

Patient perception of disease burden in diffuse cutaneous systemic sclerosis

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Journal of Scleroderma and Related Disorders
2020, Vol. 5(1) 66–76
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DOI: 10.1177/2397198319866615
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Abstract

Purpose: Systemic sclerosis is a rare multi-organ autoimmune rheumatic disease, resulting in progressive fibrosis of the skin/internal organs. This study aimed to understand the impact of diffuse cutaneous systemic sclerosis symptoms and disease burden from the patient's perspective.

Methods: This was a mixed methodology, market research study involving ethnography, structured interviews, video diaries, and patient tasks. Patients had been diagnosed with diffuse cutaneous systemic sclerosis for ≥ 6 months and were recruited via healthcare professionals or patient associations (France, Italy, the United Kingdom, and the United States). Patients filmed short (~15 min) daily video diaries about their lives over 7 days and participated in ethnographic sessions, patient tasks, and structured video interviews. In Germany and Spain, patients participated in 60-min telephone interviews.

Results: Twenty-three patients (mean age: 54 years; 83% women; minimum disease duration: 6 months) participated in the study. Time to diagnosis was prolonged, as patients overlooked their symptoms and some healthcare professionals attributed symptoms to other causes. Patients rarely received additional information or support services at diagnosis. Importantly, although patients were aware of the seriousness of organ involvement, they reported that skin changes, pain, and fatigue impaired their ability to perform routine tasks. Patients had a high prescription treatment burden (mean: 10 tablets/day; up to >25 tablets/day) with additional non-prescription medication taken for other comorbidities. Treatment discontinuation was common due to side effects. Patients experienced diffuse cutaneous systemic sclerosis as a loss of independence and self-esteem. Moreover, patients tended to have small support networks, and emotional support services were not offered as standard care.

Conclusion: Patients with diffuse cutaneous systemic sclerosis had high treatment and disease burdens, with skin changes, pain, and fatigue profoundly affecting their lives. There is an unmet need for patient information at the time of diagnosis and emotional support services throughout the patient's journey with diffuse cutaneous systemic sclerosis. Based on the results of this study, we provide recommendations for improving diffuse cutaneous systemic sclerosis care.

Keywords

Ethnography, scleroderma, quality of life, dcSSc, systemic sclerosis

Date received: 12 March 2019; accepted: 6 July 2019

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Introduction

Systemic sclerosis (SSc) is a rare multi-organ autoimmune rheumatic disease, often resulting in progressive fibrosis of the skin and internal organs.¹ The prevalence of SSc varies widely both within and between countries,¹ affecting an estimated 240 people per million in the United States and 35 per million in the United Kingdom and Japan. SSc is classified into two subsets by the degree of skin involvement: diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc.² Complications of dcSSc include interstitial lung disease,^{3,4} pulmonary arterial hypertension,^{3,5,6} cardiac involvement,^{3,7,8} renal involvement,^{3,8} and gastrointestinal (GI) problems. The cause of death in patients with dcSSc is often related to lung and heart complications. Currently, no therapies are approved to prevent the progression of dcSSc; European League Against Rheumatism treatment guidelines recommend methotrexate or other immune-suppressive drugs only in early dcSSc and therapies to treat specific symptoms such as Raynaud's phenomenon,⁹ digital ulcers, and renal crisis.¹⁰ Tocilizumab has previously been evaluated in a phase II trial; however, the reduction in skin thickening was not statistically significant compared with placebo.¹¹

The physical and psychological effects of SSc can severely impact the daily lives of patients and their families.^{12–16} Many studies and trials have considered the quality of life (QoL) of patients with SSc; however, few have focused on the subset of patients with dcSSc, and those that have used standardized questionnaires as measurements of QoL.^{17–19} Such assessments typically focus on the physical and functional status of patients and do not evaluate how disease burden shapes their daily lives. Ethnography is a qualitative technique based primarily on patient observation, often complemented by interviews, with detailed analysis yielding insights into the impact of disease on patients' lives.^{20–24}

In this study, ethnography was used in combination with structured interviews, video diaries, and patient tasks to evaluate the impact of dcSSc symptoms on the daily lives of patients, to understand how patients view the disease, and to map the disease journey from the patient's perspective.

