

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,³ 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,⁵⁻⁷ but the duration of elevated granulysin and Fas ligand levels is limited^{6,7}; 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.

Saeko Nakajima, MD
Hideaki Watanabe, MD, PhD
Mikiko Tohyama, MD, PhD
Kazunari Sugita, MD, PhD
Masafumi Iijima, MD, PhD
Koji Hashimoto, MD, PhD
Yoshiki Tokura, MD, PhD
Youichi Nishimura, MD, PhD
Hiromi Doi, MS
Miki Tanioka, MD, PhD
Yoshiki Miyachi, MD, PhD
Kenji Kabashima, MD, PhD

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Author Affiliations: Departments of Dermatology at Kyoto University Graduate School of Medicine, Kyoto (Drs Nakajima, Tanioka, Miyachi, and Kabashima and Ms Doi), Showa University School of Medicine, Tokyo (Drs Watanabe and Iijima), Ehime University School of Medicine, Toon (Drs Tohyama and Hashimoto), and University of Occupational and Environmental Health, Kitakyushu (Drs Sugita and Tokura), Japan; and Nishimura Skin Clinic, Fukui, Japan (Dr Nishimura).

Correspondence: Dr Kabashima, Department of Dermatology, Kyoto University Graduate School of Medicine, 54 Shogoin-Kawara, Sakyo-ku, Kyoto 606-8507, Japan (kaba@kuhp.kyoto-u.ac.jp).

Author Contributions: Drs Nakajima and Kabashima had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Watanabe, Sugita, Hashimoto, Tokura, Miyachi, and Kabashima. *Acquisition of data:* Nakajima, Tohyama, Iijima, Nishimura, Doi, and Tanioka. *Analysis and interpretation of data:* Nakajima, Watanabe, Hashimoto, and Kabashima. *Drafting of the manuscript:* Nakajima, Watanabe, Tohyama, Sugita, Hashimoto, Tokura, Nishimura, Doi, Miyachi, and Kabashima. *Critical revision of the manuscript for important intellectual content:* Nakajima, Iijima, Tanioka, Miyachi, and Kabashima. *Obtained funding:* Tanioka and Kabashima. *Administrative, technical, and material sup-*

port: Nakajima, Watanabe, Tohyama, Sugita, Hashimoto, Nishimura, Doi, and Miyachi. *Study supervision:* Iijima, Hashimoto, Tokura, and Kabashima.

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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.^{1,2} Outside of the United States, 20- to 25-MHz ultrasonography has demonstrated its validity, reproducibility, and responsiveness to change.³ Preliminary studies on the lower-frequency ultrasonography available in the United States (10-15 MHz) demonstrate that it may have similar attributes.⁴⁻⁶ 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

Table. Patient Demographic and Clinical Characteristics

Sex/Age, y	Disease Subtype	Clinical Stage	Site of Lesion		Dermal Echogenicity on Ultrasonogram
			Case	Site-Matched Control	
F/50	Gen	Atrophic	L medial thigh	R medial thigh	Isoechogenic
F/55	LS/M, Gen	Sclerotic	L flank	L flank	Hyperechogenic
F/16	Linear	Sclerotic	R hip	L hip	Hyperechogenic
M/12	Gen	Sclerotic	R arm	R arm	Hyperechogenic
F/7	Plaque	Inflammatory	L lateral thigh	R lateral thigh	Isoechogenic ^a
M/44	LS/M, Gen	Inflammatory	R thigh	L thigh	Isoechogenic ^a
M/34	Linear	Atrophic	L lower chin	R lower chin	Hypoechogenic
M/34	Linear	Inflammatory	L upper chin	R upper chin	Isoechogenic ^a
F/46	Plaque	Sclerotic	L abdomen	Central abd	Hyperechogenic ^a
F/22	Plaque	Inflammatory	R breast	R axilla above	Hyperechogenic
F/48	LS/M, Gen	Inflammatory	L forearm	R forearm	Isoechogenic dermis, ^a hyperechogenic in SQ
F/48	LS/M, Gen	Inflammatory	L lateral hip	L hip below	Isoechogenic
F/15	Plaque	Inflammatory	L post auric	R post auric	Isoechogenic ^a
F/60	Gen	Sclerotic	Left abdomen	Mid lower abdomen	Hyperechogenic ^a
F/20	Linear	Atrophic	R leg	L leg	Hypoechogenic ^a
F/20	Gen	Sclerotic	L thigh	R thigh	Isoechogenic

Abbreviations: abd, abdomen; Gen, generalized; L, left; LS, lichen sclerosis; M, morphea; post auric, postauricular; R, right; SQ, subcutaneous.
^aSite not biopsied owing to patient preference, age, or cosmetic ramifications.

