Assessment of skin, joint, tendon and muscle involvement

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ABSTRACT

This report makes recommendations for standardized techniques of data gathering and collection regarding: 1) skin involvement 2) joint and tendon involvement, and 3) involvement of the skeletal muscles. The recommendations in this report derive from a critical review of the available literature and group discussion. Committee recommendations are considered appropriate for descriptive clinical investigation, translational studies and as standards for clinical practice.

Skin involvement should be assessed using the modified Rodnan skin score. Joint involvement, when symmetric synovitis is present, could be best assessed by the DAS-28 as is utilized in rheumatoid arthritis. Clinical assessment should include a routinized evaluation for the presence and number of palpable tendon friction rubs. Muscle involvement should be screened for by performance of the serum creatine phosphokinase assay and assessment of proximal weakness. More specific testing including EMG, magnetic resonance imaging and muscle biopsy should be employed in those patients with clinically significant myopathy only.

Skin involvement

Tightening and thickening of the skin (scleroderma) is a cardinal clinical feature of systemic sclerosis (SSc). There are rare patients with characteristic serologic, vascular and visceral features of SSc who lack skin thickening (systemic sclerosis sine scleroderma) and there are many other disorders only superficially related to SSc in which skin thickening is a cardinal clinical feature (1), as for example, sclerodema adultorum or eosinophilic fasciitis.

Extent of change

The extent of skin involvement is the single major criterion for the classification of SSc in comparison to other major connective tissue disorders (2). The extent of skin involvement is also the prime clinical criterion for the subclassification of SSc into its two principal subsets – SSc with diffuse cutaneous involvement (diffuse scleroderma) and SSc with limited cutaneous involvement (limited scleroderma – previously termed the “CREST syndrome”) (3). By consensus and convention, patients with skin involvement restricted to sites distal to the elbows and knees, exclusive of the face, are considered to have limited scleroderma whereas patients with involvement of sites proximal to the elbows and knees and inclusive of the chest and abdomen are said to have diffuse scleroderma. Some investigators hold that an intermediate syndrome exists, which is described as skin involvement involving the upper arms and thighs but sparing the chest and abdomen (4, 5).

This subclassification of SSc is closely related to the time of onset, pace of development, and patterns of internal organ involvement and is accordingly strongly linked to survival. All descriptive clinical investigations in SSc today should require the performance of a clinical assessment of the extent of skin involvement.

Severity of change

Severity of skin involvement is highly relevant to the study of individuals with diffuse scleroderma. Consensus observations by veteran observers hold that skin change in diffuse scleroderma evolves in three sequential stages: 1) early progression, 2) plateau or stabilization, and 3) late improvement (1, 3, 6, 7). Early progressive skin changes appear to correlate with both tissue and systemic immune activation and inflammatory changes (1). The stabilization of skin involvement is associated with evidence of reduced local and systemic inflammation. Later improvement of skin involvement is thought to reflect an admixture of post-inflammatory and post-fibrotic atrophy as well as...
the remodeling of previously fibrosed tissue. A variety of techniques have been investigated to estimate the degree of skin thickening and/or tethering in discrete anatomic areas (6). The most widely used technique is the modified Rodnan skin score (mRSS) in which 17 body areas are examined by clinical palpation and scored based on examiner judgment of skin thickness on a 4-point ordinal scale (0 = normal thickness; 1 = mild thickening; 2 = moderate thickening; and 3 = severe thickening). The range of the mRSS is thus from 0 (no skin thickening) to 51 (grade 3 change in all 17 body areas) (6-8). The areas examined in the mRSS scheme include the right and left fingers, hands, forearms, upper arms, thighs, lower legs and feet, as well as the face, anterior chest and abdomen. The modified Rodnan skin score is recommended as the core assessment technique for all international descriptive clinical investigations in SSc. The reasons for selection of the mRSS are numerous and compelling.

