Concise Report

A systematic comparison of fatigue levels in systemic sclerosis with general population, cancer and rheumatic disease samples

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Objectives. There are no studies of fatigue levels in patients with SSc. The objective of this study was to compare fatigue in SSc to general population samples and patients with rheumatic diseases and cancer, where fatigue has been researched extensively.
Methods. SSc patients completed the General Fatigue Index (GFI) of the Multidimensional Fatigue Inventory. A systematic review was conducted to select comparison samples. Mean GFI scores from SSc patients were compared with mean scores from comparison samples with t-tests and Bonferroni corrections (family-wise $P < 0.05$).
Results. A total of 106 SSc patients were sampled (97 females; 28 diffuse SSc; 11.9 ± 7.9 yrs since diagnosis). Based on comparisons from the systematic review, mean GFI scores in SSc (13.3 ± 4.6) were significantly higher (greater fatigue; $P < 0.05$) than in two large population samples (8.7 and 9.6) and than in two samples of cancer patients in remission (9.4 and 10.0). Scores for the SSc sample were significantly lower (less fatigue) compared with two samples of cancer patients in palliative care (16.8 and 17.0). SSc GFI scores were similar to scores from patients with RA (13.4), AS (13.0) and SLE (13.1) and to scores from six studies of cancer patients in active treatment (11.1–13.5).
Conclusions. The high levels of fatigue reported in SSc were similar to patients with varying types and treatment stages of cancer and patients with other rheumatic diseases when assessed with the GFI, demonstrating that fatigue warrants greater attention in SSc.

KEY WORDS: Systemic sclerosis, Fatigue, Systematic review, Multidimensional Fatigue Inventory.

Introduction

Fatigue is defined as the experience of feeling weak, tired and lacking energy that often comes and goes in normal circumstances. Persistent fatigue from chronic illness involves ongoing exhaustion that is disproportionate to exertion and not alleviated by rest [1]. Fatigue from chronic illness decreases quality of life (QOL) by diminishing the ability to engage in meaningful personal and social activities and has important implications for employment, compliance with medical treatments and the use of healthcare services [2–8].

Patients with SSc report substantial disability and poor QOL [9–18]. Only three studies have examined frequency or impact of fatigue in SSc [19–21], and patients in one of these studies rated fatigue as more bothersome than any other symptom, including pain [20]. All three studies, however, used single-item assessments with unknown psychometric characteristics, and thus no conclusions could be drawn about fatigue levels in SSc compared with the general population or with patients in disease groups where it has received greater attention.

The objective of this study was to compare fatigue levels in SSc with fatigue levels from population samples and among patients with cancer and other rheumatic diseases. Fatigue has been more extensively researched in cancer patients than any other patient group. We used the Multidimensional Fatigue Inventory (MFI) [22] because its General Fatigue Index (GFI) provides a single indicator of overall fatigue with strong psychometric properties in multiple patient groups and because general population data are available.

Patients and methods

SSc patient data

We analysed data from SSc patients who were treated at the Johns Hopkins and University of Maryland Scleroderma Center between August 2004 and January 2006 and had a diagnosis of lcSSc or dcSSc based on ACR criteria. Detailed study procedures are documented elsewhere [9, 23–25]. The study was approved by the Johns Hopkins University School of Medicine Internal Review Board. All patients provided informed consent.

Search strategy and study selection

The MEDLINE®, CINAHL® and PsycINFO® databases were searched on 12 October 2007 for studies in any language that included ≥50 subjects and reported GFI means and S.D. for general population samples, patients with rheumatic disease or patients with cancer. Studies that used abbreviated versions of the MFI or an early version with different item scaling [22] were excluded due to incomparability of scores. In the case of multiple articles published on the same cohort, the most recent article with complete data was included. Studies with mixed patient populations were included only if data for patients with cancer or a rheumatic disease were reported separately. Two investigators evaluated studies for inclusion and recorded relevant study data. Discrepancies were resolved by consensus.

Assessments

The MFI [22] is a 20-item measure designed for medically ill patients that includes five subscales of four items each: the GFI, Physical Fatigue, Reduced Motivation, Reduced Activity and Mental Fatigue. Items are worded both positively and negatively and responses are recorded on a 5-point Likert scale (1–5; 'no, that is not true' to 'yes, that is true'). Scores range from 4 to 20 on each subscale/index. Higher scores indicate greater fatigue. The GFI is used when a single fatigue score is sought [26]. It is comprised of four statements ('I feel fit', 'I feel tired', 'I am rested', 'I tire easily') that assess fatigue during the previous days.

