



# Esophageal Involvement and Gastroesophageal Reflux Disease in Systemic Sclerosis: A Tertiary Center Experience

## Sistemik Skleroz'da Özofagus Tutulumu ve Gastroözofageal Reflü Hastalığı: Üçüncü Basamak Deneyimi

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### Abstract

**Aim:** In this study, we investigated the demographic features, endoscopic, manometric, and 24-hour pH monitoring findings of patients with SS.

**Materials and Method:** Twenty-six patients with SS who presented with dysphagia or heartburn complaints were identified. Patients' files, endoscopic, manometric, and 24-hour pH monitoring findings of the esophagus were examined.

**Results:** All of the patients were symptomatic. The average age of 26 patients was 47.9 years and 96% were women. 46.1% of them applied with the complaint of heartburn and 53.9% with the complaint of dysphagia. The frequency of esophagitis in patients with SS was found to be significantly higher ( $p=0.005$ ). Pathological reflux was detected in 90% of the patients with SS who underwent 24-hour pH monitoring and it was significantly higher ( $p=0.013$ ). The mean esophageal body resting pressure in the patient with SS group was  $-0.73$  mmHg and was significantly lower than that of control group ( $p<0.001$ ). The mean resting LES pressure in the patient with SS group was  $3.3$  mmHg and was significantly lower than that of control group ( $p=0.028$ ).

**Conclusion:** Esophageal involvement is a hallmark manifestation of SS and typically occurs secondary to heartburn and dysphagia. In our society, the incidence of Gastroesophageal Reflux Disease (GERD) and GERD-related complications is high in SS patients with esophageal symptoms. It is important to refer these patients to experienced gastroenterology centers to be evaluated by endoscopic and then other diagnostic methods.

**Keywords:** Esophageal motility disorder, gastroesophageal reflux disease, systemic sclerosis.

### Öz

**Amaç:** Bu çalışmamızda Sistemik Skleroz (SS) tanılı hastaların demografik özelliklerini, endoskopik, manometrik ve 24 saatlik pH monitorizasyonu bulgularını araştırdık.

**Gereç ve Yöntem:** Disfaji veya heartburn şikayetleri ile başvurmuş olan 26 SS tanılı hasta tespit edildi. Hastaların, dosyaları, endoskopik, manometrik ve özofagusun 24 saatlik pH monitorizasyonu bulguları incelendi.

**Bulgular:** SS tanılı hastaların tamamı semptomatikti, 26 Hastanın yaş ortalaması 47,9 idi, %96'sı kadındı. %46,1'i heartburn şikayetiyle, %53,9'u disfaji şikayetiyle başvurmuştu. SS tanılı hastalarda özofajit sıklığı anlamlı ölçüde yüksek saptandı ( $p=0,005$ ). SS tanılı hastalarda, 24 saatlik pH monitorizasyonu yapılan hastaların %90'ında patolojik reflü tespit edilmişti ve anlamlı derecede yüksekti ( $p=0,013$ ). SS tanılı hastaların ortalama Özofagus Gövde Dinlenim Basıncı  $-0,73$  mmHg olup kontrol grubuna göre anlamlı olarak düştü ( $p<0,001$ ). SS tanılı hastaların ortalama LES Dinlenim Basıncı  $3,3$  mmHg olup anlamlı derecede düştü ( $p=0,028$ ).

**Sonuç:** Özofageal tutulum SS' nin karakteristik tutulumlarından biridir. Özofagus tutulumu, heartburn ve disfaji gibi şikayetler ile kendini gösterir. Toplumumuzda, özofagus semptomları olan SS hastalarında Gastroözofageal Reflü Hastalığı (GÖRH) ve GÖRH ile ilişkili komplikasyonların görülme sıklığı yüksektir. Bu hastaların endoskopi ve diğer tanı yöntemleriyle değerlendirilmesi için deneyimli gastroenteroloji merkezlerine yönlendirilmesi önem arz etmektedir.

