Arch Rheumatol 2023;38(4):556-565
doi: 10.46497/ArchRheumatol.2023.9835

ORIGINAL ARTICLE

The evaluation of tibial nerve using shear-wave elastography and ultrasound in patients with systemic sclerosis: A cross-sectional study

Serdar Kaymaz[1], Murat Yiğit[1], Furkan Ufuk[2], Burak Sarılar[2], Uğur Karasu[1], Veli Çobankara[1], Nuran Sabir[2], Hakan Alkan[3]

[1]*Department of Internal Medicine, Division of Rheumatology, Pamukkale University Faculty of Medicine, Denizli, Türkiye*
[2]*Department of Radiology, Pamukkale University Faculty of Medicine, Denizli, Türkiye*
[3]*Department of Physical Medicine and Rehabilitation, Pamukkale University Faculty of Medicine, Denizli, Türkiye*

Correspondence: Serdar Kaymaz, MD.
E-mail: dr.serdarkymaz@gmail.com

Received: July 24, 2022
Accepted: February 23, 2023
Published online: July 04, 2023

Citation: Kaymaz S, Yiğit M, Ufuk F, Sarılar B, Karasu U, Çobankara V, et al. The evaluation of tibial nerve using shear-wave elastography and ultrasound in patients with systemic sclerosis: A cross-sectional study. Arch Rheumatol 2023;38(4):556-565. doi: 10.46497/ArchRheumatol.2023.9835.

ABSTRACT

Objectives: The study aimed to evaluate stiffness and the cross-sectional area (CSA) of the tibial nerve (TN) using shear wave elastography (SWE) and ultrasound (US) and investigate the relationship of these with disease activity, quality of life, and severity of neuropathic pain in patients with systemic sclerosis (SSc).

Patients and methods: This cross-sectional study included 28 SSc patients (1 male, 27 females; mean age: 50±11 years; range, 28 to 67 years) and 22 age- and sex-matched healthy controls (4 males, 18 females; mean age: 48±6 years; range, 37 to 66 years) between March and April 2022. US and SWE were performed on the TN, and CSA and nerve stiffness were measured. The TN was examined by a radiologist, 4 cm proximal to the medial malleolus. A few days later, an evaluation was performed in the second session by a second observer to investigate inter-and intraobserver agreement. Interobserver agreement was evaluated using the intraclass correlation coefficient (ICC). The Scleroderma Health Assessment Questionnaire, European League Against Rheumatism European Scleroderma Trial and Research (EUSTAR) group activity index, and Douleur-Neuropathique 4 scores of the patients were evaluated. Correlations between the questionnaires and measurements of nerve stiffness and CSA were assessed.

Results: Patients with SSc had significantly higher stiffness and CSA values of the right TN compared to healthy controls ($p<0.001$ and $p=0.015$, respectively). The nerve stiffness values of the right TN were positively correlated with the EUSTAR activity index ($p=0.004$, $r=0.552$). The CSA of the left TN was larger in patients with SSc (21.3±4.9 mm^2) than in controls (12.8±3.4 mm^2), and the nerve elasticity was positively correlated with the EUSTAR activity index ($p=0.001$, $r=0.618$). The interobserver agreement was moderate to good for measuring stiffness and CSA of the TN (ICC were 0.660 and 0.818, respectively). There was a good to excellent intraobserver agreement for measuring stiffness and CSA of TN (ICC were 0.843 and 0.940, respectively).

Conclusion: The increased disease activity in patients with SSc is associated with TN involvement, which can be demonstrated by US and SWE.

Keywords: Elastography, nerve, shear-wave, systemic sclerosis, tibial, ultrasound.

Systemic sclerosis (SSc) is an autoimmune disease of unknown etiology characterized by atypical growth of connective tissues.[1] The prognosis is mainly affected by the involvement of visceral organs. However, the involvement of the musculoskeletal system can play a significant part in the disability caused by the disease.[2] The peripheral nervous system can be involved in SSc. Nevertheless, debates remain on the frequency and significance of neurologic involvement in patients with SSc. A systematic review reported the most common forms of peripheral nervous system involvement in SSc as follows: trigeminal neuropathy (16.5%), peripheral sensorimotor polyneuropathy (14.3%), and carpal tunnel syndrome (6.6%), respectively.[3] There are some suggested possible pathophysiological mechanisms that contribute to peripheral neuropathy.[4] The first of these hypotheses is the mechanism of vascular-dependent neuropathy involvement secondary to vasculitis or inflammation of the vasa nervorum accompanied by vessel wall injury.[4] The second proposed hypothesis is direct nerve compression damage by calcinosis or edema in the early phase

of the disease and fibrosis in the advanced stage. The third hypothesis is that the presence of SSc-associated anti-neuronal antibodies could suggest an immune-mediated mechanism directed toward the peripheral nerve.[4]

