fatigue (MAF) [14] is a revision of the Piper Fatigue scale, a 41-item scale originally developed for cancer patients [24]. The MAF consists of 16 items and measures four dimensions of fatigue: severity, distress, degree of interference in activities of daily living and timing (i.e. frequency). The fatigue severity subscale consists of two items assessed on a numerical rating scale ranging from 1 (not at all) to 10 (a great deal) for a maximum possible score of 20. One item comprises the distress subscale, which ranges from 1 (no distress) to 10 (a great deal of distress). Degree of interference in activities of daily living consists of 11 items assessed on a numerical rating scale ranging from 1 (not at all) to 10 (a great deal). Scores can range from 11 to 110. The timing subscale consists of two items and asks respondents how often they have been fatigued on a 4-point Likert scale (1 = hardly any days, 2 = occasionally, 3 = most, but not all days, 4 = every day) and to what degree their fatigue has changed over the past week on a 4-point Likert scale (1 = decreased, 2 = stayed the same, 3 = fatigue has gone up and down, 4 = increased). A global fatigue index is calculated by summing the total scores for the fatigue severity and distress subscales, the average score of the degree of interference in activities of daily living and one timing item (how often they have been fatigued over the past week), which has been converted to a numerical rating scale ranging from 1 to 10. This index ranges from 5 to 50 with higher scores reflecting greater fatigue. In the current study, Cronbach's-α for the MAF global fatigue index was excellent ($\alpha = 0.94$).

Scleroderma symptoms. The scleroderma symptom ranking questionnaire was developed by the authors to assess the patient-rated importance of symptoms that scleroderma patients commonly experience. It consists of 14 problems: fatigue, pain, sleep difficulties, depression, loss of strength, upset stomach, concern about appearance changes, sore eyes, stiff joints, changes in social and recreational activities, weight loss, breathlessness, nausea and skin discolouration. Patients report whether they currently experience any of the 14 problems, and then rank the importance of each problem they experienced relative to the other endorsed items. In giving a rank, patients were instructed to consider how severe the problem was, how often it occurred, and the impact it had on their activities of daily living.

Pain. Pain was assessed with the short form of the McGill Pain Questionnaire (MPQ-SF) [25], a 15-item measure that targets sensory and affective dimensions of pain. These items are rated on an intensity scale ranging from 0 (no pain) to 3 (severe pain). Scores for each item are summed for the total scale (0–45) [26]. The internal consistency of the total score in our sample of scleroderma patients was excellent ($\alpha = 0.91$).

Depressive symptoms. Depressive symptoms were assessed with the Center for Epidemiologic Studies-Depression Scale (CES-D) [27]. The CES-D is a 20-item measure that reflects the major dimensions of depression including depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite and sleep disturbance. Each of the 20 items are assessed on a 3-point Likert scale ranging from 0 (rarely or none of the time) to 3 (most or all of the time). A total depression score is calculated by summing the 20 items (0–60). The CES-D has shown good reliability and validity with a wide variety of populations, including RA patients [28]. The internal consistency of the CES-D in the current study was adequate ($\alpha = 0.70$).

Sleep. Patients' sleep quality was examined with the Pittsburgh Sleep Quality Index (PSQI), a 19-item questionnaire that assesses factors related to sleep quality in the previous month [29]. The 19 items are grouped into seven component scores, with each being weighted equally. The seven components are summed to yield a global PSQI score (0–21). Higher scores indicate worse sleep quality and greater sleep disturbances. The seven components of the PSQI include: sleep quality, sleep onset latency, sleep duration, sleeping efficiency, sleep disturbances, use of sleep medication and daytime activity dysfunction. In this study, one of the components, a single-item sleep quality rating, was unable to be used in the total score due to missing data. Thus, we used a modified total PSQI score (0–18) for all subjects. Cronbach's-α coefficient was 0.74 for this modified version of the PSQI.

Statistical analyses

T-tests were used to compare patients with limited and diffuse scleroderma subtypes on fatigue. To examine fatigue correlates, Pearson or point-biserial correlations were conducted between global fatigue and demographic variables [i.e. age, ethnicity (White *vs* non-White), marital status (married/living in a marital like relationship *vs* not married and not living in a marital like relationship), education level (did not graduate from highschool *vs* graduated highschool)], disease-related variables [i.e. disease subtype (limited *vs* diffuse), duration of illness] and the study measures of pain, sleep, depressive symptoms, physical function and social function. Regression analyses examined whether global fatigue was a significant, independent correlate of poorer physical and social functioning. Pearson or point-biserial correlations were conducted between physical and social function and demographic variables (i.e. age, ethnicity, marital status, education level), disease-related variables (i.e. disease subtype, duration of illness) and the study measures of pain, sleep and depressive symptoms to determine relevant covariates to include in the regression models.