**Anahtar Kelimeler:** Gastroözofageal reflü hastalığı, özofagus motilite bozuklukları, sistemik skleroz



## INTRODUCTION

Systemic Sclerosis (SS) is a rare multisystemic disease of an unclear etiology, characterized by microvascular damage and excessive collagen synthesis and deposition in the skin and visceral organs.<sup>[1]</sup> The gastrointestinal tract (GI) is affected in almost 90% of the patients with SS and the disease may also involve any part of the GI, from the oral aperture to the rectum.<sup>[2]</sup> Esophageal motility disorder (EMD), lower esophageal sphincter (LES) incompetence, and the accompanying gastroparesis in some patients are considered as the primary causes of increased frequency of acid reflux. Additionally, dysphagia and gastroesophageal reflux disease (GERD) are commonly seen serious comorbidities in patients with SS.<sup>[3]</sup> GERD may result in numerous complications including esophagitis, peptic stricture, and Barrett's esophagus (BE).<sup>[4]</sup> Moreover, if left uncontrolled, GERD may form a basis for recurrent aspiration pneumonia, thereby leading to pulmonary fibrosis.<sup>[5]</sup> GER and dysphagia have been found to be associated with depressive symptoms in patients with SS.<sup>[6]</sup> In patients with SS, early assessment of esophageal involvement may create awareness of aggressive treatments for GERD. Additionally, administering treatment protocols involving antacid and prokinetic agents and taking simple precautions such as bedhead elevation may prevent long-term complications including recurrent aspirations and lung injury, thereby improving patients' quality of life.<sup>[7]</sup> The aim of this study was to evaluate the demographic, endoscopic, manometric, and 24-hour esophageal pH test results in SS patients presenting with esophageal symptoms in our society.

## MATERIAL AND METHOD

This study was approved ethically by the local ethics committee (Date: 27.11.2019, Study No: 12) of from Ministry of Health Ankara City Hospital Clinical Research Ethics Committee, Ankara, Turkey. The study retrospectively reviewed the medical records of 1,827 patients that underwent conventional esophageal manometry at Ankara Training and Research Hospital Gastroenterology Department Motility Polyclinic over the period between January 2008 and December 2018. Twenty-six patients diagnosed with SS were included in the study. For each patient, medical records were reviewed for demographic characteristics including age, gender, and body mass index (BMI) and also for clinical characteristics including 24-hour esophageal pH test results and endoscopic and manometric findings. The patients included in the study had a diagnosis of SS, underwent esophageal manometry, and were aged over 18 years. Patients aged under 18 years and those with no prior manometric evaluation, suspicious signs of other esophageal motility disorders, active cardiovascular, cerebrovascular and psychopathological disorders, morbid obesity, thyroid diseases, malignancies, other rheumatological diseases involving the esophagus, and a history of surgery for reflux, esophagus, and stomach were excluded from the study. Additionally, a control group of 26

age- and gender-matched patients was also included in the study, who were randomly chosen from among patients that presented to the same department with similar complaints and had normal manometry results.

### Statistical analysis

Data were analyzed using SPSS for Windows version 22.0 (IBM SPSS Inc., Armonk, NY, USA). Continuous variables were expressed as mean±standard deviation (SD) and categorical variables were expressed as frequencies (n) and percentages (%). Two groups were compared using Pearson's Chi-square test and Fisher's Exact Test. A p value of <0.05 was considered significant.

## RESULTS

The 26 patients in the patient group comprised 25 (96.2%) women and 1 (3.8%) man with a mean age of 47.9 years. All of these patients were symptomatic and the most common presenting complaint in the patients was dysphagia (53.9%) followed by heartburn (46.1%). The mean BMI in the patient group was 24.1 kg/m<sup>2</sup> and was significantly lower than that of control group (p=0.017). **Table 1** presents the demographic characteristics of the patients in both groups.

**Table 1.** Demographic characteristics of patients.

	SS group (n=26)	Control group (n=26)	p
Mean age (± SD) (years)	47.9±1.43	48.4±1.53	0.90
Female n (%)	25 (96.1%)	25 (96.1%)	0.75
Presenting Symptom n (%)	Heartburn=12 (46.1%) Dysphagia= 14 (53.9%)	Heartburn=13 (50%) Dysphagia=13 (50%)	0.78
Mean BMI (kg/m <sup>2</sup> ) (± SD)	24.1±5.6	28.1±5.1	0.017

SS: Systemic Sclerosis SD: standard deviation, BMI: body mass index

### Endoscopy and 24-hour esophageal pH test results

In the patient group, 18 (69.2%) patients underwent endoscopic evaluation. Endoscopic findings indicated that the frequency of esophagitis was significantly higher in the patient group compared to the control group (61.1% vs. 18.2%) (p=0.005). In the patient group, 54.5% of the patients had Los Angeles (LA) grade A and B esophagitis and 45.5% of them had LA grade C and D esophagitis. Moreover, no patient had peptic stricture and the frequency of hiatal hernia was almost significantly higher in the patient group compared to the control group. On endoscopy, only one patient was detected with BE and no significant difference was found between the two groups with regard to the frequency of LES incompetence (p>0.05).

