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**Original Article**

# Audiological involvement in patients with systemic sclerosis

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## ABSTRACT

**Objectives:** The aim of the present study was to evaluate hearing loss in patients diagnosed with systemic sclerosis (SSc) and to investigate the relation between hearing loss, subtypes of the disease, its duration and clinical findings, and antibody positivity.

**Methods:** The study included 47 patients with SSc and 44 healthy controls. Audiometric, tympanometric, and otoacoustic emission measurements were applied to both groups.

**Results:** The evaluation of the participants medical history showed that among the patients with SSc, 19.1% experienced ear fullness, 27.7% experienced vertigo, and 36.2% experienced tinnitus. Hearing loss was detected in 23.4% of the patients with SSc. The corresponding result was 4.3% in the control group with a statistically significant difference ($p = 0.001$). Transient-evoked otoacoustic emission amplitude values were significantly lower in the patients' both ears with SSc than the control group ($p < 0.005$). Duration of disease was significantly longer, and diffusing capacity of the lungs for carbon monoxide values were significantly higher in the patients with SSc and sensorineural hearing loss.

**Conclusions:** The present study found that the incidence of hearing loss was significantly higher in the study group than in the healthy control group. In addition to other organ involvements, cochlear involvement occurs in these patients, and further studies are required.

**KEYWORDS:** Audiometry; ear; hearing loss; otoacoustic emission; systemic sclerosis

## Introduction

Systemic sclerosis (SSc) is a connective tissue disease that can present with widespread organ involvement, especially skin, lung, gastrointestinal system (GIS), kidney, and heart, and can lead to morbidity and mortality [1]. Hearing loss in SSc was demonstrated in a few studies before.

There are studies stating that inner ear involvement can be observed in various connective tissue diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), granulomatous polyangiitis (GPA), and Sjogren's syndrome. These studies found that subjective and objective hearing losses in patients were significantly higher than in the control groups [2–7]. Vasculitis and autoimmune mechanisms can be regarded as the major causes of audiological involvement in these diseases [8]. Hearing loss in these patients is generally in sensorineural type, but mixed-type hearing loss can rarely occur. Hearing loss can be frequently observed in patients diagnosed with SSc. The number of studies on middle and inner ear involvement in SSc is limited. Considering the patients with diffuse cutaneous systemic sclerosis (dcSSc), the patients with limited cutaneous systemic sclerosis (lcSSc) and the studies in which the two groups are included together, the hearing loss frequency in SSc was higher than in the control group [9–13]. In addition to sensorineural hearing loss, middle ear dysfunction with abnormal tympanometry findings can be observed in patients with SSc. Although the mechanism is not known clearly, hearing loss in SSc can occur based on focal strial atrophy due to vasculopathy or inner/outer hair cell dysfunction in the organ of corti or both situations [8]. The aim of the present study was to evaluate hearing loss in patients diagnosed with SSc and to investigate the relation between hearing loss and subtype of disease, its duration and clinical findings, and antibody positivity.

## Material and methods

### Patients

The current study was designed as a prospective matched case–control study between May 2018 and January 2019 and included 47 patients with SSc who consulted to Ankara

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University Faculty of Medicine, Department of Rheumatology outpatient clinic. Patients older than 18 years of age who were diagnosed with SSc according to the 2013 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria and accepted the study were included [14], and who agreed to participate in the study. Forty-four healthy individuals, who had similar age and gender characteristics with the SSc patient group, had no known connective tissue disease, and agreed to participate in the study, were included in the study as a control group. The individuals in the study and control groups were given informed consent forms, and they were included in the study after signing. Individuals who were under the age of 18 years, had a history of previous ear surgery, had a history of head and neck surgery trauma and radiotherapy, had a history of acoustic trauma and another connective tissue disease, used ototoxic drugs (such as high-dose aspirin, cisplatin, bleomycin and aminoglycoside), had a history of upper respiratory tract infections, and a family history of hearing loss were excluded from the study. This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by the Ankara University Faculty of Medicine Ethics Committee with the decision numbered 06-350-18 dated 26 March 2018.

## Clinical and laboratory findings of systemic sclerosis

The age of disease onset was accepted as the first symptom release time except for Raynaud's phenomenon in patients with SSc. Nailfold capillaroscopy examination was performed on SSc patients under 200× magnification with the Dino-lite Capillaroscope Pro 200 (MEDL4N Pro) videocapillaroscopy device. Interstitial lung disease was accepted as having at least one lung finding (reticular pattern, honeycomb appearance, and subpleural opacity) detected on computed tomography. GIS involvement was accepted as the presence of symptoms indicating motility disorder as a result of manometric tests or endoscopic interventions along with dysphagia-like symptoms. Cardiac involvement was considered to be symptoms suggestive of heart failure (such as dyspnoea and orthopnoea), echocardiography findings, and arrhythmia on electrocardiography. The antinuclear antibody (ANA) results which were determined from the patients' record with indirect immunofluorescence method were evaluated.

