Exploratory study on quantitative assessment of skin hardness in patients with systemic sclerosis using SOFTGRAM

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Abstract

Objective

There is a lack of quantitative and objective methods for measuring skin hardness. This study aimed to verify whether SOFTGRAM, a device that can measure elastic modulus using the Hertz elastic contact theory, could be used to evaluate skin hardness in systemic sclerosis (SSc).

Methods

Skin score according to the modified Rodnan total skin thickness score and elastic modulus of the skin using SOFTGRAM were measured for 20 patients with SSc and 20 healthy controls on 8 parts of the body, both of the cheeks, forearms, fingers, and hands. Five observers shared to measure skin score 320 times (40 participants × 8 parts). Elastic modulus was measured 1600 times (40 participants × 8 parts × 5 times each). As an additional examination to compare differences between observers, the skin score of another healthy control was measured 40 times (5 observers × 8 parts). Elastic modulus was measured 200 times (5 observers × 8 parts × 5 times each).

Results

There was a significant correlation between elastic modulus and skin score (correlation coefficient=0.67, $p<0.001$) and a significant difference in elastic modulus (8 parts: healthy controls vs. limited cutaneous SSc vs. diffuse cutaneous SSc: 22.6±15.7 vs. 32.0±27.7 vs. 44.8±39.8, $p<0.001$). Intraobserver reliabilities were sufficient in 6 out of 7 observers; however, interobserver was less satisfactory.

Conclusion

This study showed the practicality of SOFTGRAM as an accurate measurement method of skin hardness but also revealed points to be improved. More studies are needed to find an accurate measurement method of skin hardness.

Key words

modified Rodnan's total skin thickness score, skin hardness, systemic sclerosis

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Introduction

Modified Rodnan's total skin thickness score (mRSS) has been widely used for scoring the skin hardness of patients with systemic sclerosis (SSc) since the 1990s (1). However, it is a semiquantitative scoring system using a 0-3 scale, where 0=normal, 1=mild (thickened skin), 2=moderate (thickened and unable to pinch small skin), and 3=severe (thickened and unable to pinch big skin or move skin). Other quantitative and objective methods for measuring skin hardness are desirable, especially for clinical trials and research. This study aimed to verify whether measuring equipment called SOFTGRAM could be applied to evaluate skin hardness, which is the elastic modulus of the skin using the principle of a tuning fork. A recent study have also reported on research conducted to measure the skin force-displacement characteristics when applying a lateral stretch (2). As a far-reaching effect, this study might be one of the triggers to advance a diagnosis with medical artificial intelligence systems for various diseases, including subcutaneous tumours, lymphedema, and compartment syndrome.

This study analysed the association between elastic modulus measured by SOFTGRAM and skin score for 20 healthy controls and 20 patients with SSc. As an additional examination, a healthy Japanese female volunteer, was added to compare differences between observers.

Patients and methods

Sensing device

The SOFTGRAM device is shown in Figure 1. SOFTGRAM can measure elastic modulus using the Hertz elastic contact theory. It is small and battery-powered and can be easily used anytime, anywhere. It comprises a force sensor, an indenter, and a touch sensor. The tip of the indenter is spherical with a diameter of 3 mm, and the touch sensor makes contact when the indenter is pushed into the target to a depth of 0.5 mm. The probe is placed perpendicular to the measurement point, and the probe is pushed into the target at a constant speed. Elastic modulus is calculated from the reaction force when the target touches the touch sensors. Because the measurement result is affected by the pushing speed, the pushing speed is detected; if the speed is out of range, the measurement cannot be performed. Measurement results are affected by hardness up to 10 times the depth of displacement. When there is something hard like a bone up to 5 mm deep, a high value will appear. The measurement accuracy of the device is tested using test samples made of silicone gel of known modulus.

