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Improvement in Skin Thickening in Systemic Sclerosis Associated With Improved Survival

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Objective. **The natural history of changes in skin thickening in diffuse scleroderma is quite variable, but the significance of these changes is not clear. Clinical trials are using changes in skin thickening as the primary outcome measure, and thus it would be helpful to determine the significance of improvement in skin thickening. The purpose of the present study was to determine whether improvement in skin thickening over time was associated with improved survival.**

Methods. **Patients with early (<3 years) diffuse scleroderma who had a baseline evaluation and a repeat skin assessment (modified Rodnan skin score) performed 2 years later (i.e., they had to live for 2 years) were identified from the prospective, observational Pittsburgh Scleroderma Databank. The percentage of improvement and rate of change in the skin score during that time were determined. Patients with an improvement in their skin thickening of >25% of their peak skin score and a rate of change of at least 5 units/year were defined as the improved group; patients with increased skin thickening or no improvement were termed the no improvement group. Demographic and clinical features, organ system involvement, and survival rates were determined and the groups were compared. Regression and Cox regression analyses were used to determine what features were associated with improved skin thickness and survival.**

Results. **Two hundred seventy-eight patients fulfilled the entry criteria, 63% in the improved group and 36% in the no improvement group. The groups were similar in terms of clinical and demographic characteristics at the initial visit. The improved group had an average improvement of 50% of their peak skin score at 2 years after the initial visit. Survival was significantly better in the improved group compared with the unimproved group at 5 and 10 years, with rates of 90% and 80%, respectively, in the improved group and 77% and 60%, respectively, in the no improvement group ($P < 0.0001$). There were no significant differences in the occurrence of severe organ involvement during the first 2 years to account for the later differences in survival. The duration of the use of D-penicillamine was significantly associated with improved skin thickness and improved survival.**

Conclusion. **Among patients surviving the first few years of diffuse scleroderma, striking improvement in skin thickening may occur in up to two-thirds. This improvement in skin thickening is associated with improved survival. Improvement in skin thickening may be useful as a surrogate for improvement in survival in clinical trials.**

Systemic sclerosis is a multisystem disease that has considerable variability in its presentation, course, and prognosis. The 2 major disease subsets, limited cutaneous and diffuse cutaneous scleroderma, have symptoms for varying lengths of time prior to diagnosis, different types and severity of internal organ involvement, and variable survival (1). Skin thickening is the hallmark of systemic sclerosis, and the extent and severity of skin thickening is one of the major ways to differentiate these 2 variants. Diffuse cutaneous involvement and rapidly increasing skin thickening have been associated with the development of renal crisis as well as decreased survival (2,3). Patients with less extensive skin thickening who have either limited scleroderma or mild,

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diffuse cutaneous disease tend to have an improved survival compared with those with more severe skin thickening (4).

Variability in the extent and severity of scleroderma has made therapy particularly challenging. Recently, there have been major advances in the treatment of specific organ system complications, including treatment of reflux esophagitis with proton pump inhibitors (5), active alveolitis in interstitial lung disease with cyclophosphamide (6), and acute renal crisis with angiotensin-converting enzyme inhibitor (7). Many reports have attributed improvement in skin thickening to certain medications, but controlled trials have not confirmed these observational studies (8,9).

Several problems have made clinical therapeutic trials in scleroderma particularly difficult to perform and interpret, although recent guidelines for the treatment of scleroderma have been made by a National Institutes of Health panel (10). Great variability in the disease makes it hard to identify an adequate number of patients with similar disease features. The method of evaluating the extent and severity of skin thickening has also been variable. However, over the last 15 years, the description, standardization, and validation of a semiquantitative method of evaluating skin thickening (modified Rodnan method) has led to uniformity in this aspect of the physical examination (11,12). Changes in skin thickening as measured by this skin thickness score method are associated with changes in function as measured by the Health Assessment Questionnaire disability index (HAQ DI) (13).

