may act to stimulate inflammation and/or regeneration of the skin lesions. Increased levels of serum HMGB1 have been reported in several diseases such as severe infection and/or sepsis, trauma, cancers, and systemic lupus erythematosus, which were not observed in our patients with MPE, EM, and SJS and/or TEN.

It has been reported that granulysin and Fas ligand are possible candidates as biomarkers for early diagnosis of SJS and/or TEN, but the duration of elevated granulysin and Fas ligand levels is limited; therefore, false-negative results for SJS and/or TEN could occur. In this regard, HMGB1 levels were high at the early stage of SJS and/or TEN and remained elevated even after the onset, which is in contrast to the kinetics of granulysin and Fas ligand. Although the numbers of patients with SJS and/or TEN were limited in this study, we propose that measurements of HMGB1 in combination with granulysin and/or Fas ligand would be a useful diagnostic tool for cases of SJS and/or TEN that require early diagnosis and treatment.

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Accepted for Publication: April 13, 2011.

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Financial Disclosure: None reported.

Funding/Support: This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, and Health and Labor Sciences Research Grants (Research on Intractable Diseases) from the Ministry of Health, Labor, and Welfare of Japan.


14-MHz Ultrasonography as an Outcome Measure in Morphea (Localized Scleroderma)

The determination of therapeutic efficacy in morphea (aka, localized scleroderma) is difficult owing to a lack of validated outcome measures. Outside of the United States, 20- to 25-MHz ultrasonography has demonstrated its validity, reproducibility, and responsiveness to change. Preliminary studies on the lower-frequency ultrasonography available in the United States (10-15 MHz) demonstrate that it may have similar attributes. However, studies correlating ultrasonographic findings with lesion stage (inflammatory, sclerotic, or atrophic), clinical scoring systems, or histologic traits have not been conducted.

See Practice Gaps at end of letter

Methods. We identified 14 patients with 16 morphea lesions (Table) from the University of Texas Southwestern Medical Center Morphea Registry and DNA repository. Each patient and lesion was assessed for morphea subtype and clinical stage and was assigned a Modified Rodnan Skin Score (mRSS) by a single board-certified dermatologist (H.T.J.).

A single site for ultrasonography and biopsy, as well as a control site, was chosen by the dermatologist and marked with a surgical pen. Ultrasonographic examination was performed by 2 radiologists blinded to the results of the clinical assessment of each patient. Each lesion had dermal thickness measured and echogenicity determined as compared...
with site-matched, unaffected skin (hypoechogenic, isoecho-
genic, and hyperechogenic) (Figure 1 and Figure 2).

One board-certified dermatopathologist (J.S.S.),
blinded to both clinical and sonographic data, graded each
specimen for inflammation, edema, and sclerosis using
a previously published scoring system7 and calculated der-
nal thickness.

To examine the correlation between ultrasonographic
finding and clinical stage, mRSS, dermal thickness, and grade
of fibrosis, the Fisher exact test was used. To examine the
correlation between thickness on ultrasonography and his-
tologic findings, the Spearman correlation coefficient was
used. The intrarater correlation and interrater correlation
of ultrasonographic measurements was analyzed using the
intraclass correlation coefficient.

### Results

Prior studies identified assessment of disease stage as important features in the evaluation and treatment of
morphea.8 Ultrasonography was able to reliably differ-
entiate between the clinical stages of morphea. A signifi-
cant number of inflammatory lesions were isoechogenic
(5 of 6) ($P = .04$). Most sclerotic lesions were hyperecho-
genic (5 of 6) ($P = .01$). Atrophy appeared on ultrasonog-
raphy as hypoechoic in 2 of 3 lesions that were
determined to be atrophic on the clinical examination ($P = .03$
(Figure 3A).

No significant relationship was found between mRSS
and ultrasonography findings of echogenicity or dermal
depth measurement ($P = .60$ and $P = .40$, respectively).

Ultrasonography measurements of dermal thickness
were reproducible by a single clinician and between cli-