Patients and controls

This study enrolled patients with SSc who visited the Department of Dermatology of Shiga University of Medical Science from March 2022 to February 2023. Twenty healthy Japanese volunteers of the same age and gender as the 20 patients with SSc were included. This study is exploratory in nature, and the sample size was determined based on feasibility. Considering the study duration and the anticipated number of eligible patients, a sample size of 20 was estimated. Due to the higher prevalence of SSc in females, we aimed to recruit healthy controls with a balanced gender distribution. Exclusion criteria were <20 years old, a person who refused consent, and a skin lesion in the parts for evaluation, except for SSc lesions. As an additional examination to compare differences between observers, a healthy female volunteer was added.

The experimental protocol was established according to the Declaration of Helsinki and approved by the Ethics Committee of Shiga University of Medical Science (reference no. R2021-181).

Study design

This study collected case data and performed univariate analysis on age, gender, type and duration of SSc, skin score according to mRSS, and elastic modulus of the skin using SOFTGRAM. Each examiner was given a simple training using silicone gel samples with known elastic modulus beforehand, in order to achieve similar elastic modulus readings. Elastic modulus was measured 5 times, and the observer recorded each value and calculated the average. Skin score for mRSS was

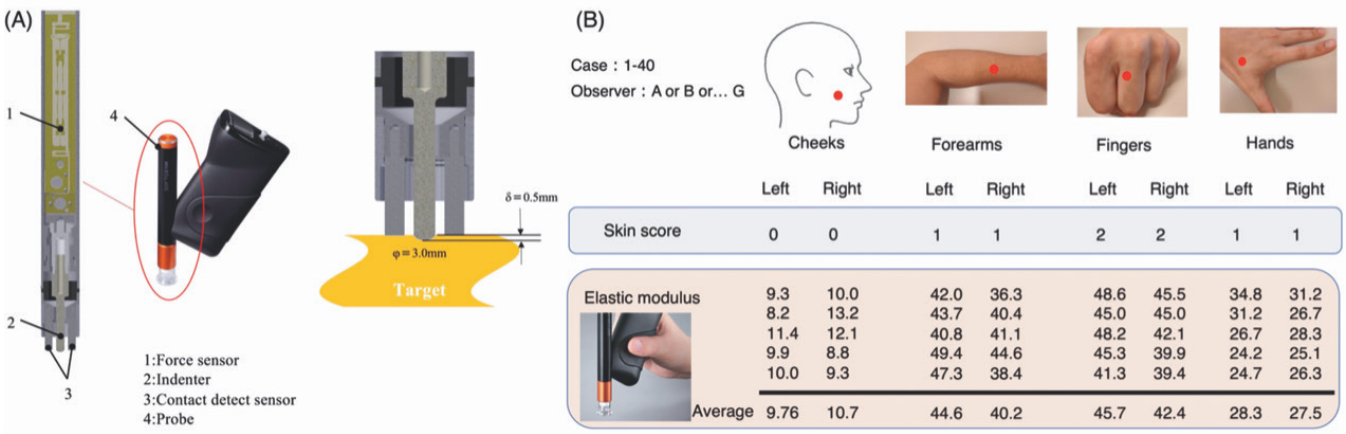

Fig. 1. (**A**) Sensing device. (**B**) Measurement points and an example.

measured in 17 parts to evaluate the extent of the disease. Considering the reduction burden for participants, one observer measured the skin score and elastic modulus of one participant at the same time only in the 8 parts: both midpoints between malar arches and mental region (defined as "Cheeks"), outside trisections of the forearms ("Forearms"), midpoints between the proximal interphalangeal and metacarpophalangeal joints of the middle fingers ("Fingers"), and radial fossae on back of the hands ("Hands"). The periphery of the upper limb and the face can be skin lesions of diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc). In Supplementary Table S1, seven observers combined to measure skin score 320 times (40 participants × 8 parts). Elastic modulus was measured 1600 times (40 participants × 8 parts × 5 times each). The primary endpoint was set to evaluate the correlation between elastic modulus and skin score. Secondary endpoints compared the differences between healthy controls and SSc patients, between observers, in terms of the duration of SSc, age, and body mass index (BMI).