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TABLE 1. Summary of General Fatigue Index scores for scleroderma and comparison samples

Reference	Population	Timing of assessment	n	Percentage of females	Mean age	General fatigue Index ± S.D.	P-values
Thombs (2008)	SSc	Mean disease duration 11.9 yrs	106	91	56	13.3 ± 4.6	
	dcSSc	Mean disease duration 9.4 yrs	28	86	54	13.8 ± 4.7	
	lcSSc	Mean disease duration 12.9 yrs	78	93	56	13.1 ± 4.6	
General population							
Schwarz *et al.* [27]	German adults (≥14 yrs)	NA	2037	56	–	8.7 ± 3.4*	< 0.001
Watt *et al.* [28]	Danish adults (20–77 yrs)	NA	1082	51	–	9.6 ± 4.5*	< 0.001
Rheumatic disease							
Da Costa *et al.* [37]	SLE	Mean disease duration 13.8 yrs	130	100	45	13.1 ± 4.5	0.801
Rupp *et al.* [36]	RA	Mean disease duration 10.7 yrs	490	73	61	13.4 ± 4.9	0.773
Van Tubergen *et al.* [38]	AS	Mean disease duration 12.5 yrs	776	30	45	13.0 ± 3.4	0.212
Cancer							
Active Treatment							
Hagelin *et al.* [56]	Heterogeneous cancer—radiation therapy	End of treatment	81	90	59	13.5 ± 5.1	0.725
Holzner *et al.* [42]	Heterogeneous cancer—chemotherapy	Beginning of 3rd cycle	60	43	61	13.4 ± 5.8	0.870
Fürst and berg [39]	Heterogeneous cancer radiation therapy	Last week of radiotherapy	81	90	56	13.5 ± 5.1	0.726
Meek *et al.* [44]	Heterogeneous cancer—chemo-, radiation or transplant therapies	End of treatment	148	NR	NR	11.1 ± 5.0*	< 0.001
Visser and Smets [46]	Heterogeneous cancer—radiation therapy	2 weeks post-treatment	216	42	64	11.7 ± 5.9	0.015
Schneider [43]	Heterogeneous cancer—radiation/chemotherapy	Current treatment	54	78	60	13.1 ± 4.0	0.786
Palliative care							
Hagelin *et al.* [56]	Heterogeneous cancer—palliative care	On admission to clinic	229	60	68	16.8 ± 3.7*	< 0.001
Munch *et al.* [40]	Heterogeneous cancer—palliative care	On referral to clinic	130	42	62	17.0 ± 3.0*	< 0.001
Non-active treatment							
Holzner *et al.* [41]	Ovarian cancer—no active treatment	>3 months since treatment	98	100	57	9.4 ± 4.4*	< 0.001
Rüffer *et al.* [47]	Hodgkin's lymphoma —complete remission	Median 5.2 yrs since treatment	818	48	31	10.0 ± 4.7*	< 0.001
Mixed stages:							
Bartsch *et al.* [45]	Heterogeneous cancer —mixed stages	68% remission 8% part remission 10% progression 14% unclear	144	70	56	12.1 ± 4.3*	0.044

*Significantly different from mean scores for SSc patients ($n = 106$) at $P < 0.05$ using Bonferroni correction for family-wise error for each subgroup comparison.

Some studies linearly transformed the GFI score, to convert the 4–20 scale into a 0–100 scale. For those studies, we re-transformed the reported subscale score into the standard 4–20 scale. Data from the GFI have been published for general population samples [27, 28], for healthy non-patient groups [26, 29–35], and for multiple patient groups, including RA [36], SLE [37], AS [38], cancer [22, 26, 39–48], Parkinson's disease [49], multiple sclerosis [50], heart failure [31, 51], chronic fatigue syndrome [26, 52] and chronic lung disease [53]. Internal consistency reliability (Cronbach's α) for the GFI ranges from 0.74 to 0.93 [22, 26, 27, 29, 31, 35, 39, 43, 44, 52, 54]. Convergent validity is 0.77–0.79 with visual analogue fatigue scales [26, 36, 44], 0.78 with the Fatigue Severity Scale [50] and 0.84 with the Piper Fatigue Scale [55]. In addition to fatigue, depressive symptoms were measured in our SSc sample with the Center for Epidemiological Studies Depression Scale; pain with a numerical rating scale (0–10); and disability with the HAQ Disability Index.