Changes in skin thickening have been the primary outcome measure in recent therapy trials in scleroderma (9,14). However, most of these studies have been relatively short. It has not been determined whether improvement in skin thickening is independent of or associated with significant improvement in survival. The number of patients necessary to show an improvement in survival as part of a drug study is considerably larger than is feasible for most trials, and the typical duration of followup required (4 or more years) is beyond the scope of almost all such studies.

The purpose of the present study was to determine whether improvement in skin thickening early in the course of disease in patients with diffuse scleroderma was associated with improvement in long-term survival. Documentation that there is a strong association between improvement in skin thickening and improved survival would allow changes in this simple physical examination measure to be used as a surrogate for prognosis.

PATIENTS AND METHODS

Patients were identified from the Pittsburgh Scleroderma Databank, a prospective study of more than 2,500 scleroderma patients seen at the University of Pittsburgh since January 1, 1972. All patients had a standardized baseline evaluation, which includes general history, physical examination, scleroderma-specific examination, and laboratory studies including pulmonary function, cardiac, and renal testing as well as determination of scleroderma-associated serum autoantibodies. A modified Rodnan skin score was determined for all patients at the first visit (11). Followup visits at the University of Pittsburgh Scleroderma Clinic included a repeat skin examination, medication history, and visceral studies as clinically indicated. Annual or biannual contact was made with all patients to determine the natural history and course of their disease, with special focus on organ system involvement, medication use, and survival. As of May 1997, there was 95% accountability for these patients.

Severe organ involvement was defined as described in other studies (15) using the following criteria: 1) gastrointestinal malabsorption, pseudoobstruction, or hyperalimentation, 2) lung-pulmonary fibrosis with a forced vital capacity $<55\%$ of predicted, 3) heart-symptomatic pericarditis, congestive heart failure, or arrhythmias requiring treatment (8), and 4) kidney-renal crisis with the acute onset of malignant hypertension associated with a rising serum creatinine. The presence and timing of severe organ system involvement and the timing and causes of death were determined for each patient as part of the prospectively collected information.

Patients who had the diagnosis of diffuse scleroderma with skin thickening involving the upper arms, legs, or trunk and had the first symptom attributable to scleroderma <3 years before the time of their initial visit were eligible for the study. In addition, patients had to have survived for 2 years following the first visit and were required to have 1 or more followup skin examinations between 12 months and 28 months after the first visit. Comparisons of clinical features in patients who did and did not have repeat skin scores were performed to determine if the study patients were representative of all patients with diffuse scleroderma.

For each eligible patient, the rate of change in skin thickening and the percentage improvement in skin thickness score were determined for the 2-year time period after the initial visit. The peak skin score, which typically occurred during the first year, was used in those patients who had an increase in their skin score after the initial visit. To calculate the rate of change in the skin score, the value closest to 24 months after the initial visit (SS2) was subtracted from the initial (or peak) skin score (SS1) and then divided by the time between the 2 skin scores. The formula for this measure is as follows:

$$\text{Rate of change in skin score} = \frac{\text{SS1 (or peak score)} - \text{SS2 (score closest to 24 months)}}{\text{Time 2} - \text{time 1}}.$$

In patients who had improvement, the amount of improvement was defined as a percentage of the initial or peak skin score. Improvement required a reduction in their skin score of at least 5 units per year and a $>25\%$ overall improvement from

their initial or peak skin score. No improvement was defined as no change or an increase in the skin score during the first 2 years after the first visit. Patients with minimal improvement, i.e., from 1 to 4 units of change per year or <25% improvement during the 2 years, were excluded from further aspects of the study.

Patients in the improved and no improvement groups were compared at the time of the initial visit using standard descriptive statistics. A summary of events, presence of severe organ involvement, and medications used during the 2 years were also compared. Survival from the time of the first Pittsburgh visit was determined for the 2 groups using Kaplan-Meier survival curves and compared using log-rank analysis. Finally, logistic regression analysis and Cox survival analysis were performed to identify those factors which best predicted improvements in skin thickening and survival.