Methods

This research study was designed with input from all authors, in collaboration with the sponsor and an independent agency with extensive experience in qualitative market research in specialist medical indications (Blueprint Partnership, Manchester, UK). Recruitment, recording, data collection, and analysis were conducted by Blueprint Partnership, and all research materials were designed by this team (led by S.D.). The study was compliant with the legal and ethical healthcare market research guidelines of the British Healthcare Business Intelligence Association

and the code of conduct of the European Pharmaceutical Market Research Association.^{25,26}

Patient recruitment

Sampling was purposive; patients diagnosed with dcSSc for ≥ 6 months were recruited in six countries (France, Germany, Italy, Spain, the United Kingdom, and the United States) via healthcare professionals (HCPs) or patient associations. For patients recruited via their HCP, diagnosis was confirmed by the recruiting physician. For patients recruited via patient associations, photographic identification of the patient and a letter from the patient's hospital or physician confirming diagnosis of dcSSc were required. As the aim of the research was to focus in depth on qualitative information, there was no sample size calculation or data saturation. Five patients per country were felt to be an appropriate number for recruitment. All patients provided written informed consent before participation. Consent forms outlined the objectives and format of the research, and how the findings would be used. Detailed descriptions of the video-recording patient consent form and the patient briefing materials are included in the Supplementary Data.

Data collection and analysis

Data were collected from September to December 2014 and analyzed in January and February 2015. A mixed methodology was employed (Figure 1). Interviews were conducted in France, Italy, the United Kingdom, Germany, Spain, and the United States. In France, Italy, the United Kingdom, and the United States, patients participated in structured face-to-face interviews of a total duration of 165 min (in two sessions: the first 90 min and the second 75 min) with a native-language-speaking, experienced qualitative researcher (one per country) to explore key events within their disease journey (a description of the interview guide is included in the Supplementary Data). In some cases, the patient's caregiver (e.g. spouse) was also present during the interviews. Interviews were conducted by experts on ethnographic research. All interviewers were female. Details of the interviewers are provided in the "Acknowledgments" section. The discussion guide materials were piloted during initial interviews to test timings and to ensure that the line of questioning was appropriate and understood by patients. Following these initial interviews, the discussion guide was refined accordingly. The structured nature of the interviews limited the potential for bias and reflected the specific research goals identified by the researchers when developing the interview guide.

Ethnographic sessions lasting up to 175 min (in two sessions: the first 75 min and the second 100 min) were incorporated to increase the understanding of patient behaviors and to analyze how actual behaviors are compared with

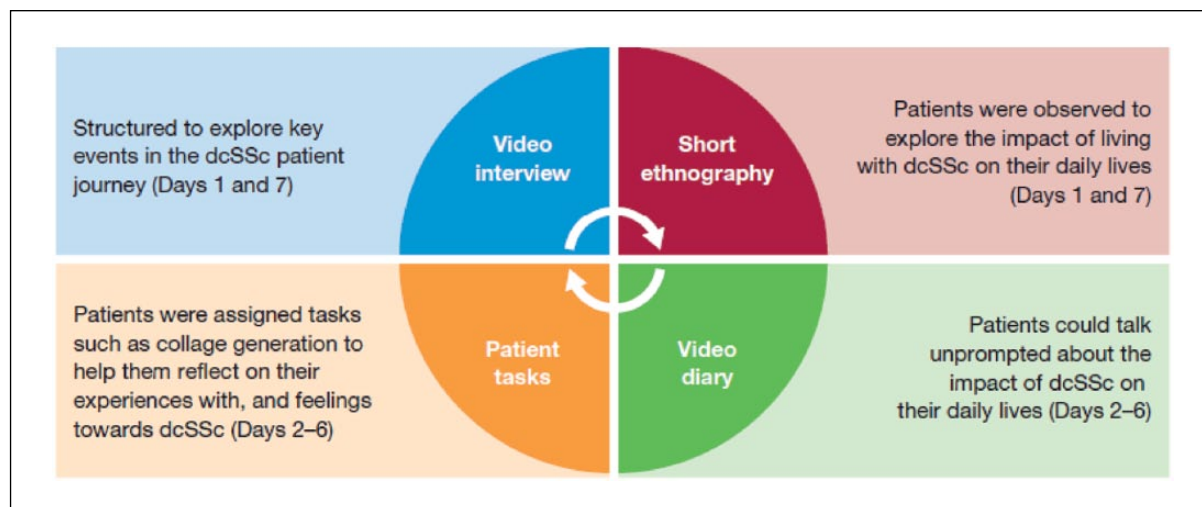


Figure 1. Methodology employed to evaluate the impact of dcSSc. No ethnography sessions were conducted in Germany and Spain. DcSSc: diffuse cutaneous systemic sclerosis.

reported behaviors. Patients were free to choose where the ethnographic sessions took place (e.g. at home, at work, or in the local area); these sessions were observed by an experienced ethnographer (one per country). Patients were also provided with a video camera to record video diaries and talk unprompted about the impact of dcSSc on their lives. Video diaries were a total duration of approximately 75 min (5×15 min), and no specific instructions were given to respondents about where they should complete their video diaries. Finally, patients were asked to complete tasks (90 min maximum; 3×15 –30 min) including drawings and collages to help them reflect on their current feelings toward dcSSc and their disease journey. In Germany and Spain, patients participated in 60-min telephone interviews (Supplementary Data) with a reduced discussion guide compared with that of the patients undergoing face-to-face interviews. No ethnography sessions were conducted in these countries because local market research guidelines and codes of conduct related to data protection laws do not allow for an ethnographic approach.