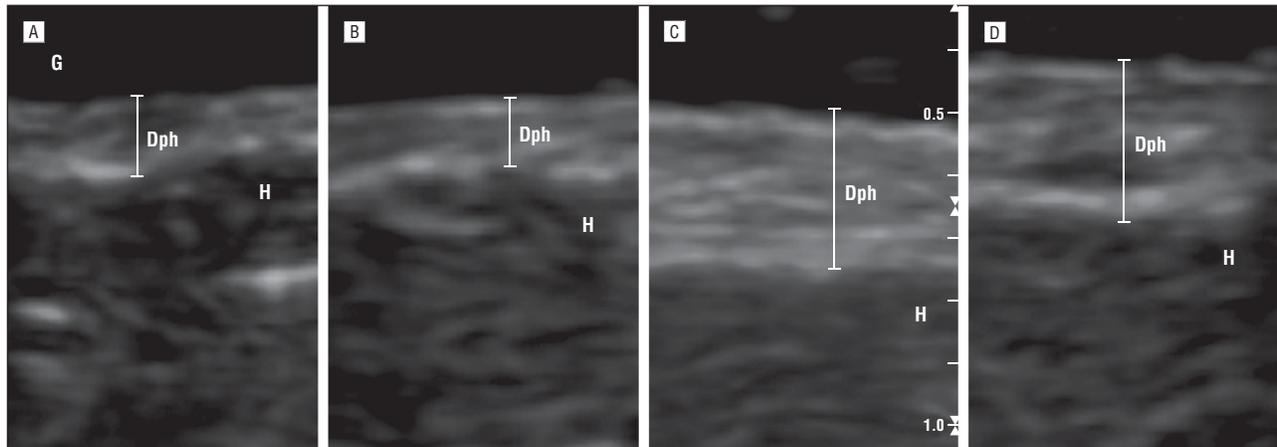


Figure 1. Morphea lesions and their controls were imaged using 14-MHz ultrasonography. The interface between the dermis and the subcutaneous fat, or hypodermis (H), is easily seen by this technique. Measurements of dermal depth (Dph) were obtained by 2 blinded observers. Lesions were compared with controls 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).

with site-matched, unaffected skin (hypoechoic, isoechogenic, 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 dermal 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 histologic 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 differentiate between the clinical stages of morphea. A significant number of inflammatory lesions were isoechogenic (5 of 6) ($P = .04$). Most sclerotic lesions were hyperechogenic (5 of 6) ($P = .01$). Atrophy appeared on ultrasonography as hypoechoic in 2 of 3 lesions that were deemed 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-

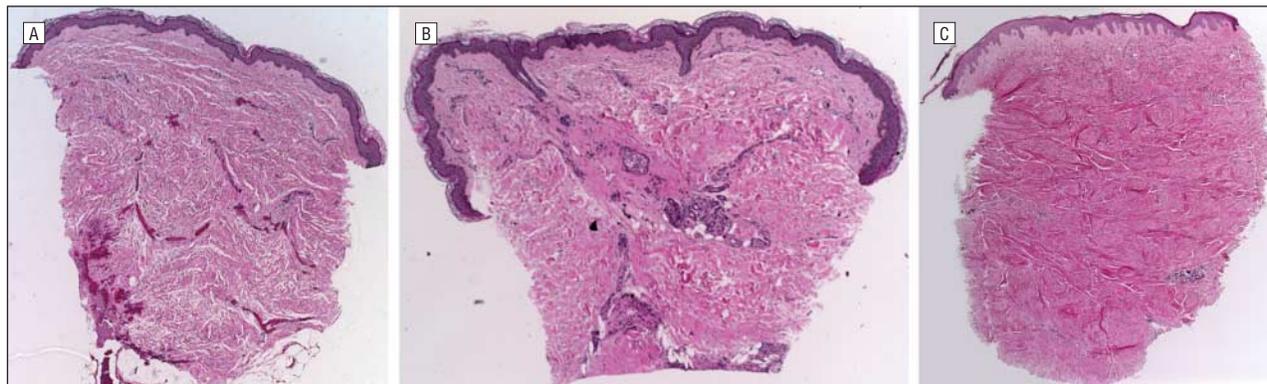


Figure 2. Morphea lesions were biopsied in the same location that ultrasonographic examination was performed. The specimens were graded by a single dermatopathologist who was blinded to the clinical and ultrasonographic data. Representative specimens of lesions from each of the 3 clinical stages of a morphea lesion are shown. A, Clinically atrophic lesions were found to be hypoechoic compared with their controls (Figure 1A and B) ($P=.03$). B, Clinically sclerotic lesions of morphea were found to be hyperechoic compared with their controls (Figure 1C and D) ($P=.01$). C, Clinically inflammatory lesions were found to have an echogenicity similar to controls (isoechogenic) ($P=.04$).