Only 10 (38.5%) patients had 24-hour esophageal pH test results. Of these, 9 (90%) patients were detected with reflux, including 6 (60%) patients with distal reflux and 3 (30%) patients with both distal and proximal reflux. In the control group, however, reflux was detected in 9 (42.9%) out of 21

patients, including 8 (38.1%) patients with distal reflux and 1 (4.8%) patient with both distal and proximal reflux. The frequency of pathological reflux was significantly higher in the patient group compared to the control group ( $p=0.013$ ). **Table 2** and **3** present the endoscopic and 24-hour esophageal pH test results in both groups.

**Table 2.** Endoscopic findings of patients.

	SS group (n=18)	Control group (n=22)	p
Esophagitis n (%)	11 (61.1%)	4 (18.2%)	0.005
Peptic stricture n (%)	-	-	-
Barrett's esophagus (%)	1 (5.5%)	-	-
Hiatal hernia n (%)	6 (33.3%)	2 (9.1%)	0.57
LES incompetence n (%)	7 (38.9%)	5 (22.7%)	0.31
Gastric ulcer n (%)	0 %	2 (9.1%)	0.18
Duodenal ulcer n (%)	0 %	2 (9.1%)	0.18

SS: Systemic Sclerosis

**Table 3.** 24-hour esophageal pH test results of patients.

	SS group (n=10)	Control group (n=21)	p
Reflux	9 (90%)	9 (42.9%)	0.013
Distal reflux	6 (60%)	8 (38.1%)	
Distal + Proximal reflux	3 (30%)	1 (4.8%)	

SS: Systemic Sclerosis

### Esophageal manometry findings

In manometric evaluation, the LES was situated at a mean distance of 43.6 cm in the patient group and 43.03 cm in the control group ( $p>0.05$ ). The mean esophageal body resting pressure in the patient group was  $-0.73$  mmHg and was significantly lower than that of control group ( $p<0.001$ ). The mean resting LES pressure in the patient group was  $3.3$  mmHg and was significantly lower than that of control group ( $p=0.028$ ). **Table 4** presents the esophageal manometry findings in both groups.

**Table 4.** Esophageal manometry results of patients.

	SS group (n=26)	Control group (n=26)	p
Resting LES pressure (mm/Hg) ( $\pm$ SD)	$3.3\pm 3$	$20.3\pm 4.94$	$<0.001$
Esophageal body resting pressure (mm/Hg) ( $\pm$ SD)	$-0.73\pm 2.4$	$0.46\pm 1.21$	0.028
LES distance (cm) ( $\pm$ SD)	$43.6\pm 3.6$	$43.03\pm 2.1$	0.43

SS: Systemic Sclerosis LES: Lower esophageal sphincter

## DISCUSSION

In the present study, GERD and complications were detected in most of the patients with SS. Moreover, a significant portion of the patients presented with both distal and proximal reflux. Given that all the patients were symptomatic, it is tempting to consider that reflux could be the primary cause of these complications.

Literature indicates that patients with SS have a higher frequency of GERD complications such as reflux esophagitis, esophageal stricture, and BE compared to the general population.<sup>[8]</sup> Katzka et al.<sup>[9]</sup> reported that patients with scleroderma are at increased risk of BE and esophageal adenocarcinoma. Wipff et al.<sup>[10]</sup> also noted that patients with SS have an increased risk of esophageal adenocarcinoma and should be closely monitored. Lahcene et al.<sup>[11]</sup> detected reflux esophagitis in 38% and esophageal stricture and BE in 10% of their patients. In our patients, although the frequency of reflux was higher compared to those reported in the literature and esophageal reflux was detected in 61% of the patients, no esophageal stricture was detected in any patient and BE was detected in only one patient.

Some previous studies found no significant association between esophageal symptoms and EMD.<sup>[12,13]</sup> Another study reported that some patients presented no manometric signs of esophageal involvement despite presenting numerous esophageal symptoms and concluded that esophageal symptoms have low sensitivity, specificity, and predictive values in the diagnosis of SS.<sup>[14]</sup> In contrast, Lahcene et al.<sup>[11]</sup> reported that the frequency of esophageal symptoms was significantly higher in the presence of esophageal dysmotility and, therefore, these symptoms could be a simple warning sign necessitating prompt search of EMDs by manometry.<sup>[12]</sup> Similarly, in our study, all the patients with SS were symptomatic and were detected with EMD on manometry. It is commonly known that patients with SS mostly present to or are referred to gastroenterology polyclinics when their complaints of dysphagia and heartburn become symptomatic. Accordingly, in these patients, an assessment of esophageal involvement in the symptomatic period may allow early diagnosis and treatment of the patients and also prevent potential complications.