Additional regression analyses were used to test a mediational model involving global fatigue, pain and functioning. Baron and Kenny [30] have outlined four criteria in establishing mediation. In the first regression equation, the independent variable (pain) must be significantly associated with the dependent variable (physical function). In the second regression equation, the independent variable (pain) must be significantly associated with the mediator (global fatigue). If this second step is significant, the analysis can proceed to the third regression equation, in which the mediator (global fatigue) must be significantly associated with the dependent variable (physical function) after controlling for the independent variable (pain). The fourth step involves using Sobel's test [31] to determine whether the strength of the relationship between the independent variable (pain) and dependent variable (physical function) is significantly reduced after controlling for the mediator (global fatigue).

Results

Patient characteristics

Of the 324 scleroderma patients invited to participate in the study, 52 were deceased and 16 were unable to be located due to outdated addresses. Forty-two percent of eligible patients ($n = 107$) completed the questionnaire packet. The final sample of 107 patients (90% women) had a mean age of 55.68 (S.D. = 11.4). Seventy-one percent were married or currently living with someone in a marital-like relationship and 32% reported having a high school or lower level of education. In addition, 42% of scleroderma patients reported being employed, 27% of patients were unemployed or unable to work, 20% were retired and 11% were homemakers. The sample was 82% White, 13% African American, 4% Asian and 1% Hispanic. Patients reported being diagnosed with scleroderma from 1 to 37 yrs (*Median* = 10.0; *Interquartile range* = 8.0). Seventy-five percent of patients received a diagnosis of limited scleroderma while 25% of the sample received a diagnosis of diffuse scleroderma.

Frequency of fatigue

In this sample of scleroderma patients, 76% reported that they currently experienced fatigue, as assessed by the scleroderma symptom ranking questionnaire. Other current symptoms reported included stiff joints (74%), loss of strength (68%), pain (67%), sleep difficulties (66%), skin discoloration (47%), changes in social and recreational activities (47%), concern about appearance changes (47%), breathlessness (41%), upset stomach (37%), sore eyes (26%), depressive symptoms (25%), nausea (21%) and weight loss (16%). Of the subset of patients who reported fatigue, 21% ranked fatigue as their number one complaint, followed by stiff joints (13%) and pain (12%). Additionally, fatigue was ranked as one of the three most distressing complaints by 61% of scleroderma patients who reported experiencing fatigue.

Fatigue correlates

Means and standard deviations of the dimensions of fatigue assessed by the MAF and other key study measures used in the current study are presented in Table 1. Patients with limited and diffuse disease subtypes did not significantly differ in any of the fatigue dimensions. Greater global fatigue, as assessed by the MAF, was significantly correlated with greater pain ($r = 0.46$, $P < 0.01$), greater depressive symptoms ($r = 0.54$, $P < 0.01$), poor sleep quality ($r = 0.46$, $P < 0.01$), poorer physical function ($r = 0.44$, $P < 0.01$), smaller social network size ($r = -0.24$, $P < 0.01$) and smaller social network diversity ($r = -0.20$, $P < 0.05$). Global fatigue was not significantly associated with age, ethnicity, marital status, education level, disease duration or limited *vs* diffuse disease subtype (all r's < 0.09, all P's > 0.74).

Impact of fatigue on physical function

Regression analysis was conducted to investigate whether global fatigue was a significant predictor of poorer physical function. Pearson or point-biserial correlations examined the association between physical function and potential covariate demographic variables (i.e. age, ethnicity, marital status, education level), disease-related variables (i.e. disease subtype, duration of illness), and the study measures of sleep and depressive symptoms. Poorer physical function was significantly associated with diffuse scleroderma subtype ($r_{PB} = 0.31$, $P < 0.001$), lower education ($r_{PB} = -0.29$, $P < 0.01$), greater depressive symptoms ($r = 0.36$, $P < 0.01$), and poorer sleep quality ($r = 0.41$, $P < 0.01$). Thus, these variables were included as covariates in regression models predicting physical function. Results of the regression analysis predicting physical function are summarized in Table 2. The regression model was significant and accounted for 39% of the variance in physical functioning. In addition to diffuse disease subtype ($P < 0.01$) and lower level of education ($P < 0.05$), greater global fatigue was a significant predictor of poorer physical function ($P < 0.01$).