### Table. Patient Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Sex/Age, y</th>
<th>Disease Subtype</th>
<th>Clinical Stage</th>
<th>Case</th>
<th>Site-Matched Control</th>
<th>Dermal Echogenicity on Ultrasonogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/50</td>
<td>Gen</td>
<td>Atrophic</td>
<td>L medial thigh</td>
<td>R medial thigh</td>
<td>Isoechnogenic</td>
</tr>
<tr>
<td>F/55</td>
<td>LS/M, Gen</td>
<td>Sclerotic</td>
<td>L flank</td>
<td>L flank</td>
<td>Hyperechogenic</td>
</tr>
<tr>
<td>F/16</td>
<td>Linear</td>
<td>Sclerotic</td>
<td>R hip</td>
<td>L hip</td>
<td>Hyperechogenic</td>
</tr>
<tr>
<td>M/12</td>
<td>Gen</td>
<td>Sclerotic</td>
<td>R arm</td>
<td>R arm</td>
<td>Hyperechogenic</td>
</tr>
<tr>
<td>F/7</td>
<td>Plaque</td>
<td>Inflammatory</td>
<td>L lateral thigh</td>
<td>R lateral thigh</td>
<td>IsoechnogenicA</td>
</tr>
<tr>
<td>M/44</td>
<td>LS/M, Gen</td>
<td>Inflammatory</td>
<td>R thigh</td>
<td>L thigh</td>
<td>IsoechnogenicA</td>
</tr>
<tr>
<td>M/34</td>
<td>Linear</td>
<td>Atrophic</td>
<td>L lower chin</td>
<td>R lower chin</td>
<td>Hypoechoenic</td>
</tr>
<tr>
<td>M/34</td>
<td>Linear</td>
<td>Inflammatory</td>
<td>L upper chin</td>
<td>R upper chin</td>
<td>IsoechnogenicA</td>
</tr>
<tr>
<td>F/46</td>
<td>Plaque</td>
<td>Sclerotic</td>
<td>L abdomen</td>
<td>Central Abd</td>
<td>HyperechogenicA</td>
</tr>
<tr>
<td>F/22</td>
<td>Plaque</td>
<td>Inflammatory</td>
<td>R breast</td>
<td>R axilla above</td>
<td>Hyperechogenic</td>
</tr>
<tr>
<td>F/46</td>
<td>LS/M, Gen</td>
<td>Inflammatory</td>
<td>L forearm</td>
<td>R forearm</td>
<td>Isoechnogenic dermis,A, hyperechogenic</td>
</tr>
<tr>
<td>F/48</td>
<td>LS/M, Gen</td>
<td>Inflammatory</td>
<td>L lateral hip</td>
<td>L hip below</td>
<td>Isoechnogenic</td>
</tr>
<tr>
<td>F/15</td>
<td>Plaque</td>
<td>Inflammatory</td>
<td>L post auric</td>
<td>R post auric</td>
<td>IsoechnogenicA</td>
</tr>
<tr>
<td>F/60</td>
<td>Gen</td>
<td>Sclerotic</td>
<td>Left abdomen</td>
<td>Mid lower abdomen</td>
<td>HyperechogenicA</td>
</tr>
<tr>
<td>F/20</td>
<td>Linear</td>
<td>Atrophic</td>
<td>R leg</td>
<td>L leg</td>
<td>HyperechogenicA</td>
</tr>
<tr>
<td>F/20</td>
<td>Gen</td>
<td>Sclerotic</td>
<td>L thigh</td>
<td>R thigh</td>
<td>Isoechnogenic</td>
</tr>
</tbody>
</table>

Abbreviations: abd, abdomen; Gen, generalized; L, left; LS, lichen sclerosis; M, morphea; post auric, postauricular; R, right; SQ, subcutaneous.

*Site not biopsied owing to patient preference, age, or cosmetic ramifications.

Figure 1. Morphea lesions and their controls were imaged using 14-MHz ultrasonography. The interface between the dermis and the subcutaneous fat, or
hypodermis (H), is easily seen by this technique. Measurements of dermal depth (Dph) were obtained by 2 blinded observers. Lesions were compared with
controls to determine dermal echogenicity. The echogenicity or brightness of a structure depends on the acoustic impedances at a tissue interface. Structures with
greater acoustic impedances will be displayed as brighter and hyperechogenic. To increase the accuracy of the measurements, a thick layer of hypoechoic
ultrasonography gel (G) was applied to the skin to clearly depict the surface. The gel is invisible by ultrasonography (dark zone superficial to the surface). A and B,
Morphea lesion in the atrophic phase in which the dermis demonstrates decreased echogenicity (A) compared with its control (B). C and D. By contrast a morphea
lesion in the sclerotic phase shows substantial hyperechogenicity (C) compared with its control (D).
Ultrasonography findings were compared with the putative gold standard for evaluation of morphea, histologic analysis. Hyperechogenicity on ultrasonography was significantly associated ($P=0.04$) with grades of moderate or extensive sclerosis on dermatopathologic examination (Figure 3B). There was not a significant relationship between the depth of sclerosis as measured by ultrasonography and histologic analysis ($R=0.75; P=0.33$).

Comment. The high validity and reliability demonstrated by 14-MHz ultrasonography in this study indicates it might be a useful outcome measure. Fourteen-MHz ultrasonography could differentiate between all the clinical stages of disease. It could also differentiate active disease, which appeared hyperechoic (sclerosis) or isoechogenic (inflammation), from atrophy or damage, which appeared hypoechoic. We also found that ultrasonography demonstrated a significant correlation between the amount of sclerosis on histologic examination and degree of echogenicity.

