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Original article

Correlation between skin and clinical features in systemic sclerosis

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Summary

Introduction. Systemic sclerosis (SS) is a complex autoimmune disease characterized by chronic progressive organic sclerosis. The aim of this paper is to show the correlation of ultrasound (US) parameters with Rodnan skin score (mRSS), as well as the clinical involvement of other organ systems. Methods. Our study included 24 patients diagnosed with SS and 24 healthy controls. We included demographic, clinical and laboratory parameters, individually and included in the European Scleroderma Trial and Research Disease Activity Index (EUSTAR-DAI) score. To measure skin involvement, we used the modified mRSS and skin ultrasound.

Results. The skin thickness of patients and healthy controls measured by ultrasound showed statistically significant differences ($p<0.001$). Correlations between mRSS and anti-Scl-70 antibody ($p=0.02$) and between mRSS and diffusion capacity for carbon monoxide (DLCO) ($p=0.03$) were shown.

Conclusion. In recent years, the importance of using skin ultrasound in patients with systemic sclerosis has been increasing, due to the fact that this technique can detect skin involvement in the early stages of the disease. The advantages of the method are availability and non-invasiveness, unlike skin biopsy. By standardizing ultrasound skin measurement, it would be possible to implement the method in daily clinical practice.

Key words: ultrasound, scleroderma, skin

Introduction

Systemic sclerosis (SS) is a complex autoimmune disease characterized by chronic progressive organic fibrosis. The disease includes three phases: edematous, indurative and atrophic phase. Thickened skin is the main clinical manifestation in SS [1]. The most frequently used method of the evaluation of skin involvement is the modified Rodnan skin score (mRSS). Considering that mRSS is a subjective method, there are frequent variations during consecutively measurements even up to 30% [2]. In recent years, researchers have focused on ultrasound (US) measurement of skin thickness, as well as its correlation with mRSS [3]. The aim of this study is to show the correlation of US parameters with mRSS, as well as the clinical manifestation of other organ systems.

Methods

Patients

Our study included 24 patients diagnosed with SS and 24 age- and sex-matched healthy controls. Our patients were treated in the Department of Rheumatology of the University Clinical Center of Republic of Srpska (UCC RS) in the period from January 2021 to January 2022. The patients were diagnosed according to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) from 2013 [4]. Exclusion criteria were: overlapping syndromes with other systemic connective tissue diseases, thickenings caused by other conditions (morphea, myxedema, eosinophilic fasciitis, diabetes mellitus), skin ulcerations caused by nephrotic syndrome and congestive heart failure and venous peripheral disease. The implementation of the study was approved by the Ethics Committee of UCC RS. Each patient confirmed their participation by signing an informed consent.

Clinical parameters

We included demographic, clinical features, laboratory parameters and the disease activity score- European Scleroderma Trial and Research Disease Activity Index (EUSTAR-DAI). This score includes six items: difference in skin equals 1.5, mRSS ≥18 equals 1.5, finger ulceration (FU) equals 1.5, tendon friction (TF) 2.25, C-reactive protein (CRP) >1 mg/dL equals 2.25, diffusion capacity for carbon monoxide (DLCO) < 70% equals 1. By adding, a maximum sum of 10 is gotten, and active disease means a score of 2.5 or more [5].

mRSS

For skin involvement, mRSS was used, performed by an experienced rheumatologist, in three attempts, whereby the mean value was taken as final. It covers 17 skin regions: face, chest, abdomen, upper arms, forearms, dorsum of hands, fingers, upper legs, lower legs, dorsum of feet and feet. The thickness of the skin is ranked from 0 to 3, 0 indicating normal skin and 3 severe thickening of the skin. The maximum value is 51 [6].

US of the skin

Skin thickness was measured on an eSaote US machine with a 15 Mhz probe at five anatomical locations: the dorsum of the right forearm 3 cm proximal to the right wrist (RC), the area between the metacarpophalangeal (MCP) joints II and III of the right hand, the dorsal skin of the proximal phalanx of the II finger right, skin of the right leg 12 cm proximal to the ankle joint (TC) and sternum 2 cm distal to the upper edge of the manubrium [7]. The average values of regional skin thickness and total skin thickness (TST) were measured at three assessments performed horizontally and vertically, and they were recorded in millimeters. The measurement was accomplished in the subjects and in the control group.

Statistical analysis

Statistical analyses were performed with SPSS program version 22.0. Descriptive statistics were expressed as mean value, standard deviation and median for quantitative parameters, while percentages were used for qualitative parameters. The Kolmogorov Smirnov test was used for data distribution. The Mann-Whitney U test was used for non-parametric data analysis, while the Student's t test was used for parametric data analysis. Pearson's and Spierman's correlation tests were also performed. P values <0.05 were considered statistically significant.