The Modified Rodnan Skin Score (MRSS) was calculated in the physical examination of the patients [15]. In the patient group diagnosed with SSc, the Medsger severity scale [16], and Valentini disease activity index [17] were investigated. The patient and control groups were inquired in terms of symptoms such as ear fullness, tinnitus, hearing loss, and vertigo.

## Audiological evaluation

Patients and healthy control group were evaluated through physical examination in terms of pathologies that may cause hearing defects in the Ankara University Faculty of Medicine otolaryngology clinic. If the patient had cerumen impaction, it was removed by appropriate otoscopy with the patient's consent, and then pure tone audiometry, speech audiometry, tympanometry, and otoacoustic emission tests were performed. Audiological tests were performed in the soundproof rooms (Industrial Acoustic Company) using the Interacoustics (Assens, Denmark) AC40 clinical audiometry device. Air conduction thresholds in both ears were evaluated at octave frequencies of 125–8000 Hz, and bone conduction thresholds were evaluated at octave frequencies of 500–4000 Hz. Pure tone average (PTA) was calculated by averaging the air conduction thresholds of 500, 1000, 2000, and 4000 Hz. Hearing loss degree of the participants based on PTA was evaluated according to the following classification system [18]:

0–20 dB hearing level (HL) as normal, 21–40 dB HL as mild hearing loss, 41–60 dB HL as moderate hearing loss, and >60 dB HL as severe hearing loss.

Hearing loss type was classified as conductive type (the presence of an air–bone gap >10 dB, with preserved bone conduction), sensorineural type (degradation of both bone and air conduction, the air–bone gap is <10 dB), and mixed type (degradation of both air and bone conduction, the air–bone gap is >10 dB).

226-Hz tympanometry was used for tympanometric measurements with 85 dB sound pressure level (SPL). We used two normality criteria for the tympanometric evaluation: peak amplitude (between 0.39 and 1.30 ml) and peak pressure value (−100 to +50 decapascal) in our study. All tympanograms were classified to Jerger and explained as follows:

Type A tympanogram, normal amplitude and pressure values.

Type As ('stiffness'), a peak in the normal pressure area, but its static compliance value is below 0.35 cc (typical finding of otosclerosis).

Type Ad ('discontinuity'), a peak in the normal pressure area, but its static compliance value is above 1.30 cc typical finding of ossicular chain disarticulation.

Type C tympanogram, a peak in the negative pressure area with normal or low compliance.

Type B tympanogram, no peak, obstruction of the auditory canal, ruptured (perforated) eardrum, and middle ear tumours [19].

Since audiological evaluation and emission evaluation cannot be performed in individuals with type B tympanogram, these individuals were excluded from the study. The tympanometric measurements were performed using the Interacoustics (Assens, Denmark) AZ26 immittance meter.

Otoacoustic emission measurements were made using full Autodynamics ILO88DP OAE V5.6y version and adult transient-evoked otoacoustic emission (TEOAE) probe. The transient click stimulus was used at the level of 83 ± 3 dB SPL with a duration of 80 ms. Signal-to-noise ratio of >3 dB in at least three frequency bands out of five frequency bands (700, 1500, 2200, 3000, and 3700 Hz) indicates the presence of otoacoustic emission [20]. We excluded the subjects when the TEOAE reproducibility and reliability was <70% [21, 22].

## Statistical analysis

The study data were transferred into the computer environment through SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL) and evaluated. Descriptive statistics were presented as mean ± standard deviation, median (min–max), frequency distribution and percentage. Categorical variables were evaluated using Pearson's chi-square test or Fisher's exact test. The variables' fitness to normal distribution were examined using visual (histogram and probability graphics) and analytic methods (Shapiro–Wilk test). Mann–Whitney U test was used to determine the

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statistical significance between two independent groups in terms of variables that did not meet normal distribution. Student's *t* test was used to determine the statistical significance between two independent groups in terms of variables that met normal distribution. Correlation analysis was performed between pure tone average and Valentini activity index, Medsger disease severity score, and MRSS, which are indicators of disease activity and severity, as well as diffusing capacity of the lungs for carbon monoxide (DLCO) value, which can show the severity of the disease clinically, disease duration. Multiple linear regression analysis was performed by evaluating these variables together, and their effect on pure tone average was investigated. The model fit was assessed using appropriate residual and goodness-of-fit statistics. The statistical significance level was regarded as $p < 0.05$.

