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Original article

Role of skin ultrasound in diagnosis of systemic sclerosis compared to Modified Rodnan skin score, inflammatory markers and disease activity indices

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Abstract:

The goal of this study To assess if high frequency ultrasound correlates with modified Rodnan skin score and inflammatory markers and if it can differentiate between Systemic sclerosis and healthy individuals and if HFU can detect subclinical skin thickening. We recruited 30 consecutive patients with SSc and 40 controls in this case control study. Skin thickness was measured by 20-22 MHz ultrasonic probe at 3 different skin sites bilaterally (at third proximal interphalyngeal, third metacarpophalyngeal and wrist joints bilaterally). Total skin thickness (TST) by HFU and skin thickness using mRSS were recorded and compared to HFU.

The final results of our work show that total skin thickness in patients with SSc was higher than in healthy controls ($P < 0.001$), and correlated positively with total mRSS and correlated negatively with CRP. Patients with higher TST had higher mRSS . The area under the receiver operator characteristic (ROC) curve yielded sensitivity of 90% and specificity of 85% at the predicted probability of 1.4 mm as the optimal cut off point to access of mean skin thickness.

1. Introduction:

Systemic sclerosis is a disease of unknown etiology affecting the connective tissue and characterized by sclerotic alteration of the skin and some other organ systems. Histological findings on the skin are massive deposition of synthesized collagen, perivascular mononuclear cell infiltrate and vascular damages[1].

The resultant skin tightening is the hallmark of this disease and causes significant morbidity due to limitation of finger movements, mouth opening, and restriction of chest expansion. There are two variants of SSc, limited and diffuse, the latter involves skin proximal to the elbows and the knees[2]. Clinical quantification of skin tightening is usually done by the modified Rodnan skin score)mRSS([3], which grades skin tightening from 0 to 3 in seventeen areas of the body (fingers, hands, forearms, arms, face and neck, chest, abdomen, thighs, legs, feet) with maximal score of 51. The mRSS was established by Rodnan in 1979 and is a validated method to evaluate skin thickening in SSc worldwide [4-6].

The mRSS is a popular parameter for reflecting changes in cutaneous involvement in patients with SSc because it is intuitive, comprehensive and repeatable in studies [6-8].The role of ultrasound (US) is becoming more and more relevant in the assessment of rheumatic diseases with wide availability and recent improvement in technology coupled with portability, low cost. and safety, which makes it the first-choice imaging investigation for the evaluation of musculoskeletal diseases [9].

2. Patient and Methods:

This was a case control study performed in Beni-Suef university hospital and within 1 year from November 2020 to November 2021 involving 70 case verbal consents were obtained.

Inclusion criteria:

Systemic sclerosis patient from 18 to 70 years old.

Exclusion criteria:

- Mixed connective tissue disease.
- Patient below 18 and after 70 years old.
- Patients with other diseases known to affect the skin.

Methodology

All patients recruited for the review were exposed to clinical assessment in the form of cautious history taking including age ,sex , medications and infection and clinical examination ,clinical labs as CRP, ESR An expert physician assessed the mRSS on 0±3 ordinal scale in 17 physical destinations. The 17 locales were reciprocal center finger, hand dorsum, lower arm, upper arm, thigh, lower leg, foot dorsum, brow, front of the chest.

The patient will be examined by using [LOGIq p9] ultrasound device equipped by high frequency probe 20- 22 MHZ linear array to asses skin thickness and echogenicity on wrist , third metacarpophalyngeal and

third proximal interphalyngeal joints on both hands.

The ethics committee of Beni-Suef university approved the study(approval no 05012020) . and all participants signed informed consent.

Statistical methodology:

Sample size was calculated based on online openepi calculator. The required sample was calculated at 95% two sided confidence interval (CI), 80% power and 1:1 controls to cases ratio; so the sample size will be 30 cases and 40 controls

Results from OpenEpi, Version 3, open source calculator--SSCC.

3. Results:

The study conducted in Beni-Suef university within one year from November 2020 to November 2021 included 30 cases including 28 females ,2 males with systemic sclerosis and 40 controls including 38 females, 2 males who were prospectively recruited from Beni- suef university hospital immunology clinic .