As an additional examination, another healthy control was measured in 8 parts to compare differences between observers by five out of seven observers, considering the reduction burden for the healthy control. Skin score was measured 40 times (1 participant × 8 parts × 5 observers), and elastic modulus was measured 200 times (1 participant × 8 parts × 5 times each × 5 observers).

Table I. Characteristics of healthy controls and SSc patients.

	Healthy controls (n=20)	lcSSc lcSSc x (n=10)	dcSSc patients (n=10)	*p*
Age (years old)	63.2 ± 12.3	65.9 ± 6.3	58.8 ± 14.9	0.460
Gender (M/F)	1/19	0/10	1/9	0.599
BMI	21.3 ± 2.9	22.3 ± 4.7	21.2 ± 3.2	0.785
Duration of SSc (months)	—	156.5 ± 124.4	156.5 ± 94.8	0.597
Antibody				
Antinuclear	—	9	10	1.000
Anti-Scl-70	—	0	3	0.211
Anti-RNA polymerase III	—	0	1	1.000
Anti-RNP	—	0	1	1.000
Anti-centromere	—	10	1	<0.001
Unidentified	—	0	4	0.087

dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; RNA: ribonucleic acid; RNP: ribonucleoprotein; Scl-70: anti-topoisomerase-I antibodies; SSc: systemic sclerosis.

Statistical analysis

To compare characteristic data, Fisher's exact test (gender, each antibody) and Mann-Whitney U-test (duration of SSc) were performed. Kruskal-Wallis rank-sum and Dwass multiple comparison tests were performed to compare characteristic data (age and BMI) and elastic modulus in each skin score and among healthy controls, lcSSc, and dcSSc. Spearman's rank and Pearson product-moment correlation coefficients were used to examine the relationship between elastic modulus and skin score, elastic modulus and age, elastic modulus and BMI, skin score and age, and skin score and BMI. Intraclass correlation coefficient (ICC) was used to examine intra- and inter-observer reliabilities. Data were the average ± standard deviation. $p<0.05$ was considered statistically significant. The experimental protocol was established according to the Declaration of Helsinki and approved by the Ethics Committee of Shiga University of Medical Science (reference no. R2021-181).

Results

Patient characteristics

Data were collected from 20 healthy Japanese controls (1 male and 19 females; 63.2±12.3 years old), 10 lcSSc patients (10 females; 65.9±6.3 years old), and 10 dcSSc patients (1 male and 9 females; 58.8±14.9 years old) (Table I). No significant difference was observed in BMI (healthy controls: 21.5±2.7; lcSSc: 22.3±4.7; dcSSc: 21.2±3.2; $p=0.785$) and duration of SSc (lcSSc: 156.5±124.4 months; dcSSc: 156.5±94.8 months; $p=0.597$). Supplementary Table S2 shows the number of measurement parts in each skin score. Each part had two sides (right and left) per participant.

Correlation between elastic modulus with SOFTGRAM and skin score

Figure 2 is a box-and-whisker plot showing differences between elastic modulus (logarithmic scale) and skin score of 20 patients. There were clear differences between elastic modulus and skin score, especially in forearms, hands and total. In Supplementary Table S3, Spearman's rank and Pearson product-moment correlation coefficients also showed a significant correlation (p<0.001) between elastic modulus and skin score of 20 patients (Spearman's rank and Pearson product-moment correlation coefficients; cheeks: 0.62 and 0.72; forearms: 0.64 and 0.75; fingers: 0.64 and 0.65; hands: 0.75 and 0.77; Total: 0.67 and 0.70). The same statistical tests were conducted for all 40 participants (Spearman's rank and Pearson product-moment correlation coefficients; cheeks: 0.53 and 0.58; forearms: 0.46 and 0.65; fingers: 0.45 and 0.53; hands: 0.52 and 0.65; total: 0.43 and 0.57). Kruskal-Wallis rank-sum test also revealed a significant difference in elastic modulus (logarithmic scale) between different skin scores in each part (cheeks: p=0.001, others: p<0.001). As a *post-hoc* test, Dwass multiple comparison test showed which groups had a significant difference between elastic modulus (logarithmic scale) between different skin scores (Fig. 2). There were significant differences between skin score=0 *vs*. 2 and 1 *vs*. 2 but not in 0 *vs*. 1 in cheeks. The difference between skin score=2 *vs*. 3 was smaller in Fingers than in Others. Supplementary Figure S1 shows a scatter plot of the correlation between elastic modulus (logarithmic scale) and average skin score for 20 patients with SSc.