RESULTS

There were 1,065 patients with diffuse cutaneous scleroderma who were initially seen at the University of Pittsburgh Scleroderma Clinic between January 1, 1972 and December 31, 1994. Of these, 766 (72%) had <3 years of symptoms related to scleroderma at the time of the initial visit, and 124 of these patients died. Of the 642 patients (60%) who survived for the first 2 years after the initial visit, 147 had only 1 skin score and 217 had repeat skin scores but these were not within the required 2 years.

The 124 patients who did not survive for the required 2 years died a mean of 0.7 years after the first visit. Seventy-two of these patients (58%) were started on D-penicillamine, but remained on this drug only briefly (mean 0.4 years). Forty-three (35%) had a repeat skin score prior to their death which, in most cases, was less than a year after the initial skin score. Twenty-three patients had a higher score on repeated measurement of skin thickening and 11 had a lower skin score, but none of those patients fulfilled the improvement criteria for this study. Forty-seven (38%) of these patients died from renal crisis within 6 months of their first Pittsburgh visit, of which most occurred prior to the availability of angiotensin-converting enzyme inhibitors. Thus, there was a greater percentage of deaths earlier in the 23-year time period.

One hundred forty-seven patients had only 1 skin score, so we could not determine whether or not they had improvement. Of the 495 patients who had >1 skin score, 217 did not have an evaluation during the 12–24-month period after the first visit, which was part of our entry criteria. Thus, the remaining 278 patients made up the study population.

The 364 patients with diffuse scleroderma who had <3 years of symptoms and survived for 2 years but who did not have a repeat skin examination performed in the appropriate time period were compared with the study patients. At the time of the initial visit, there were no significant differences between these patients and the study patients in demographic, clinical, or laboratory manifestations. The initial mean skin score was 23.5 in the study group and 25 in the non–study group. The disease duration was identical, a mean of 1.3 years. Other initial features were also similar, including mean age, sex distribution, frequency of scleroderma-specific autoantibodies, and proportions of internal organ involvement. In both groups, ~45% of patients were initially started on D-penicillamine, and 72% of the study group and 80% of the non–study group received this drug at some point during their illness. The mean HAQ DI was 1.33 in the study patients and 1.32 in the non–study patients at entry. The 5- and 10-year cumulative survival rates were also similar, 90% and 75%, respectively, for the study group and 90% and 65%, respectively, for the non–study group (*P* not significant). The major difference was that 50% of the study patients resided within the Pittsburgh referral area (<100 miles from Pittsburgh) compared with only 30% of the non–study patients. Thus, the study group and the non–study group were very similar, strongly suggesting that the study group was representative of all patients with diffuse scleroderma.

In the 278 study patients, 174 (63%) were classified as having improved and 99 patients (36%) as having no improvement, based on the above criteria. Only 5 patients (2%) were excluded because they had only minimal improvement. There were no differences in the baseline demographic features in the improved and no improvement groups: 75% were female in both groups; the mean (±SD) age at the first visit was 46 ± 13 years in the improved group and 47 ± 13 years in the no improvement group; and the mean (±SD) duration of disease from the first symptom to first Pittsburgh visit was 1.2 ± 1.0 years in the improved group and 1.3 ± 1.3 years in the no improvement group. The mean date of the initial visit in the improved group was January 1986 and was January 1985 in the no improvement group. Clinical features in the 2 groups were similar, including the frequency of tendon friction rubs, which were present in 49% of both groups. There were no differences in the frequency of antitopoisomerase or anti–RNA polymerase III antibodies between the 2 groups, although only 20% of the patients in each group had an anti–RNA polymerase assay performed.