The table (1) illustrates that there was a statistically significant difference with p-value <0.001 between study groups with higher mean of skin thickness score at PIP, MCP, and Wrist joints on right and left sides among cases, also higher mean of total and mean skin thickness among cases **.**

Variables	Cases (N=30)		Control (N=40)		P-value	Sig.
	Mean	SD	Mean	SD		
PIP						
Right side	1.66	0.37	1.16	0.19	**<0.001**	**HS**
Left side	1.63	0.31	1.13	0.20	**<0.001**	**HS**
MCP						
Right side	1.59	0.26	1.19	0.16	**<0.001**	**HS**
Left side	1.62	0.17	1.21	0.19	**<0.001**	**HS**
Wrist						
Right side	1.54	0.25	1.22	0.24	**<0.001**	**HS**
Left side	1.55	0.27	1.24	0.21	**<0.001**	**HS**
Total skin thickness						
Mean	1.59	0.20	1.19	0.16	**<0.001**	**HS**
Total	9.59	1.2	7.15	0.96	**<0.001**	**HS**

Table (1): Comparisons of skin thickness in different joints between study groups

The table (2) illustrates that there was a statistically significant higher percentage of iso- and hyperechoice echogenicity in dermis layer at PIP joints on right and left sides among cases with p-value <0.05.On the other hand, there was no statistically significant difference with p-value >0.05 as regards epidermis layer as all cases and controls had hyperechoice echogenicity on both sides.

PIP	**Cases** (N=30)		**Control** (N=40)		**P-value**	**Sig.**
	No.	**%**	**No.**	**%**		
Epidermis (hyperechoice)						
Right side	30	100%	40	100%	----	---
Left side	30	100%	40	100%	----	---
Dermis layer on right side						
Isoechoic	4	13.3%	0	0%	**0.006**	**HS**
Hypoechoic	23	76.7%	40	100%		
Hyperechoic	3	10%	0	0%		
Dermis layer on left side						
Isoechoic	6	20%	0	0%	**0.002**	**HS**
Hypoechoic	22	73.3%	40	100%		
Hyperechoic	2	6.7%	0	0%		

Table (2): Comparisons of skin layer echogenicity of PIP joint between study group

The table(3) illustrates that there was no statistically significant difference with p-value >0.05 between study groups as regards ultrasound measures for skin layers dermis and epidermis echogenicity at MCP joints on right and left sides.

MCP	**Cases** (N=30)		**Control** (N=40)		**P-value**	**Sig.**
	No.	**%**	**No.**	**%**		
Epidermis (hyperechoice)						
Right side	30	100%	40	100%	----	---
Left side	30	100%	40	100%	----	---
Dermis layer on right side						
ISO	1	3.3%	0	0%	0.2	NS
Hypo	27	90%	40	100%		
Hyper	2	6.7%	0	0%		

Dermis layer on left side						
ISO	1	3.3%	0	0%	0.3	NS
Hypo	28	93.4%	40	100%		
Hyper	1	3.3%	0	0%		

Table (3): Comparisons of skin layer echogenicity of MCP joint between study group

The table (4) illustrates that among cases there was statistically significant **positive** correlation with p-value <0.05 between mRSS and skin thickness by HFU at MCP, and wrist joints on right side. This indicated that an **increase** in skin thickness at these joints will associate with **increase** in mRSs score. On the other hand, there was no statistically significant correlation with p-value >0.05 between mRSS and other variables among cases.

Variables	**MRSs**		
	R	**P-value**	**Sig.**
Age (year)	**-0.07**	**0.7**	**NS**
Duration of disease (years)	**-0.29**	**0.1**	**NS**
PIP			
Right side	**0.34**	**0.06**	**NS**
Left side	**0.32**	**0.08**	**NS**
MCP			
Right side	**0.57**	**0.001**	**HS**
Left side	**0.17**	**0.3**	**NS**
Wrist			
Right side	**0.45**	**0.01**	**S**
Left side	**0.34**	**0.07**	**NS**
Skin thickness			
Mean	**0.49**	**0.006**	**HS**
Total	**0.49**	**0.005**	**HS**

Table (4): Correlation between mRSS score with skin thickness scores and other variables by ultrasound among cases

The table (5) illustrates that there was a statistically significant difference with p-value <0.05 between study groups showing lower mean and total skin thickness score among cases with pulmonary hypertension and abnormal high resolution CT findings, on the other hand there was no statistically significant difference in skin thickness between CRP groups