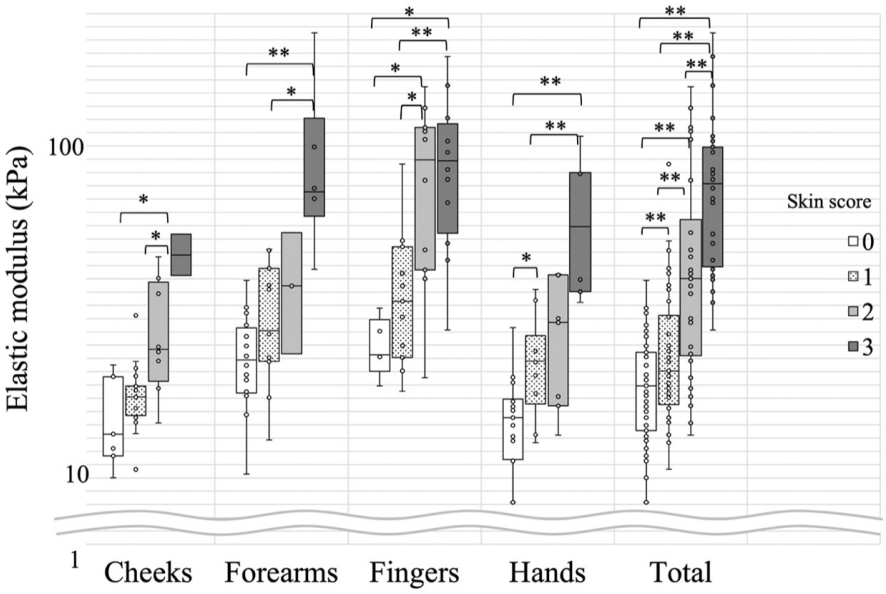

Fig. 2. A box-and-whisker plot showing differences between elastic modulus (logarithmic scale) with SOFTGRAM and skin score of 20 patients (*p<0.05, **p<0.01).

