Dear Editor,

We have read with interest the review by Li and colleagues [1] in which the pathophysiology of esophageal dysfunction (ED) in patients with systemic sclerosis (scleroderma, SSc) has been discussed, providing valuable data on vascular, inflammatory, and pro-fibrotic factors possibly related to this visceral involvement.

In line with the instructive observations made by the authors, we would like to make some comments not based on new studies with human or animal participants, but on previously known data. In this regard, we recommend keeping in mind the effect that some drugs usually prescribed in SSc might have on ED. In fact, polypharmacy is not uncommon in this rheumatic disease and patients often receive therapies that may promote esophageal dysmotility by decreasing the lower esophageal sphincter pressure (LESP) or impairing peristalsis, with the subsequent detrimental effect on esophageal clearance and the potential onset of remarkable complications during the follow-up, such as Barrett’s esophagus (BE) or esophageal adenocarcinoma (EAC). Indeed, a higher prevalence of both conditions has been previously reported in SSc patients compared to controls from the general population [2].

As briefly stated by Li et al., the potential link between drugs and ED in SSc has been suggested for dihydropyridine calcium channel blockers (CCB), which are widely used in the treatment of some major and long-term manifestations of scleroderma [3, 4]. Similar considerations can be made regarding other non-immunosuppressive drugs, such as phosphodiesterase-5 (PDE-5) inhibitors, nitrates, or some therapies for depression or sleep disturbances (Table 1). Moreover, immunosuppressants have also been linked to some esophageal infectious complications [5] and an increased incidence of overall malignancy, probably due to their cytotoxicity and the modulation on immunosurveillance. Although no specific drug has been associated with esophageal tumors yet, this hypothetical link cannot be completely ruled out in view of a rate of BE-to-dysplasia or EAC progression higher than expected in other immunosuppression clinical scenarios such as transplant recipients [6].
**Table 1** Potential effect on ED of drugs commonly prescribed in SSc [4]

| Drug                        | Main indications in SSc | Potential effect on ED                                                                 |
|-----------------------------|-------------------------|---------------------------------------------------------------------------------------|
| Dihydropyridine-CCB         | RP, cardiac involvement | LESP reduction, esophageal contractions reduction, esophageal clearance impairment, exacerbation of GERD symptoms [3, 7, 8] |
| Non dihydropyridine-CCB     | RP, PAH, calcinosis     | Not reported or low risk [8]                                                           |
| PDE-5 inhibitors            | RP, DUs, PAH            | LESP reduction, esophageal bolus transit slowing down [9, 10]                         |
| Nitrates                    | RP                      | LESP reduction [11, 12]                                                               |
| ACE inhibitors / ARB        | SRC, RP                 | Not reported or unknown                                                               |
| Prostacyclin analogues      | DUs, PAH, RP            | Not reported or unknown                                                               |
| Endothelin receptor antagonists | DUs, PAH, RP         | Low risk of GERD [13]                                                                |
| Mycophenolate mofetil       | SSc-ILD                 | Ulcerative esophagitis and esophageal strictures [14–16]                              |
| Cyclophosphamide            | SSc-ILD, SD             | Association with GERD-related symptoms [17]                                           |
| Methotrexate                | Arthritis, SD           | Not reported or unknown                                                               |
| Corticosteroids             | Arthritis, muscular involvement | Predisposition to erosions and ulceration [18]                                 |
|                            |                         | Increased esophageal acid contact time [19]                                           |
| NSAIDs                      | Arthralgia/arthritis, serositis | Pill-induced esophagitis [20, 21]                                                 |
| Bisphosphonates             | Osteoporosis, calcinosis | Pill-induced esophagitis [22]                                                        |
| Antidepressants             |                         |                                                                                        |
| TCA                         | Depression, mood disorders | LESP reduction, increased risk of GERD [23]                                        |
| SSRI                        | Depression, mood disorders, RP | Not reported [24]                                                                          |
| Benzodiazepines             | Anxiety, sleep disturbances | LESP reduction [25, 26]                                                                   |

ED esophageal dysfunction, SSc systemic sclerosis, CCB calcium channel blockers, RP Raynaud’s phenomenon, LESP lower esophageal sphincter pressure, GERD gastroesophageal reflux disease, PAH pulmonary arterial hypertension, PDE-5 phosphodiesterase type 5, DUs digital ulcers, ACE angiotensin-converting enzyme, ARB angiotensin receptor blockers, SRC scleroderma renal crisis, SSc-ILD SSc-related interstitial lung disease, SD skin disease, NSAID nonsteroidal anti-inflammatory drugs, TCA tricyclic antidepressants, SSRI selective serotonin reuptake inhibitors

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Unfortunately, the effect of treatment has been scarcely assessed when analyzing risk factors for ED, BE, or progression to dysplasia and EAC in scleroderma. Therefore, clinicians caring for patients with this autoimmune disease should be aware of the possible deleterious consequences on ED and its related complications when prescribing some drugs commonly used for other visceral or cutaneous involvement. In our opinion, a judicious evaluation of these potential risks should be made at any clinical encounter with our SSc patients, as well as the continuous revision of the appropriateness of all administered therapies, which could lead to readjustment of the prescribed medication or to a higher dose of proton pump inhibitors, aiming for greater acid suppression.

Likewise, an in-depth analysis of the concomitant treatments might also be valuable in future studies assessing the pathophysiology of ED in subjects with SSc.

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