Wrist	**Mean skin thickness**		**P-value**	**Sig.**	**Total skin thickness**		**P-value**	**Sig.**
	Mean	SD			**Mean**	**SD**		
ECHO								
Normal	1.64	0.19	0.04	S	9.84	1.1	0.03	S
PHTN	1.46	0.19			8.75	1.1		
HRCT								
Normal	1.71	0.19	0.01	S	10.3	1.2	**0.01**	**S**
Abnormal	1.52	0.18			9.1	1.1		
CRP								
Negative	1.55	0.14	0.4	NS	9.30	0.81	**0.4**	**NS**
Positive	1.62	0.23			9.7	1.4		

Table (5): Comparisons of skin thickness in different radiological and CRP findin

Table (6) illustrates that the skin thickness at PIP joints shows higher sensitivity and specificity with a sensitivity of (86.7 %,) and a specificity of (95%) at cut off value (1.38 mm) versus a sensitivity of (80%, and 76.7%) and specificity of (95%, and 87.5%) at cut off 1.45, and 1.43 respectively for MCP, and wrist joints.

Variable	**Sensitivity**	**Specificity**	**AUC**	**Cut off point**	**p-value**	**CI**
PIP	86.7%	95%	94.7%	1.38	**<0.001**	98-100
MCP	80%	95%	95.2%	1.45	**<0.001**	88.9-100
Wrist	76.7%	87.5%	83.8%	1.43	**<0.001**	73.5-94
Mean skin thickness	90%	85%	94.6%	1.34	**<0.001**	88-100
Total skin thickness	90%	85%	94.6%	8.05	**<0.001**	88-100

Table (6): Sensitivity and specificity of skin thickness at each joint in diagnosis of cases .

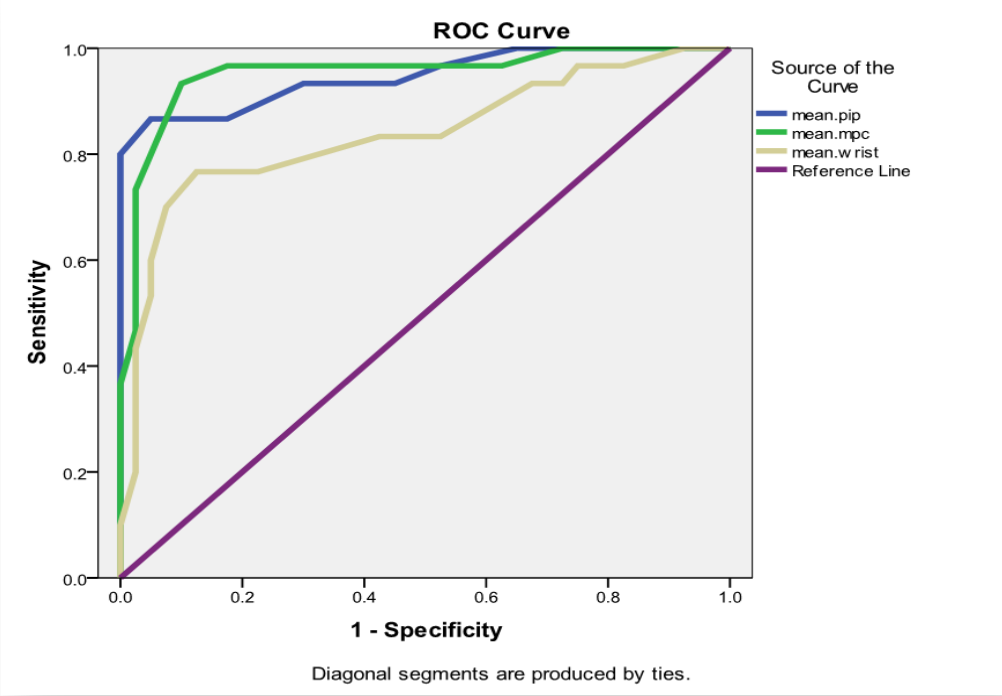

Figure (1): ROC curve for ultrasound different joints skin thickness in diagnosis of scleroderma cases.