Performance of the modified Rodnan Skin Score
The mRSS can be easily taught and yet its broad use in clinical settings outside of the core of investigators who actively participate in trials has been limited. While investigator training sessions have validated the utility of mRSS, the following practical guidelines have evolved that enhance the understanding and application of the measure. We believe that adherence to this methodology of mRSS will improve both the accuracy and the measurement of sensitivity to change. The mRSS is a measure of skin thickening and not of skin tethering. Clinicians and investigators should not attempt to assess the potential contributions of edema, tethering, inflammation and fibrosis as they assign regional skin thickness scores. In the later stages of SSc, skin can atrophy and become abnormally thin. Even though such patients may have considerable underlying tethering of the skin (adherence of skin to underlying subcutaneous tissue, making it difficult to “pick up”), the local skin score should be recorded as 0. If the local skin is so tethered as to preclude confident assessment, the examiner should use his/her best judgment. Patients in whom areas of atrophic skin (tethered, but not thickened) predominate are not considered appropriate choices for clinical trial participation even if they might otherwise fulfill the criteria for inclusion and not those for exclusion. Experience has demonstrated that individual investigators, while consistent, differ in their reporting of the skin score. Some are “maximizers” and assign scores to individual anatomic areas according to the most severe local involvement. Others tend to “average” skin involvement over a given surface area. For the purposes of multicenter trials, investigators should be encouraged to score individual areas with a score that is most representative at the area under examination. For example, if the distal forearm has a patch considered 2+ whereas the remainder of the forearm is 1+, then 1+ would be the most representative score. Alternatively, if the area rated 2+ was relatively extensive, then 2+ would be the recommended score for the forearm.

Recommendations for patient positioning and assessment of the individual areas of examination are as follows:

1. Face: Assess the area between the zygomatic arch and the lower mandible. Do not assess the forehead.
2. Fingers: Concentrate on the skin of the dorsum of the fingers. Do not assess the palmar aspect. Skin distal to the DIP joints is difficult to judge. If the area distal to the PIP joints is excessively tethered and invaluable, score the area between the PIP and MCP joints only.
3. Hands: Assess the dorsum of the hands only. The area is defined as the skin between the MCP joints and the wrists.
4. Forearms and Upper Arms: Examination may include the volar surfaces but scoring should emphasize the findings on the dorsal aspect of the forearms and upper arms.
5. Chest: Assess from the manubrial notch to the xiphoid, including the breasts. The chest should be assessed with the subject in a sitting position.
6. Abdomen: Assess from the xiphoid to the pelvic brim. The abdomen should be assessed with the subject supine.
7. Thighs and Legs: Assess with the subject lying down with the hips, knees and ankles comfortably flexed.
8. Feet: Assess the dorsum only. Feet should be examined with the subject lying down with the hips, knees, and ankles comfortably flexed.

Critique of the Modified Rodnan Skin Score
The mRSS is regarded as a measure of the degree of fibrosis, yet it does not discriminate between the contributions to skin thickening of fibrosis, edema and inflammation. Ignoring the element of tethering of the skin to deeper structures can be seen as underestimating the total burden of skin involvement on the function and mobility of patients in the later atrophic stages of disease (9).

There is controversy within the investigative community as to the robustness of mRSS as a primary outcome measure. It is recognized that worsening skin scores are associated with a higher risk of renal involvement and death (10-12) and that improving the skin score is associated with better functional capacity and survival (13). These data argue that the mRSS is a surrogate but perhaps not a primary measure of outcome. Nevertheless, the mRSS or a similar technique remains a crucial parameter in determining whether an SSc patient is the same, better or worse.

Other measures and future directions
Other approaches are under study which include techniques to objectively assess skin thickness (durometer) (14); skin tethering (elastometer) (15); and to assess the relative contributions of fibrosis versus edema (high frequency ultrasound) (16).
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ity to change is attractive. All risk the problem of sampling error, not unlike the use of skin biopsy. Local skin scores by MRSS have been validated in terms of their correlation with core skin biopsy weights but not in terms of local differences in histopathology, fibroblast behaviour or gene expression (17, 18).

Joint involvement
Proliferative synovitis and other forms of primary joint involvement have been described in scleroderma but may be overestimated. Local skin thickening and involvement of the tendons and tendons sheaths are frequently a better, albeit underappreciated, explanation for loss of joint mobility, local pain and impaired function.

In multicenter interventional trials, the presence of synovitis has been measured as a “modified Ritchie index” where the presence of swelling and tenderness of the metacarpophalangeal joints, wrists, elbows and knees have been recorded. This simplified approach remains unvalidated and probably insufficiently precise (19).

