

# Helpful, albeit hazardous! Esophageal stem-cell injection in systemic sclerosis

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## Abstract

**Background:** Over 90% of patients with systemic sclerosis suffer from gastroesophageal reflux. Esophageal motility disturbances are associated with a reduced life quality and may force interstitial lung disease progression. We wanted to determine whether we can improve gastroesophageal reflux in these patients by esophageal stem-cell injection.

**Methods:** We performed a pilot study including eight patients with systemic sclerosis and symptomatic gastroesophageal reflux. Sampling of adipose tissue was performed by an experienced plastic surgeon under local anesthesia. The collected fat was injected into the submucosa of the distal esophagus, each time 1 ml in all four quadrants starting 2, 4 and 6 cm proximal to the Z line (ending up to a total volume of 12 ml). Before the intervention, 3, 6 and finally 12 months after the procedure, patients answered the Gastroesophageal Reflux Disease Health-Related Quality of Life Questionnaire (GERD HRQL) and a high-resolution manometry was performed to quantify changes in motility function.

**Results:** All patients showed an improvement in the GERD HRQL score after the stem-cell injection and a lower dosage of proton-pump inhibitors. The manometric findings showed no change throughout the time. A serious adverse event occurred, as one patient developed multiple cerebellar embolic infarcts.

**Conclusion:** Because of the favorable effect in all patients, a safe route for esophageal fat injection needs to be developed.

**Keywords:** gastroesophageal reflux, stem cell injection, systemic sclerosis

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## Introduction

Systemic sclerosis (SSc) is a chronic and complex connective tissue disease with esophageal manifestation in up to 90% of all patients.<sup>1</sup> The esophageal dysfunction affects mainly the distal two thirds of the esophagus, resulting in a hypotensive lower esophageal sphincter (LES) and aperistalsis.<sup>2</sup> While not life threatening, gastroesophageal reflux and dysphagia result in worsening quality of life, worsening in lung function tests due to microaspiration, and can represent a real challenge for physicians.<sup>1</sup> In recent years, autologous fat transplantation (AFT) has become a promising technique to treat cutaneous manifestations of SSc.<sup>3,4</sup> Injected adipose-derived stromal cells (ADSCs) are multipotent cells with angiogenic and immunomodulatory properties.<sup>5</sup>

## Methods

We performed a single-center, prospective study to determine the effect of AFT in the distal esophagus in SSc patients with symptomatic esophageal involvement. Eight patients (one male patient, median age 51 years), fulfilling the American College of Rheumatology criteria for SSc, were enrolled from the outpatient clinic of the Department of Rheumatology of the Medical University of Graz (Austria). Every patient agreed by written, informed consent, to participate in the study approved by our ethics committee (27-117 ex 14/15). Six out of eight patients had diffuse systemic sclerosis (dSSc); five out of six dSSc patients had antitopoisomerase 1 antibodies; two out of eight had limited disease (lSSc) and a