Table 1. Study measures

Measure	Mean (S.D.)		
	Total sample	Diffuse	Limited
MAF severity	9.77 (5.62)	9.91 (5.39)	9.33 (6.34)
MAF distress	3.31 (2.91)	3.38 (2.91)	3.11 (2.97)
MAF interference	4.56 (3.11)	4.69 (3.02)	4.19 (3.41)
MAF timing	4.63 (2.11)	4.79 (1.99)	4.19 (2.42)
MAF global fatigue index	20.57 (11.69)	21.07 (11.27)	19.10 (12.95)
PSQI total	6.93 (3.73)		
MPQ-SF total	8.47 (9.22)		
CES-D total	19.26 (5.39)		
HAQ-DI	1.84 (0.74)		
SNI size	17.87 (8.34)		
SNI diversity	5.94 (1.64)		

Table 2. Regression analysis predicting physical function

	Variable				
	B^a	SEB^b	β^c	t	P
Physical function					
Full model: $R^2 = 0.39$, $F(5,97) = 12.51$, $P < 0.01$					
Global fatigue	0.03	0.01	0.39	3.62	0.001
Depressive symptoms	−0.01	0.02	−0.06	−0.58	0.758
Disease subtype	0.52	0.14	0.30	3.59	0.001
Level of education	−0.35	0.14	−0.22	−2.48	0.015
Poor sleep quality	0.04	0.02	0.19	1.74	0.091

[a]Unstandardized regression coefficient. [b]Standard error of the unstandardized regression coefficient. [c]Standardized regression coefficient.

Impact of fatigue on social function

Two parallel regressions examined the association between global fatigue and social function, one model examining network size and one model examining network diversity. Pearson or point-biserial correlations examined the associations between social network size and diversity and potential covariate demographic variables (i.e. age, ethnicity, marital status, education level), disease-related variables (i.e. disease subtype, duration of illness), and the study measures of sleep and depressive symptoms. Smaller social network size was significantly associated with lower education ($r_{PB} = 0.43$, $P < 0.001$) and greater depressive symptoms ($r = -0.27$, $P < 0.01$); thus education level and depressive symptoms were included as covariates in the social network size regression model. Smaller network diversity was significantly associated with lower education ($r_{PB} = 0.35$, $P < 0.001$), older age ($r = -0.23$, $P < 0.05$) and marital status ($r_{PB} = -0.46$, $P < 0.001$); thus education level, age and marital status were included as covariates in the social network diversity regression model. Global fatigue was not a significant predictor of either social network size, $t(96) = -1.98$, $P = 0.06$, or social network diversity, $t(91) = -1.95$, $P = 0.07$, in the regression models.

Mediation analyses

A series of regression equations tested whether global fatigue was mediating the effect of pain on physical function. Four criteria must be met in order to support the mediating role for global fatigue. Table 3 summarizes the results of these regression analyses, which do not support global fatigue as a mediator of the aforementioned relationship between pain and physical function. Specifically, pain was significantly related to physical function ($P < 0.01$) and global fatigue ($P < 0.01$) after controlling for

TABLE 3. Regression analyses testing global fatigue as a mediator of the effect of pain on physical function

	Variable				
	B[a]	*SEB*[b]	β[c]	*t*	*P*
Dependent measure—physical function					
Pain	0.03	0.01	0.39	4.45	0.001
Disease subtype	0.39	0.14	0.23	2.83	0.001
Depressive symptoms	0.01	0.01	0.05	0.53	0.44
Level of education	−0.30	0.13	−0.18	−2.26	0.02
Poor sleep quality	0.03	0.02	0.17	1.71	0.07
Dependent measure—global fatigue					
Pain	0.38	0.11	0.30	3.49	0.01
Disease subtype	−3.96	2.10	−0.15	−1.73	0.90
Depressive symptoms	0.91	0.22	0.41	4.24	0.001
Level of education	2.29	0.10	0.09	1.14	0.14
Poor sleep quality	0.38	0.31	0.12	1.22	0.14
Dependent measure—physical function					
Global fatigue	0.02	0.01	0.23	1.77	0.09
Pain	0.03	0.01	0.31	3.48	0.01
Disease subtype	0.46	0.13	0.27	3.39	0.01
Depressive symptoms	0.01	0.02	−0.06	−0.58	0.73
Level of education	−0.34	0.13	−0.21	−2.51	0.02
Poor sleep quality	0.03	0.02	0.14	1.14	0.28

[a]Unstandardized regression coefficient. [b]Standard error of the unstandardized regression coefficient. [c]Standardized regression coefficient.

the covariates noted above; diffuse scleroderma subtype, lower education, greater depressive symptoms, and poorer sleep quality. In the third regression equation, global fatigue was no longer significantly associated with physical function after controlling for pain $t(96) = 1.77$, $P = 0.09$. Sobel's test was not conducted given the results of the third regression equation.