All the tasks took place over a 7-day period. No repeat interviews were carried out. No field notes were made; verbatim transcripts of all discussions with time codes were produced and, when appropriate, were translated into English by medical translators.

Data analysis and preliminary interpretation were conducted by the Blueprint research team. Three experienced ethnographers immersed themselves in the research data through observation of recorded behaviors and review of the verbatim transcripts. Information from the footage and transcripts was categorized and assessed for themes, patterns, and indicators of emotion, ambivalence, and conflict. One member of the team read the transcripts for each country, and a five-step analysis process (adapted

from Ereaut²⁷) was adopted: (1) The research team met before starting the analysis to agree the analysis framework and to ensure consistent focus on the anticipated key themes. (2) Transcripts were reviewed, and content analysis was conducted. Additional themes that had not been anticipated in Step 1 were also recorded. (3) Each researcher grouped and clustered the findings for their country to reveal key themes and postulated findings. (4) The research team came together to discuss and interpret their overall findings, identifying patterns that emerged, and similarities and differences between respondents and countries. (5) The team worked together in a hermeneutic process of questioning their data and arriving at answers to achieve an overall perspective on their research findings. Data coding was not applied, and no data management software was used.

Patient involvement

Patients were not contacted by the researchers before commencement of the interviews. Patients were not involved in the design, recruitment, or conduct of the study. Interview transcripts were not shared with participants and they did not provide feedback on the findings.

Results

Patient demographics and data collection

In total, 23 patients from 6 countries were enrolled. Patients were recruited via HCP referral ($n=19$), patient associations ($n=3$), and advertisement ($n=1$; recruited from a database to which their physician had previously contributed information supporting the diagnosis of dcSSc). Mean

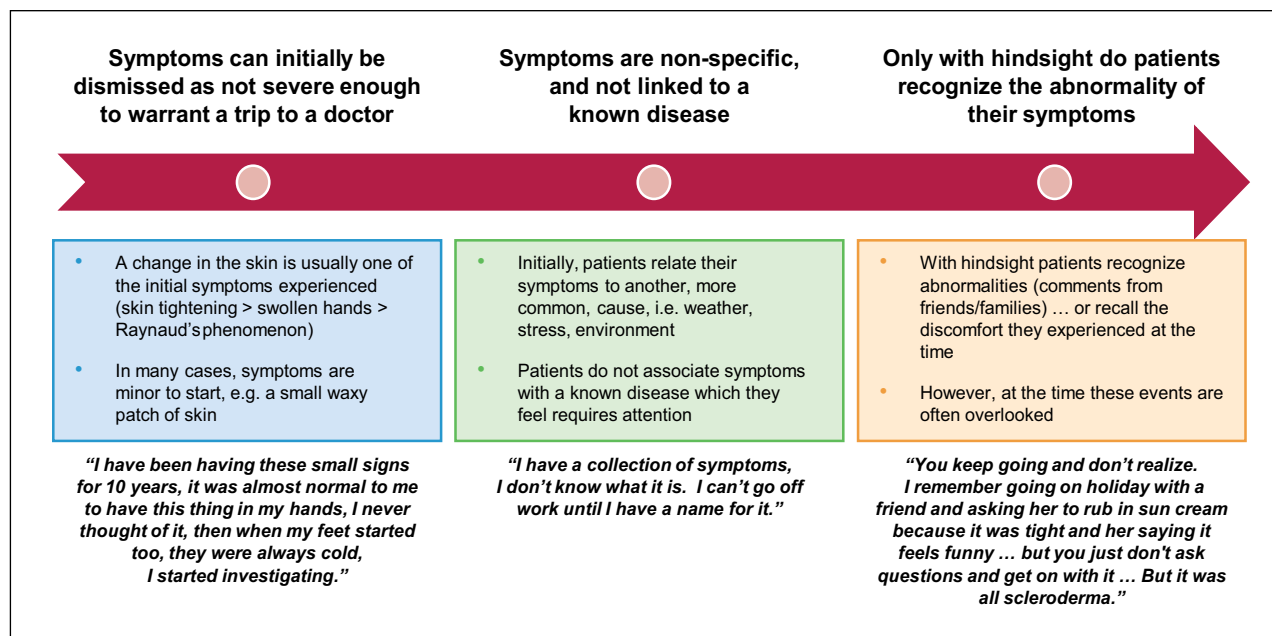


Figure 2. Patients' descriptions of their initial diffuse cutaneous systemic sclerosis symptoms, lack of awareness, and disease progression.

patient age was 54 years, 39% (n=9) were aged 29–49 years, 26% (n=6) 50–59 years, 26% (n=6) 60–69 years, and 9% (n=2) ≥ 70 years. Most patients were female (n=19; 83%) and had been diagnosed for >3 years (n=19; 83%). Seven patients (30%) included in the study were members of patient associations. Of the 23 patients enrolled in the study, 1 patient failed to complete the study due to severe health problems.