Our subcommittee recommended the DAS-28 (20) as a core assessment technique in all clinical descriptive investigations in patients with scleroderma. This instrument has evolved to serve as a core clinical measurement for rheumatoid arthritis and is widely used and understood by the general community of rheumatologists (21).

Tendon involvement
A tendon friction rub is defined as “leathery crepitus” noted on palpation during active or passive motion of a joint. Their presence has been ascribed to fibrous or fibrinous tendinitis or tenosynovitis (22, 23).

The presence of one or more tendon friction rubs is thus a crucial core variable in clinical descriptive investigation in scleroderma. These rubs confer strong predictive value regarding classification, severity and progression and should be incorporated into both clinical practice and descriptive clinical investigation. All patients should be assessed by palpation during active and/or passive motion in the following areas: extensors and flexors of both the fingers and the wrists; the olecranon bursae; the shoulder capsule; the knee extensors; and the extensors and flexors of the ankles, including the Achille tendons.

Muscle involvement
Proximal muscle weakness, principally of the shoulder and hip girdles, is a common clinical feature of SSc, most notably in patients with diffuse scleroderma. Insidious onset of weakness, flexor greater than extensor, but in the absence of significant muscle pain and tenderness is the most typical scenario (24).

Detailed studies have revealed that a simple inflammatory myopathy is the most prevalent lesion, although overlap with polymyositis, piecemeal infarction from scleroderma vasculopathy, fibrous myopathy (24-26) and myopathies of uncertain pathogenic relationship are also well described. Weakness can be attributed to the adverse effects of therapy, e.g. corticosteroids, but may also be related to articular/tendinous involvement, disuse and sedentary activity levels.

Assessment of muscle strength by confrontational testing is difficult to interpret in the setting of local tendon inflammation and reduced mobility. Serum muscle enzyme assays, most notably creatine phosphokinase (CPK), are both sensitive and specific. Elevations above 3 to 4 times the upper limit of normal are indicative of polymyositis (24, 27).

A core assessment for the presence or absence of muscle disease must consider the multiple methodologies that offer high precision, e.g. magnetic resonance imaging or electromyography, but should also recognize that these techniques are neither broadly nor uniformly accessible and that they are expensive.

The recommendation for descriptive core assessments applicable to all patients with systemic sclerosis is to perform the following: 1) physical examination of proximal muscles for weakness (neck flexion, shoulder girdle, hip girdle); 2) serum CPK level; and 3) if indicated, EMG, MRI or muscle biopsy.

Table I. Core set variables for the assessment of skin, joint, tendon and muscle involvement.

<table>
<thead>
<tr>
<th>Skin</th>
<th>modified Rodnan Skin Score</th>
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<tbody>
<tr>
<td>Joints</td>
<td>DAS 28 (when synovitis occurs)</td>
</tr>
<tr>
<td>Tendons</td>
<td>Tendon friction rubs</td>
</tr>
<tr>
<td>Muscle</td>
<td>CPK, proximal weakness</td>
</tr>
</tbody>
</table>

Discussion
Identification of core set variables
After a critical review of the available literature and group discussion, the subcommittee propose as core set variables for the assessment of skin, joint, tendon and muscle involvement those listed in Table I.

Rationale for selecting the core set variables
The mRSS has evolved to serve as the primary outcome measure in virtually all clinical interventional trials by the community of international scleroderma researchers. The mRSS has been thoroughly studied (6-8) and has been found to be accurate (inter-observer variability of 5 units) and reproducible (intra-observer variability of 3 units) (8). This standard of utility exceeds that of techniques utilized in studies of rheumatoid arthritis (joint count). The MRSS is accessible and cost effective, in that it is a simple bedside examination requiring less than 5 minutes to perform.

The DAS-28 is accessible, validated and sensitive to change in non-scleroderma populations. Prospective multicenter data gathering on scleroderma patients can test the usefulness of this measure. Tendon rubs are highly specific for scleroderma with diffuse cutaneous involvement which is early and active. Their presence correlates with more severe skin thickening, more frequent heart and kidney involvement and decreased survival.

The detection of proximal weakness and the evaluation of serum CPK can identify SSc patients with muscle disease, even if its nature may require further investigations.
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Rationale for excluding other variables

Other variables were not selected because of either poor feasibility (e.g. durometer) or reproducibility (e.g. change in the Ritchie index), or the lack of standardization (e.g. skin ultrasonography).

References