Is there a Correlation between Seventeen Site Sonologic Skin Thickness and Severity of Interstitial Lung Disease in Patients with Scleroderma Related Interstitial Lung Disease ?

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ABSTRACT

Introduction: Scleroderma, also known as Systemic Sclerosis (SSc), is an autoimmune disease characterized by diffuse fibrosis of skin and internal organs. Pulmonary involvement is commonly silent, whereas skin fibrosis is the usual clinical feature drawing patient's attention. Interstitial lung disease (ILD) is a common and serious complication of Scleroderma. The aim of this study was to investigate the relationship between seventeen site sonologic skin thickness and severity of Interstitial lung disease (ILD) as determined by high resolution computed tomography score for ILD in patients with Scleroderma related interstitial lung disease (SSc- ILD) and thus reducing patients exposure to radiation.

Material and Methods: The study comprised of 30 consecutive patients of scleroderma with pulmonary involvement. All patients underwent high resolution computed tomography (HRCT) scan of the lungs, pulmonary function test (PFT) and high resolution ultrasonography (USG) of the skin. The severity and extent of SSc – ILD was evaluated by a semi – quantitative scoring system. Full skin' thickness was measured on high resolution USG at seventeen sites corresponding to those of modified Rodnan skin score and total sonologic skin thickness was obtained by summing the skin thickness of all the seventeen sites in each patient.

Results: The sum of seventeen site sonologic skin thickness was 26.41 +/- 4.27mm.The "total HRCT score" for ILD was 25+/- 4

Conclusion: The current study failed to establish any definite correlation between seventeen site sonologic skin thickness and severity of ILD as determined by "total HRCT score". However, a multi-centric study involving a larger number of patients is required to further investigate the relationship

Keywords: Systemic Sclerosis; SSC-ILD-Scleroderma-interstitial lung disease; Skin ultrasound; Computed tomography; Scoring methods.

INTRODUCTION

Scleroderma, also known as Systemic Sclerosis (SSc), is an autoimmune disease of small vessels and connective tissue,which is characterised by diffuse fibrosis of skin and internal organs; most frequently the lungs and gastro-intestinal tract. SSc typically occurs in 3rd to 5th decade of life and has a 3:1 female predilection. The fibrosis occurs due to the release of cytokines by various immune cells, including macrophages, T- cells and platelets at the site of vascular injury. This in turn, stimulates fibroblast production of extracellular matrix.[1] Almost all patients have cutaneous involvement. Based on the extent of skin involvement, Systemic sclerosis has been subdivided into diffuse cutaneous scleroderma, limited cutaneous scleroderma and systemic sclerosis sine Scleroderma.[2] Upto 80% of the patients have limited cutaneous sclerosis with skin changes confined to face and extremities. The degree of cutaneous involvement is an important prognostic factor in these patients, as it predicts mortality.[3] Rodnan skin score.[4] (introduced by Rodnan in 1979) or a modified Rodnan skin score is the established method to assess skin thickness in these patients. Despite its simplicity and usefulness, the Rodnan skin score has its drawbacks. High resolution Ultrasonography (USG) is a more reliable and sensitive method for measuring skin thickness. It shows thickening of the so-called uninvolved skin, suggesting that palpation underestimates the skin fibrosis. A seventeen – site skin ultrasound has been found to be a reliable measure of skin thickness in SSc patients.[5] Pulmonary involvement is common in patients with Scleroderma. Currently, ILD is the leading causes of death and accounts for about 60 % of SSc-related deaths. Most patients have a gradual deterioration in pulmonary function while some have a rapidly progressive course. The greatest decline in pulmonary function occurs within the first four years of disease and moderate or severe restrictive lung disease is detectable in approximately 40 % of these patients. High resolution computed tomography (HRCT) is currently the 'gold standard' for non – invasive diagnosis of ILD.[6] In this study,we investigated the relationship between seventeen site sonologic skin thickness and total HRCT score for ILD to find if sonologic skin thick-

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ness allows prediction of the severity of ILD in SSc - ILD patients. The ability to predict the severity of ILD by sonologic skin thickness will help in avoiding CT scans and thus reduce patients exposure to radiation.