The use of classical ultrasound (US) as a simple tool for supplementary diagnostic evaluation of distinct peripheral nerve disorders has been increasingly popular over the last two decades. US offers some advantages such as faster image acquisition, less patient discomfort, noninvasiveness, cost-effectiveness, and wide availability.[5] With the use of conventional US, the cross-sectional area (CSA) of the peripheral nerves can be quantified easily.[6] Peripheral neuropathy results in a relevant increase in intraneural pressure, microvascular compromise, and nerve edema, a common response to nerve injury.[5] However, classical US is unable to demonstrate these histological changes. Further, US has a low sensitivity and specificity for evaluating neuropathy. On the other hand, it has been reported that elastography gives more detailed information on the elastic and biomechanical features of peripheral nerves and that nerve stiffness tends to increase in peripheral neuropathy.[5] Shear-wave elastography (SWE) is widely used to evaluate the musculoskeletal system since it produces quantitative results and has high reproducibility and less operator dependency compared to strain elastography.[5-7] It has been reported that SWE can demonstrate the involvement of peripheral nerves in diabetic polyneuropathy and carpal tunnel syndrome.[7-9] A recently published study showed increased stiffness of the median nerve in SSc.[10]

The tibial nerve (TN) takes its origin from L4-S3 spinal nerve roots and provides sensory and motor innervation to a large part of the posterior aspect of the leg and foot. It is the larger distal extension of the sciatic nerve, which is the largest and longest nerve in the body.[11] TN is involved in various types of neuropathies. Knowledge of the anatomical details along with biomechanical properties will be helpful in assessing and managing these conditions. To the best of our knowledge, SWE and CSA of TN and the factors affecting them have not been previously studied in SSc patients. Therefore, we aimed to evaluate the stiffness and CSA of TN in SSc patients and healthy controls and to determine the relationship of stiffness and CSA of nerves with disease activity, quality of life, and severity of neuropathic pain.

PATIENTS AND METHODS

The cross-sectional study was conducted with SSc patients classified by the 2013 American College of Rheumatology criteria and age- and sex-matched healthy controls between March and April 2022.[12] The study recruited patients from the rheumatology outpatient clinics of the Pamukkale University Faculty of Medicine and healthy controls who were blood donors from the blood bank of the institution or who were university hospital staff and their family members. A total of 33 patients with SSc were evaluated for eligibility. Five patients were excluded since they did not meet the inclusion criteria. Of the excluded patients, one had overlap syndrome, one had diabetes mellitus, one had a history of malignancy, and two had hypothyroidism. Thus, the study included 28 SSc patients (1 male, 27 females; mean age: 50±11 years; range, 28 to 67 years) and 22 healthy controls (4 males, 18 females; mean age: 48±6 years; range, 37 to 66 years) (Table 1).

The participants filled out a sociodemographic data form to collect data on sex, age, and body mass index. A detailed history was obtained from patients with SSc. The modified Rodnan skin score (mRSS), disease duration, medical treatment, and comorbidity of the patients were recorded. The inclusion criteria for patient and control groups were having complete blood count, fasting blood glucose levels, and liver and kidney function tests within normal limits. Patients with an etiology that could cause neuropathy, such as hypothyroidism, overlap syndrome, mixed connective tissue disease, history of malignancy, a metabolic or inflammatory disorder, pregnancy, and diabetes mellitus, were excluded from the study.

The Scleroderma Health Assessment Questionnaire (SHAQ) was used to evaluate health-related quality of life.[13] SHAQ was constructed by the addition of the five following questions related to symptoms: “In the past week, how much have your-Raynaud's phenomenon, digital ulcers, gastrointestinal symptoms, lung

symptoms, and overall scleroderma symptoms-interfered with your activity?" The response was evaluated by the Visual Analog Scale (VAS) on a 15-cm line, with anchor statements "does not interfere" on the left and "very severe limitations" on the right. The final VAS score was calculated by multiplying the value by 0.2. The score ranged from 0 to 3 points, representing a minimum to maximum limitation.

The European League Against Rheumatism European Scleroderma Trial and Research (EUSTAR) activity index was used to assess disease activity. EUSTAR is a weighted 10-point activity index to measure disease activity, the