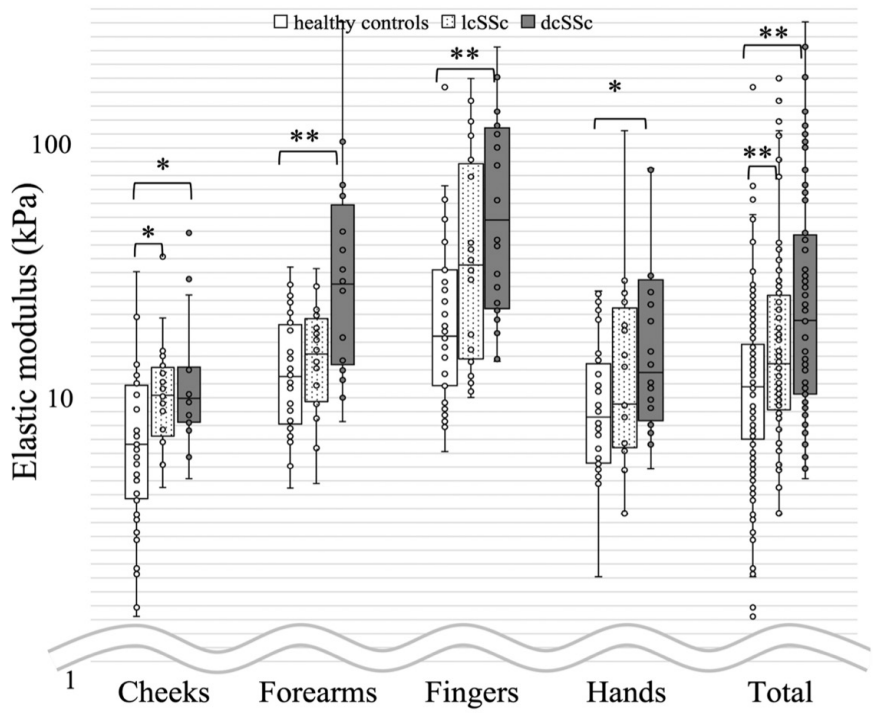

Fig. 3. A box-and-whisker plot showing differences among elastic modulus of healthy controls, lcSSc, and dcSSc patients (*p<0.05, **p<0.01).

Comparison of the differences between healthy controls and SSc patients

Figure 3 shows the elastic modulus (logarithmic scale) of healthy controls, lcSSc, and dcSSc. Kruskal-Wallis rank-sum test showed a significant difference among healthy controls, lcSSc, and dcSSc patients in each part (total of elastic modulus: healthy controls *vs*. lcSSc *vs*. dcSSc: 22.6±15.7 *vs*. 32.0±27.7 *vs*. 44.8±39.8, p<0.001, hands: p=0.035, others: p<0.001). As a *post-hoc* test, Dwass multiple comparison test was performed to determine which groups had a significant difference between elastic modulus (logarithmic scale) and skin score (Fig. 3). Supplementary Table S4 shows the elastic modulus and 95% confidence interval of healthy controls, lcSSc, and dcSSc.

Comparison of the differences in duration of SSc, age, and BMI

Supplementary Figure S2 is a scatter plot of the average elastic modulus (logarithmic scale) and skin score in each duration of lcSSc and dcSSc. There is no relationship between the average elastic modulus and age [Pearson product-moment correlation coef-

Table II. Previous methods to evaluate skin involvement in SSc patients.

Year	Measurement	Outcome	Quantitative	Objectivity	Portability	Time per one site(s)	Painlessly	Unnecessary of training
1969, (5)	X-ray	Thickness	Yes	Yes	No	10	Yes	No
1985, (9)	Dynamic admittance	Elastic modulus	Yes	Yes	NA	120	NA	NA
1990, (10)	Elastometer	Elastic modulus	Yes	Yes	NA	120	Yes	NA
1991, (6)	Magnetic resonance	Thickness	Yes	Yes	No	1200	Yes	No
1993, (12)	Durometer	Stiffness	Yes	Yes	Yes	3	Yes	Yes
1995, (1-3)	mRSS	Thickness and stiffness	No	No	Yes	3	Yes	No
1996, (11)	Cutometer	Elastic modulus	Yes	Yes	No	10	Yes	Yes
1997, (13)	Plicometer	Thickness	Yes	Yes	Yes	10	No	Yes
2003, (7, 8)	Ultrasound	Thickness	Yes	Yes	No	10	Yes	No
2008, (14)	Vesmeter	hardness, elasticity, and viscosity	Yes	Yes	Yes	6	Yes	Yes
2008, (15)	Twistometer	Response of skin to a torsional stimulus	Yes	Yes	Yes	10	No	Yes
2010, (16, 17)	Ultrasound elastography	Stiffness and elasticity	Yes	Yes	No	10	Yes	No
2023	SOFTGRAM	Elastic modulus	Yes	Yes	Yes	1	Yes	No

NA: not acquired.

ficient: 0.248; 95% confidence interval (95% CI), -0.519 to 0.07; p=0.123], average skin score and age (Pearson product-moment correlation coefficient; -0.128; 95% CI, -0.423 to 0.191; p=0.430), average elastic modulus and BMI (Pearson product-moment correlation coefficient: -0.017; 95% CI, -0.331 to 0.300; p=0.916), and average skin score and BMI (Pearson product-moment correlation coefficient; -0.059; 95% CI, -0.261 to 0.368; p=0.721) in 40 participants.