Table 1 summarizes the course of the skin

Table 1. Changes in skin thickening during the course of disease in patients who experienced improvement or who had no improvement in skin thickening during the first 2 years after the initial visit*

	Improved (n = 174)	No improvement (n = 99)
Initial skin score	25 ± 11.8	22 ± 13.1
Peak skin score	31 ± 10.7	33 ± 12.9
Time to peak skin score, years	0.5†	1.2
Skin score closest to 2 years	16 ± 15.5†	31 ± 12.4
Rate of skin score change/year‡	−11 (median −9)	+8 (median +5)
Percentage improvement from peak‡	52 ± 20	1.8 ± 5.2
Final recorded skin score	11 ± 86†	24 ± 10.5
Time to final skin score, years	7.2	6.2

* Except where otherwise indicated, values are the mean ± SD.
† $P < 0.001$ versus no improvement.
‡ During the first 2 years.

changes in the 2 groups during their illness. Patients in the improved group started with a mean skin score of 25 that increased to a mean peak skin score of 31 during the first 12 months, and this was reached a mean of 0.5 years after the first visit. The final mean skin score in this group at the evaluation closest to the 24-month followup time was 16, a mean improvement of almost 50% of the peak skin score. The mean rate of change was a decrease of 11 skin score units per year.

In contrast, the no improvement group began with a mean total skin score of 22, which increased to 28 during the first 12 months, but, for many patients, that was not their peak skin score. The mean peak skin score in the no improvement patients during the 2 years was 33. This was not significantly different from the mean peak skin score of 31 in the improved group. However, the mean time to reach the peak skin score in the no improvement patients was 1.2 years after the initial visit, compared with 0.5 years in the improved group ($P < 0.001$). The mean skin score nearest to the 2-year time after the initial visit in the no improvement patients was 31. This was significantly greater than the mean skin score of 16 at the same time in the improved group ($P < 0.001$). The overall mean rate of change in skin score in the no improvement group during this time was an increase of 8 skin score units per year.

The skin score in the improved group showed continued improvement from a mean score of 16 at the 2-year time point to a score of 11 at a mean of 7.2 years after the initial visit. The no improvement group did experience some further improvement in their skin thickening. At the time that their final skin score was determined at a mean of 6.2 years after the initial visit, the final mean score for skin thickening was 24, still somewhat greater than the initial mean skin score of 22. The difference in the mean final skin scores in these groups, which was determined at a similar point in time, was highly significant ($P < 0.001$).

During followup, there were significantly more deaths in the no improvement group, 47% versus only 18% in the improved group. Figure 1 shows the dramatic differences in the overall survival in the 2 groups. The cumulative survival rate from the time of first visit in the improved group was 90% at 5 years and 80% at 10 years. In contrast, the no improvement group had a 5-year cumulative survival rate of 77% and 10-year cumulative survival rate of 60% ($P < 0.0001$).

Table 2 summarizes the internal organ system involvement that occurred throughout the course of disease in the 2 groups of patients. An FVC <65% of predicted was used for the first part of the evaluation, but when used as a definition of severe organ involvement, the FVC was <55% of predicted (as described in Patients and Methods). Severe gastrointestinal involvement was included only in new severe organ involvement because of the small numbers.

These organ system involvements were similar in the 2 groups at the baseline evaluation, as shown in Table 2. Furthermore, new internal organ involvement that developed during the first 2 years of the study also occurred with similar frequency in both groups, and the presence of any one of these severe organ involvements was not significantly different between the 2 groups during that time. At the time of the final followup, and in spite of similar frequencies of severe organ involvements in the early part of the study, the cumulative

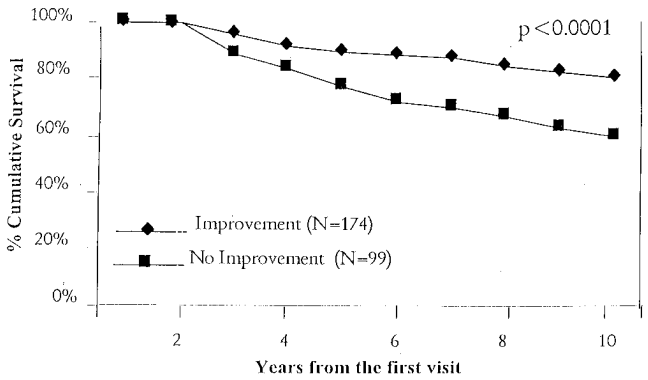

Figure 1. The percentage of cumulative survival in patients with skin improvement compared with those with no skin improvement in the first 2 years after the initial visit.