Table 1. Demographic and clinical characteristics of the groups

	Patients with SSc (n=28)			Healthy controls (n=22)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			50±11			48±6	0.614
Sex							0.116
Male	1	4		4	18		
Female	27	96		18	82		
Body mass index (kg/m^2)			25.6±4.4			26.9±4.1	0.320
Skin variables							
Diffuse SSc	18	64					
Limited SSc	10	36					
Disease duration (year)			13.04±11				
mRSS score			17.9±13.6				
SSc autoantibodies							
Anti-ScL-70	18	64					
Anti-centromere	10	36					
Anti-SSA	3	11					
Anti-SSB	0	0					
Anti-RNP	3	11					
Anti-Ro52	2	7					
Anti-fibrillarin	1	3.5					
Clinical features							
Digital ulcer	5	38					
Raynaud's phenomenon	26	92					
Telangiectasia	5	18					
Inflammatory arthritis	1	3.5					
Myositis	0	0					
Calcinosis	1	3.5					
Interstitial lung disease	17	61					
Pulmonary arterial hypertension	15	53.5					
Gastroesophageal reflux disease	22	78.5					
Small intestinal bacterial overgrowth	1	3.5					
Medical treatment							
Azathioprine	4	14					
Prednisolone	19	68					
Methotrexate	5	19					
Mycophenolate mofetil	12	43					
Hydroxychloroquine	10	36					
Endothelin receptor antagonist	11	39					
Iloprost	7	25					
Assessment questionnaire							
Douleur Neuropathique 4			1.2±0.8				
EUSTAR			3.4±2.6				
SHAQ			1.2±0.8				

SD: Standard deviation; SSc: Systemic sclerosis; mRSS: Modified Rodnan skin score; Scl-70: Anti-topoisomerase I; SSA: Sjögren syndrome type A antigen; SSB: Sjögren syndrome type B antigen; RNP: Ribonucleoprotein; Ro52: Sjögren syndrome (SS)A; EUSTAR: European League Against Rheumatism Scleroderma Trial and Research group; SHAQ: Scleroderma Health Assessment Questionnaire; * $p<0.05$, statistically significant.

score of which is composed of Δ-skin (1.5 points; Δ=patient assessed worsening during the previous month), mRSS >18 (1.5 points), digital ulcers (1.5 points), tendon friction rubs (2.25 points), C-reactive protein >1 mg/dL (2.25 points), and diffusing capacity of the lung for carbon monoxide predicted <70% (1.0 points).[14]

The DN4 is a simple questionnaire used to differentiate neuropathic pain from nonneuropathic pain. It consists of seven sensory descriptors (burning, painful cold, electric shocks, tingling, pins and needles, numbness, and itching) and three signs related to sensory examination (hypoesthesia to touch, hypoesthesia to prick, and pain increased by brushing).[15] The total score is calculated as the sum of the 10 items, and a total score of ≥4 out of 10 suggests neuropathic pain.

A radiologist with seven years of experience in US, who was blinded to the clinical and laboratory data of all patients (Observer 1), examined both ankles of all participants using a new generation US system (Aplioi800, Canon Medical Systems Corporation, Otawara, Japan) with an 18 MHz linear transducer. All participants underwent US examinations in the supine position in a quiet, temperature-controlled room. The examination was performed by slightly externally rotating the ankle in a slight plantar flexion position with the lower leg stabilized. The position of all participants was standardized to allow comparison and to avoid any ankle movement that may increase ankle soft tissue pressure. The participants were instructed to keep their feet or ankles still during the examination.

Tibial nerve was examined in the transverse and longitudinal planes at a distance of 4 cm proximal to the tip of the medial malleolus. The correct imaging plane was confirmed by tendinous landmarks, such as the flexor digitorum longus and flexor hallucis longus tendons, and the posterior tibial vessels.[16] CSA was measured by the use of a continuous boundary trace of the nerve directly over the epineurium on transverse images (Figures 1, 2).

Shear-wave elastography was performed by careful handling of the transducer during transport and mounting to avoid compression force. The skin surface was coated with ample coupling gel before placing the transducer, which was used with light force and kept stable during image acquisition. TN was first identified transversely, and then the transducer was rotated 90° to acquire a longitudinal image of the nerve in the parallel direction to the fiber orientation.[16]

Ultrasound measurements of the first 12 participants were performed by two observers (Observer 1, a board-certified radiologist with >9 years of experience in US and elastographic studies, and Observer 2, a third-year radiology resident with 12 months of training in US and elastographic studies). The observers consecutively examined the participants during the same visit. There was only one radiologist in the room during the examination of the participants at any time. To ensure that the radiologists were blinded to each other's measurements, the US screen was cleared before the other radiologist entered the room. The images were not read by the radiologists and were saved on a hard drive for future analyses. Observer 1 repeated elastographic and CSA measurements of the same participants three days after the initial interpretation to evaluate intraobserver variation. Both radiologists were blinded to the initial measurement results and clinical information of the participants.