Diagnosis

In many cases, initial symptoms were minor, for example, a small patch of waxy skin. Patients tended to overlook their symptoms and did not associate them with a known disease that they felt required attention, thereby leading to delayed presentation (Figure 2). Only in hindsight did patients recognize the abnormality of their symptoms. Patients tended to present to HCPs as a result of prolongation or an increase in symptoms. The most common presenting symptoms recalled by patients were Raynaud's phenomenon (n=9), swelling of the hands and feet (n=6), and joint pain (n=6).

Most patients presented to primary HCPs, who in some cases attributed symptoms to other causes, for example, detergent allergy, stress, hormonal changes, arthritis, or venous insufficiency. Some patients were referred to the correct specialist (rheumatologist, internal medicine specialist (in France), or dermatologist) and a diagnosis was made quickly. However, others reported being "passed around" and seeing five or more HCPs. Therefore, the time to diagnosis was highly variable. Patients reported feeling

frustrated if they did not reach the appropriate specialist quickly and their diagnosis was delayed.

The initial reaction of patients to diagnosis was one of relief and freedom from uncertainty as to the cause of their symptoms. However, patients were often unprepared for the diagnosis as it was more serious than they anticipated, particularly if they had overlooked their initial symptoms. Some patients became depressed and, as they accepted the implications of the disease, began to grieve for their previous life. Many patients did not have a good understanding of their condition at diagnosis. Most patients received information about dcSSc via a combination of leaflets and verbal explanation from HCPs. However, the information provided was often limited and/or generalized, leaving patients without a good understanding of dcSSc. Of the 23 patients enrolled in the study, only 2 (9%) mentioned attending patient education conferences. Patients and families often tried to increase their understanding by research on the Internet; however, with no guidance on where to look, this often resulted in finding information that focused on worst-case scenarios.

Treatment

Patients with dcSSc had a high prescription treatment burden (mean: 10 tablets/day), with some patients taking >25 tablets/day. In addition to their prescribed dcSSc medication, patients often took vitamins, over-the-counter analgesics, and medication for other comorbidities. Patients generally claimed to be compliant with medication, although some would make conscious decisions to miss

doses. Side effects were common, often resulting in treatment discontinuation and the feeling that all treatment options had been exhausted. Various medications were described as having problematic side effects; the most frequently mentioned included iloprost, mycophenolate mofetil, and methotrexate. Frequently, patients did not “struggle through” if they experienced side effects; instead they discontinued treatment, making a conscious decision to prioritize their QoL. Patients had a low awareness of treatments in development (e.g. clinical trials) and sometimes used or considered massage, physiotherapy, acupuncture, hot wax, and other alternative or “natural” therapies. Many patients described these treatments as effective and would like HCPs to advocate alternative therapies to enable their earlier and more widespread use.

Follow-up

Most patients had a good relationship with their HCPs and considered that their doctors were making the correct decisions for their well-being. However, patients from the United Kingdom were hesitant to visit local hospitals, instead preferring specialist centers. Patients managed by multidisciplinary teams appreciated the expertise of the different specialists but would have preferred better coordination of clinics to avoid multiple trips to various specialists. Patients found follow-up appointments to be logistically, physically, and emotionally demanding, although they were recognized as a necessity. Traveling long distances to attend follow-up visits led to logistical problems, particularly for patients without a full-time caregiver. Fatigue, exhaustion, and physical limitations meant that a follow-up appointment could be the only activity patients were able to accomplish on that day. In patients with more severe symptoms, an appointment could result in fatigue for several days. Follow-up appointments also led to feelings of anxiety, as patients feared disease progression. Some patients found it traumatic to see others with more severe symptoms, such as patients in wheelchairs, patients receiving oxygen, or those with visible amputations or skin changes.