Results

Demographics

Twenty one patients (87.5%) were females, three patients were males and the mean age was 55.5 ± 10.8 years. The average duration of the disease (appearance of the first symptoms) was 5.3 ± 5.07 years, with maximum of 22 years, minimum of one year. Arthritis was present in four subjects (16.7%), while FU was found in nine subjects (37.5%). Anti-Scl-70 antibody was present in 13 (54.2%) subjects. The mean value of mRSS was 20.92 ± 10.06, maximum was 43 and minimum was 8. As for DLCO, four subjects had normal results, 10 (41.7 %) had mild disorder, five subjects (20, 8%) had medium, and severe diffusion disorder was present in five patients (20.8%). The mean CRP value was 4.34±5.3. The mean value of the EUSTAR DAI score was 4.28 ± 2.22, maximum was 9.92 while minimum was 0,92. Detailed demographic data and clinical parameters are presented in Table 1.

US correlation

In our subjects, the values of mentioned locations were measured, as well as the TST. Skin measurements were compared with the control group. Sex and age distributions are shown in Table 2.

Table 3 shows a statistically significant difference (<0.001) in skin thickness between the subjects and the control group. The highest measured values of skin thickness were in the metacarpophalangeal and phalangeal regions of the hand.

Table 1. Demographics and clinical parameters

	N=24
Sex (M/F)	3/21
Age (SD)	55.5 (±10.8)
Disease duration (SD)	5.3 (±5.07)
Raynaud phenomenon (Y/N)	19/5
Arthritis (Y/N)	4/20
Finger ulceration (Y/N)	9/15
Rodnan skin score	20.9 (±10.1)
Anti-Scl-70 (pos/neg)	13/11
CRP	4.3 (±5.3)
DLCO	
Normal	4
Mild	10
Medium	5
Severe	5
EUSTAR DAI (min-max)	4.6 (0.92-9.92)

CRP - C-reactive protein; DLCO - diffusion capacity for carbon monoxide; EUSTAR DAI = European Scleroderma Trial and Research Disease Activity Index

Table 2. Sex and age distribution of subjects and control group

	SS	Control group
Sex (M/F)	3/21	5/19
Age (SD)	55.5 (±10.8)	55.29 (±13,24)

SS - systemic sclerosis

Table 3. Skin thickness in subjects and control group

	SS	control	range SS	control range	p
RC	1.99±0.66	1,14±0,12	1.00-3.90	0.89-1.32	<0.001**
MCP	2.25±0.68	1.07±0.24	1.00-3.70	0.92-1.40	<0.001**
Ph	3.12±0.82	1.27±0.09	1.40-4.20	1.10-1.50	<0.001**
TC	1.89±0.92	1.21±0.15	1.00-4.40	0.87-1.47	<0.001**
Sternum	1.58±0.49	0.96±0.15	1.00-3.00	0.60-0.87	<0.001*
TST	2.17±0.46	1.13±0.12	0.94-1.30	1.48-3.12	<0.001**

MCP - metacarpophalangeal joint; Ph - phanges; RC - radiocarpal joint; SS - systemic sclerosis; TC - talocrural joint; TST - total skin thickness

*Student T-test, **Mann-Whitney test

TST and clinical parameters

TST and mRSS were compared, and there was no statistical significance (r=0.155, p=0.468) between them. We compared TSS and mRSS separate with other clinical parameters (EUSTAR DAI, FU, Arthritis, anti Scl-70 antibody, DLCO, CRP). No significant correlation was found between TST and the listed clinical parameters, while for mRSS, relationships with anti Scl-70 (p=0.024, r=0.472) and DLCO degree (p=0.03, r=0.329) were statistically significant. More details are shown in Table 4.

Table 4. Correlation between clinical parameters and skin involvement

	TST p-value	mRSS p-value, r-value
EUSTAR DAI	0.375	0.095
Finger ulceration	0.31	0.083
Arthritis	0.13	0.58
Anti-Scl-70	0.75	0.024, 0.472*
DLCO	0.34	0.03, 0.329*
CRP	0.09	0.96

CRP - C-reactive protein; DLCO - diffusion capacity for carbon monoxide; EUSTAR DAI = European Scleroderma Trial and Research Disease Activity Index, mRSS - modified Rodnan skin score; TST - total skin thickness

*statistical significant, p<0.05

Also, we individually compared the US measured skin thickness at the targeted points with clinical features. None of the parameters were statistically significant.