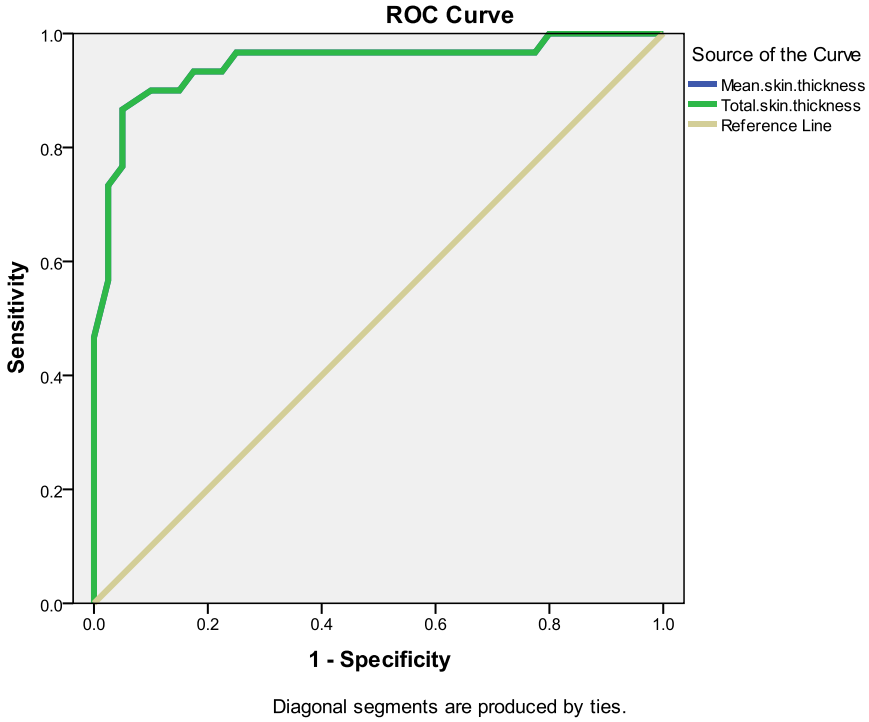

Figure (2): ROC curve for ultrasound skin thickness in diagnosis of systemic sclerosis cases.

