Objective: An important barrier in the study of systemic sclerosis (SSc) is the difficulty in measuring disease activity. We reviewed the literature on currently available global measures of disease activity in SSc.

Methods: The PubMed database (1950-2006) was searched for the key words “scleroderma” in conjunction with “disease activity” and then “disease severity.” All relevant original and review articles in English and French were reviewed. Textbooks in rheumatology and pertinent secondary references were also reviewed.

Results: There are currently 3 tools that are used to measure disease activity globally in SSc. Physician global assessments have been commonly used but have not been formally evaluated. The Valentini Disease Activity Index is a new measure that consists of 10 variables and a resulting score ranging from 0 to 10. It appears easy to use but lacks some face and content validity and responsiveness to change has yet to be demonstrated. The Medsger Disease Severity Scale measures disease severity in 9 organ systems. However, it assesses mostly damage and is difficult to score.

Conclusions: There is currently no gold standard measure of disease activity in SSc. Given the need to measure disease activity in SSc and the limitations of the currently available instruments, efforts are ongoing to develop new ones. This represents a major challenge but one that remains particularly important to undertake.

© 2007 Elsevier Inc. All rights reserved. Semin Arthritis Rheum 37:93-98

Keywords: disease activity, scleroderma, outcome measures, review

Systemic sclerosis (SSc) is a chronic, multisystem disorder characterized by thickening and fibrosis of the skin and internal organs (1,2). It affects mainly women (3,4) in the prime of their life (3,4) and is associated with significant morbidity, including pain, disability, depression (5,6), and reduced quality of life (7,8), increased mortality (relative survival as low as 35% at 20 years, compared with age-, sex-, and race-matched individuals) (9) and high costs (10). Although it is a heterogeneous disorder, 2 common clinical subsets are recognized in terms of skin involvement, either limited (skin involvement distal to the elbows and knees) or diffuse (skin involvement proximal to the elbows and knees in addition to the trunk) (11). SSc is thought to affect over 16,000 Canadians and up to 100,000 Americans (12-16). There is currently no known cure (17).

An important barrier in the study of SSc has been and continues to be the difficulty in measuring disease activity (18-20). Disease activity (20-23) usually measures the aspect of disease that varies over time and is potentially reversible spontaneously or under drug treatment. This is in contradistinction to disease damage and severity. Damage measures irreversible tissue injury that results from disease (20-23). Disease severity lacks an accepted definition (21). Some (24,25) use it as a modifier of activity and incorporate it into ratings of activity (does the disease manifestation require treatment, does it impose functional limitations). Some (21) equate it to a measure of prognosis. Others (22) take it to represent the total effect of disease on organ function at a given point in time, including both reversible (activity) and irreversible components (damage).
Measuring disease activity in SSc has been particularly difficult, especially compared with diseases such as systemic lupus erythematosus and rheumatoid arthritis that are characterized by episodes of inflammation, such as synovitis, pleuritis, dermatitis, and nephritis, that can be easily differentiated from quiescent phases (20,23). The difficulty arises from several facts, as follows:

- First, many patients, especially those with limited skin involvement, have an indolent course without clear signs of inflammation (20,23).
- Second, from a laboratory point of view, only a few acute phase proteins are elevated in patients with early SSc (26), albeit in small studies, leading some to argue that patients with SSc may have an impaired acute phase response (19).
- Third, the clinical features of SSc are attributable to vascular and connective tissue fibrosis that is more difficult to appreciate and quantitate than inflammation (20) and, when it becomes measurable, has often progressed to permanent damage.

Indeed, Clements noted more than a decade ago that we have failed to measure activity in SSc in large part due to the fact that we have relied on measures of organ dysfunction, such as serum creatinine, forced vital capacity, left ventricular ejection fraction, and lower esophageal sphincter pressure, that reflect damage and severity rather than activity (18). He suggested that true activity in SSc should be that which is abnormal when the disease is worsening and then normalizes as the disease quiets. He identified several clinical (increasing skin score, inflammatory foci in skin, joint tenderness count, ground-glass changes on high resolution computed tomography of the chest) and laboratory (von Willebrand factor VIII antigen, various cytokines, and other soluble protein markers) variables that follow this pattern.

As it still stands, there is no “gold standard” measure of disease activity in SSc. However, in recent years, some global measures of disease activity in SSc have been proposed and are increasingly being used. We therefore undertook a review of these instruments and identified their relative strengths and limitations.

**METHODS**

The PubMed database (1950-2006) was searched for the keywords “scleroderma” in conjunction with “disease activity” and then “disease severity.” All relevant original and review articles in English and French were examined. Textbooks in rheumatology and pertinent secondary references, including meeting abstracts, were also reviewed.