Table 2. Organ system involvement throughout the disease course of patients with and without improvement in skin thickening*

	Findings at initial (baseline) visit		New findings during 2 years after initial visit		Cumulative frequency of findings at final visit	
	Improved	No improvement	Improved	No improvement	Improved	No improvement
FVC <65% of predicted	11 (n = 151)	11 (n = 99)	3 (n = 92)	3 (n = 52)	14	20
Scleroderma heart	3	4	2	4	5	8
Renal crisis	7	11	5	7	11	18
Any severe organ involvement						
% of patients	21	23	10	13	30	46
Odds ratio	1.46		1.55		2.04	
95% CI	0.61–3.19		0.62–3.87		1.18–3.51	
P	NS		NS		<0.0005	

* Except where otherwise indicated, values are the percentage of patients. FVC = forced vital capacity; 95% CI = 95% confidence interval; NS = not significant.

frequency of severe organ involvement was significantly greater in those patients whose skin had not improved during the first 2 years. As shown in Table 2, severe internal organ involvement occurred cumulatively in 46% of the no improvement group compared with only 30% of the improved group (odds ratio 2.04, 95% confidence interval 1.18–3.51, $P < 0.0005$).

We next examined the potentially disease-modifying medications that were used during the 2-year study period (Table 3). There were small numbers in each group who received cytotoxic agents including methotrexate, cyclophosphamide, cyclosporin A, or FK-506, and thus these drugs were combined into one category. Prednisone was also used in small doses in small numbers of patients in each group. The majority of patients in both groups were treated with D-penicillamine, although there were significantly more patients in the improved group who ever received D-penicillamine during the first 2-year study period ($P < 0.002$). Also during this initial 2 years early in the disease, the patients in the improved group received D-penicillamine for a mean of 1.3 years, which was significantly longer than the mean of 0.7 years in the no improvement group ($P < 0.001$). More than half of the no improvement group discontinued D-penicillamine during the 2-year study period. Thirty-eight percent of these patients discontinued it because of toxicity within the first year of treatment, compared with 25% of the improved patients. Fourteen percent of the no improvement patients discontinued D-penicillamine because of failure to respond, but they had only taken the drug for 3–6 months. Another 15% discontinued it after 6 or more months of unresponsive treatment. There were no significant differences between the improved and no improvement groups in the frequency of the use of other medications in those patients who had never taken D-penicillamine or those who had discontinued D-penicillamine.

Tables 4 and 5 summarize the significant findings from multiple regression and Cox regression analyses using improvement in skin and deaths as outcome variables. The major factor that was significantly associated with the improvement in skin thickening was >1 year of treatment with D-penicillamine. Severe organ involvement did not correlate with improvement in skin thickness. The peak skin score was negatively associated with improvement; that is, patients with the highest peak skin scores were least likely to improve. Other variables, such as the age, sex, initial skin score, and disease duration at first visit, were not associated with the skin score improvement seen in these patients. The Cox regression analysis demonstrated that younger age at first visit, a lower peak skin score, increased duration of

Table 3. Possible disease-modifying medications used during the first 2 years after initial visit in patients with early diffuse scleroderma whose skin score improved or did not improve*

Medication	Improved (n =174)	No improvement (n = 99)
Methotrexate, cyclophosphamide, cyclosporine, or FK-506	10	12
Prednisone >15 mg/day	11	8
D-penicillamine use	82†	66
Duration of D-penicillamine during first 2 years, mean no. of years	1.3‡	0.7

* Except where otherwise indicated, values are the percentage of patients.
† Odds ratio 2.41 (95% confidence interval 1.32–4.43), $P < 0.002$ versus no improvement.
‡ $P < 0.001$ versus no improvement.