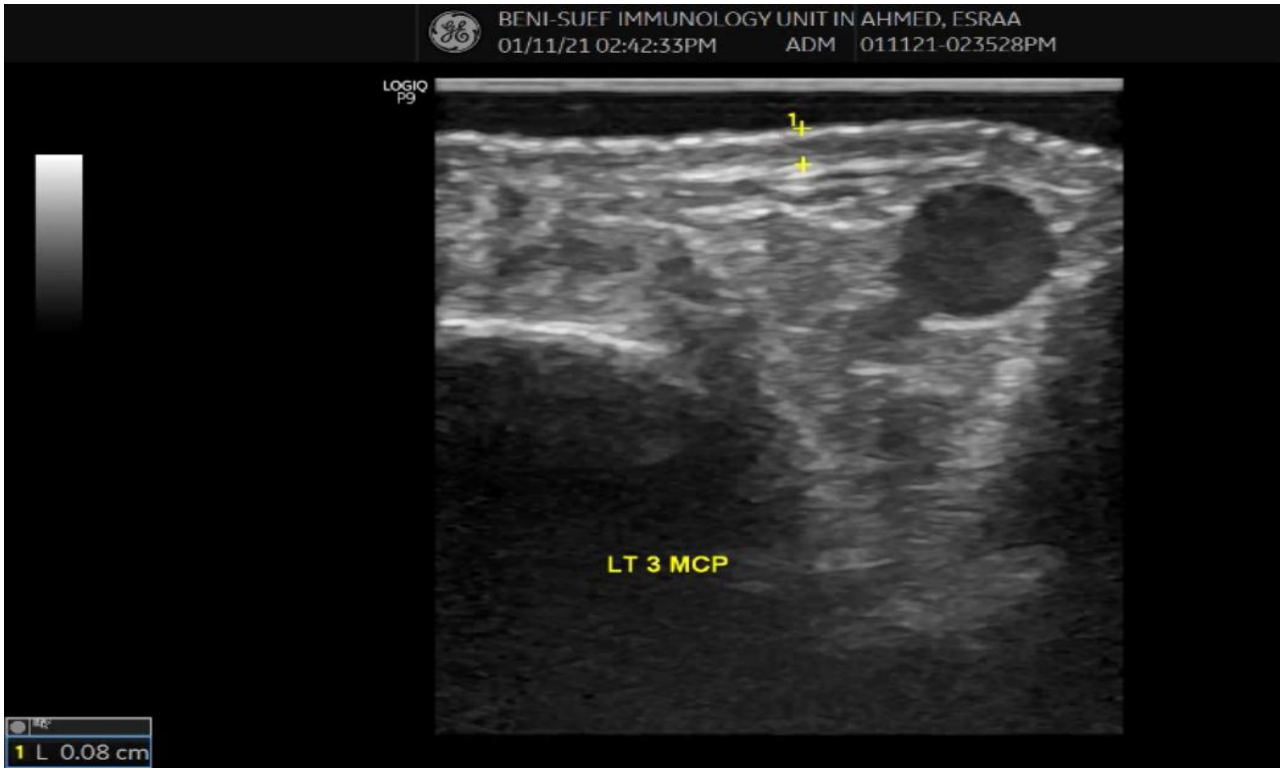

Figure (3): skin ultra sound over left third Metacarpophalyngeal joint in a control showing: skin thickness:0.08 cm

isoechoic epidermis ,Hypoechoic dermis

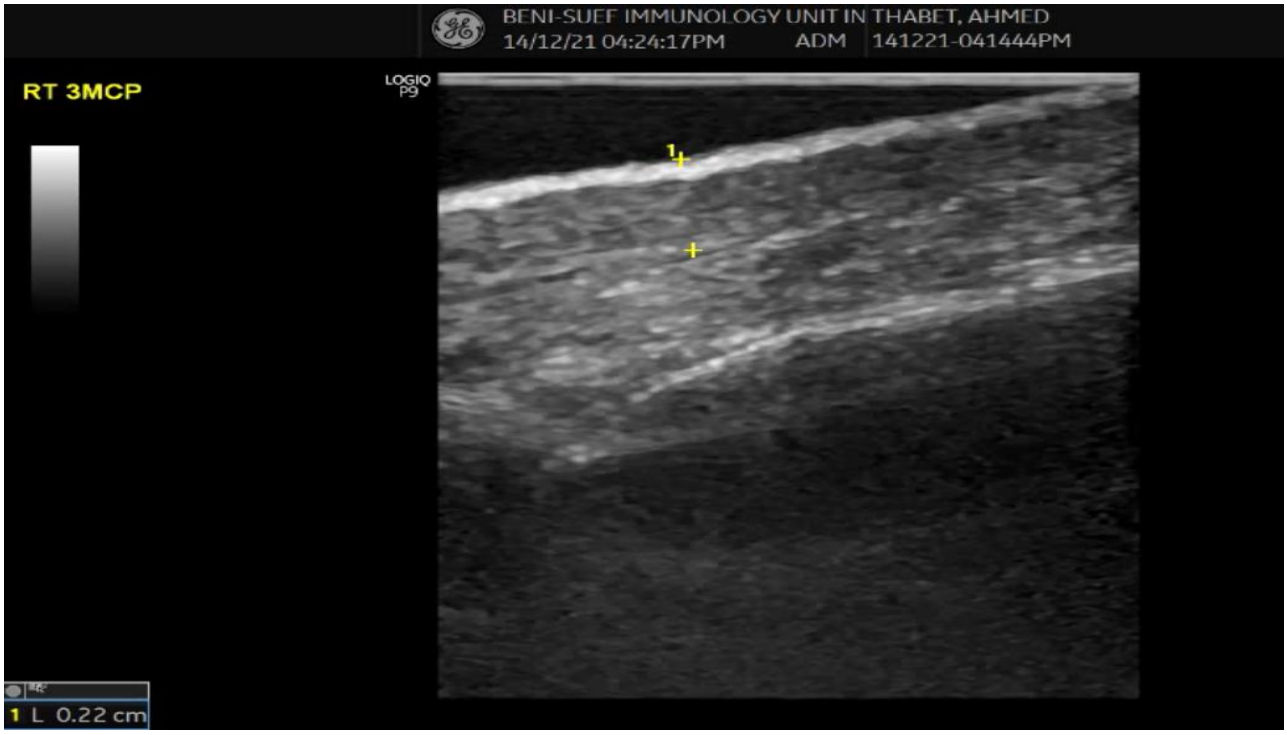

Figure (4): skin ultra sound over right third mcp in systemic sclerosis patient showing: skin thickness 0.22 cm

hyperechoic epidermis, Hypoechoic dermis

Statistical Analysis

Data collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis performed using the Statistical Package of Social Science **(SPSS)** software version 22 in windows 7 (SPSS Inc., Chicago, IL, USA). Simple descriptive analysis in the form of numbers and percentages of qualitative data, and arithmetic means as central tendency measurement, standard deviations as a measure of dispersion of quantitative parametric data.