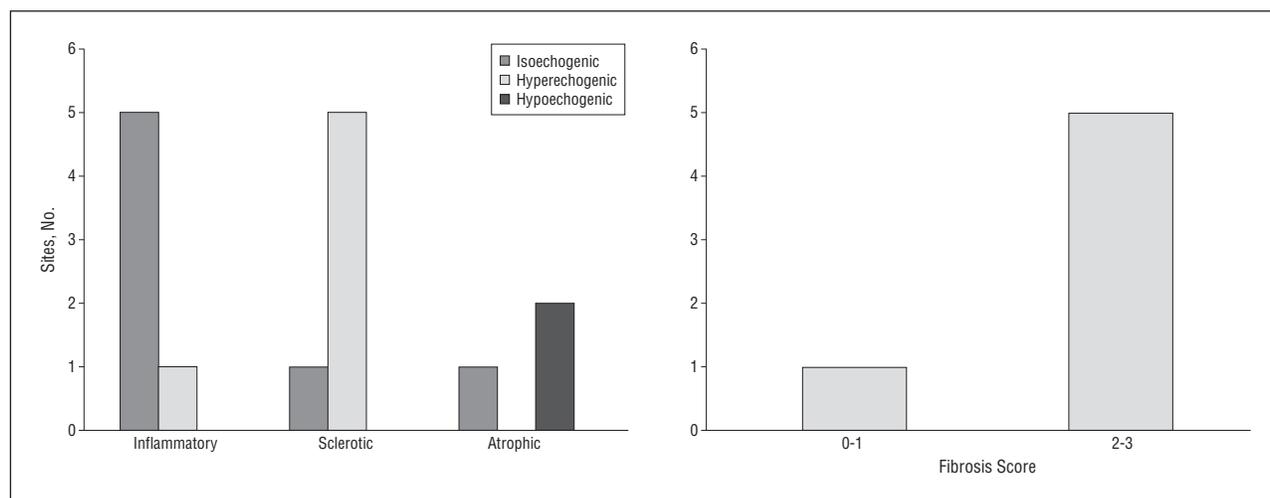


Figure 3. Ultrasonography is capable of differentiating between disease activity (inflammation and sclerosis) and damage (atrophy). A, In our study, early inflammatory lesions of morphea appeared isoechogenic ($P=.04$); sclerosis appeared hyperechoic ($P=.01$), while atrophic lesions appeared hypoechoic ($P=.03$). 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 ($P=.04$).

nicians (intrarater and interrater correlation, 0.99 and 0.97, respectively).

Ultrasonography findings were compared with the putative gold standard for evaluation of morphea, histologic analysis. Hyperechogenicity on ultrasonography was significantly associated ($P=.04$) 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 ($R=0.75$; $P=.33$).

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 isoechoic (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.

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.

Kaveh A. Nezaferati, MD
Rachael L. Cayce, MD
Joseph S. Susa, DO
Anthony T. Setiawan, MD
Temel Tirkes, MD
Sandra E. Bendeck, MD
Heidi T. Jacobe, MD

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Author Affiliations: Departments of Dermatology (Drs Nezaferati, Cayce, Susa, Bendeck, and Jacobe) and Radiology (Drs Setiawan and Tirkes), University of Texas Southwestern Medical Center, Dallas. Dr Tirkes is now in private practice in Bloomington, Indiana; Dr Bendeck is now with Kaiser Permanente, Hayward/Fremont Medical Centers, Department of Dermatology, Union City, California.

Correspondence: Dr Jacobe, Department of Dermatology, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Ste JA5.120H, Dallas, TX 75390-9069 (Heidi.Jacob@utsouthwestern.edu).

Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Cayce, Tirkes, Bendeck, and Jacobe. **Acquisition of data:** Nezaferati, Cayce, Susa, Setiawan, Tirkes, and Jacobe. **Analysis and interpretation of data:** Nezaferati, Cayce, Susa, Setiawan, and Jacobe. **Drafting of the manuscript:** Nezaferati and Cayce. **Critical revision of the manuscript for important intellectual content:** Nezaferati, Susa, Setiawan, Tirkes, Bendeck, and Jacobe. **Obtained funding:** Setiawan and Jacobe. **Administrative, technical, and material support:** Susa, Tirkes, and Bendeck. **Study supervision:** Tirkes. **Financial Disclosure:** None reported.

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PRACTICE GAPS

The Hard Task of Measuring Cutaneous Fibrosis

Cutaneous fibrosing 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.¹ 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 Nezaferati et al, but each requires multiple, time-consuming measurements that are subject to significant interuser and intrauser variability as well as within-patient sampling error. Thermographic global heat mapping partially overcomes these