**RESULTS**

**Physician Global Assessments**

In SSc, as in most rheumatic diseases, disease activity may be manifested in various organs and measured using organ-specific measures (27). However, a measure that pools several findings of activity and creates a composite result is a common method of handling the variability of different findings in various body systems (21). The physician global assessment is the simplest form of a composite measure to assess disease activity. In the absence of a gold standard, the physician global assessment is often used as the next best thing to determine disease activity (21).

Physician global assessments of disease activity have often been used in SSc (20,28-30). However, these have not been formally evaluated. In the study of the construct validity of the Valentini Disease Activity Index that will be discussed shortly, the level of agreement in the assessment of disease activity among 4 SSc experts was low (lowest reported correlation coefficient r = 0.428, P, not significant) (31). Thus, although this was not the main purpose of the study, the validity of physician global assessments of disease activity in SSc remains to be demonstrated.

An alternative way of creating a single measure of disease activity is to develop an index consisting of a number of disease variables appropriately selected and weighted. Such disease activity indices exist in a number of rheumatic diseases (32,33) and there are 2 such indices currently available in SSc.

**Valentini Disease Activity Index**

In 2001, the European Scleroderma Study Group (ESSG) developed preliminary disease activity indices to be used in patients with SSc (34,35). Investigators from 19 European centers in 11 countries completed an extensive, 88-item, standardized chart for each of 290 consecutive patients with either diffuse or limited SSc. Three experts blindly evaluated each chart and, by consensus, assigned a disease activity score to each chart on a scale of 0 to 10. This constituted the “gold standard.” Univariate analysis was used to select individual items in the charts that correlated with the gold standard. Multiple linear regression analyses were performed to evaluate the combined performance of different sets of variables in predicting the gold standard and to define the relative weight of each variable. Three separate weighted 10-point indices of disease activity were constructed, 1 for the group as a whole and 1 for each of the subsets with either diffuse or limited disease.

The construct validity of the 3 preliminary indices was assessed in a subsequent report (31). The charts from a random subset of 30 of the original 290 patients were selected. Four clinical experts were asked to rank the charts from least active to most active. The disease activity index scores of each patient were calculated and compared with the ranks given by each expert, separately. The activity index scores obtained using the whole series index correlated well with the ranks given by the 4 experts (r ranging from 0.530 to 0.712, all P values <0.003). However, some of the correlations between the scores obtained using the index.
indices of the subsets of patients with diffuse and limited disease only were low (lowest $r 0.357$, $P$, not significant). Thus, based on the authors’ own conclusions, and accepted standards that correlation coefficients $> 0.5$ represent strong correlations (36), only the index for the whole cohort and not the indices for the disease subsets was judged to be valid.

The Valentini Disease Activity Index for all patients with SSc (Table 1) was adopted by the ESSG and the Scleroderma Clinical Trials Consortium at a symposium held in 2002 (23,37). It consists of 10 variables with weights ranging from 0.5 to 2.0 and resulting in a total score ranging from 0 to 10. This index appears simple and easy to use and is now increasingly being used in research settings (7,38-40). This attests to the need to have a measure of disease activity in SSc.

Despite the major advance that the Valentini Disease Activity Index for SSc represents, there are issues that require further study:

1. The cohort used to develop the index had longstanding disease. However, SSc often progresses rapidly within the first 2 to 4 years of onset and slows or stabilizes thereafter (41,42). Thus, the index needs to be studied in patients with early onset disease, before damage has occurred (18).

2. The development of the index was hampered by a high number of missing values and a high degree of variability among centers in the reported frequency of various disease manifestations. Although this could be due to true geographic differences in prevalence of different disease manifestations, it may also reflect a lack of consistency and reliability in the clinical assessment of patients with SSc. In the end, the investigators appropriately excluded from the analysis items that were either missing or reported differently in the various centers. However, in so doing, they were forced to exclude several items that prima facie could be related to disease activity, such as alveolitis (43). In the future, issues of missing data and reliability need to be considered.

3. Certain items included in the index lack face validity. For example, hypocomplementemia is retained as an element of disease activity but this does not seem intuitively appropriate as complement fixation is not commonly thought to be important in SSc.

4. Three items in the index relate to change, namely change in skin, vascular and cardiopulmonary symptoms in the past month. Such change items in activity indices are problematic because they fail to capture persistent activity (20). Others have addressed how to capture persistent disease activity in similar diseases, namely systemic lupus erythematosus (44), and this needs to be considered in SSc.