Impact of dcSSc on the patient's daily life

Skin symptoms. Patients reported that dcSSc-associated skin complications impacted their daily lives including pruritus, neuropathy, increased sensitivity to touch (allodynia), skin thickening and tightening, calcinosis, Raynaud's phenomenon (with subsequent burning), and digital ulcers. Skin tightening around the mouth caused problems with eating and dental hygiene. Patients reported being unable to recognize themselves because of skin tightening on the face, leading to low self-esteem, social withdrawal, and depression (Figure 3). Skin changes required an extensive regimen of moisturizing to maintain

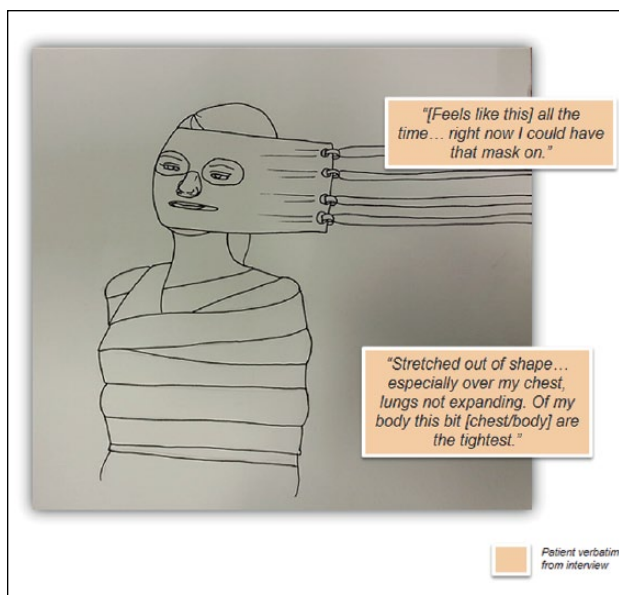


Figure 3. A patient's illustration depicting their experience of skin symptoms of diffuse cutaneous systemic sclerosis.

skin comfort. Creams and lotions were used by nearly all patients to maintain elasticity, prevent tightness or dryness, and prevent the formation of digital ulcers. Patients applied lotions multiple times throughout the day, particularly after contact with water.

Episodes of Raynaud's phenomenon are associated with the development of painful digital ulcers in patients with dcSSc²⁸ and were of great concern to them. Episodes were common in colder temperatures and patients actively avoided the cold. Digital ulcers were described as excruciatingly painful and took extended time to heal (6 months to 1 year). Furthermore, digital ulcers severely limited the ability of patients to conduct daily activities, such as driving, dressing, and carrying objects, and led to a reliance on others. Complications were reported in some patients, including infections, gangrene, and in some cases, amputations of the whole finger or removal of fingernails (n=3). Patients, therefore, actively tried to avoid development of digital ulcers with massage and moisturizers and ensured effective management of existing ulcers by wearing gloves to avoid trauma or infection, and to limit pain.

Non-skin symptoms. The most commonly experienced symptoms within the patient sample were pain, joint problems, fatigue, and GI complications. Patients reported problems in all the major joints including shoulders, elbows, hips, knees, ankles, and neck, causing severe pain. Joint pain affected patients' ability to sit or stand comfortably. Anticipatory anxiety about future tasks due to joint pain was common, further limiting patient movement. Patients' ability to rest and sleep properly was also affected by joint pain. Some patients had organ



Figure 4. Representative examples of how patients described the emotional burden caused by symptoms of diffuse cutaneous systemic sclerosis.

Examples were selected by the qualitative researchers.

complications including pulmonary fibrosis (n=6), cardiac complications (n=4), pulmonary hypertension (n=3), and renal involvement (n=3). Although patients recognized the seriousness of organ involvement, they stated that it was fatigue and pain alongside their skin complications that restricted their daily activity. Lung problems could further exacerbate the reduced activity levels of some patients but were not the primary contributor in this sample. GI complications were typically well managed and, therefore, were not the most concerning for patients; however, in some patients, gastroesophageal reflux impaired enjoyment of food and disturbed sleep.

Interviews with patients suggested that pain management is a key component of dcSSc care and patients were typically receiving multiple medications for pain (including tablets, topical gels, and transcutaneous patches), which could necessitate the involvement of a pain management team. Medication helped to alleviate pain; however, it was by no means eradicated and patients continued to experience daily pain. There were concerns regarding dependency on and tolerance of pain medications, leading to increased dosages. Some patients considered surgical procedures to reduce pain, such as joint fusions or lumbar sympathetic nerve blocks.

Fatigue occurred early in the course of dcSSc and represented a continuous, debilitating burden. Patients spent much of the day sleeping, leading to a perceived loss of the day and time wasted. Patients needed to recuperate for several days after activity, leading to loss of spontaneity and excessive planning for simple activities.

Effect of dcSSc on patient outlook

Patients experienced a series of losses throughout their disease journey, representing a large emotional burden (Figure 4) and were acutely aware at all times of their physical limitations, leading to feelings of inadequacy, depression, and social withdrawal (Figure 5). The unpredictability of dcSSc made the patient journey and acceptance of the condition difficult. Premature retirement from work was common in patients with dcSSc, and patients who were informed they would not return to work often felt a diminished hope of recovery.