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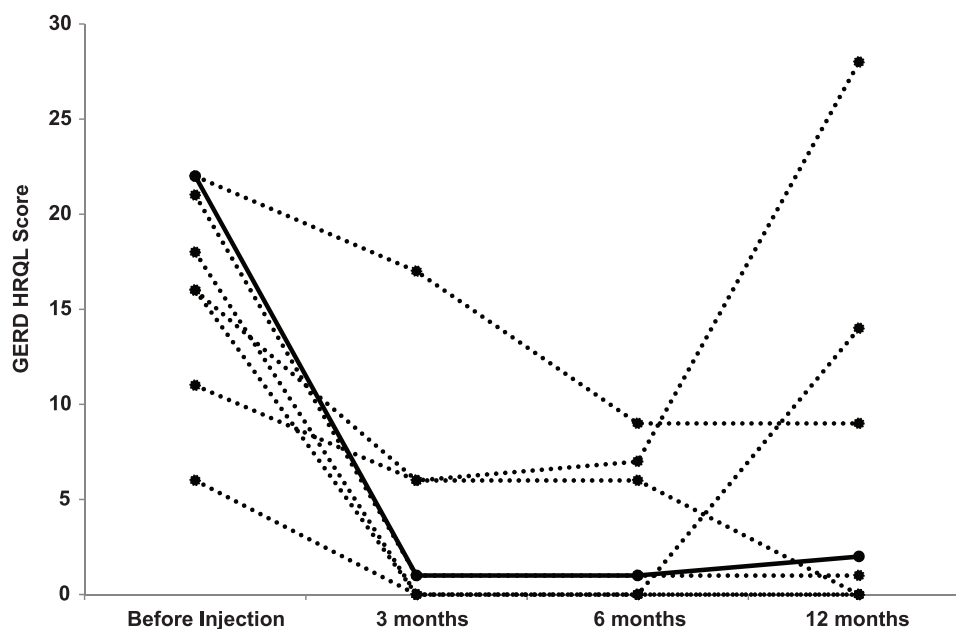
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**Figure 1.** Course of the GERD HRQL scores before, 3, 6 and 12 months after the esophageal fat injection of the eight patients.

The thick line represents the score values of the patient with the adverse event.

GERD HRQL, Gastroesophageal Disease Health-Related Quality of Life Questionnaire.

positive anticentromere antibody. All patients had a disease duration of >5 years.

Sampling of adipose tissue was performed by an experienced plastic surgeon under local anesthesia. The collected fat was injected into the submucosa of the distal esophagus, each time 1 ml in all four quadrants starting 2, 4 and 6 cm proximal to the Z line (ending up to a total volume of 12 ml). Before the intervention, 3, 6 and finally 12 months after the procedure, patients had to answer the GERD HRQL score (Gastroesophageal Reflux Disease Health-Related Quality of Life Questionnaire, Figure 1) and a high-resolution manometry was performed to quantify changes in motility function.

### Results

At the start of the study, all patients showed an absent contractility, with a weak lower esophageal sphincter (LES) and a median GERD HRQL score of 17. The course of the GERD HRQL scores showed a decrease in all patients. Seven of eight decreased below a GERD HRQL score of 6 points within 3 months. Almost all patients gained body weight during the follow up (median body weight gain 3.6 kg). The manometric findings showed no change throughout the time.

Unfortunately, the study had to be stopped because of a serious adverse event during the eighth study patient. A 48-year-old female patient developed an epileptic seizure after the esophageal fat injection, was intubated and admitted to the intensive care unit. A cranial computer tomography showed multiple infarcts in both cerebellar hemispheres, both occipital and frontal regions, as well as in the thalamus bilaterally. A cardiac ultrasound showed an atrial septal defect and initially, a cerebral fat embolism was suspected. Despite an unfavorable prognosis, the patient was extubated 8 days later, recovered completely with only a slight weakness of the left arm as a residual symptom. A subsequently performed cranial magnetic resonance showed multiple embolic infarcts not typical for fat embolism. In the follow up, this patient also had a significant reduction of the GERD HRQL score from initially 22 points to 1, 1 and 2 points after 3, 6 and 12 months, respectively.

### Discussion

This was the first study evaluating the effect of ADSC injection in the distal esophagus of SSC patients with symptomatic esophageal involvement. All patients showed a clinical improvement of their symptoms. The reason for the adverse event

of our study is still not clear. The rapid clinical improvement of our patient, as well as the cranial magnetic resonance argues against a cerebral fat embolism. The event was however directly associated with the esophageal fat injection and the distribution of the multiple cerebral infarcts are consistent with a cerebral fat embolism.

Because of the favorable effect in all patients, a safe route for esophageal fat injection needs to be developed.

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#### Conflict of interest statement

The authors declare that there is no conflict of interest.

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#### Availability of data and material

Not applicable

#### Supplemental material

Supplemental material for this article is available online.

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