Table 4. Regression analysis for variables predicting an improvement in skin thickening

	Coefficient	Odds ratio	95% confidence interval	*P*
Disease duration at first visit	0.021	0.79	0.62–1.25	0.62
Skin score at first visit	0.071	1.13	0.95–1.14	0.16
Peak skin score	−0.081	0.87	0.80–0.96	0.21
D-penicillamine duration	0.799	2.43	1.45–3.31	0.0001
Age at first visit	−0.006	0.99	0.97–1.01	0.52
Sex	0.018	1.17	0.60–2.27	0.78
Severe organ involvement	0.039	1.09	0.83–1.34	0.52

D-penicillamine treatment, and a lower frequency of severe organ involvement were associated with improved survival.

DISCUSSION

A number of studies have shown that severe skin thickening in scleroderma is associated with renal crisis and decreased survival (2,3). Progressive skin thickening was considered the norm until recently, when the entity of regressive scleroderma was described (16). More recently, clinical trials have suggested that many untreated patients with diffuse scleroderma have spontaneous improvement in the degree of skin thickening over time (9). However, the frequency and significance of this type of improvement are not known.

Observational therapeutic studies in scleroderma have suggested that improved skin thickening is associated with an improved survival (8,17). This has led recent clinical trials to use skin thickening as the primary end point, since a much larger and longer study (up to 4 years) would be necessary if survival was used as the end point. The purpose of the present study was to examine the relationships between improvement in skin thickening and improved survival and to identify what variables were associated with this skin improvement.

We identified patients with early (<3 years) diffuse scleroderma who experienced improvement in the extent and severity of skin thickening during the first 2 years after their initial Pittsburgh visit. At the time of this study, we were following up nearly 500 patients with diffuse scleroderma who had <3 years of scleroderma symptoms at their initial visit and had lived for 2 years after the initial evaluation. Although only half of these patients had 2 or more skin scores obtained during the 2-year period after the initial visit, we did not identify any meaningful differences between those with and those without repeat skin scores that would otherwise bias the findings of this study.

The initial skin score (23.5 in study patients and 25 in non–study patients), duration of disease (1.3 years in both study patients and non–study patients), and frequency of severe internal organ involvement (33% in study patients in the first 2 years and 31% in the non–study patients) were virtually identical. Seventy-two percent of the study patients and 80% of the non–study patients were taking D-penicillamine. The cumulative survival rate was similar between the groups, 75% at 10 years in the study group and 65% at 10 years in the non–study group. The only difference between patients fulfilling the criteria for the study and those who did not was whether they were from the Pittsburgh referral area. Thus, we believe that the 278 study patients with diffuse scleroderma were representative of all patients with diffuse scleroderma.

This study focused on the subset of patients with early diffuse scleroderma who experienced significant skin improvement during the first 2 years after the initial visit. Sixty-three percent of the patients with diffuse scleroderma fulfilling the initial criteria experienced a significant improvement in skin thickening. The mean

Table 5. Cox regression analysis for variables predicting death

	Coefficient	Odds ratio	95% confidence interval	*P*
Age at first visit	−0.42	0.96	0.93–0.98	0.006
Peak skin score	−0.008	0.92	0.88–0.97	0.07
D-penicillamine duration	0.05	1.29	1.16–2.45	0.05
Skin score at first visit	0.001	1.05	1.01–1.08	0.80
Sex	0.50	1.64	0.82–3.28	0.16
Disease duration	0.06	0.94	0.58–1.52	0.17
Severe organ involvement	0.42	1.65	1.12–2.01	0.01

skin score at 2 years in these patients was ~50% of the peak skin score. Patients showing skin improvement also had a significantly improved survival. The 5- and 10-year cumulative survival rates of 90% and 80%, respectively, in the improved group was significantly better than the 77% and 60% rates in the patients without skin improvement. Thus, this study demonstrates that improvement in skin thickening is associated with improved survival. Improved skin thickening is thus a good prognostic feature and may be an acceptable surrogate for improved survival. It is possible that using changes in skin score in the future will allow therapeutic trials to be adequately powered using fewer patients. The guidelines for doing controlled trials in scleroderma suggest that 4 years is needed if survival is used as an end point (10). Perhaps this study will allow improved skin thickening to represent improved survival. This information also should be helpful for both patients and physicians to better understand the natural history of diffuse scleroderma.