## Results

### Patient characteristics

In our study, the sociodemographic characteristics of both groups were similar. The mean age of the patients with SSc was $49.8 \pm 10.6$ years, and the mean age of the control group was $46.8 \pm 7.9$ years ($p = 0.126$). Of the patients, 85.1% were female, and 75% of the control group were female. The median duration of disease of the patients was 7 (min: 1 to max: 23) years, and the medians of MRSS, Valentini index and Medsger score were 10 (min: 2 to max: 34), 3 (min: 0 to max: 11), and 4 (min: 0 to max: 15), respectively. Among the patients, the capillaroscopy findings were normal in 4.7% and were compatible with the early period in 18.6%, with the active period in 46.5% and with the late period in 30.2%. Of the patients, 95.7% had Raynaud's phenomenon, 83% had sclerodactyly, 70.2% had telangiectasia, 31.9% had digital ulcer, and 8.5% had amputation. In the subtypes of the patients with SSc, 55.2% were lcSSc and 44.7% were dcSSc.

### Symptoms and signs of the patients

The patients with SSc had the symptoms of hearing loss (23.4% vs 2.3%, $p = 0.003$), ear fullness (19.1% vs 0, $p = 0.003$), vertigo (27.7% vs 4.5%, $p = 0.003$), and tinnitus (36.2% vs 9.1%, $p = 0.002$) significantly frequent (Table 1). The percentage of those with sensorineural hearing loss (23.4% vs 4.5%, $p = 0.001$) was significantly higher than in the control group. PTA in both right and left ears of the patients with SSc were significantly higher than in the health control group ($p = 0.009$; $p = 0.001$, respectively). On the other hand, no significant differences were found between groups in terms of conductive hearing loss, mixed-type hearing loss, and tympanogram findings (Table 1).

The air conduction threshold values at 500, 1000, and 2000 Hz in both ears of the patients with SSc and air conduction threshold value in their left ear at 4000 Hz were significantly higher than in the healthy control group (Table 2). TEOAE values at 700, 1500, 2200, 3000, and 3700 Hz in both right and left ears of the patients with SSc were significantly lower than the healthy control group (Table 3).

Comparing the patients with lcSSc and patients with dcSSc, the sensorineural hearing loss was statistically more common in patients with dcSSc ($p = 0.043$) and the right ear PTA was higher ($p = 0.026$) than the left ears. Hearing loss, ear fullness, vertigo and tinnitus symptoms' incidence frequencies of conductive and mixed-type hearing loss and left ear PTA in SSc subtypes were similar (Table 4).

### Comparison of clinical and serological characteristics of SSc patients with and without sensorineural hearing loss

The duration of disease in patients with SSc and sensorineural hearing loss ($14.0 \pm 6.6$ years) was longer than the patients without sensorineural hearing loss ($6.4 \pm 4.8$ years), and their DLCO values were lower ($p = 0.003$). The mean age of patients with SSc and sensorineural hearing loss was higher ($p = 0.005$). Among patients with SSc and hearing loss, those who had amputation ($p = 0.035$) and those who received immunosuppressive treatment ($p = 0.029$) were more frequent (Table 5). MRSS, Valentini index, Medsger scores, capillaroscopy result, Raynaud's phenomenon, sclerodactyly, telangiectasia, digital ulcer, GIS involvement, cardiac involvement, arthralgia and arthritis presence, anti-nuclear antibody (ANA), topoisomerase 1 (SCL-70), anti-major centromere autoantigen B (CENP-B), and anti-PM/Scl antibody positivity, calcium channel blocker, steroid, PDE5 inhibitor, prostacyclin analog, and the state using endothelin receptor antagonist were similar between groups (Table 5).

There was a positive correlation between right and left PTA and Valentini index and Medsger scores of patients with SSc, while there was a negative correlation with DLCO values. In multiple linear regression analysis, a statistically significant relationship was found only between Medsger score and PTA (Table 6).

## Discussion

SSc is a disease known to be able to involve almost any organ, especially GIS, lung, kidney, heart, and skin, but data on hearing loss and inner ear involvement in SSc are limited. Although there are studies showing that audiological involvement can be observed in various connective tissue diseases such as RA, SLE, GPA, and Sjogren syndrome, the number of studies on middle and inner ear involvement in SSc is limited [2–7]. The study compared 47 patients with SSc and 44 healthy controls and assessed the effect of SSc on hearing threshold level, middle ear structures and otoacoustic emission test. The study tried to clarify whether there is relation between these effects and duration and severity of disease, subtype, and autoantibody positivity.

The earliest pathogenic event in SSc is regarded as vascular damage. Vascular changes can be detected even in pre-clinic period. Vascular damage is most likely caused by oxidative stress due to viruses, autoantibodies, or free radicals. Endothelial cell damage especially occurs in arterioles [23, 24]. Kahaleh and Le Roy asserted that the deficiency of protease inhibitors in SSc may cause cytotoxic activity. They also asserted that humoral and cellular dysregulation can be responsible for endothelial injury and vasculopathy [25]. Abou-Taleb *et al.* determined that the blood vessels in the stria vascularis were wider than normal and focal strial atrophy occurred in the histopathology of a patient diagnosed with SSc who underwent surgery due to sensorineural hearing loss. The study showed that the number of outer hair cells and ganglion cells decreased by ~50% compared to normal. Additionally, vascular fibrosis was shown in small arterioles and venules [8]. Cochleovestibular changes, loss of the organ