Statistical analyses

The minimum sample size was calculated using MedCalc version 21.1 software (MedCalc Software Ltd., Ostend Belgium) based on 85% power and a two-sided significance level of 0.05. The sample size capable of detecting a change in difference between groups was estimated using the mean and expected standard deviation of change in stiffness measurements and CSA obtained from a previous study.[16]

Statistical analysis was performed using the IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 21.1 (MedCalc Software Ltd, Ostend, Belgium) software. The Kolmogorov-Smirnov test was used to examine the normality distribution of variables. Nonparametric tests were used for nonnormally distributed variables. The Mann-Whitney U test was used to assess significant differences in continuous variables, while the chi-square test was used to analyze categorical variables at baseline. Spearman's correlation analysis evaluated the correlation between nonparametric variables. A correlation coefficient (r) of <0.2 was considered

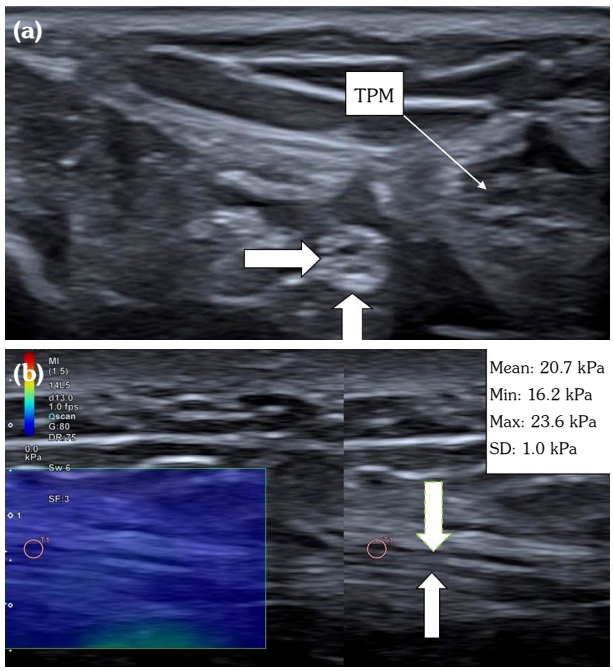

Figure 1. CSA measurement and SWE assessment of a healthy female control subject. **(a)** Cross-sectional gray-scale US scan of the tibial nerve (arrows) at 4 cm proximal to the medial malleolar level (CSA=9 mm^2). **(b)** Longitudinal view SWE of the tibial nerve, with color map, minimum, maximum, and mean stiffness in kilopascal (kPa).

CSA: Cross-sectional area; SWE: Shear-wave elastography; US: Ultrasound; TPM: Tendon of tibialis posterior muscle.

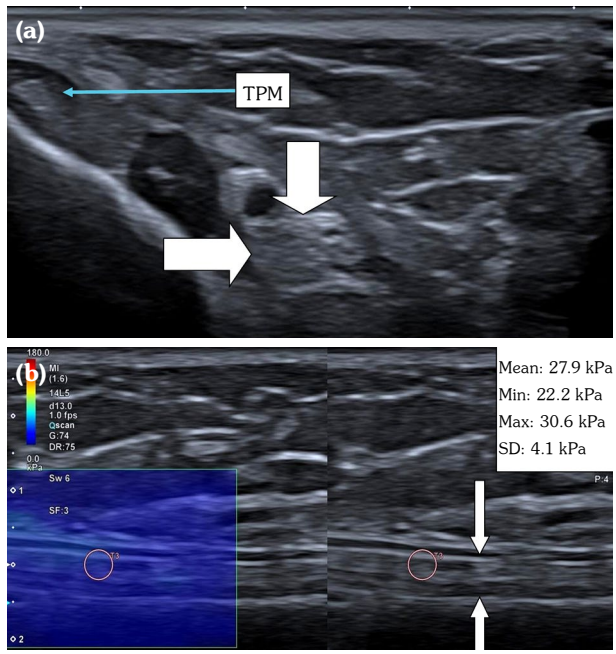

Figure 2. CSA measurement and SWE technique in a female patient with systemic sclerosis. **(a)** Cross-sectional gray-scale US scan of the tibial nerve (arrows) at 4 cm proximal to the medial malleolar level (CSA=17 mm^2). **(b)** Longitudinal view SWE of the tibial nerve, with color map, minimum, maximum, and mean stiffness in kPa.

CSA: Cross-sectional area; SWE: Shear-wave elastography; US: Ultrasound; TPM: Tendon of tibialis posterior muscle.

negligible, 0.2 to 0.4 was fair, 0.41 to 0.60 was moderate, 0.61 to 0.80 was good, and >0.8 was considered excellent agreement. Intraclass correlation coefficient (ICC) with 95% confidence interval (CI) levels was used to assess the intra- and interobserver agreement for CSA and stiffness measurements. An ICC score of 0.81-1.0 indicated excellent agreement, 0.61-0.80 suggested good agreement, 0.41-0.6 showed moderate agreement, 0.21-0.40 indicated fair agreement, and 0-0.20 suggested slight agreement.[17] Moreover, the Bland-Altman plot was used to evaluate the interobserver agreement. A p-value <0.05 was considered statistically significant.