Discussion

The present study investigated the relationships among fatigue and physical and social function in patients with scleroderma. While previous research has investigated and confirmed the presence of depressive symptoms [8–10] and pain [8] in scleroderma patients, prior work has not examined the impact of fatigue on physical and social functioning. In this sample, 76% of the scleroderma patients reported experiencing fatigue, and fatigue was ranked as one of the top three most important problems by 61% of scleroderma patients reporting fatigue. Using the MAF, the mean level of global fatigue (20.6) experienced by our sample of scleroderma patients is less than the average level of fatigue reported by patients with RA (29.2), but greater than the average fatigue reported by healthy individuals (17.0) [32].

Greater fatigue, as assessed by the MAF, was significantly associated with poorer sleep quality, greater pain and greater depressive symptoms. These findings are consistent with studies of patients with RA [14, 32, 33]. Previous research shows a significant detrimental impact of depression and pain on physical functioning in scleroderma [8–10, 34]. Our finding of the negative effect of fatigue on physical functioning after controlling for disease subtype, level of education, poor sleep quality and depressive symptoms is consistent with studies involving other rheumatic diseases [35–37] and suggests fatigue is another common and disabling symptom in scleroderma. However, our mediation analyses showed global fatigue was not significantly associated with physical function when pain was included in the analyses. As we have shown previously [8], the influence of pain on physical functioning is substantial and these results further confirm this earlier finding. Although scleroderma patients frequently report fatigue, which is correlated with pain and physical function, these results suggest that fatigue has less of an impact on physical function than does pain. The clinical implications of this finding suggest that the aggressive management of pain, even mild to moderate pain, may impact physical functioning. Since pain and fatigue are clearly correlated, treatment of pain may also influence ratings of fatigue. Given that so little is known about the relationship between pain and fatigue, monitoring the natural course of both of these disabling symptoms over time may lead to a better understanding of their relationship. Ideally, longitudinal studies will extend our cross-sectional analyses to further explore the relationships among pain, fatigue, depressive symptoms and sleep disturbance in scleroderma patients. Indeed, management of scleroderma may be less than optimal if attention is given only to one rather than a cluster of symptoms that appear to often co-occur in these patients.

Regression analyses revealed that global fatigue was not a significant unique predictor of social network diversity or size. This is somewhat surprising given that decreases in physical functioning often lead to declines in mobility, resulting in both qualitative and quantitative changes in social relationships [38]. Future work should examine whether disruption may occur in a different component of social function (e.g. social support) given that social function is a broad, multidimensional concept [19, 35, 39]. The lack of relationship between limited and diffuse disease subtype and fatigue also deserves mention. Given the variability of scleroderma symptoms between and within limited and diffuse disease subtypes, risk for fatigue may be better explained by disease severity. For example, severity scores that incorporate scleroderma patients' skin, cardiac function, gastrointestinal tract function, renal function and lung function, and define overall organ damage may be useful markers of disease severity [40, 41] that add to our understanding of scleroderma-related fatigue.

This study has several limitations that should be noted. If patients with less severe symptoms were more likely to participate in this questionnaire study, then symptoms of fatigue, pain, depression and physical and social functioning may be underestimated. Additionally, the cross-sectional nature of this study prevents conclusions from being drawn regarding the direction of observed relationships, particularly the proposed fatigue → functioning pathway examined in the current study. Prospective studies are needed to truly establish causal relationships.

In summary, we found that fatigue is a common and disabling symptom associated with poor sleep quality, greater pain and depressive symptoms, and poor physical and social functioning. Global fatigue was a significant predictor of physical, but not social, functioning when relevant covariates were considered. However, global fatigue no longer significantly predicted physical function when pain was included in the regression model; pain had significant effects on physical function beyond the effects of fatigue. This study is an important first step to understanding the impact of fatigue in this patient population and suggests that the interventions that target both pain and fatigue may improve the quality of life in scleroderma.

Rheumatology key messages

- Patients with scleroderma rate fatigue as common and important.
- Fatigue is associated with poorer physical function and greater pain.
- Optimal management of scleroderma may require treatment targeted to fatigue and pain.

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