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**Table 1.** Distribution of hearing symptom and findings between the study and control groups.

| | | SSc ($n=47$) | Control ($n=44$) | |
|---|---|---|---|---|
| | | *n* (%) | *n* (%) | *p* |
| Age (year) mean ± SD/median (min–max) | | 49.8 ± 10.6/50 (25–72) | 46.8 ± 7.9/45 (30–66) | 0.126[a] |
| Gender, female | | 40 (85.1) | 33 (75) | 0.226[b] |
| BMI (kg/m$^2$) mean ± SD/median (min–max) | | 25.9 ± 4.2/25.7 (18.5–37.6) | 26.9 ± 3.8/27.3 (19.3–35.6) | 0.169[c] |
| Hearing loss | | 11 (23.4) | 1 (2.3) | 0.003[b] |
| Ear fullness | | 9 (19.1) | 0 | 0.003[d] |
| Vertigo | | 13 (27.7) | 2 (4.5) | 0.003[b] |
| Tinnitus | | 17 (36.2) | 4 (9.1) | 0.002[b] |
| Right ear | Conductive hearing loss | 0 | 1 (2.3) | 0.484[d] |
| | Sensorineural hearing loss | 11 (23.4) | 2 (4.5) | 0.010[b] |
| | Mixed-type hearing loss | 2 (4.3) | 0 | 0.495[d] |
| | Tympanogram findings | | | |
| | A | 32 (68.1) | 30 (68.2) | 0.751[b] |
| | As | 12 (25.5) | 11 (25.0) | |
| | Ad | 2 (4.3) | 3 (6.8) | |
| | C | 1 (2.1) | 0 | |
| | Pure tone average mean ± SD/median (min–max) | 16.4 ± 9.3/16 (2–45) | 11.8 ± 6.5/11 (−3;34) | 0.009[c] |
| Left ear | Conductive hearing loss | 0 | 0 | – |
| | Sensorineural hearing loss | 11 (23.4) | 2 (4.5) | 0.010[b] |
| | Mixed-type hearing loss | 2 (4.3) | 0 | 0.495[d] |
| | Tympanogram findings | | | |
| | A | 33 (70.2) | 29 (65.9) | 0.864[b] |
| | As | 10 (21.2) | 11 (25.0) | |
| | Ad | 2 (4.3) | 3 (6.8) | |
| | C | 2 (4.3) | 1 (2.3) | |
| | Pure tone average mean ± SD/median (min–max) | 17.0 ± 9.9/16 (3–45) | 11.0 ± 6.7/10 (0–39) | 0.001[c] |

*n*: number of individuals; %: column percentage; SD: standard deviation.
[a]Student's *t* test.
[b]Chi-square test.
[c]Mann–Whitney U test.
[d]Fisher's exact test; BMI; body mass index; SSc: systemic sclerosis.

**Table 2.** Distribution of right and left ear air conduction threshold values at different frequencies between the study and control groups.

| | | SSc ($n=47$) | | Control ($n=44$) | | |
|---|---|---|---|---|---|---|
| Ear | Air conduction threshold (Hz) | Mean ± SD | Median (min–max) | Mean ± SD | Median (min–max) | $p$[a] |
| Left | 125 | 9.4 ± 7.1 | 10 (0–25) | 9.7 ± 8.1 | 7.5 (0–30) | 0.977 |
| | 250 | 10.7 ± 7.9 | 10 (0–30) | 9.2 ± 8.2 | 5 (0–35) | 0.276 |
| | 500 | 11.5 ± 8.2 | 10 (0–30) | 7.7 ± 6.7 | 5 (0–30) | 0.021 |
| | 1000 | 15.0 ± 9.5 | 15 (0–40) | 8.5 ± 6.5 | 5 (0–35) | <0.001 |
| | 2000 | 15.8 ± 10.8 | 15 (0–45) | 10.3 ± 8.6 | 10 (0–50) | 0.012 |
| | 4000 | 24.4 ± 15.4 | 20 (0–65) | 16.8 ± 11.2 | 15 (0–55) | 0.012 |
| | 6000 | 30.6 ± 17.4 | 30 (0–75) | 24.1 ± 14.0 | 22.5 (0–65) | 0.066 |
| | 8000 | 29.8 ± 21.0 | 25 (0–90) | 23.8 ± 17.2 | 20 (0–70) | 0.184 |
| Right | 125 | 9.2 ± 6.9 | 10 (0–25) | 11.4 ± 10.2 | 10 (−5;50) | 0.360 |
| | 250 | 10.8 ± 6.8 | 10 (0–25) | 10.2 ± 9.3 | 10 (−5;45) | 0.428 |
| | 500 | 12.6 ± 8.7 | 10 (0–40) | 8.8 ± 7.6 | 10 (−5;40) | 0.024 |
| | 1000 | 15.5 ± 8.1 | 15 (0–35) | 10.3 ± 5.4 | 10 (−5;25) | 0.001 |
| | 2000 | 15.6 ± 10.0 | 15 (0–50) | 10.4 ± 8.5 | 10 (0–40) | 0.005 |
| | 4000 | 22.6 ± 14.4 | 20 (0–65) | 18.8 ± 12.0 | 15 (0–60) | 0.185 |
| | 6000 | 27.4 ± 16.7 | 25 (0–75) | 22.2 ± 12.0 | 20 (0–60) | 0.134 |
| | 8000 | 28.2 ± 19.3 | 20 (0–80) | 22.3 ± 14.4 | 20 (0–60) | 0.177 |