Data analysis

In the table and text, mean ± S.D. are presented. GFI scores were compared using two-tailed *t*-tests based on published means and S.D. A Bonferroni correction was used to maintain the family-wise Type I error rate <0.05 within each set of comparisons (e.g. SSc *vs* general population studies, SSc *vs* studies of patients with rheumatic disease). Kendall's τ correlations were used to assess the bivariate association between demographic (age, gender, race/ethnicity), socioeconomic (education, marital status), medical (disease duration, diffuse/limited classification) and psychosocial variables (pain, depressive symptoms, disability) with fatigue.

Results

SSc sample characteristics

A total of 106 patients with lcSSc or dcSSc completed the MFI. The mean age was 55.5 ± 11.4 yrs; mean time since SSc diagnosis was 11.9 ± 7.9 yrs; 91.3% were females; 83.7% were non-Hispanic white; 67.9% were married; 67.9% completed at least some college; 73.6% had lcSSc; and 26.0% reported that they were disabled and unable to work. GFI total scores are shown in Table 1 for all patients, patients with diffuse disease and patients with limited disease. Patients with dcSSc scored higher than patients with lcSSc on the GFI, albeit not significantly so
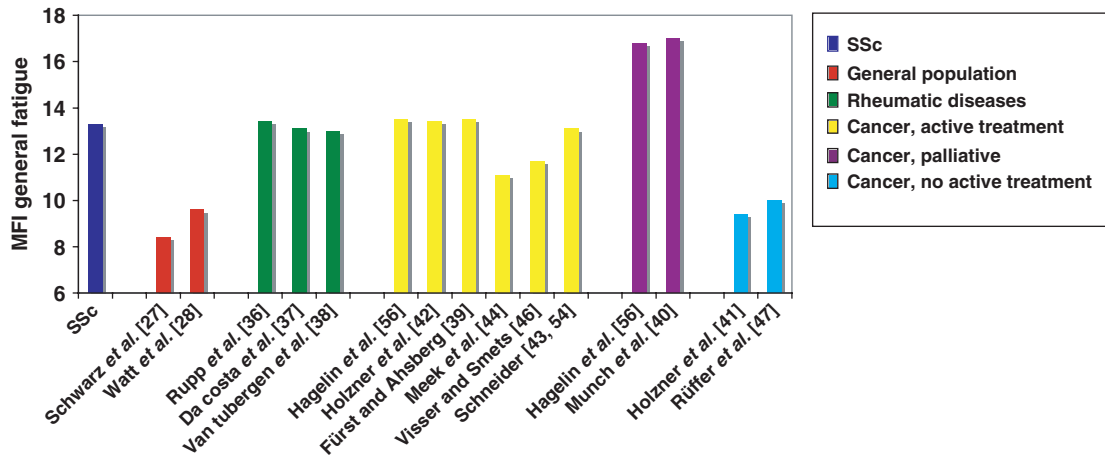
FIG. 1. General Fatigue Index scores for SSc and comparison samples.

($P = 0.494$). Female SSc patients had significantly higher fatigue scores than male patients ($\tau = 0.19$, $P = 0.024$), but no other demographic, socioeconomic or medical variables were related to fatigue. Patient ratings of pain ($\tau = 0.38$), depressive symptoms ($\tau = 0.36$) and disability ($\tau = 0.39$) were all significantly associated with fatigue ($P < 0.001$).

Search results

The search process identified 114 unique studies that used the MFI. Upon review, 99 articles were excluded, including 24 reports on patients without chronic illness, 43 on patients with chronic illness other than cancer or rheumatic disease, 10 with <50 patients, 18 that did not report GFI scores, two with duplicate data, one that only reported GFI scores for patients with high fatigue scores on another fatigue measure and one that reported scores only for patients who were selected for rehabilitation based on criteria that included fatigue.

Characteristics of studies reviewed are shown in Table 1. A total of 15 studies published from 1995 to 2007 were reviewed, including 12 studies from Europe [27, 28, 36, 38–42, 45–47, 56] and three studies from North America [37, 43, 44]. There were two studies on fatigue in the general population [27, 28] and three on patients with rheumatic disease, including RA [36], SLE [37] and AS [38]. There were 10 studies (11 separate cohorts) on patients with cancer [39–47, 56, 57], including six cohorts of patients in active treatment [39, 42–44, 46, 56], two that assessed fatigue post-treatment [41, 47], two of patients in palliative care [40, 56] and one that included patients in mixed stages, which was not classified as active, non-active or palliative care [45].