MATERIAL AND METHODS

Our study included 30 consecutive patients (26 females and 4 males) of Scleroderma related interstitial lung disease (SSc-ILD) who presented to the Department of Dermatology of SKIMS, Medical College, Srinagar from March 2011 to July 2014.The diagnosis of Scleroderma was made according to the American College of Rheumatology criteria.[7] Patients were considered to have limited SSc if their skin thickness was confined to areas of extremities below the elbows and knees and above the clavicles. Patients were considered to have diffuse SSc if their skin thickness involved proximal extremities and /or torso. The diagnosis of ILD was made on basis of HRCT scan of the lungs. The HRCT scan eligibility was determined by the presence of ground glass opacities and / or reticular intralobular thickening with or without bronchiolectasis, traction bronchiectasis and honey- combing. Informed consent was obtained from all the patients. The study was approved by the institute ethical committee.

A detailed history was obtained in all the patients. Patient's age, sex and duration of disease were documented. The duration of disease was defined as the time from the outset of first non- Raynaud's phenomenon manifestation.History of smoking (defined as current smoker or ex- smoker with greater than 10 pack – years), dry cough and exertional dyspnea were recorded. Detailed general and systematic examination was done and modified Rodnan skin score was assessed. Besides routine baseline investigations, levels of anti-nuclear antibodies (ANA), anti-centromere antibodies (ACA) and anti-topoisomerase I antibodies (Anti- Scl-70) were done. High resolution computed tomography (HRCT) of the lungs was performed in all the patients on128 – slice spiral CT scanner (Siemens Somatom Definition AS), in full inspiration in supine position. A bone reconstruction algorithm with lung window was used. No intravenous contrast was administered. Prone scans were performed to exclude gravity dependent perfusion, whenever required. All the HRCT examinations were studied by an experienced Radiologist.The following HRCT scan findings were recorded: ground glass opacities, irregular pleural margin,septal or subpleural lines, honey combing, subpleural cyst, intralobular thickening, bronchiolectasis and traction bronchiectasis. A semi-quantitative scoring system proposed by Warrick etal,[8] was used to assess the severity and extent of ILD. The index includes a 'severity score` ranging from 0 (normal) to 15 (all lesions present) and an 'extension score` ranging from 0 (normal) to 15 (more than nine pulmonary segments involved). The grading of abnormalities of 'severity score` is: ground glass opacities (1), irregular pleural margin (2), septal or subpleural lines (3), honey combing (4) and subpleural cyst (5). The grading of 'extension score` for each abnormality is: 1 to 3 bronchopulmonary segments involved (1), 4 to 9 segments involved (2) and more than 9 segments involved (3). A total HRCT score was obtained by summing the 'severity' and 'extension' scores. Pulmonary function tests (PFT) were performed within one month of the HRCT scan in all the patents using standardized methods. Total lung capacity (TLC), forced vital capacity (FVC) and forced expiratory volume in 1- sec to forced vital capacity ratio were recorded and expressed as percentage of predicted normal. Predicted normals were obtained from published standards.[9] High resolution ultrasonography (USG) of the skin was done by another trained Radiologist who was unaware of the results of other investigations. A Philips IU-22 ultrasound machine fitted with a 20 MHz linear transducer was used. All USG examinations were done, within one week of the HRCT scan of the lungs, before noon to avoid diurnal variation in skin edema. The transducer was placed perpendicular to the skin surface using moderate thickness of ultrasonic gel so as to separate the epidermal echo from probe echo on the image. An electronic calliper was used to measures the 'full skin' thickness by identifying surface-skin and skin-subcutis interfaces on two –dimensional B-mode image. Skin thickness was measured at seventeen sites corresponding to those of the modified Rodnan skin score. The seventeen sites examined were: dorsum of middle phalanx of middle finger (2 sites); dorsum of hand (2sites); anterior aspect of middle portion of upper arm (2 sites); centre of forehead (1 site);anterior chest between sternal angle and sternal notch (1 site); anterior aspect of mid abdomen (1 site); anterior aspect of mid -thigh (2 sites); antero – lateral aspect of middle portion of lower leg (2 sites) and dorsum of foot (2 sites).The total sonologic skin thickness was obtained by summing the thickness of all the seventeen sites in each patient.

