

To the Reviewers,

We thank you for taking the time to read our manuscript and offer suggestions for improvement. Below is a list of the stated concerns with an explanation of how they were addressed in the manuscript.

Reviewer 1:

General comments Dr. Kadakuntla and Dr. Tadras, et al. reviewed ‘Altered Physiology in Scleroderma Patients Leading to Dysphasia’. This article is well presented. The reviewer has some comments.

1. In CAUSES OF PHARYNGEAL DYSPHAGIA IN SSc PATIENTS, Cricopharyngeal Muscle Disorder, please show manometry findings of swallowing in SSc patients with pharyngeal dysphagia.

We have look carefully in our records and unfortunately have no good quality images suitable for publication. We have had 2 patients that have pharyngeal dysphagia in our practice but we do not have their manometry imaging pictures as they were diagnosed with speech evaluation and antibodies rather than imaging.

Reviewer 2:

This paper is written to provide functional and anatomical understanding of dysphagia in SSc patients. The review is very interesting to me, but I have several comments.

1. Figure 1 is not mentioned in the text.

We have edited this and mentioned it in the text.

2. Table 2 is mentioned before Table 1 in main text. Please devise the Table number.

We have edited this and reordered the tables.

3. About Table 1 score, this score is only associated in lower esophageal obstruction especially in achalasia disease. In SSc patients, LES is almost dilated. So, If there are any scoring system of esophageal dysphagia, please consider to adapt other.

We have adapted a different scoring system from Khanna et al. [14] that is more relevant to SSc patients. This scoring system assesses GI symptom severity in SSc based on a questionnaire that is given to patients.

4. Please add the refference to lines 1-2 of section PHYSIOLOGY OF SWALLOWING, and lines 14-15 of section Esophageal Dysmotility. Esophageal dysmotility is not commonly known cause of dysphagia because any papers had not proven it.

We added the references as some authors believe difficulty swallowing may be a clinical presentation of dysmotility. These references include Adigun et al. [1] and Shreiner et al. [17]. However, we have rephrased the text as this is not well studied as it is not clearly established that esophageal dysmotility is a cause of dysphagia.

5. If you have any references or hypothesis why the esophagus is affected first in GI involvement, please mention or add it in CAUSES OF ESOPHAGEAL DYSPHAGIA IN SSc PATIENTS section. -Sam

We have detailed hypotheses as to why esophagus is commonly cited as first affected location of the GI tract in SSc. This includes the possibility that esophageal changes are sensed more readily due to daily frequency of swallowing. Changes in other parts of the GI tract may become noticeable later in time. Furthermore, we have included that the 2-layered muscularis of the esophagus may be affected more rapidly than the thicker 3-layered muscularis of the stomach.

6. This review is very important to assess the dysphagia in SSc patients TO MANAGEMENT the symptoms or complications. There were few suggestions about treatment or management in esophageal dysmotility and GERD sections. So I suggest to describe it briefly.

We have described lifestyle and medical management of esophageal dysmotility and GERD. Information about these treatment options were also elaborated in Table 3. We mention GERD treatments of medications (PPIs and H2RAs) as well as lifestyle changes (avoiding acidic foods, alcohol, and smoking; losing weight; eating smaller meals; elevating the head of the bed). We also discuss lifestyle management for esophageal dysmotility, which includes taking smaller bites, chewing food thoroughly, and hydrating with water.

Reviewer 3:

The reviewed manuscript is indeed a well-written structured review on the upper GI manifestations in patients with Systemic sclerosis (SS). Still, there are minor inconsistencies that may require attention of the authors.

1. First, the title of the paper assumes the influence of the disease on dysphagia. However, some of the conditions (like gastroesophageal reflux and oesophageal candidosis) are not accompanied by dysphagia, usually.

We have changed the title to “**Dysphagia, Reflux and Related Sequelae Due to Altered Physiology in Scleroderma**” as this encompasses the other conditions as well.

2. Moreover, the influence of SS on types of disturbances revealed with pharyngeal and oesophageal motility diagnostic procedures (like high-resolution manometry) is mentioned just in a few words.

We have elaborated on diagnostic procedures such as pharyngeal manometry in the text. We have also added pharyngeal manometry to Table 1 and describe its role in assessing for UES relaxation and pharyngeal propulsion to evaluate for oropharyngeal dysphagia.

3. As the paper rather clinically oriented, and involves the description of wider spectrum of the conditions than just dysphagia (which is good, actually), I would suggest to make changes in the title to make it correspond with the text.

We have adjusted the title to correspond better with the text to “**Dysphagia, Reflux and Related Sequelae Due to Altered Physiology in Scleroderma**” as this is more comprehensive.

4. Please, consider to provide the readers with the definition of dysphagia, as it may somewhat differ case by case.

We have provided a definition of dysphagia in the “Physiology of Swallowing” section. We define it as “difficulty in swallowing that results in delayed passage of food or liquid bolus”.

5. There are more than one scoring systems to assess the presence and severity of dysphagia. One, mentioned in the table 1 is difficult for practical use as it requires assessment of passage through lower oesophageal sphincter.

We have included a different scoring system that does not require impractical assessment for patients. This scoring system by Khanna et al. [14] is based on a questionnaire that takes about 6-8 minutes to complete. It assesses severity of SSc GI symptoms based on the answers on this questionnaire.

6. Moreover, the reference [14], provided along with the description of the diagnostic tests on the page 6 is not fully relevant, as it describes not the diagnostic performance of the scale, but the results of botulinum toxin injections in patients with dysphagia. Please, consider revision

We have removed this reference as it is not applicable and used a different reference to describe a different scoring system. This scoring system is by Khanna et al. [14]

7. Could you please provide the pathophysiology of dysphagia in patients with Barrett oesophagus? I can imagine, that it may be present in some cases, however, it is really rare.

The pathophysiology of dysphagia in patients with Barrett’s esophagus is unclear. We have clarified in the text that this association may be correlation rather than causation, as patients with risk factors for Barrett’s esophagus may be predisposed to other causes of dysphagia as well.

8. Although oesophageal candidosis may naturally be present in patients with SS who receive immunosuppression, it seems to be not directly related to the disease.

We have discussed how candida esophagitis may be a complication of SSc and its treatment. SSc patients are commonly on acid suppression medication and immunosuppression which may predispose to Candida esophagitis. In addition, esophageal stasis in SSc can promote Candida colonization.

9. To avoid text reduction, I would suggest to re-organize the text and add a heading with the sequelae of SS treatment (or secondary manifestations) and described candidiasis and drug-induced oesophagitis in this section.

We have re-organized the text to show that candida esophagitis and pill esophagitis are sequela of SSc treatment. Both of these sections are now under the new heading “Sequelae of SSc Treatment”

10. Please, pay attention that [66] is not relevant here, as it describes Candida infection in patients with achalasia.

We have removed this reference as it is not fully relevant. Included is reference by Sam et al. [72] that describes disease that cause stasis, such as SSc, may be complicated by candida esophagitis.

11. Please, consider to add pharyngeal manometry to the diagnostic procedures described in the table 2.


We have included pharyngeal manometry to table 2 and describe its role in evaluating for oropharyngeal dysphagia.

Reviewer 4:

I would like to thank the authors for bringing up an important topic. The article is well structured, written in clear and understandable language. It can be highly recommended due to actuality of the problem among children, the interesting presentation of the article.

We again thank the reviewers for their time and for the helpful suggestions that they offered. Please let us know if we have adequately addressed all concerns.

Sincerely,

A handwritten signature in black ink, appearing to read 'Anusri Kadakuntla', with a stylized, flowing script.

Anusri Kadakuntla