There was no significant association between mRSS and echogenicity or dermal depth on ultrasonography. This discrepancy highlights the inadequacy of the mRSS, which relies solely on the investigator’s ability to pinch or move skin.

As in prior studies, the measurements obtained by 14-MHz ultrasonography demonstrated extremely high reliability. Both the intrarater and interrater reliability of ultrasonography exceeded the reliability of existing clinical sclerosis scores.$^{9,10}$

The main limitation of this study was the small number of patients included and the smaller number of lesions with suitable, full-thickness biopsies. Depth of disease is important for selection of therapy. Biopsies, which are both invasive and unreliable in their ability to assess the depth of sclerosis, are not always helpful. Fourteen-MHz ultrasonography, which penetrates up to 40 mm, may be a useful, noninvasive tool to investigate the depth of involvement beyond the dermis. Fourteen-MHz ultrasonography is likely better suited than 20-MHz for this function owing to its deeper penetration.

Figure 2. Morphea lesions were biopsied in the same location that ultrasonographic examination was performed. The specimens were graded by a single dermatopathologist who was blinded to the clinical and ultrasonographic data. Representative specimens of lesions from each of the 3 clinical stages of a morphea lesion are shown. A, Clinically atrophic lesions were found to be hypoechoic compared with their controls (Figure 1A and B) ($P=0.03$). B, Clinically sclerotic lesions of morphea were found to be hyperechoic compared with their controls (Figure 1C and D) ($P=0.01$). C, Clinically inflammatory lesions were found to have an echogenicity similar to controls (isoechogenic) ($P=0.04$).

Figure 3. Ultrasonography is capable of differentiating between disease activity (inflammation and sclerosis) and damage (atrophy). A, In our study, early inflammatory lesions of morphea appeared isoechogenic ($P=0.04$); sclerosis appeared hyperechogenic ($P=0.01$), while atrophic lesions appeared hypoechoic ($P=0.03$). B, Hyperechogenicity seen on ultrasonogram correlates with the presence of histologic sclerosis. Sixteen lesions were examined by ultrasonography and histologic analysis. Hyperechogenicity was associated with moderate or severe grades of histologic sclerosis ($P=0.04$).
The value of ultrasonography as an outcome measure will depend on its ability to demonstrate that it can detect changes in lesions over time. If ultrasonography assessment is found to distinguish longitudinal changes in plaque sclerosis and depth, it could be a very valuable tool in following up entire cohorts of patients in a clinical trial, or it could give the clinical dermatologist a follow-up tool for individual patients with morphea.

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Accepted for Publication: January 24, 2011.

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Financial Disclosure: None reported.

Funding/Support: This study was supported in part by the Dermatology Foundation Clinical Development Award in Medical Dermatology and National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases K23 Award (Dr Jacobe).

Role of the Sponsors: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; or in the preparation, review, or approval of the manuscript.

PRACTICE GAPS

The Hard Task of Measuring Cutaneous Fibrosis

Cutaneous fibroelastic disorders (CFDs) — including scleroderma, chronic graft-vs-host disease, and nephrogenic systemic fibrosis — are devastating skin diseases, variably involving subcutaneous tissues and internal organs and potentially resulting in debilitating morbidity and substantial mortality. Provision of effective interventions for management of cutaneous complications of CFDs, including progressive skin induration, joint restriction, cutaneous dysesthesias, and recalcitrant pruritus, remains challenging. Fortunately, several pharmacologic agents in development purportedly inhibit the underlying cytokine cascades that lead to abnormal collagen production, and others may potentially even permit the reversal of established fibrosis.

Evaluating the response of patients with CFD to these novel therapies will require accurate and reproducible assessment of skin disease activity and damage — measures that, to date, are largely lacking. However, the dermatologic community has developed reliable clinical instruments for quantifying skin disease activity in several other chronic skin conditions, notably the Psoriasis Area and Severity Index (PASI) for psoriasis and the Severity Weighted Assessment Tool (SWAT) for mycosis fungoides. Moreover, use of full-body digital imaging and analysis to identify and precisely quantify areas of involved skin has continued to improve the accuracy of these tools.

Unfortunately, such instruments have proven difficult to export to the realm of CFD, which may harbor dermal, subcutaneous, and fascial involvement that is often not easily appreciated by visual inspection and palpation alone. Various technologies have been developed to address these challenges, including durometers for measuring skin hardness and/or tautness, cutometers for quantifying skin elasticity, and ultrasonographic devices for assessing local dermal and subcutaneous blood flow, as outlined by Nezafati et al, but each requires multiple, time-consuming measurements that are subject to significant interuser and intruser variability as well as within-patient sampling error. Thermographic global heat mapping partially overcomes these...