- **For quantitative parametric data:**
  - Independent samples **t test** was used to compare quantitative measures between two independent groups
- **For qualitative data**
  - **Chi square** test used to compare between two of more than two qualitative groups.
- **Bivariate Pearson correlation test** to test the association between variables
- **Sensitivity and specificity test for testing a new test with ROC curve** "Receiver Operating Characteristic".
  - The **P-value< 0.05** was considered as statistical significant

4. Discussion:

Our study showed statistically significant difference in skin thickness between study groups which showed more total skin thickness (TST) in SSc patients at PIP ,MCP and Wrist joints on right and left sides with (p-value < 0.001) and higher mean skin thickness (the mean thickness of all areas in every patient) with (p- value < 0.001) and this goes in accordance with the result of Hongyan Li et al, who examined 31 patients compared to 31 healthy controls, age matched by 18 MHZ probe and found that TST in patients with SSc (phalynx, hand, forearm and chest) was significantly greater than in healthy controls (P < 0.001) but there was no difference in skin thickness on the legs in patients with SSc and normal controls [10]

Regarding skin echogenicity , our study showed statistically significant higher percentage of isoechoic and hyperechoic echogenicity in dermis layer at PIP and wrist joints on right and left side among cases with (p_ value< 0.05) but no statistically significant difference at MCP joint echogenicity .

On the other hand, there was no statistically significant difference with (p_value >0.05) as regards epidermis layer as all cases and control had hyperechoic echogenicity on both sides in controversy with Li H et al,. and Hesselstrand et al, who reported that patients in the edematous phase of their disease had increased skin thickness assessed by HFU, but with low echogenicity, while Liu H et al,. reported

that the thickness increased as the echogenicity changed on the order of isoechoic, hypoechoic and hyperechoic [11]. Our results differ regarding echogenicity from Hesselstrand et al,. This may be explained by the longstanding disease in our patients while they examined the patients in early edematous phase [12].

In our study, there was significant positive correlation with (p_value< 0.05) between MRSs and skin thickness by HFU at MCP and wrist joints on right side. This indicated an increase in skin thickness at these joints will associate with increase in MRSs. On the other hand, there was no statistically significant correlation with (p-value >0.05) between MRSs and skin thickness at other areas among cases which goes in accordance to Li H et al, who reported positive correlation between TST and MRSs and Hesselstrand et al. who found a mild-to-moderate positive correlation between local skin thickness and the local/total mRSS. We found that skin ultrasound in SSc patients has high sensitivity (86.7%) and specificity (95%) at PIP joints with cut off value of mean TST (1.38 mm) versus sensitivity (80, 76.7%) and specificity of (98% , 87.5%) and cut off (1.45),(1.43) for MCP and wrist joint, so HFUS may be alternative to skin clinical examination later on.

In our study, there was a statistically significant difference with (p-value <0.05) between study groups with lower mean and total skin thickness score among cases with PHTN and abnormal HRCT findings compared to those without P.HTN or HRCT abnormalities respectively, so HFUS may be a predictive tool for these complications of SSc .

On the other hand, there was no statistically significant difference in skin thickness by HFU between SSc patients with positive vs negative CRP in our study which contradicts the results of Li H et al, study that reported that there was low-to-moderate, positive correlation between HFU-TST and the EUSTAR-DAI, (P = 0.014) in patients with SSc.

Limitations:

Some limitations were present in this study:

1. Elastography is not included in this study.
2. Age of the control was not matched with the cases.
3. We compared TST by HFU with the total MRSs not with local skin thickness in each area in the MRSs.

5. Conclusion:

- Skin ultrasound is considered a valuable tool for differentiation of systemic sclerosis from normal .

- Skin thickness by ultrasound may predict pulmonary hypertension and interstitial lung disease.
- 1.34 mm for the mean TST and 8.05 mm for the sum of TST at pip , mcp and wrist joints bilaterally are a suggested cut off point for differentiating SSc patients from normal ,but further studies with larger sample size are needed for validation.

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