RESULTS

The mean CSA value was 22±5.7 mm^2 in patients with SSc and 12.65±3.4 mm^2 in healthy controls. The mean stiffness value was 23.12±14.5 kilopascal (kPa) in patients with SSc and 15.5±3.27 kPa in healthy controls. The CSA and stiffness values of the right TN were significantly higher in SSc patients than in healthy control subjects (p<0.001 and p=0.015, respectively; Table 2).

The elasticity measurements of the right TN were positively correlated with the EUSTAR activity index and mRSS (p=0.004, r=0.552, and p=0.023, r=0.453, respectively). Similarly, the nerve elasticity of the left TN was positively correlated with the EUSTAR activity scale and mRSS (p=0.001, r=0.618, and p=0.006, r=0.530, respectively). However, both the right and left TN had no correlation with DN4 and SHAQ-global scores (Table 3).

There was a good interobserver agreement for assessing TN stiffness (ICC score 0.660, 95% CI: 0.354–0.839) and an excellent interobserver agreement for the CSA evaluation of TN (ICC score 0.818, 95% CI: 0.623–0.918). There was an excellent intraobserver agreement for

Table 2. The comparison of CSA and stiffness values in the tibial nerve between SSc patients and healthy controls

	CSA (mm)		SWE (kPa)	
	Right tibial nerve	Left tibial nerve	Right tibial nerve	Left tibial nerve
Comparison	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Patients with SSc	22.7±6.5	21.3±4.9	23.2±14.7	23.04±14.3
Healthy Controls	12.5±3.4	12.8±3.4	15.1±3.03	15.9±3.5
p value	<0.001*	<0.001*	0.015*	0.030*

CSA: Cross-sectional area; SSc: Systemic sclerosis; SD: Standard deviation; SWE: Shear-wave elastography; * p<0.05 statistically significant. The Mann-Whitney U test was used.

Table 3. The relationship between disease activity, quality of life, neuropathic pain severity, and the CSA and stiffness values of the tibial nerve

	EUSTAR		DN4		SHAQ		mRSS	
	r	*p*	r	*p*	r	*p*	r	*p*
CSA (mm)								
Right	0.97	0.644	0.123	0.559	0.214	0.304	0.107	0.612
Left	0.172	0.410	0.198	0.343	0.245	0.238	0.181	0.387
SWE (kPa)								
Right	0.552	**0.004***	0.077	0.714	0.077	0.714	0.453	**0.023***
Left	0.618	**0.001***	0.037	0.859	0.037	0.859	0.530	**0.006***

CSA: Cross-sectional area; EUSTAR: European League Against Rheumatism Scleroderma Trial and Research group; DN4: Douleur Neuropathique 4; SHAQ: Scleroderma Health Assessment Questionnaire; mRSS: Modified Rodnan Skin Score; * p<0.05 statistically significant.

stiffness and CSA measurements. The ICC score was 0.843 (95% CI: 0.670–0.930) and 0.940 (95% CI: 0.867–0.974) for stiffness and CSA of TN, respectively (Figure 3).

DISCUSSION

The prevalence of peripheral neuropathy has not been well-defined in patients with SSc. A systematic review of the literature yielded an estimated prevalence of 14.5% for peripheral neuropathy in SSc, suggesting that peripheral nervous system involvement may be common.[18] The diagnosis of neuropathy by neurophysiological examinations has been recommended.[19] However, these examinations do not provide information on the pathological or biomechanical changes of the affected nerves. Our study showed stiffer TN and significantly higher CSA in patients with SSc compared to healthy controls. Moreover, the elasticity measurements of TN had a positive correlation with disease activity. These results suggest that SWE-based stiffness measurements of TN indirectly reflect the changes associated with the effect of SSc on the nerve. This is the first study to report SWE and CSA of TN and their association with disease activity, quality of life, and severity of neuropathic pain in patients with SSc.

Many studies in the literature have evaluated stiffness and CSA measurements of peripheral nerves using US. However, the majority of these studies were conducted on diabetic patients. Dikici et al.[16] found stiffer TN in diabetic polyneuropathies compared to healthy controls. Ishibashi et al.[20] stated that the elasticity of TN could be a new parameter for determining early biomechanical changes and characterizing diabetic neuropathy. Our study showed an increase in stiffness and CSA of TN in patients with SSc compared to healthy