Comparison of SSc patients with selected cohorts

As shown in Fig. 1, there was a high level of consistency of GFI scores within patient groups. There were no significant differences (family-wise error, $P < 0.05$; Bonferroni adjustment) in mean GFI scores between cohorts within general population studies; rheumatic disease studies; non-active cancer treatment studies; or palliative cancer care studies. Of the six cohorts in the active cancer-treatment group, four had similar mean GFI scores (13.1–13.5) [39, 42, 43, 56], which were higher than in the other two studies (11.1 and 11.7) [44, 46].

Based on the GFI, the SSc sample reported significantly more fatigue than both the Danish and German general population samples [27, 28]. GFI scores for the SSc sample were significantly higher than all age groups in each population sample, including the oldest age groups of Danish subjects aged 70–79 yrs and German subjects aged >75 yrs (data not shown). There were no

significant differences between the SSc patients and samples of patients with other rheumatic diseases, including RA [36], SLE [37] and AS [38]. The SSc sample had significantly lower GFI scores than the two samples of cancer patients in palliative care [40, 56] and significantly higher scores than patients in remission [41, 47]. Compared with cancer patients in active treatment, the SSc patients had significantly higher scores than patients in one of the samples [44], but were not significantly different from the other five samples [39, 42, 43, 46, 56].

Discussion

This is the first study to report levels of fatigue among patients with SSc using a standardized fatigue assessment instrument. The levels of fatigue reported in SSc were significantly higher than in general population samples and similar to samples of patients with other rheumatic diseases identified through systematic review. Fatigue in SSc was similar to patients in active treatment for cancer, higher than remitted cancer patients and lower than cancer patients in palliative care.

Although patients with SSc identify fatigue as a highly debilitating problem [19, 20], it has been largely ignored in the assessment and intervention literatures. The development and testing of interventions to reduce fatigue in SSc and the viability of their application in clinical settings are dependent upon fatigue assessment. Types of assessment tools that would be useful for clinical and research purposes include structured interviews based on case-definition criteria, continuous measurement scales and brief screening tools. Case-definition criteria define consensual understandings of fixed criteria to identify patients with clinically significant conditions. Measurement scales are rating scales or questionnaires that facilitate research on aetiological factors, symptom impact or change. Brief screening tools are quick, easily administered instruments to identify patients likely to meet case-definition criteria with more extensive evaluation. Research in cancer has laid the groundwork to develop fatigue case-definition criteria [58] and case-definition criteria for cancer-related fatigue appear in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Clinical Modification (ICD-10-CM). Research in RA has identified a set of valid and reliable fatigue measurement scales based on rigorous evaluative standards [59], and recently the final plenary session of the Outcome Measures in Rheumatology Clinical Trials group (OMERACT 8) endorsed the proposal that fatigue should be measured in future studies of RA [60]. Finally, research on screening for fatigue in cancer and for major depression in primary care has shown that brief 1–3 question screening tools

can facilitate effective, low-burden case detection in clinical settings [61–63]. Similar methods should be used to develop case definition, continuous assessment and screening tools that can be applied in SSc with the goal of facilitating research on intervention and subsequent implementation in clinical settings.

Limitations that should be considered in this study include the relatively small sample of SSc patients from a single centre and the large proportion of patients with lcSSc, which may have lowered fatigue estimates. Due to the small sample, the predominance of patients with lcSSc, and the lack of available data on important disease aspects, such as a measure of physician-rated disease severity, assessment of factors related to fatigue in SSc was limited. In addition, for the comparative analyses, the limited number of studies in each disease group and varied patient characteristics within and across comparison groups did not allow for assessment across samples of factors, such as age and sex, that may influence fatigue [27].

In summary, the results demonstrate that fatigue is a significant problem for patients with SSc, similar in magnitude to fatigue among patients with heterogeneous types of cancer and other rheumatic diseases. Research is needed on assessment tools to accurately screen and measure fatigue in patients with SSc, which will then lead to the creation of interventions aimed at treating fatigue in SSc.

Rheumatology key messages

- Fatigue is largely ignored in SSc.
- Levels of fatigue in SSc are similar to levels of patients in active treatment for cancer, a group for which fatigue is recognized as an important problem that warrants assessment and intervention.

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