Intra- and inter-observer reliabilities of elastic modulus measurement with SOFTGRAM

Intraobserver reliability is shown in Supplementary Table S5. Intraobserver reliability between seven observers was 0.697±0.299 (95% CI, -0.018 to 0.904) for 8 parts of 40 participants. Interobserver reliability was 0.387 (95% CI, 0.108–0.769) for five observers calculated by measuring one healthy control.

Discussion

SOFTGRAM has many advantages compared to previous methods; the six advantages are shown in Table II. First, it is quantitative and can evaluate unmovable skin. Second, this is an objective method and useful for clinical trials and research. Third, the device is not more expensive than an echo machine. Fourth, it is rechargeable and portable, weighing 150 g. Fifth, each measurement can be finished in 1 s. Sixth, it can be measured without pain. Based on our results, SOFTGRAM could quantify a high elastic modulus for the parts of skin score=3 that could be evaluated only as unable to pinch big skin without SOFTGRAM, especially in forearms and fingers (Fig. 2). There were no clear differences in elastic modulus between skin score=0 and 1 of cheeks and skin score=2 and 3 of fingers. The former would be because dented cheeks could not accurately evaluate skin score. In 40 cheeks of healthy controls, there were 3 cheeks with skin score=1. The latter would be because some parts of skin score=2 were misclassified as skin score=3 in fingers, owing to the existence of bones and tendons. There was a possibility that bone hyperreflection interfered with the accuracy of elastic modulus like ultrasound elastography (3). We believe that an update to the measurement range of SOFTGRAM to make it shallower could potentially mitigate these concerns. Supplementary Table S3 shows a low correlation coefficient between elastic modulus and skin score. Although it is difficult to say which better evaluates the skin lesion of SSc patients, elastic modulus and skin score seemed to differ slightly in getting information from the skin. There is no significant difference in elastic modulus between healthy controls and lcSSc in forearms (Fig. 3), probably because the lcSSc patients in this study had mild lesions in the Forearms as shown in the skin score (healthy controls: 0; lcSSc: 0.4±0.6; dcSSc: 1.4±1.2). There have been few reports showing graphs between skin score and duration of SSc, such as in Supplementary Figure S2. There is a tendency that the average elastic modulus had a slightly upper trend in lcSSc and a steadily decline in dcSSc, except for fingers. There seemed to be no great influence of age and BMI on the average elastic modulus and skin score. If participants are recruited for a similar study next time, I believe there is no need to be overly concerned about age and BMI disparities. Intraobserver reliability in Supplementary Table S4 was very low only in Observer A, who measured only one healthy control out of 40 participants. Low reliability means variation in elastic modulus of five times. It was thought that the use of SOFTGRAM did not require any training, however, it did not apply to everyone. Elastic modulus would depend on the skin position and the speed to push by SOFTGRAM. If a robotic arm was combined with SOFTGRAM, intraobserver reliability would be very high in exchange for ease of measurement. Actually, the average elastic modulus measured five times was not abnormal (from 20.02 in the left Face to 28.42 in the left Forearm). Using an average value of five times for elastic modulus, the low intraobserver reliability of Observer A would not affect the results of this study. Interobserver reliability for five observers was low, meaning that elastic modulus depended on the observers. It would also be because elas-

tic modulus depended on the skin position and the power and speed to push by SOFTGRAM. Regarding the skin position, bone hyperreflection might affect elastic modulus. If SOFTGRAM is improved to measure only the more shallow parts, the effect of bone hyperreflection might be minimal.