Prior investigators have shown that the severity of skin thickening, per se, is a bad prognostic sign. In this study, the initial and peak skin scores in the 2 groups were not statistically significantly different. Also, there were no differences in the disease duration, age, sex, or serum autoantibody status that would likely affect survival. The patients who did not improve started out with slightly lower skin scores and increased to slightly higher skin scores than those of the improved patients (neither difference was significant). However, it took longer for patients in the no improvement group to reach their peak score, an average of 1.2 years after the initial visit compared with the 0.5 years in the patients who experienced improvement. The final skin score at 2 years in the no improvement group was 31, which was similar to their peak score of 33.

Thus, these skin scores suggest that patients with slower development of diffuse skin thickening are less likely to improve compared with those who have an earlier, more rapid course to the peak skin score. Conversely, those with a rapid increase in skin thickening are more likely to have skin improvement subsequently. However, there were many patients who died within the first 2 years after the initial visit who were not eligible for this study and who also had an early rapid increase in the skin thickening. This is likely to explain the findings of prior studies that concluded that a severe rapid increase in skin thickening was a poor prognostic sign (2,3).

As stated above, patients in the 2 study groups were very similar at the time of their initial visit. Recent studies have suggested that spontaneous improvement in skin thickening occurs in some patients with diffuse scleroderma (16). This may have occurred in our patients, but they had very impressive improvement in skin thickening which was more than has been documented in other studies. Generally, patients with severe skin thickening, such as that seen in our patients, who had mean maximum skin scores of 31–33, have a poor prognosis, but in this study, the improved skin group had a significantly improved survival. We carefully examined other factors that could be influencing the improvement experienced in these patients. Improved general medical treatment and better survival following scleroderma renal crisis may be playing a role. The frequency of severe organ involvement was similar, both at the initial visit and during the first 2 years. It was only after the 2-year followup period that the nonimproved group overall had significantly more severe organ involvement. This is likely to account for their late decrease in survival. The high frequency of D-penicillamine use during the first 2 years after the initial evaluation shows our bias in using it as a remittive agent. D-penicillamine was the principal factor that was associated with improvement in skin thickening. If all of the skin improvement in this study was spontaneous, as has been suggested, it would be unlikely to be associated with survival.

Uncontrolled series of patients treated with methotrexate, minocycline, anti–thymocyte globulin, and D-penicillamine have shown varying degrees of improvement (8,17–20). Recently, a controlled study of high-dose versus low-dose D-penicillamine did not find any significant skin score differences between the 2 groups after 2 years (9) and suggested that the patients all had spontaneous improvement. However, the patients who completed the study tended to have mild skin disease (skin score 20), and half of all patients who entered the study withdrew prior to completing the study. The mean improvement in skin score in both groups was 30%, suggesting that both low- and high-dose D-penicillamine could be effective or that this was spontaneous improvement. The present study demonstrates that a subset of scleroderma patients with severe skin involvement had a dramatic improvement in skin thickening and survival. The regression analysis for improved skin found that of the factors studied, the use of D-penicillamine during the first 2 years after the initial evaluation was the best predictor of skin improvement. A similar analysis showed that both severe organ involvement and D-penicillamine use were good predictors of survival.

Several recent clinical trials (9,14,18) have shown that patients may have had spontaneous improvement, but few had the impressive 50% improvement seen in many of our patients at 2 years. Thus, our patients had a greater amount of improvement in skin thickening compared with that seen in the controlled clinical trials. The explanation for this impressive improvement is not clear.

In summary, this study demonstrated that a large group of patients with early diffuse scleroderma who experienced significant improvement in skin thickening during the first 2 years after initial evaluation also had improved survival compared with the group of patients who did not experience improvement in skin thickening. There were no significant differences in organ system involvement initially or at 2 years to account for these skin thickening and survival differences. Regression analysis suggested that D-penicillamine use could be a predictor of skin improvement. Skin improvement is strongly associated with improved survival and may be able to be used as a survival surrogate in future clinical trials.

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