Patients tended to have small support networks, driving a sense of isolation. Friends and family struggled to comprehend the seriousness of the disease. Furthermore, patients relied on partners or children as care providers, leading to changes in their relationships. Emotional support services were not offered by HCPs as part of standard care, and most support services (e.g. therapists, support groups, and patient associations) were identified by patients themselves. Patients in the United Kingdom and the United States tended to be more involved in patient societies and online communities than those in France, Germany, Italy, and Spain.

Discussion

This study reports a number of important initial findings, including patients' high treatment and emotional burdens, the profound impact on patients' daily lives of pain, fatigue, and skin and Raynaud's phenomenon complications, and

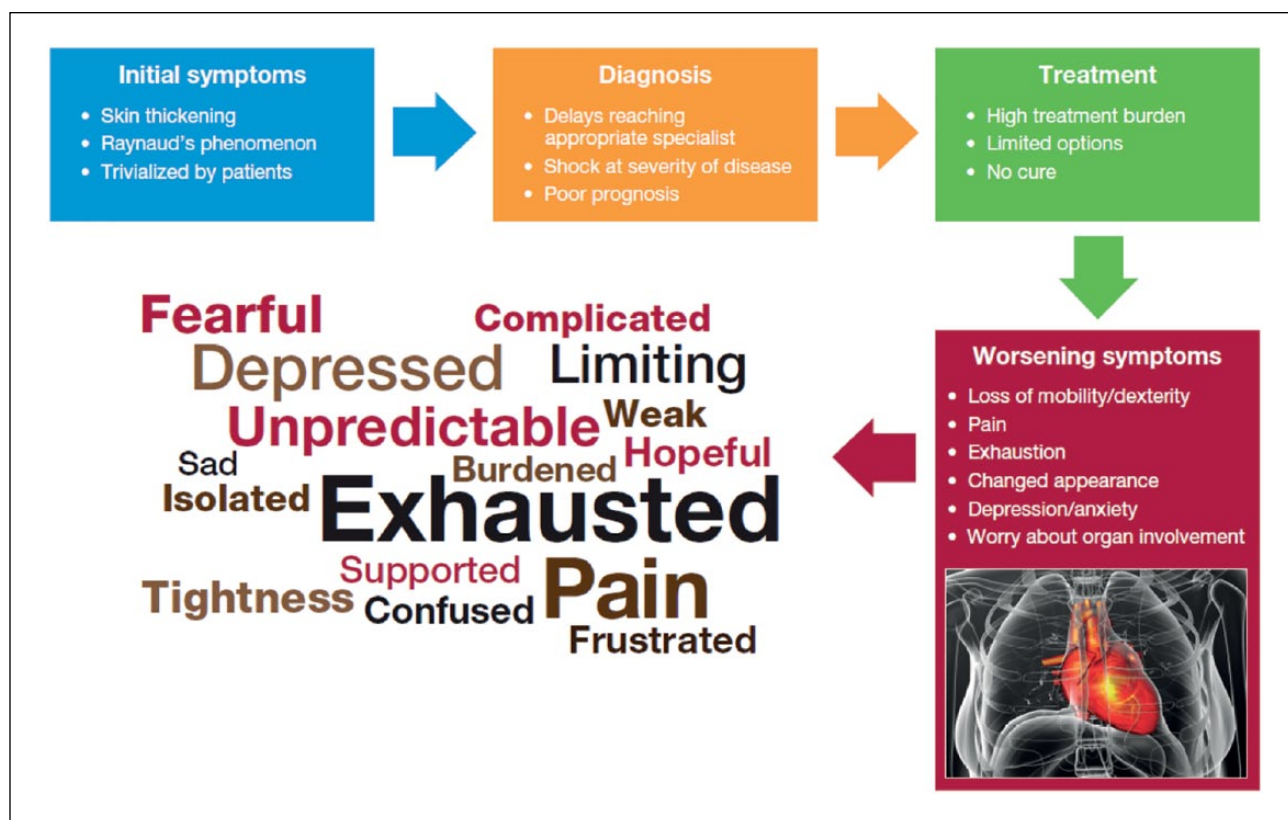


Figure 5. Patient journey with dcSSc from initial symptoms to progressive disease.

Word cloud generated from words spontaneously associated with dcSSc in patients' diaries ($n = 16$) and those selected from a pre-generated list during telephone interviews ($n = 6$). Only words mentioned more than once are included in the word cloud; size of word is related to the frequency of mentions.

