The relationship between the degree of skin fibrosis by sonoelastography and the degree of pulmonary involvement in scleroderma

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Background/aim: This study aimed to assess the relationship between skin fibrosis as determined by sonoelastography and the degree of pulmonary involvement as determined by high-resolution computed tomography (HRCT) in patients with diffuse cutaneous systemic sclerosis (dcSSc).

Materials and methods: This prospective study included 40 patients with dcSSc. All patients with HRCT scans underwent conventional ultrasonography and sonoelastography to determine skin thickness and degree of fibrosis. The degree of fibrosis was classified according to color-scale sonoelastography. The degree of pulmonary involvement was classified according to HRCT grading groups. The relationship between skin fibrosis and pulmonary involvement was investigated.

Results: There was a statistically significant difference between HRCT grading groups according to the sonoelastographic color scale (P < 0.001). Sonoelastographic color-scale groups showed a statistically significant difference in duration of disease (P = 0.013). No significant difference was found between the sonoelastographic color-scale groups in age, sex, or skin thickness.

Conclusion: Sonoelastography is a useful and reliable tool for assessing skin involvement in dcSSc. We found a good correlation between the degree of skin fibrosis as determined by sonoelastography and the degree of pulmonary involvement.

Key words: Pulmonary involvement, scleroderma, skin fibrosis, sonoelastography

1. Introduction
Scleroderma (Ssc) is a chronic multisystem disease characterized by vascular dysfunction, immune activation, and tissue fibrosis (1). Patients exhibiting fibrosis distal to the elbows and knees are included in the limited cutaneous disease subset (2). An increased risk of pulmonary arterial hypertension is recognized in this group (3,4). More extensive skin fibrosis involving the proximal portion of the limbs or the trunk is classified as diffuse cutaneous scleroderma (dcSSc), and patients with dcSSc have an increased risk of restrictive lung disease (3–5). Lung involvement is currently the leading cause of morbidity and mortality in SSc, with a prevalence ranging between 30% and 90% of patients (5,6). A relationship between skin and internal organ involvement has been shown in some studies (7,8). Sonoelastography is an emerging technology of ultrasonic imaging of soft tissue strain and elasticity aimed at providing information about the mechanical properties of tissues, such as their hardness or stiffness. This technique has been used in breast, thyroid, prostate, pancreas, lymph nodes, testes, and liver imaging; recently some studies have also used sonoelastography for the assessment of scleroderma (9–12).

We aimed to evaluate the relationship between skin fibrosis as determined by sonoelastography and the degree of pulmonary involvement as determined by high-resolution computed tomography (HRCT) in patients with scleroderma.

2. Materials and methods
This cross-sectional observational study was approved by the local ethics committee of the School of Medicine of Adnan Menderes University. The study included patients with dcSSc who were classified according to the American College of Rheumatology criteria (13). Eligible patients with dcSSc were those who underwent HRCT for the determination of interstitial lung involvement during the last month. Patients with a disease that could cause interstitial lung involvement other than dcSSc were excluded. Patients’ demographic and clinical data including age, sex, and disease duration were recorded.

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Sonoelastography was performed using an Aplio 500 (Toshiba Medical System Corporation, Tokyo, Japan) machine with a 15-MHz linear probe. The target site was the volar aspect of the middle forearm. Sonoelastographic evaluation started after a conventional ultrasound examination, which was performed to identify the interface between the epidermis, dermis, and subcutis. Vertical thickness of the skin was assessed in a B-mode two-dimensional longitudinal image using a setting for superficial structures with a single focal zone set at the interface between the skin and subcutaneous fat. A gel pad was used to provide an acoustic interface and to prevent local artifacts from interposition of air. Sonoelastography examinations were performed by applying slight compression to the region of interest with the ultrasound probe. The pressures and speeds of the manual compressions were adjusted to view the subcutaneous fat tissue as a mix of red and green. Both the B-mode and the elastographic images were displayed on the screen during the sonoelastographic examinations. The elastograms were obtained by superimposing the color-scale images on the B-mode images. The elastographic images were considered related to the degree of tissue elasticity in accordance with a color scale varying from red to blue, in which red corresponds to soft tissue, green corresponds to intermediate tissue, and blue corresponds to hard tissue (9). Patients were divided into groups according to the color scale in sonoelastography: group 1 - red pattern; group 2 - green pattern; and group 3 - blue pattern (9,12).