mRSS has been widely used for scoring skin hardness worldwide (4). It is a great method to evaluate the extent of the disease easily but not enough to evaluate skin involvement strictly for the following reasons. First, it is semi-quantitative, and small changes within the same skin score will be neglected. Second, it lacks objectivity and is inappropriate for clinical trials and research, as a recent review have also pointed out (4). Third, skin thickness varies not only by the SSc stage (oedema, fibrosis, and atrophy) but also by age, sex, obesity, and skin tension. The tight and creaseless skin of young and fatty patients could be assessed as severe even if the skin is soft. Skin thickness and stiffness are inseparable when we pinch the skin. Fourth, mRSS requires knowledge and experience to evaluate skin score accurately. One study reported that repeated teaching courses improved the reliability of mRSS (5). The other study reported a skin model for improving the reliability of mRSS for SSc (6). These studies also involve the necessity of training. The Scleroderma Clinical Trials Consortium offers formal training in mRSS including video demonstration, review articles, and trainees examine at least 3 patients with SSc (7). It is sometimes difficult for even trained dermatologists, especially in the case of borderline severities.

Previous studies have reported some methods to evaluate skin involvement in patients with SSc (Table II). Image evaluations, x-rays (8), magnetic resonance imaging (9) and ultrasound (10, 11), involve the cost of the device, training, and moving a patient to the machine. Moreover, skin thickness alone measured by image evaluation is insufficient to evaluate skin involvement in patients with SSc. Measurement for the elastic modulus of the skin has been reported as a dynamic admittance (12), an elastometer (13), and a cutometer, which proved its high inter- and intraobserver ICCs, as published 1996 (14). However, these measurements did not become popular as methods to evaluate skin involvement in patients with SSc. It might be because these measurements lacked portability and speed for measurement. Durometer, a handheld device that measures only skin stiffness, was also published in 1993 (15). Plicometer is a medical device that measures skin thickness by pinching skin fold (16). Pinching skin fold with a plicometer is time-consuming and painful. Vesmeter is a computer-linked sensing device measuring hardness, elasticity, and viscosity (17). It takes ~6 s per site because it needs time to push the skin and relaxation time, which is related to the time taken by the deformed material to return to its original state. Twistometer is a device that measures the skin response to a torsional stimulus (18). It also takes ~10 s to twist the skin. Ultrasound elastography can measure skin stiffness and elasticity (3, 19). It is challenging to directly compare the accuracy of these previous evaluation methods due to differences in measurement targets, conditions, and the semi-quantitative nature of skin score. This exploratory study represents the first application of SOFTGRAM in patients with SSc. By elucidating the correlation coefficients between elastic modulus and skin score, this study may provide valuable insights for future research, such as setting conditions and sample sizes, in similar investigations.

Limitations

First, the measurement points were narrowed down from 17 to 8 parts compared to mRSS considering the participants' burden. In order to collect data more efficiently, we selected the measurement sites which are common in both lcSSc and dcSSc. 1800 times would be enough to verify whether SOFTGRAM could be applied to evaluate skin hardness. In this study, to minimise inter-observer variability, we designated specific points within the measurement sites for assessing both skin scores and elasticity, even when different points of a single part had varying sclerosis scores. Second, the SSc patients in this study were established SSc with longstanding disease duration; hence, data to accurately assess the early oedematous phase of the disease are not available. Third, this study lacked ethnic diversity. Fourth, the statistical analysis might have been better performed with the average of left and right parts because they are not completely independent. We chose not to use a graph based on the average skin score to avoid introducing decimal points and making the graph less readable.

Conclusion

This study showed the practicality of SOFTGRAM as an accurate measurement method of skin hardness but also revealed points to be improved. It is unlikely that SOFTGRAM will become commonly used worldwide in a short time. Further improvements will be made to SOFTGRAM, and sensing devices can be used, especially for clinical trials and research. We hope that this study will encourage the development of a medical diagnosis system using artificial intelligence.

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