*n*: number of individuals; SD: standard deviation; [a]Mann–Whitney U test; SSc: systemic sclerosis.

of corti and atrophy of the stria vascularis were observed in patients with hearing loss with vasculitis such as GPA and PAN [26]. In the light of this information, it can be thought that hearing loss in SSc is related to vasculopathy. However, we do not know the exact mechanism of hearing pathologies.

The present study found that among the patients with SSc, 23.4% had subjective hearing loss, 19.1% had ear fullness, 27.7% had vertigo, and 36.2% had tinnitus. We detected sensorinoral hearing loss in 23.4% of our patients diagnosed with SSc (38.1% of dcSSc and 11.5% of lcSSc). These symptoms and sensorineural hearing loss were more significantly common among the study group than in the control group. When we examine the studies of other researchers on this subject, Kastanioudakis *et al.* [10] determined that 20% of 30 patients with SSc experienced sensorineural hearing loss, Maciaszczyk

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**Table 3.** TEOAE measurements of right and left ears at different frequencies between the study and control groups.

| Ear | Frequency (Hz) | SSc ($n=47$) | | Control ($n=44$) | | $p$[a] |
|---|---|---|---|---|---|---|
| | | Mean ± SD dB | Median (min–max) | Mean ± SD dB | Median (min–max) | |
| Left | 700 | 2.5 ± 3.7 | 0 (0–13) | 6.2 ± 5.4 | 6.5 (0–18) | 0.002 |
| | 1500 | 9.4 ± 5.4 | 9 (0–21) | 14.9 ± 6.4 | 15.5 (0–25) | <0.001 |
| | 2200 | 8.5 ± 6.6 | 7 (0–28) | 15.7 ± 6.5 | 15.5 (0–29) | <0.001 |
| | 3000 | 6.4 ± 5.3 | 5 (0–22) | 11.4 ± 6.8 | 11 (0–26) | <0.001 |
| | 3700 | 5.8 ± 5.6 | 5 (0–16) | 10.3 ± 7.1 | 10 (0–26) | 0.002 |
| Right | 700 | 2.7 ± 4.2 | 0 (0–17) | 5.7 ± 6.1 | 3 (0–20) | 0.010 |
| | 1500 | 10.4 ± 6.6 | 9 (0–25) | 15.1 ± 5.0 | 15 (5–30) | <0.001 |
| | 2200 | 10.0 ± 6.4 | 9 (0–24) | 15.3 ± 5.7 | 15 (2–34) | <0.001 |
| | 3000 | 7.4 ± 6.1 | 7 (0–24) | 11.0 ± 6.6 | 10.5 (0–25) | 0.008 |
| | 3700 | 5.4 ± 5.6 | 4 (0–20) | 9.9 ± 6.5 | 10 (0–23) | 0.001 |

*n*: umber of individuals; SD: standard deviation; TEOAE: transient-evoked otoacoustic emission values.
[a]Mann–Whitney U test; SSc: systemic sclerosis.

**Table 4.** Hearing symptom and findings between patients with lcSSc and patients with dcSSc.

| | | lcSSc ($n=26$) | dcSSc ($n=21$) | |
|---|---|---|---|---|
| | | *n* (%) | *n* (%) | *p* |
| Hearing loss | | 4 (15.4) | 7 (33.3) | 0.181[a] |
| Ear fullness | | 4 (15.4) | 5 (23.8) | 0.486[a] |
| Vertigo | | 6 (23.1) | 7 (33.3) | 0.435[b] |
| Tinnitus | | 9 (34.6) | 8 (38.1) | 0.805[b] |
| Right ear | Conductive hearing loss | 0 | 0 | – |
| | Sensorineural hearing loss | 3 (11.5) | 8 (38.1) | 0.043[a] |
| | Mixed-type hearing loss | 1 (3.8) | 1 (4.8) | 1.000[a] |
| | Tympanogram findings | | | |
| | A | 18 (69.2) | 14 (66.7) | 0.342[b] |
| | As | 7 (26.9) | 5 (23.8) | |
| | Ad | 0 | 2 (9.5) | |
| | C | 1 (3.8) | 0 | |
| | Pure tone average mean ± SD/median (min–max) | 14.5 ± 10.1/12.5 (2–45) | 18.9 ± 7.9/17 (6–35) | 0.026[c] |
| Left ear | Conductive hearing loss | 0 | 0 | – |
| | Sensorineural hearing loss | 3 (11.5) | 8 (38.1) | 0.043[a] |
| | Mixed-type hearing loss | 1 (3.8) | 1 (4.8) | 1.000[a] |
| | Tympanogram findings | | | |
| | A | 18 (69.2) | 15 (71.4) | 0.242[b] |
| | As | 6 (23.1) | 4 (19.0) | |
| | Ad | 0 | 2 (9.5) | |
| | C | 2 (7.7) | 0 | |
| | Pure tone average mean ± SD/median (min–max) | 15.2 ± 9.6/15.5 (3–41) | 19.3 ± 9.9/18 (6–45) | 0.099[c] |