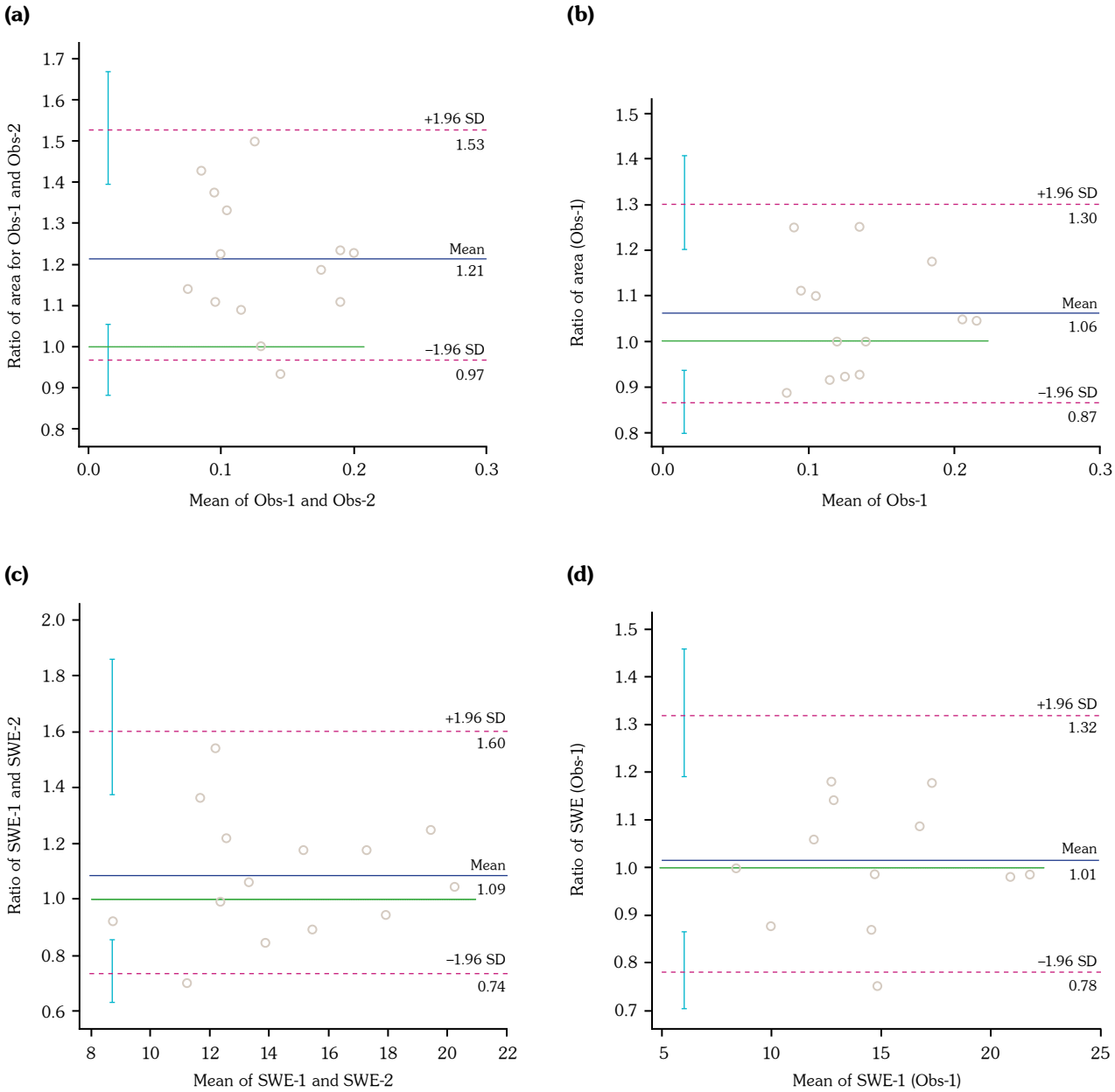

Figure 3. Bland-Altman plot for interobserver and intraobserver agreement. **(a, c)** Bland-Altman plots demonstrating interobserver variability of CSA and stiffness of TN, respectively. **(b, d)** Bland-Altman plots demonstrating intraobserver variability of CSA and stiffness of TN, respectively.

CSA: Cross-sectional area; SWE: Shear-wave elastography; TN: Tibial nerve; SD: Standard deviation.

controls, while limited data from previous studies have yielded mixed results. Yagci et al.[10] reported decreased median nerve elasticity compared to healthy controls. Sousa-Neves et al.[21] stated that CSA and perimeter of the median nerve of both sides were higher in patients with SSc than in healthy controls when measured at the level of the carpal tunnel inlet in the transverse plane between the scaphoid tubercle and the pisiform bone. Another study reported a reduced median nerve density in patients with limited cutaneous SSc compared to control subjects.[22] Nevertheless, the pathophysiology of nerve involvement in SSc patients is still unknown. Two published studies have stated that microvascular abnormalities are effective in the development of neuropathy in

patients with SSc.[23,24] Another study reported that the same vascular lesions as in Raynaud's phenomenon might occur in the small peripheral vessels vascularizing peripheral nerves that contribute to neuropathy.[25] Therefore, larger studies are needed to confirm the pathophysiology of the disease and the results of the mentioned studies.