Discussion

Measured by ultrasound, TST in our subjects with SS was thicker than in the control group (p=0.001). Also, there was significantly thicker skin in the other target sites: MCP, RC, phalanx, sternum and TC with the same statistical significance as in TST (p=0.001). Similar data were obtained by researchers who included the measurement of skin thickness in their research [8, 9]. In addition to the thickness of the skin, some researchers also compared the echogenicity and composition of the skin itself. In the study by Liu et al, it was confirmed that increased echogenicity was proportional to the increase in skin thickness [10].

The importance of measuring these parameters is reflected in the possibility of early detection of transition from limited systemic sclerosis to diffuse one. This refers to the measurement of the sternum region, especially if echogenicity is also taken into account. Few years ago one study concluded that the progression of skin thickness was followed by the progression of the disease itself [7]. By trying to improve and standardize this method, a simple non-invasive tool would be obtained, which could be used to monitor patients during regular check-ups. A group of scientists tried to express their views on standardization, but without success. After extensive analysis, they concluded that there were still significant gaps in knowledge about echogenicity and thickness assessment [11]. An unexpected fact was that the duration of the disease was not correlated with the thickness of the skin, meaning that the thickness of the skin was greatest in the edematous phase, not in the atrophic phase. Similar results were obtained by other researchers. Because they used serial measurements on the same patient, these results were more significant [3, 8].

When comparing mRSS with clinical manifestations, we obtained significant correlations with DLCO (p=0.03) and anti-Scl-70 antibodies (p=0.024). Unlike mRSS, there was no statistical significance in TST when correlating with clinical features. This differs from the study where the TST relationship was statistically significant in correlations with disease duration, EUSTAR DAI, mRSS and CRP [12].

This small research is only a part of a greater research. The disadvantage of this research is, first of all, the small sample. Another disadvantage is the small number of clinical

features that would indicate greater systemic involvement, such as gastrointestinal and cardiovascular. The third disadvantage is not using elastography when in US.

The use of US is currently an orientation method. Based on the obtained results, we concluded that anti-Scl-70 and DLCO were correlated with skin involvement, although only with mRSS. It is necessary to pay more attention to the US measurement, taking into account that the thickening of the skin is the hallmark of SS.

Conclusion

The importance of using skin ultrasound in patients with systemic sclerosis has been increasing in recent years, because this technique can detect skin involvement in early stages of the disease. Also, the method is useful in monitoring the progression of skin changes in patients with systemic sclerosis. Unlike skin biopsy, ultrasound is available and non-invasive. By standardization of ultrasound skin measurements it would be possible to implement this method in everyday clinical practice.

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Ethical approval. The Ethics Committee of the University Clinical Center of Republic of Srpska, Banja Luka, Republic of Srpska, Bosnia and Herzegovina, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Korelacija debljine kože i aktivnosti bolesti kod oboljelih od sistemske skleroze

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Uvod. Sistemska skleroza (SS) je kompleksna autoimuna bolest koja je obilježena hroničnom progresivnom organskom sklerozom. Cilj ovog rada jeste prikazati korelaciju ultrazvučnih (UZ) parametara sa *Rodnan skin score* (mRSS), kao i kliničko zahvatanje ostalih organskih sistema.

Metode. Naša studija je obuhvatila 24 pacijenta kojima je postavljena dijagnoza SS i 24 zdrave kontrole. Obuhvatili smo demografske, kliničke i laboratorijske parametre, pojedinačno i uvrštene u skor za izračunavanje aktivnosti bolesti - *European Scleroderma Trial and Research Disease Activity Index* (EUSTAR-DAI). Za mjerenje kožnog zahvatanja koristili smo modifikovani mRSS i ultrazvuk kože.

Rezultati. Uočena je statistički značajna razlika debljine kože između ispitanika i kontrolne grupe ($p<0,001$). Prikazana je korelacija mRSS i prisustva anti Scl-70 antitijela ($p=0,02$), kao i odnos mRSS i difuzionog kapaciteta za ugljen monoksid (DLCO) ($p=0,03$).

Zaključak. Posljednjih godina raste značaj upotrebe ultrazvuka kože kod oboljelih od sistemske skleroze, budući da se ovom tehnikom može otkriti zahvatanje kože u ranoj fazi bolesti. Prednost metode je dostupnost i neinvazivnost, za razliku od biopsije kože. Standardizacijom ultrazvučnog mjerenja kože bilo bi moguće primijeniti metodu u svakodnevnoj kliničkoj praksi.

Ključne riječi: ultrazvuk, skleroderma, koža