All patients underwent HRCT examinations using a 128-detector, 160-slice computed tomography device (Prime Aquilion, Toshiba Medical Systems, Otawara, Japan). Scans were obtained at full inspiration from the apex to the lung base with patients in the supine position. Scanning parameters were as follows: 120 kV, 300 mAs, acquisition time 0.8 s, slice thickness 1 mm with 0.6-mm reconstructions, and the smallest possible field of view (FOV) covering both lungs. The scans were viewed with a window level of 600 Hounsfield units (HU) and a width of 1600 HU. HRCT grading of the thorax included: 0 - normal; I - ground-glass appearance more than reticular; II - equal ground-glass and reticular areas; III - reticular area more than ground-glass; and IV - diffuse honeycomb lesions in the upper and central zones. Due to the low number of patients in each subgroup, HRCT grade 0 was considered as no pulmonary involvement, grades I and II were considered the low-grade group, and grades III and IV were considered the high-grade group (14).

2.1. Statistical analysis
All statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). The Mann-Whitney U test was used to compare nonparametric continuous variables in independent groups based on the color scale. Descriptive data were given as frequencies, percentages, means, and standard deviations. P < 0.05 was considered statistically significant.

3. Results
The study included 40 patients with dcSSc: 28 women (70%) and 12 men (30%), with or without pulmonary involvement. The study period lasted from January 2015 to September 2016. The mean age of the patients was 58.8 years (range: 40–70), and the mean duration of disease was 202 months (range: 36–328). There was smoking history in three patients. Six patients had comorbid diseases such as diabetes mellitus, hypertension, and coronary artery diseases. All patients were receiving treatment according to EULAR recommendations (15). According to the color scale, there were no patients with the red pattern (group 1); 14 patients had the green pattern (group 2) and 26 patients had the blue pattern (group 3). The mean skin thickness for all patients was 1.5 ± 0.35 mm. Patients were further subdivided according to their HRCT findings; 10 patients (25%) were in the group with no pulmonary involvement; 16 patients (40%) were in the low-grade group and 14 patients (35%) were in the high-grade group. There was a statistically significant difference between HRCT grading groups according to the sonoelastographic color scale (P < 0.001). A higher rate of the blue pattern was seen in the high-grade pulmonary involvement group. There was also a statistically significant difference in duration of disease between the sonoelastographic color-scale groups (P = 0.013). There was no significant difference in age, sex, or skin thickness between the sonoelastographic color-scale groups (P = 0.16, P = 0.88, and P = 0.63, respectively). The demographic features of patients and HRCT findings by color pattern groups are shown in the Table.

4. Discussion
We believe that this is the first study to indicate a relationship between the degree of pulmonary involvement and skin involvement as detected by sonoelastography in patients with dcSSc. We also found that color-scale patterns determined by sonoelastography are able to distinguish the degree of pulmonary involvement as shown by HRCT (Figures 1 and 2). In sonoelastography, the blue pattern group indicating hardness showed excessive pulmonary involvement. There was also a relationship between the duration of disease and the color pattern in sonoelastography.