5. Responsiveness to change of the index has yet to be assessed.

### Medsger Disease Severity Scale

As previously mentioned, disease severity is defined by some as the sum of both reversible (activity) and irreversible (damage) components of disease at any given time (22). Using this definition, there are few scales to measure disease severity, either in an individual organ system or globally in SSc (22,45,46). Although it has not been widely tested, the scale developed by Medsger and the International SSc Study Group (Table 2) (22,47) has emerged as the most frequently used (6,20,42). It assesses disease involvement in 9 organ systems, namely, general health, peripheral vascular, skin, joint/tendon, muscle, gastrointestinal tract, lungs, heart, and kidneys. Each organ system is scored separately from 0 to 4, depending on whether there is no, mild, moderate, severe, or end-stage involvement.

This severity scale has limitations as a measure of disease activity. First, although the stated objective of the severity scale was to include components of activity and damage, in preparing the final scale, the variables felt to represent disease activity (eg, sedimentation rate, tendon friction rubs, creatinine kinase, diastolic blood pressure) were excluded. Second, as it stands, the scale results in 9 separate severity scores, 1 for each organ assessed, rather than an overall score. Thus, this scale is not easy to use. The absence of an overall score is a limitation that the authors of the scale specifically acknowledged (22). Finally, its responsiveness to change is unknown.

### DISCUSSION

Given the need to measure disease activity in SSc and given the limitations of the available instruments, work is ongoing to develop new ones. The Canadian Scleroderma Research Group (CSRG) is a unique consortium of the major Canadian stakeholders in SSc research, including rheumatologist, basic scientists, and patient representatives, who have established a multicentered registry to recruit large numbers of patients for longitudinal studies.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rodnan skin score $&gt;14$</td>
<td>1.0</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>0.5</td>
</tr>
<tr>
<td>Change in skin symptoms in the last month*</td>
<td>2.0</td>
</tr>
<tr>
<td>Digital necrosis</td>
<td>0.5</td>
</tr>
<tr>
<td>Change in vascular symptoms in the last month*</td>
<td>0.5</td>
</tr>
<tr>
<td>Arthritis</td>
<td>0.5</td>
</tr>
<tr>
<td>Lung diffusion capacity $&lt;80%$ predicted</td>
<td>0.5</td>
</tr>
<tr>
<td>Change in cardiopulmonary symptoms*</td>
<td>2.0</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate $&gt;30$ mm/1st hour</td>
<td>1.5</td>
</tr>
<tr>
<td>Hypocomplementemia</td>
<td>1.0</td>
</tr>
<tr>
<td>Total disease activity index score</td>
<td>10.0</td>
</tr>
</tbody>
</table>

*Assessed by the patient.
in SSc. As of January 2007, 15 centers were involved and over 500 patients had been enrolled. The CSRG is in the process of developing a SSc disease activity index and proposes to evaluate its psychometric properties (in particular, reliability, validity, and responsiveness) using this cohort.

The Scleroderma Clinical Trials Consortium has also undertaken preliminary studies to define disease activity. Using a Delphi method (48) and data on 96 patients from 10 centers worldwide, they have identified numerous clinical and laboratory variables that appeared to be related to disease activity (49). However, there are very few published details of their study to date.

Experts have commented that a self-administered measure of disease activity could make disease monitoring more practical (13). Such self-administered instruments to measure disease activity exist in other rheumatic diseases, namely rheumatoid arthritis and ankylosing spondylitis (50-55), and are useful complements to traditional biomedical assessments of disease activity based on clinical and laboratory measures (56). In addition, in the absence of a gold standard to define disease activity, both physician and patient assessments of disease activity can be used together (57,58). For example, in a study of Raynaud’s phenomenon in patients with SSc, both physician and patient assessments of Raynaud’s phenomenon activity were found to be valid and reliable and the authors recommended that both be included in the core set of measures for use in future clinical trials in this area (59). Nevertheless, although SSc patients are able to self-report symptoms and function accurately (60-62), it remains to be shown whether they can

Table 2 Medsger Disease Severity Scale (22,47)