DcSSc: diffuse cutaneous systemic sclerosis.

the need for information and emotional support services for patients with dcSSc throughout their disease course. Patients with dcSSc described a state of continual loss during their disease journey and many said their lives were no longer recognizable.

In common with other ethnographic studies,^{29,30} strict sampling procedures (e.g. ensuring geographical and ethnic diversity of referring physicians and patients) were not applied due to the laborious and time-consuming nature of this type of study. Recruitment can be challenging³¹ and sample sizes were necessarily small, resulting in a limited number of patients from different countries. Additional limitations include that the study only included patients who were willing to talk at length about their condition, and patients who participated were based in Europe and the United States. There may also be a potential recall bias as the study included a large proportion (83%) of patients with intermediate-stage dcSSc, who had experienced symptoms for more than 3 years. These patients may have developed coping skills, unlike newly diagnosed patients, that could have affected the reporting of symptoms at onset. Furthermore, due to local research guidelines and codes of conduct pertaining to

data protection laws, patients in Germany and Spain were not asked to provide as much detail as those in the other countries. It should also be noted that, although the interviewers and moderators who conducted the interviews and ethnographic research were highly experienced in qualitative research, they had no specific medical or clinical qualifications related to SSc. Finally, no repeated analysis or assessments of inter-rater reliability were conducted. However, the strength of the study is that all patients had their diagnosis confirmed before enrollment, and piloting of the discussion guides allowed refinement of the questions to ensure comprehension by all participants. The structured nature of the surveys also limited the potential for questioning bias.

Patients living with dcSSc often experience delays in their diagnosis or misdiagnosis due to poor awareness of the disease by HCPs.^{32–35} Delays in diagnosis and treatment can result in disease progression due to irreversible end-organ damage and can increase patient anxiety.^{32,34,36,37} In this study, time to diagnosis from first symptoms was highly variable, and many patients reported frustration at multiple referrals before final diagnosis. Late diagnosis may also be attributed to patients trivializing symptoms

and postponing visits to primary HCPs; indeed, we observed that many patients in this study had overlooked their initial symptoms.

Acceptance of the diagnosis is a further emotional challenge for many patients; although some patients felt a sense of relief, others reported experiencing shock followed by depression. As highlighted here, and consistent with findings from other qualitative studies of SSc,^{33,38–40} this situation is often made worse by a lack of access to practical information and poor provision of emotional support. Participants in our study reported that, in general, HCPs did not discuss the emotional consequences of dcSSc, nor did they actively refer patients to support services or patient associations. Interestingly, in a survey of patients with SSc, participants did not always ask for counseling and were not sure what counseling should focus on, emphasizing the limited understanding of the disease.⁴⁰ In our study, many patients and their families attempted to increase their understanding of the condition through research on the Internet, although this often created more anxiety and uncertainty, a finding also reported previously.⁴⁰

The finding that skin complications, Raynaud's phenomenon, pain, and fatigue have a profound impact on the QoL and emotional well-being of patients with dcSSc is also in agreement with previous studies.^{9,18,33,39–46} Our patients recognized the seriousness of the organ-related symptoms of dcSSc (particularly cardiac and pulmonary) but felt that these were not the most bothersome complications of the disease on a daily basis. The social impact of physical manifestations is likely to be a key component of a patient's perception of impact, often leading to feelings of embarrassment and withdrawal.

The lack of a cure and need for lifelong treatment, specialist referral, and follow-up visits also impose emotional burden and frustration on patients.³³ Existing treatment regimens are burdensome, have significant side effects, and offer limited perceived benefits to patients, highlighting an unmet need for new treatments. Our interviews highlighted pain management as a key component of dcSSc care. Interestingly, in a qualitative survey by Mouthon et al.,⁴⁰ patients with SSc commented that pain and fatigue were specific issues that they felt were insufficiently addressed by physicians.

The feeling of continual loss experienced by the participants in our study was not unexpected, as depression, anxiety, and anger are common emotions in patients with SSc, with 20%–80% of patients experiencing mild-to-severe psychological distress.^{12,33,38,40,44,47,48} Several studies report reliance on family and/or social support.^{38,40,44} This was also evidenced in the current study; many patients claimed to be heavily reliant on family or external support as care providers. Although the ability to cope with SSc is reported to be greater among patients who have sustained social support,⁴⁴ reliance on family and friends can be challenging

and, as demonstrated in our study, puts a strain on relationships. An important finding from this study is the lack of emotional support services provided for patients with dcSSc. Rather than being offered as a standard of care by HCPs, support services were typically sought by patients themselves. Implementing online support groups may be an economical and effective option for delivering support for patients with dcSSc.⁴⁹