Advanced diffuse illness, ischemia of the vasa nervorum, and reduced nerve density have been identified as risk factors for neuropathy in patients with SSc.[26] AlMehmadi et al.[27] reported an association between peripheral neuropathy and the severity and progression of skin involvement. Martin et al.[28] stated that disease activity was associated with the severity of skin involvement. A published study suggested a relationship between the severity of skin involvement, disease activity, and neuropathy, albeit indirectly.[29] Another study assessing patients with higher skin thickness by mRSS showed a higher median nerve area.[21] In line with the literature, the results of our study revealed a significant relationship between disease activity, severity of skin involvement, and TN stiffness. This relationship might be explained by increasing connective tissue of the endo- and perineurium or microangiopathy of the vasa nervorum. Therefore, patients with an advanced diffuse disease or excessive skin involvement should be screened for neuropathy.

The present study has three potential limitations. First, although statistically sufficient, the number of patients included in the study was small due to the pandemic. Second, peripheral neuropathy was not evaluated by a nerve conduction study, and it would be more valuable had a nerve conduction study been performed with US and SHE to arrive at a conclusion about peripheral neuropathy. Third, the deeper location of TN in some patients and control subjects with a high body mass index did not allow us to obtain a high-spatial-resolution image as with the superficially located median nerve. Therefore, we attempted to measure the CSA of TN over the epineurium, where a high spatial resolution image could not be obtained.

In conclusion, Tibial nerve was stiffer and CSA was higher in patients with SSc than in healthy controls. The disease activity of SSc was significantly associated with TN elasticity. However, no correlation was found between severity of neuropathic pain and quality of life. The involvement of peripheral nerves in patients with SSc can be demonstrated using US and SWE with high reproducibility.

Ethics Committee Approval: The study protocol was approved by the Pamukkale University Non-Interventional Clinical Research Ethics Committee (date: 15.02.2022, no: 179799). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, analysis and/or interpretation, writing the article, references and fundings, materials: K.S.; Design: K.S., Y.M., U.F., S.B., K.U., C.V., S.N., A.H.; Control/supervision: K.S., Y.M., U.F.; Data collection and/or processing: K.S., C.V., S.N., A.H.; Literature review: K.S., Y.M., U.F., S.B., K.U., C.V.; Critical review: K.S., U.F.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390:1685-99. doi: 10.1016/S0140-6736(17)30933-9.
2. Lóránd V, Czirják L, Minier T. Musculoskeletal involvement in systemic sclerosis. Presse Med 2014;43:e315-28. doi: 10.1016/j.lpm.2014.03.027.
3. Amaral TN, Peres FA, Lapa AT, Marques-Neto JF, Appenzeller S. Neurologic involvement in scleroderma: A systematic review. Semin Arthritis Rheum 2013;43:335-47. doi: 10.1016/j.semarthrit.2013.05.002.
4. Raja J, Balaikerisnan T, Ramanaidu LP, Goh KJ. Large fiber peripheral neuropathy in systemic sclerosis: A prospective study using clinical and electrophysiological definition. Int J Rheum Dis 2021;24:347-54. doi: 10.1111/1756-185X.14042.
5. Zakrzewski J, Zakrzewska K, Pluta K, Nowak O, Miłoszewska-Paluch A. Ultrasound elastography in the evaluation of peripheral neuropathies: A systematic review of the literature. Pol J Radiol 2019;84:e581-91. doi: 10.5114/pjr.2019.91439.