*n*: number of individuals; %: column percentage; SD: standard deviation; lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis.
[a]Fisher's exact test.
[b]Chi-square test.
[c]Mann–Whitney U test.

*et al.* [27] conducted a study on 20 patients with SSc sensorineural hearing loss was detected in eight (40%) patients. Monteiro *et al.* [11] assessed the audiological symptoms of 24 patients with dcSSc and found that 46% of the patients had sensorineural hearing loss while no mixed-type or conductive-type hearing loss was observed. Similar to the study of Monteiro *et al.* [11], we did not detect conductive hearing loss in our study, but we found mixed-type hearing loss in two patients. However, this was not statistically significant. Amor-Dorado *et al.* assessed the audiovestibular involvement in 35 patients with lcSSc and found abnormal tympanometric findings in 20% of the patients while the tympanometric findings of the control group were normal [9]. Considering the tympanogram findings of the patients with SSc in our study, 29.8% of the patients with SSc had abnormal tympanogram findings. However, this was not statistically significant compared to the control group. Amor-Dorado *et al.* [9] also found that 54% of the patients had subjective hearing loss while 27 patients (77%) had abnormal hearing symptoms. Of 27 patients with hearing loss, 24 (89%) had sensorineural hearing loss and 3 (11%) had mixed-type hearing loss. Hearing loss was found to be asymmetrical or unilateral in 11 patients with sensorineural hearing loss. These patients were examined with magnetic resonance imaging in terms of central nervous system lesions [9]. Compared to the study of Amor-Dorado *et al.*, we found a lower rate of sensorineural hearing loss (11.5%) in our patients with lcSSc. In addition, asymmetric hearing loss was not present in our study. No significant differences were found between individuals with or without hearing loss in terms of age, sex, disease

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**Table 5.** Distribution of some clinical features among SSc patients with and without sensorineural hearing loss.

| Patients diagnosed with SSc | Without sensorineural hearing loss ($n = 36$) | With sensorineural hearing loss ($n = 11$) | $p$ |
|---|---|---|---|
| Sex, *n* (%) | | | |
| Female | 30 (83.3) | 10 (90.9) | 1.000[b] |
| Male | 6 (16.7) | 1 (9.1) | |
| Age (years), mean ± SD/median (min–max) | 47.6 ± 10.4/48 (25–72) | 57.4 ± 7.9/57 (49–68) | 0.005[a] |
| BMI (kg/m$^2$), mean ± SD/median (min–max) | 25.4 ± 3.9/25.1 (18.5–35.8) | 27.6 ± 4.7/27.0 (19.3–37.6) | 0.085[a] |
| MRSS, mean ± SD/median (min–max) | 11.9 ± 7.8/12 (2–34) | 10.3 ± 6.6/9 (2–22) | 0.560[a] |
| Valentini ($n = 42$), mean ± SD/median (min–max) | 2.9 ± 2.2/3 (0–11) | 3.4 ± 2.4/3 (0.5–7.5) | 0.546[a] |
| Medsger ($n = 43$), mean ± SD/median (min–max) | 4.6 ± 3.0/4 (0–15) | 5.1 ± 3.5/4 (2–14) | 0.872[a] |
| Capillaroscopy ($n = 43$), *n* (%) | | | |
| Normal | 2 (5.9) | 0 | 0.649[b] |
| Early period | 7 (20.5) | 1 (11.2) | |
| Active pattern | 16 (47.1) | 4 (44.4) | |
| Advanced period | 9 (26.5) | 4 (44.4) | |
| Raynaud's phenomena, *n* (%) | 34 (94.4) | 11 (100) | 1.000[c] |
| Sclerodactylia, *n* (%) | 30 (83.3) | 9 (81.8) | 1.000[c] |
| Telangiectasia, *n* (%) | 26 (72.2) | 7 (63.6) | 0.710[c] |
| Digital ulcer, *n* (%) | 10 (27.8) | 5 (45.5) | 0.292[c] |
| Amputation, *n* (%) | 1 (2.8) | 3 (27.3) | 0.035[c] |
| ILD, *n* (%) | 15 (41.7) | 8 (72.7) | 0.071[b] |
| DLCO ($n = 42$), mean ± SD/median (min–max) | 68.5 ± 15.3/70.5 (33–112) | 54.2 ± 20.3/55 (27–103) | 0.003[a] |
| Normal, *n* (%) | 20 (62.5) | 1 (10.0) | 0.004[b] |
| Low, n (%) | 12 (37.5) | 9 (90.0) | |
| GIS involvement, *n* (%) | 5 (13.9) | 3 (27.3) | 0.367[c] |
| Cardiac involvement, *n* (%) | 0 | 1 (9.1) | 0.234[c] |
| Arthralgia, *n* (%) | 23 (63.9) | 9 (81.8) | 0.461[c] |
| Arthritis, *n* (%) | 1 (2.8) | 0 | 1.000[c] |
| ANA positivity ($n = 46$), *n* (%) | 32 (91.4) | 11 (100) | 1.000[c] |
| SCL-70 positivity ($n = 46$), *n* (%) | 14 (40.0) | 5 (45.5) | 1.000[c] |
| CENP-B positivity ($n = 46$), *n* (%) | 11 (31.4) | 2 (18.2) | 0.473[c] |
| PM-SCL positivity ($n = 46$), *n* (%) | 1 (2.9) | 0 | 1.000[c] |
| Calcium channel blocker, *n* (%) | 28 (77.8) | 8 (72.7) | 0.703[c] |
| Immunosuppressive, *n* (%) | 9 (25.0) | 7 (63.6) | 0.029[c] |
| Steroid, *n* (%) | 12 (33.3) | 2 (18.2) | 0.464[c] |
| PDE5 inhibitor, *n* (%) | 2 (5.6) | 0 | 1.000[c] |
| Prostacyclin analogue, *n* (%) | 6 (16.7) | 1 (9.1) | 1.000[c] |
| Endothelin receptor antagonist, *n* (%) | 3 (8.3) | 1 (9.1) | 1.000[c] |