In systemic sclerosis, skin involvement is a characteristic manifestation. It can range from edema to fibrosis and eventually to atrophy because of the excessive dermal deposition of collagen and changes in the architecture of the connective tissue (16). Several studies have shown that the extent of skin involvement predicts internal organ...
involvement and general outcome of patients (17,18). Skin thickness assessment by palpation (modified Rodnan skin score) is widely used in SSc, but it is a qualitative method and has interobserver variability. High-frequency ultrasound has been suggested for the determination of skin thickness and echogenicity (16,19). However, it is not useful for assessment of skin elasticity. Elastosonography allows for the examination of the elastic properties of the skin with a color scale superimposed on a gray-scale image produced by conventional ultrasound (9–12). The principle behind this technique is that the excessive dermal deposition of collagenous and noncollagenous extracellular matrix causing fibrosis reduces skin elasticity. Initial studies carried out with elastosonography in systemic sclerosis, such as that of Iagnocco et al. (9), indicated that dermal stiffness is greater in patients with systemic sclerosis than in controls. Specific color patterns of the dermis have been identified in SSc patients compared to healthy subjects, but several aspects need to be further confirmed and studied. Cannàò et al. (12) described an elastographic scale based on perioral segments and showed that perioral stiffness is greater in patients with systemic sclerosis than in controls. Hou et al. (20) used acoustic radiation force elastosonography in SSc and defined this technique as feasible and reliable for assessing skin involvement in patients with dcSSc.

Table. Demographic features and HRCT findings of patients by color pattern groups.

<table>
<thead>
<tr>
<th></th>
<th>Green pattern group, mean ± SD n = 14</th>
<th>Blue pattern group, mean ± SD n = 26</th>
<th>P -value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F)</td>
<td>n = 10</td>
<td>n = 18</td>
<td>0.88</td>
</tr>
<tr>
<td>Age, years</td>
<td>57.71 ± 10.44</td>
<td>55.19 ± 9.35</td>
<td>0.16</td>
</tr>
<tr>
<td>Disease duration, months</td>
<td>56.93 ± 42.80</td>
<td>99.08 ± 58.87</td>
<td>0.013</td>
</tr>
<tr>
<td>Skin thickness (mm)</td>
<td>1.50 ± 0.27</td>
<td>1.52 ± 0.39</td>
<td>0.63</td>
</tr>
<tr>
<td>HRCT grading groups</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>No pulmonary involvement</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Low-grade group</td>
<td>4</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>High-grade group</td>
<td>3</td>
<td>14</td>
<td></td>
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F: Female, n: number, HRCT: high-resolution computed tomography, SD: standard deviation. Statistically significant values are given in bold font.

Figure 1. A 62-year-old female patient with dcSSc showed a green pattern on color-scale sonoelastography (A, B) and a normal HRCT scan (C).
Interstitial lung disease (ILD) is a devastating and significant cause of death in patients with SSc. In early autopsy studies, up to 100% of patients were found to have parenchymal involvement (6). HRCT has now become an important part of the routine detection and evaluation of SSc-ILD (21,22). It has been shown to be more accurate than chest radiography in detecting and characterizing diffuse lung diseases, and furthermore, abnormalities on HRCT correlate more closely with physiologic parameters (23). Although pulmonary involvement is more common in dcSSc, no reliable association has been found between pulmonary involvement and severity of skin involvement (24). Cottrell et al. (25) showed that the presence of pulmonary involvement was positively associated with the pattern of skin involvement in 2205 patients with SSc. They used the modified Rodnan skin score for the severity of skin involvement. In our study, we investigated the relationship between the degree of skin fibrosis as classified by sonoelastography and the degree of pulmonary involvement. We showed that there was a good correlation between skin fibrosis and the degree of pulmonary involvement.

There are several limitations to our study. First, we had a relatively small number of patients. Second, there were no patients in the red pattern group. Third, the semiquantitative sonoelastographic method was operator-dependent. Fourth, the assessment of pulmonary involvement was made only by HRCT, not by pulmonary function tests. Further studies are needed to confirm our findings and determine the validity of this new imaging modality.

In summary, sonoelastography is a useful and reliable tool for assessing skin involvement in dcSSc. There was a good correlation between the degree of skin fibrosis determined by sonoelastography and the degree of pulmonary involvement. It seems that noninvasive sonoelastographic assessment of the skin can give us an idea about pulmonary involvement in patients with dcSSc. Further studies with larger cohorts of patients are needed to confirm the validity of sonoelastography for predicting the severity of lung involvement in systemic sclerosis.

References