6. Aslan M, Aslan A, Emeksiz HC, Candan F, Erdemli S, Tombul T, et al. Assessment of peripheral nerves with shear wave elastography in type 1 diabetic adolescents without diabetic peripheral neuropathy. J Ultrasound Med 2019;38:1583-96. doi: 10.1002/jum.14848.
7. Wei M, Ye X. Feasibility of point shear wave elastography for evaluating diabetic peripheral neuropathy. J Ultrasound Med 2020;39:1135-41. doi: 10.1002/jum.15198.
8. He Y, Xiang X, Zhu BH, Qiu L. Shear wave elastography evaluation of the median and tibial nerve in diabetic peripheral neuropathy. Quant Imaging Med Surg 2019;9:273-82. doi: 10.21037/qims.2019.02.05.
9. Dikici AS, Ustabasioglu FE, Delil S, Nalbantoglu M, Korkmaz B, Bakan S, et al. Evaluation of the tibial nerve with shear-wave elastography: A potential sonographic method for the diagnosis of diabetic peripheral neuropathy. Radiology 2017;282:494-501. doi: 10.1148/radiol.2016160135.
10. Yagci I, Kenis-Coskun O, Ozsoy T, Ozen G, Direskeneli H. Increased stiffness of median nerve in systemic sclerosis. BMC Musculoskelet Disord 2017;18:434. doi: 10.1186/s12891-017-1793-9.
11. Bedewi MA, Elsifey AA, Alfaifi T, Kotb MA, Abdelgawad MS, Bediwy AM, et al. Shear wave elastography of the tibial nerve in healthy subjects. Medicine (Baltimore) 2021;100:e23999. doi: 10.1097/MD.0000000000023999.
12. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2013;72:1747-55. doi: 10.1136/annrheumdis-2013-204424.
13. Temiz Karadag D, Karakas F, Tekeoglu S, Yazici A, Isik OO, Cefle A. Validation of Turkish version of the Scleroderma Health Assessment Questionnaire. Clin Rheumatol 2019;38:1917-23. doi: 10.1007/s10067-019-04494-5.
14. Valentini G, Iudici M, Walker UA, Jaeger VK, Baron M, Carreira P, et al. The European Scleroderma Trials and Research group (EUSTAR) task force for the development of revised activity criteria for systemic sclerosis: Derivation and validation of a preliminarily revised EUSTAR activity index. Ann Rheum Dis 2017;76:270-6. doi: 10.1136/annrheumdis-2016-209768.
15. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114:29-36. doi: 10.1016/j.pain.2004.12.010.
16. Dikici AS, Ustabasioglu FE, Delil S, Nalbantoglu M, Korkmaz B, Bakan S, et al. Evaluation of the tibial nerve with shear-wave elastography: A potential sonographic method for the diagnosis of diabetic peripheral neuropathy. Radiology 2017;282:494-501. doi: 10.1148/radiol.2016160135.
17. Viera AJ, Garrett JM. Understanding interobserver agreement: The kappa statistic. Fam Med 2005;37:360-3.
18. Amaral TN, Peres FA, Lapa AT, Marques-Neto JF, Appenzeller S. Neurologic involvement in scleroderma: A systematic review. Semin Arthritis Rheum 2013;43:335-47. doi: 10.1016/j.semarthrit.2013.05.002.
19. England JD, Gronseth GS, Franklin G, Miller RG, Asbury AK, Carter GT, et al. Distal symmetric polyneuropathy: A definition for clinical research: Report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2005;64:199-207. doi: 10.1212/01.WNL.0000149522.32823.EA.
20. Ishibashi F, Taniguchi M, Kojima R, Kawasaki A, Kosaka A, Uetake H. Elasticity of the tibial nerve assessed by sonoelastography was reduced before the development of neuropathy and further deterioration associated with the severity of neuropathy in patients with type 2 diabetes. J Diabetes Investig 2016;7:404-12. doi: 10.1111/jdi.12408.
21. Sousa-Neves J, Cerqueira M, Afonso C, Teixeira F. Median nerve ultrasound findings in systemic sclerosis patients: How do they relate to clinical features of the disease? Reumatol Clin (Engl Ed) 2018;14:312-3. doi: 10.1016/j.reuma.2017.07.019.
22. Bignotti B, Ghio M, Panico N, Tagliafico G, Martinoli C, Tagliafico A. High-resolution ultrasound of peripheral nerves in systemic sclerosis: A pilot study of computer-aided quantitative assessment of nerve density. Skeletal Radiol 2015;44:1761-7. doi: 10.1007/s00256-015-2230-5.
23. Raja J, Balaikerisnan T, Ramanaidu LP, Goh KJ. Large fiber peripheral neuropathy in systemic sclerosis: A prospective study using clinical and electrophysiological definition. Int J Rheum Dis 2021;24:347-54. doi: 10.1111/1756-185X.14042.
24. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: Update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010;33:2285-93. doi: 10.2337/dc10-1303.
25. Fleming JN, Nash RA, Mahoney WM Jr, Schwartz SM. Is scleroderma a vasculopathy? Curr Rheumatol Rep 2009;11:103-10. doi: 10.1007/s11926-009-0015-3.
26. Amaral TN, Peres FA, Lapa AT, Marques-Neto JF, Appenzeller S. Neurologic involvement in scleroderma: A systematic review. Semin Arthritis Rheum 2013;43:335-47. doi: 10.1016/j.semarthrit.2013.05.002.
27. AlMehmadi BA, To FZ, Anderson MA, Johnson SR. Epidemiology and treatment of peripheral neuropathy in systemic sclerosis. J Rheumatol 2021;48:1839-49. doi: 10.3899/jrheum.201299.

28. Martin P, Teodoro WR, Velosa AP, de Morais J, Carrasco S, Christmann RB, et al. Abnormal collagen V deposition in dermis correlates with skin thickening and disease activity in systemic sclerosis. Autoimmun Rev 2012;11:827-35. doi: 10.1016/j.autrev.2012.02.017.

29. Manneschi LI, Del Rosso A, Milia AF, Tani A, Nosi D, Pignone A, et al. Damage of cutaneous peripheral nervous system evolves differently according to the disease phase and subset of systemic sclerosis. Rheumatology (Oxford) 2005;44:607-13. doi: 10.1093/rheumatology/keh559.