*n*: number of individuals; %: column percentage; SD: standard deviation.
[a]Mann–Whitney U test.
[b]Chi-square test.
[c]Fisher's exact test; SSc: systemic sclerosis; DLCO: diffusing capacity of the lungs for carbon monoxide; BMI: body mass index; PDE5: phosphodiesterase5; ILD: interstitial lung disease; MRSS: Modified Rodnan Skin Score.

subtype, duration of disease, antibody profile, and medicine used in the above-mentioned studies [10, 11, 27]. A statistically significant difference was found in the PTA values of the study and control groups for the right and left ears. However, we do not find this difference, which is <5 dB for the right ear, clinically significant [28]. The source of this variability is a combination of variations in participants' decision process, mental status, calibration wrong, and differences in earphone placement [29].

In the present study, it was found that sensorineural hearing loss was significantly more in the patients with a longer duration of disease ($p < 0.001$). Also, in our study, sensorineural hearing loss was significantly higher in patients with low DLCO ($p = 0.003$). While the DLCO in 90% of the patients with sensorineural hearing loss was low, this rate was 37.5% among people without hearing loss ($p = 0.004$). Similar to other studies [4, 9, 13, 27], in the present study, no correlation between MRSS, Raynaud's phenomenon, telangiectasia, sclerodactyly, autoantibody positivity, and hearing loss was found (Table 5). Contrary to the study by Amor-Dorado *et al.* [9], we found no correlation between digital ulcers and hearing loss. However, three (27.3%) out of four patients with finger amputation had sensorineural hearing loss ($p = 0.03$). The mean age of patients with SSc and hearing loss was higher ($p = 0.005$). However, we considered that age-related hearing loss did not affect the study results since the study and control groups were similar in terms of age and sex.

As far as we know, the disease severity score and activity index were not examined in the relevant studies. The present study is the first study that examined the correlation between hearing loss and the activity and severity of disease using the Medsger severity scale and Valentini activity index. No significant correlation was found between sensorineural hearing loss and the severity and activity of disease. However, a positive medium-level correlation was found between the PTA in both ears and Valentini index and Medsger scores of the patients with SSc while a negative medium-level correlation was found with DLCO value. The fact that hearing loss is more frequent among patients with dcSSc and patients with high disease activity and severity scores indicates that the prevalence and severity of the

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**Table 6.** Correlation between right and left ear pure tone average and disease duration, DLCO value, MRSS, Valentini index and Medsger scores of patients with SSc and multiple linear regression analysis.

