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LETTER

Letter to the Editor Regarding Esophageal Dysfunction and Systemic Sclerosis: Drugs Should be Kept in Mind

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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].

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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

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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REFERENCES

1. Li B, Yan J, Pu J, Tang J, Xu S, Wang X. Esophageal dysfunction in systemic sclerosis: an update. Rheumatol Ther. 2021;8:1535–49.

2. Snyder DL, Crowell MD, Kahn A, Griffing WL, Umar S, Ramirez FC. Prevalence of Barrett's esophagus in female patients with scleroderma. Am J Gastroenterol. 2021;116:517–21.

3. Kahan A, Bour B, Couturier D, Amor B, Menkes CJ. Nifedipine and esophageal dysfunction in progressive systemic sclerosis. A controlled manometric study. Arthritis Rheum. 1985;28:490–5.

4. Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76:1327–39.

5. Kadakuntla A, Juneja A, Sattler S, et al. Dysphagia, reflux and related sequelae due to altered physiology in scleroderma. World J Gastroenterol. 2021;27:5201–18.

6. Biswas Roy S, Banks P, Kunz M, et al. Prevalence and natural history of Barrett's esophagus in lung

transplant: a single-center experience. Ann Thorac Surg. 2019;107:1017–23.

7. Hughes J, Lockhart J, Joyce A. Do calcium antagonists contribute to gastro-oesophageal reflux disease and concomitant noncardiac chest pain? Br J Clin Pharmacol. 2007;64:83–9.

8. Jean F, Aubert A, Bloch F, et al. Effects of diltiazem versus nifedipine on lower esophageal sphincter pressure in patients with progressive systemic sclerosis. Arthritis Rheum. 1986;29:1054–5.

9. Kim HS, Conklin JL, Park H. The effect of sildenafil on segmental oesophageal motility and gastro-oesophageal reflux. Aliment Pharmacol Ther. 2006;24:1029–36.

10. Lee TH, Lee JS, Hong SJ, et al. Examination of the effects of vardenafil on esophageal function using multichannel intraluminal impedance and manometry. J Neurogastroenterol Motil. 2012;18:399–405.

11. Kikendall JW, Mellow MH. Effect of sublingual nitroglycerin and long-acting nitrate preparations on esophageal motility. Gastroenterology. 1980;79:703–6.

12. Tutuian R, Castell DO. Esophageal motility disorders (distal esophageal spasm, nutcracker esophagus, and hypertensive lower esophageal sphincter): modern management. Curr Treat Options Gastroenterol. 2006;9:283–94.

13. Wei A, Gu Z, Li J, et al. Clinical adverse effects of endothelin receptor antagonists: insights from the meta-analysis of 4894 patients from 24 randomized double-blind placebo-controlled clinical trials. J Am Heart Assoc. 2016;5: e003896.

14. Parfitt JR, Jayakumar S, Driman DK. Mycophenolate mofetil-related gastrointestinal mucosal injury: variable injury patterns, including graft-versus-host disease-like changes. Am J Surg Pathol. 2008;32:1367–72.

15. Kim JJ, Mulki RH, Sebastian KM. Recalcitrant esophageal stricture secondary to mycophenolate mofetil. Case Rep Gastrointest Med. 2020;2020:8817801.

16. Nguyen T, Park JY, Scudiere JR, Montgomery E. Mycophenolic acid (CellCept and Myfortic) induced injury of the upper GI tract. Am J Surg Pathol. 2009;33:1355–63.

17. Matsuda R, Yamamichi N, Shimamoto T, et al. Gastroesophageal reflux disease-related disorders of systemic sclerosis based on the analysis of 66 patients. Digestion. 2018;98:201–8.

18. Seminerio J, McGrath K, Arnold CA, et al. Medication-associated lesions of the GI tract. Gastrointest Endosc. 2014;79:140–50.

19. Lazenby JP, Guzzo MR, Harding SM, et al. Oral corticosteroids increase esophageal acid contact times in patients with stable asthma. Chest. 2002;121:625–34.

20. Bigard MA, Pelletier AL. Esophageal complications of non-steroidal antiinflammatory drugs. Gastroenterol Clin Biol. 2004;28(3):58–61.

21. Avidan B, Sonnenberg A, Schnell TG, Budiman-Mak E, Sontag SJ. Risk factors of oesophagitis in arthritic patients. Eur J Gastroenterol Hepatol. 2001;13:1095–9.

22. de Groen PC, Lubbe DF, Hirsch LJ, et al. Esophagitis associated with the use of alendronate. N Engl J Med. 1996;335:1016–21.

23. Martín-Merino E, Ruigómez A, García Rodríguez LA, Wallander MA, Johansson S. Depression and treatment with antidepressants are associated with the development of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2010;31:1132–40.

24. Brahm NC, Kelly-Rehm MC. Antidepressant-mediated gastroesophageal reflux disease. Consult Pharm. 2011;26:274–8.

25. Rushnak MJ, Leevy CM. Effect of diazepam on the lower esophageal sphincter. A double-blind controlled study. Am J Gastroenterol. 1980;73:127–30.

26. Jung HK, Choung RS, Talley NJ. Gastroesophageal reflux disease and sleep disorders: evidence for a causal link and therapeutic implications. J Neurogastroenterol Motil. 2010;16:22–9.