<table>
<thead>
<tr>
<th>Organ system</th>
<th>0 (normal)</th>
<th>1 (mild)</th>
<th>2 (moderate)</th>
<th>3 (severe)</th>
<th>4 (end stage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Wt loss &lt;5%; PCV 37%+; Hb 12.3+ g/dl</td>
<td>Wt loss 5–10%; PCV 33–37%; Hb 11.0–12.2 g/dl</td>
<td>Wt loss 10–15%; PCV 29–33%; Hb 9.7–10.9 g/dl</td>
<td>Wt loss 15–20%; PCV 25–29%; Hb 8.3–9.6 g/dl</td>
<td>Wt loss 20+%; PCV 25%; Hb &lt;8.3 g/dl</td>
</tr>
<tr>
<td>Peripheral vascular</td>
<td>No Raynaud’s; Raynaud’s not requiring vasodilators</td>
<td>Raynaud’s requiring vasodilators</td>
<td>Digital pitting scars</td>
<td>Digital tip ulcerations</td>
<td>Digital gangrene</td>
</tr>
<tr>
<td>Skin</td>
<td>TSS 0; FTP 0–0.9 cm</td>
<td>TSS 1–14; FTP 1.0–1.9 cm; Proximal weakness, mild</td>
<td>TSS 15–29; FTP 2.0–3.9 cm; Proximal weakness, moderate</td>
<td>TSS 30–39; FTP 4.0–4.9 cm; Proximal weakness, severe</td>
<td>TSS 40+; FTP 5.0+ cm; Ambulation aids required</td>
</tr>
<tr>
<td>Joint/tendon</td>
<td>Normal proximal muscle strength</td>
<td>Distal esophageal hypoperistalsis; small bowel series abnormal</td>
<td>Antibiotics required for bacterial overgrowth</td>
<td>Malabsorption syndrome; episodes of pseudo-obstruction</td>
<td>Hyperalimentation required</td>
</tr>
<tr>
<td>Muscle</td>
<td>Normal esophagram; normal small bowel series</td>
<td>DLCO 80+%; FVC 80+%; No fibrosis on radiograph; sPAP &lt;35 mmHg</td>
<td>DLCO 70–79%; FVC 70–79%; Basilar rales; fibrosis on radiograph; sPAP 35–49 mmHg</td>
<td>DLCO 50–69%; FVC 50–69%; sPAP 50–64 mmHg</td>
<td>DLCO &lt;50%; FVC &lt;50%; sPAP 65+ mmHg</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>EKG normal; LVEF 50+ %</td>
<td>EKG conduction defect; LVEF 45–49 %</td>
<td>EKG arrhythmia; LVEF 40–44%</td>
<td>EKG arrhythmia requiring Rx; LVEF 30–40%</td>
<td>CHF; LVEF &lt;30%</td>
</tr>
<tr>
<td>Heart</td>
<td>No history of SRC with serum creatinine &lt;1.3 mg/dl</td>
<td>History of SRC with serum creatinine &lt;1.5 mg/dl</td>
<td>History of SRC with serum creatinine 1.5–2.4 mg/dl</td>
<td>History of SRC with serum creatinine 2.5–5.0 mg/dl</td>
<td>History of SRC with serum creatinine &gt;5.0 mg/dl or dialysis required</td>
</tr>
</tbody>
</table>

Wt, weight; PCV, packed cell volume (hematocrit); Hb, hemoglobin; TSS, total skin score; FTP, fingertip to palm distance in flexion; DLCO, diffusing capacity for carbon monoxide, % predicted; FVC, forced vital capacity, % predicted; sPAP, estimated pulmonary artery pressure by Doppler echo; EKG, electrocardiogram; LVEF, left ventricular ejection fraction; Rx, treatment; CHF, congestive heart failure; SRC, scleroderma renal crisis.
distinguish between disease activity, as opposed to severity and damage.

Measures of disease activity in SSc are needed for multiple uses (19, 21). In observational studies, they could be used to describe and compare study populations and identify potentially reversible aspects of disease. Given that research into new treatments for SSc is rapidly advancing (17), they could be used to determine eligibility and as a measure of outcome in upcoming clinical trials. Finally, there has been an increasing trend toward measuring disease activity in clinical practice in several conditions (63). This is in part the result of attempts by governments and insurance companies to regulate prescription of expensive new therapies. As new and surely expensive treatments become available for SSc (eg, bosentan), measures of disease activity also have the potential to be used in clinical practice to guide decision-making and for regulatory documentation.

Given the limitations of the currently available instruments to measure disease activity in SSc, efforts are ongoing to develop new indices. This represents a major challenge but one that remains particularly important to pursue both epidemiological and clinical research in this field.

ACKNOWLEDGMENTS

The CSRG Investigators include the following: M. Abu-Hakima, Calgary, Alberta, Canada; P. Docherty, Moncton, New Brunswick, Canada; J. Dunne, Vancouver, British Columbia, Canada; M. Fritzler, Advanced Diagnostics Laboratory, Calgary, Alberta, Canada; S. Johnson, Toronto, Ontario, Canada; N. Jones, Edmonton, Alberta, Canada; N. Khalidi, Hamilton, Ontario, Canada; S. LeClercq, Calgary, Alberta, Canada; J. Markland, Saskatoon, Saskatchewan, Canada; J-P. Mathieu, Montreal, Quebec, Canada; J. Pope, London, Ontario, Canada; P. Rahman, St John’s, Newfoundland, Canada; D. Robinson, Winnipeg, Manitoba, Canada; D. Smith, Ottawa, Ontario, Canada; E. Sutton, Halifax, Nova Scotia, Canada.

REFERENCES

Disease activity in systemic sclerosis


40. Poole JL, Steen VD. The use of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum 2002;46(9):2410-5.