| | Right ear pure tone average | | | | | |
|---|---|---|---|---|---|---|
| | | Correlation analysis | | Multiple linear regression analysis* | | |
| | *n* | rho | *p* | Standardized B | 95% CI | *p* |
| Duration of illness (year) | 47 | 0.082 | 0.583 | 0.147 | −0.31–0.76 | 0.403 |
| MRSS score | 47 | 0.089 | 0.553 | −0.410 | −1.05–0.07 | 0.084 |
| Valentini index | 42 | 0.308 | 0.048 | −0.042 | −1.95–1.60 | 0.843 |
| Medsger score | 43 | 0.361 | 0.017 | 0.482 | 0.03–3.26 | 0.046 |
| DLCO | 47 | −0.409 | 0.007 | −0.276 | −0.36–0.05 | 0.141 |
| | Left ear pure tone average | | | | | |
| | | Correlation | | Multiple linear regression analysis** | | |
| | *n* | rho | *p* | B | 95% CI | *p* |
| Duration of illness (year) | 47 | 0.191 | 0.200 | 0.264 | −0.14–0.98 | 0.136 |
| MRSS score | 47 | 0.084 | 0.574 | −0.383 | −1.06–0.10 | 0.104 |
| Valentini index | 42 | 0.309 | 0.046 | 0.024 | −1.75–1.95 | 0.910 |
| Medsger score | 43 | 0.329 | 0.031 | 0.519 | 0.17–3.54 | 0.032 |
| DLCO | 47 | −0.342 | 0.027 | −0.140 | −0.29–0.13 | 0.446 |

B: beta; DLCO: diffusing capacity of the lungs for carbon monoxide; MRSS: Modified Rodnan Skin Score; rho; Spearman's correlation coefficient; SSc: systemic sclerosis.
*$R^2 = 0.289$.
**$R^2 = 0.297$.

disease might be related to hearing loss. Moreover, the present study performed OAE evaluation in both patients with SSc and control group unlike other studies [9–13, 27]. OAE measurement, which was primarily defined by Kemp in 1977, is a clinical practice used to determine the presence of hearing loss. OAE is the sound that can be recorded from the outer hair cells of the cochlea with a microphone placed in the external auditory canal and is a simple, effective, and non-invasive objective indicator of healthy cochlear function [30]. Probst and Harris made TEOAE and DPOAE measurements in 166 ears with or without hearing loss and obtained emission response in those with hearing levels better than 30 dB [31]. No emission response was obtained in the patients with sensorineural hearing loss and control group in the present study. Although there were normal audiometric and tympanometric findings in two patients in the study group and two participants in the control group, no emission response was obtained. This finding might be due to the lack of permeability in the middle ear structures. While emission presence in those with normal middle ear structures indicates normal hearing and normal cochlear structures, there is no specific 'cut-off' value of a decrease in emission amplitudes [32]. TEOAE amplitude values of the patients with SSc were lower than the control groups at all frequencies, and this difference was statistically significant for both right and left ears ($p < 0.005$). This significant OAE amplitude lowness indicates that hearing loss in patients with SSc may be of cochlear origin.

A study that compared hearing loss in the patients with SSc to the severity of capillaroscopy findings was published in 2018 [13]. Of the patients with early period capillaroscopy findings, 71.4% had sensorineural hearing loss while 62% of the patients with active period capillaroscopy findings and 72.7% of the patients with late period capillaroscopy findings had sensorineural hearing loss. In our study, no correlation was found between capillaroscopy findings and hearing loss. Moreover, 63% of the patients with SSc experienced sensorineural hearing loss while one patient had mixed-type hearing loss. No correlation was found between the presence of early, active, and late period capillaroscopy findings in patients and hearing loss in the present study ($p = 0.649$) [13].

The study group (47 patients) with SSc consisted of 26 patients with dcSSc (55.3%) and 21 patients with lcSSc (44.7%). While there were no significant differences between two subtype terms of subjective hearing loss, tinnitus, vertigo, and ear fullness, sensorineural hearing loss was more common among the patients with dcSSc ($p = 0.04$). The right ear PTA was found as 18.9 dB HL in dcSSc and 14.5 dB HL in lcSSc ($p = 0.026$). The left ear PTA was 19.3 dB HL in dcSSc and 15.3 dB HL in lcSSc; however, this value was not statistically significant although it was slightly high in dcSSc ($p = 0.09$). dcSSc is related to more aggressive organ involvement and higher mortality than lcSSc. The fact that sensorineural hearing loss was higher in patients with dcSSc compared to the patients with lcSSc in the present study supports this finding.

The main limitation of our study was the small number of patients. However, this is also due to the fact that SSc is a very rare disease. Another limitation was that we did not compare the prevalence difference of hearing problems between SSc and other connective tissue diseases (RA, SLE, etc.). However, unlike previous studies, we used TEOAE, which is an objective method for hearing assessment. In addition, we aimed to shed light on the relationship between hearing loss and disease severity/activity by using SSc-related scales such as Medsger and Valentini in our study.

In conclusion, hearing loss is frequently observed in the patients with SSc. In addition to other organ involvements, hearing loss due to cochlear involvement in these patients appears to be an important problem; however, more extensive and comprehensive studies on this subject should be conducted.

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## Conflict of interest

None declared.

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