Statistical analyses

Statistical analyses was performed using SPSS software package, version 16. Continuous variables are expressed as mean ± SD. Categorial variables are represented as counts and percentages. Spearman's correlation coefficient was used for correlation between total sonologic skin thickness and total HRCT score for ILD. P-values above 0.05 were considered statistically insignificant.

RESULTS

We studied 30 consecutive patients (aged 29.4 to 49 years) of SSc –ILD. The clinical and demographic characteristics of the patients are given in Table 1. Twenty six (86.7%) patients were female. Eighteen (60%) patients had diffuse SSc and remaining 12 (40%) patients had limited SSc. Exertional dyspnea was present in 23 (76.7%) patients and dry cough was present in 19 (63.3%) patients. The mean duration of disease was 5.8± 2.2 years. Three patients were smokers; the mean duration of smoking was 6.2 ± 4 years. The mean per-

AverageAge (years)+/- mean	**AverageAge (years)+/- mean**
Number of female patients (%)	Number of female patients (%)
Average Disease duration (years)+/- SD	Average Disease duration (years)+/- SD
Number of patients having Exertional dyspnea (%)	Number of patients having Exertional dyspnea (%)
Number of patients having Dry cough(%)	Number of patients having Dry cough(%)
Smoking history	Smoking history
Antibody positivity	
Number of patients having ANA	24 (80%)
Number of patients having ACA	8(26.7%)
Number of patients having Anti- Scl-70	9(30%)
Pulmonary function tests	
Average FVC (%) predicted +/- SD	68.6+/- 12.9
Average TLC (%) predicted +/- SD	70.4+/- 11.9
Average FEV_1 / FVC ratio +/- SD	82.5+/-7.5
mRST score(range 0-51)+/- SD	mRST score(range 0-51)+/- SD
Seventeen site sonologic skin thickness (mm)+/- SD	Seventeen site sonologic skin thickness (mm)+/- SD
Total HRCT score range (0-30)	Total HRCT score range (0-30)

Table-1: Clinical and demographic characteristics of the patients with SSc-ILD.(n=30)

centage of predicted values of forced vital capacity was less in patients with diffuse SSc than in limited SSc (69.5±16.8 vs 67.8±15.4; p= NS). Mean percentage of predicted values of forced expiratory volume in 1-s to forced vital capacity(FEV_1/ FVC ratio) was less in patients with limited SSc compared to diffuse SSc (80.8±6.5 vs 84.3±7.5; p= NS).

Ground glass opacities were the most frequent HRCT scan findings of lungs seen in 28 (93.3 %) patients followed by reticular intralobular thickening seen in 26 (86.7%) patients. Honey combing was seen in 11 (36.6%) patients and pleural thickening in 2 (6.7 %) patients. All HRCT scan abnormalities were most common in lower lobes without right or left predominance. The total HRCT score for ILD was 25+/- 4.

Fig I and 2 show the HRCT scan of lungs in a patients with SSc- ILD.

High resolution USG of the seventeen anatomical sites showed a considerable overlap in skin thickness.