Patients with EMD are likely to experience numerous clinical problems such as early satiety, food regurgitation, progressive weight loss, malnutrition, and food impaction.<sup>[15]</sup> Unintentional weight loss is the most sensitive indicator of malnutrition and should be monitored at regular intervals. Moreover, a low BMI ( $<18.5$  kg/m<sup>2</sup>) is an indicator of protein-energy malnutrition.<sup>[16]</sup> In a 2009 study, Savarino et al.<sup>[17]</sup> evaluated a total of 40 patients with SS including 35 women and 5 men and reported the mean BMI of the patients as 23 kg/m<sup>2</sup>. Another study evaluated a group of patients with SS awaiting lung transplantation and reported that the mean BMI was 23.3 kg/m<sup>2</sup> and the men comprised 10% of the patients (18). In our study, the mean BMI in the patient group was 24.1 kg/m<sup>2</sup> and was significantly lower than that of control group. However, depending on the mean BMI in the patient group, it would be wise to assert that malnutrition could not be considered in our patients with SS. Additionally, the high frequency of reflux and other esophageal complications in such patients, as seen in our patients, could be the primary cause of food avoidance and the lower mean BMI compared to that of control subjects. Based on these findings, we suggest that an initial evaluation of esophageal involvement and nutrition

status is essential for the assessment of malnutrition in patients with SS that present to the gastroenterology clinic after the onset of first symptoms.

Literature indicates that the normal range for the resting LES pressure in response to wet swallows on esophageal manometry is 16.6-35.4 mmHg. Additionally, the reported normal ranges for mean distal and proximal amplitude are 64-154 and 33-91 mmHg, respectively.<sup>[19]</sup> The esophageal manometry findings of SS are associated with decreased esophageal motility with or without LES incompetence. Esophageal symptoms and manometric anomalies are commonly seen in patients with SS.<sup>[20]</sup> In our study, the mean resting LES pressure and the mean esophageal body resting pressure in the patient group were 3.3 mmHg and -0.73 mmHg, respectively, and were significantly lower than those of control group. In all the patients with SS, the resting LES pressure was below 10 mmHg and EMD was detected. In our study, manometric abnormalities were common in symptomatic patients, in accordance with the literature. Based on these findings, we consider that in patients with SS, a manometric evaluation of esophageal involvement followed by a 24-hour esophageal pH test in the symptomatic period will be beneficial for the detection of GERD and its complications.

The association between gender and GI involvement in SS remains controversial in the literature. A previous study found a significant association between GI manifestations and gender in SS.<sup>[21]</sup> In contrast, Abu-Shakra et al.<sup>[22]</sup> found no significant relationship between GI manifestations and demographic characteristics including gender, age at diagnosis, and disease type in patients with SS. However, a previous retrospective study that was conducted with 257 Greek patients with SS indicated that the frequency of GI involvement was higher in women than in men.<sup>[14]</sup> Our study, unlike previous studies, had a female preponderance (96%). This situation may be related to the fact that women in our society visit hospitals more than men. Taken together, all these findings implicate that SS mostly affects women and esophageal involvement may also lead to more frequent and serious complications in Turkish women.

Our study was limited in several ways. It had a retrospective design and had a small patient population since SS is a rare disease. However, no information was available in the study regarding the durations of the disease and the use of antacid-proton pump inhibitors and analgesic drugs by the patients.

## CONCLUSION

Esophageal involvement is a hallmark manifestation of SS and typically occurs secondary to heartburn and dysphagia. SS commonly causes EMD and LES incompetence, thus precipitating patients towards reflux. Reflux also leads to EMD and as this vicious circle continues, the frequency of complications increases. In conclusion, GERD and GERD-related complications have a high incidence in SS patients

with esophageal symptoms in our society. It is important to refer these patients to experienced gastroenterology centers to be evaluated by endoscopic and other diagnostic methods.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** This study was approved ethically by the local ethics committee (Date: 27.11.2019, Study No: 12) of from Ministry of Health Ankara City Hospital Clinical Research Ethics Committee, Ankara, Turkey.

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

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