These preliminary findings highlight the need for further research in this area to fully understand the impact of dcSSc on the lives of patients and their families. Based on the outcomes of this study and previous observations from traditional research based on patient-reported outcomes (PROs),¹⁷ we suggest the following actionable recommendations for physicians treating patients with dcSSc:

1. Increased awareness among primary HCPs, leading to increased referral to appropriate specialists, may assist in achieving an earlier diagnosis.
2. Treating physicians should provide overall education about the disease and increase their focus on skin and Raynaud's phenomenon complications, as patients report these symptoms significantly affect their QoL. Improvement of QoL in patients with dcSSc should be a priority objective for HCPs.
3. Physicians should incorporate PRO measures into routine care to provide information on the impact of skin complications, Raynaud's phenomenon, pain, and fatigue, as well as symptoms that traditionally concern physicians, such as organ involvement.
4. Although validated PRO instruments exist, such as the Health Assessment Questionnaire–Disability Index⁵⁰ and University of California, Los Angeles, Scleroderma Clinical Trials Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0) instrument,⁵¹ there is currently no global PRO instrument that captures symptoms and their impact specifically in patients with dcSSc. New, clinically validated tools are required that can effectively capture the complex health problems experienced by patients with this condition.
5. Patients may benefit from structured patient education, referral to patient groups, websites (scleroderma.org, fesca-scleroderma.eu, and sruk.co.uk), and emotional support services at diagnosis and throughout their journey with dcSSc.
6. Referral to multidisciplinary teams including physical therapy, occupational therapy, and massage therapy may be helpful to patients with dcSSc; however, the beneficial effects of these treatments have not yet been confirmed by clinical trials.

Acknowledgments

The authors thank the patients and patient recruiters who participated in this study. The authors also thank the interviewers: Janine

Lerat (senior recruiter and moderator; France), Sonia Icovino (moderator; Italy), Tessa Higgins (market research consultant; UK), Kelly Adell (moderator and researcher; USA), Taraneh Bahij (researcher; Germany), and Eva Calbet (moderator; Spain). Editorial assistance was provided by Adelphi Communications Ltd (Bollington, UK), supported by Bayer AG.

Author contributions

B.H., S.D., and J.d.O.P. were involved in study conception and design, and analysis of the data. All authors contributed to the interpretation of the data and preparation of the manuscript, and approved the final version for publication.

Data sharing statement

The authors were able to make research materials available to view by a third party, which include recruitment screeners and discussion guides. These extra materials are available by emailing B.H. (barbara.hinzmann@bayer.com). The authors were not able to share the transcripts of the research interviews as the research participants consented that their ethnographic footage would not enter the public domain and would only be used in communicating the research findings to Bayer AG. There may be occasions whereby a third party could audit the footage to assess findings, but this would have to be arranged under clearly defined guidelines.


Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: D.K. consults for Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Cytari, CSL Behring, EMD Merck-Serono, Genentech/Roche, GlaxoSmithKline, Genkyotex, Sanofi-Aventis, UCB, Actelion, and Gilead; has stock options in Eicos Sciences; and has received research grants from National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health/National Institute of Allergy and Infectious Diseases, Bayer, Bristol-Myers Squibb, and Pfizer. Y.A. consults for Actelion, Bayer, Roche/Genentech, Inventiva, Medac, Pfizer, Sanofi, Servier, and UCB; and has received research grants from Bristol-Myers Squibb, Roche/Genentech, Inventiva, Pfizer, Sanofi, and Servier. C.P.D. consults for Bayer, Roche, GlaxoSmithKline, Actelion, Inventiva, CSL Behring, Takeda, Merck-Serono, MedImmune, and Biogen; and has received research grants from Actelion, GlaxoSmithKline, Novartis, and CSL Behring. M.M.-C. consults for Actelion, GlaxoSmithKline, Pfizer, and Bristol-Myers Squibb. J.P. consults for and/or has research grants with Actelion, Bayer, BMS Merck, Pfizer, and Roche. B.H. is an employee of Bayer AG. S.D. is an employee of Blueprint Partnership. J.d.O.P. has been an employee of Bayer US LLC. O.D. has been a consultant for Genentech/Roche, 4D Science GmbH, Actelion, Active Biotech, Bayer, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, EpiPharm, Ergonex, espeRare Foundation, GlaxoSmithKline, Inventiva, Lilly, Mitsubishi Tanabe, Medac, MedImmune, Pfizer, Pharmacyclics, Serodapharm, and Sinoxa; and has received research funding from Actelion, Bayer, Boehringer Ingelheim, Ergonex, Pfizer, and Sanofi. O.D. has a patent for mir-29 for the treatment of systemic sclerosis.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by Bayer AG (Berlin, Germany) and carried out by Blueprint Partnership (Manchester, UK).

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Supplemental material

Supplemental material for this article is available online.

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