Fig. 3 shows high resolution USG image of skin over dorsum of hand for measuring skin thickness. Patients with diffuse SSc showed thicker skin on hands, forearms, legs and chest than did patients with limited SSc; however, the differences did not reach statistically significant values. Also, there was a considerable overlap in the USG skin thickness in patients with different mRS score.The sum seventeen site sonologic skin thickness was 26.41+/- 4.27 mm

Figure-1: HRCT image of lung showing interlobular septal thickening and bronchiolectasis

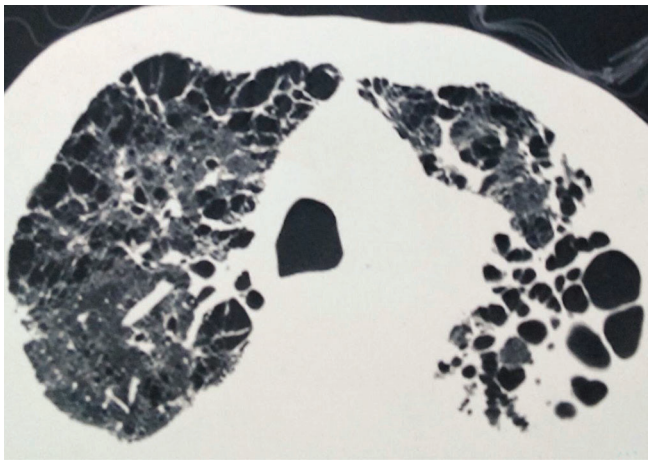

Figure-2: HRCT image of lung showing honeycombing and bronhiectasis

DISCUSSION

Scleroderma is an auto-immune disease characterised by diffuse fibrosis of skin and internal organs. The degree of cutaneous involvement is an important prognostic factor in these patients as it predicts mortality.[3] High resolution USG is a sensitive method for measuring skin thickness in these patients, as it shows thickening of so called uninvolved skin also. A seventeen site skin ultrasound has been found to be reliable in measuring skin thickness in SSc patients.[5] Pulmonary involvement is common and interstitial lung disease (ILD), occurs in approximately 80 % of these patients. HRCT is currently, the gold standard for non invasive diagnosis of ILD.[12] The HRCT features of SSc –ILD are similar to those of non specific interstitial pneumonia(NSIP). As the disease

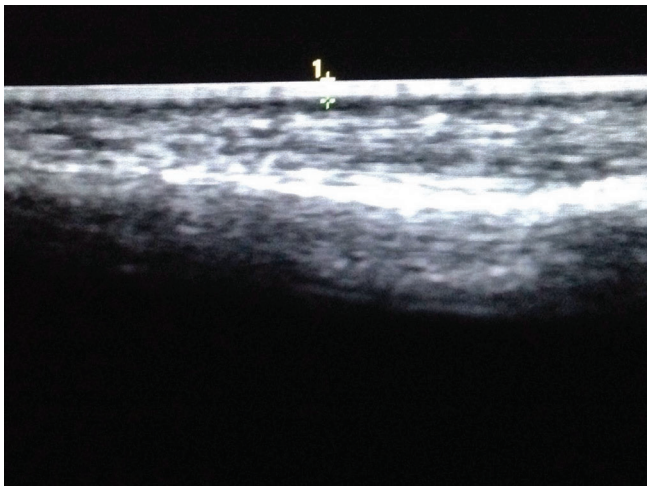

Figure-3: High resolution sonography of skin over dorsum of hand for measuring skin thickness 1 + +: thickness of skin of dorsum of hand

progresses, ground glass opacities get replaced with reticular intralobular thickening, bronchiolectasis, traction bronchiectasis and honey- combing. These findings of ILD by HRCT have been found in 91% of patients with Scleroderma.[13] Various HRCT scoring methods have been developed to quantify SSc- ILD.[14] Although, ILD represents a major complication of Scleroderma, pulmonary involvement is commonly silent, whereas the skin fibrosis is the usual clinical feature drawing patient's attention. Hence the study was undertaken to determine whether seventeen site sonologic skin thickness could predict the severity of ILD in SSc- ILD patients.

Conclusion: The present study failed to establish any definite correlation between the two. This can be explained by the fact that the skin thickness usually reaches a peak in the first three years due to skin edema that occurs early in the course of disease. However, when the early edematous phase is replaced by the indurative phase in which the skin thickness decreases. On the other hand, ILD worsens over time but shows a quite variable course

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