Digestive Dysbiosis in Systemic Scleroderma: a Review

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ABSTRACT

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by widespread microvasculopathy, inflammation, and fibrosis of the skin and internal organs. The involvement of the gastrointestinal tract is associated with a wide variety of symptoms and affects circa 90% of patients during the course of the disease. The gastrointestinal microbiota contains trillions of microbial cells and has been found to contribute to both local and systemic homeostasis. In both health and disease, a dynamic interrelationship between gut microbiome activity and the host immune system has been identified. Gastrointestinal dysbiosis has been described as having an important role in obesity, diabetes mellitus, liver disease, cardiovascular and neuropsychiatric disorders, neoplasia, as well as autoimmunity. Recent scientific data indicates a notable role of dysbiosis in the pathogenesis of SSc-related digestive involvement together with various other clinical manifestations. The present review aims to summarize the recent findings regarding digestive dysbiosis as well as the relationship between gastrointestinal microbiota and certain features of SSc.

Keywords: systemic sclerosis, microbiota, gastrointestinal involvement, dysbiosis

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune condition with a complex pathogenesis that is characterized by vasculopathy and fibrosis of the skin as well as the internal organs. Depending on the extent of cutaneous involvement, there are three distinct subsets: limited cutaneous systemic sclerosis (lcSSc), diffuse cutaneous systemic sclerosis (dcSSc), and scleroderma "sine scleroderma". The potentially severe disease-related cutaneous, cardiopulmonary, renal, and gastrointestinal changes contribute significantly to the increased morbidity and mortality risk in SSc patients, together with a lower quality of life. Up to 90% of SSc patients develop upper and/or lower digestive involvement during the course of the disease. Despite the fact that the gastrointestinal tract can be affected in every form of SSc, it is more frequent or more severe in the diffuse phenotype. According to recent findings, dysbiosis may be involved in the development of certain gastrointestinal symptoms in SSc patients.¹⁻⁷

The gastrointestinal microbiota contains trillions of microbial cells and has been found to contribute to both local and systemic homeostasis.⁸ The immune system can modulate the processes occurring within the microbial ecosystem. Additionally, the microbiota itself produces biochemically active molecules which may affect the immune system's functionality.⁹ Any disturbance of this balance may lead to dysbiosis which has been described as having an important role in obesity, diabetes mellitus, liver disease, cardiovascular and neuropsychiatric disorders, neoplasia, as well as in autoimmunity.⁸⁻¹² Numerous different interactions between the microbiota and the host immune system have been described in immune-mediated diseases including SSc.¹³

The present review aims to describe the recent findings regarding dysbiosis as well as the relationship between gastrointestinal microbiota and certain features of SSc.

MICROBIOTA CHANGES IN THE UPPER DIGESTIVE TRACT

Apart from skin fibrosis and Raynaud's phenomenon (RP), one of the most common manifestations of SSc is the involvement of the gastrointestinal tract.^{1,7} Through a wide range of symptoms, disease-related digestive involvement has a notable impact on quality of life and demonstrates a major influence on perception of disease severity in SSc patients.¹⁴

The oral cavity may be affected in SSc, leading to mucosal, dental, and periodontal changes.^{15,16} The most common orofacial changes described in these patients are microstomia, xerostomia, oral mucosal atrophy, telangiectasias, widening of the periodontal ligament, periodontitis, and bone damage involving the temporomandibular joint.¹⁷⁻¹⁹ Periodontal disease is an inflammatory condition defined by the presence of pathogenic microflora in the oral biofilm which disturbs the host immune response that may destroy the periodontium, causing bone resorption and ultimately leading to tooth loss.²⁰ SSc patients are at risk of developing periodontal disease due to microstomia, the latter leading to poor oral hygiene and subsequent dental plaque growth.²¹ During the course of periodontal disease, the facultatively anaerobic Gram-positive species may convert into anaerobic, proteolytic Gram-negative species. Moreover, potential pathogens such as *Porphyromonas gingivalis* or *Aggregatibacter actinomycetemcomitans* can trigger autoimmunity by activating autoantibody production through citrullinated antigens, this mechanism being described in autoimmune diseases such as rheumatoid arthritis. However, further research is needed to in-

vestigate the connection between the bacterial species involved in periodontal disease and autoantibody production in SSc.^{21,22}

Salivary gland involvement, clinically expressed through xerostomia, is a frequently encountered feature in SSc, more than 50% of the patients complaining of "dry mouth".¹⁵ Baron *et al.* showed that saliva production in these patients is decreased, thus facilitating the development of dysbiosis in the oral cavity.¹⁹ The fibrotic process appears around the capillaries and excretory ducts, promoting functional impairment by decreasing vascular permeability. Sjogren's syndrome can be associated with the condition and has been found in circa 30% of SSc patients, mostly due to the fibrotic process.^{17,23}

Approximately 50–90% of SSc patients may develop symptoms linked to esophageal involvement.²⁴⁻²⁶ The latter has been associated to various symptoms, such as heartburn, regurgitation, dysphagia, pain, or nausea, as a result of esophageal dysmotility.^{2,3,27,28} The combination of hypotensive esophagogastric junction pressure and absent contractility in the lower esophageal body are typical features of the classic scleroderma esophagus. SSc patients who have absent contractility on high-resolution esophageal manometry experience more severe heartburn, dysphagia, chest and abdominal pain, early satiety, bloating, and loss of appetite.²⁹⁻³¹ Moreover, up to 5% of the patients can develop Barrett's esophagus and/or adenocarcinoma.^{32,33}

It has been stated that dysbiosis at this level may also influence the appearance of symptoms. The esophagus microbiota mostly consists of bacteria from the oral cavity and from the stomach, the more prevalent species being *Streptococcus viridans*, *Fusobacterium* spp., *Neisseria* spp., and *Haemophilus* spp. The dynamics of the esophageal microbiome is not fully understood, although an increase in Gram-negative bacteria is presumed to be connected with gastroesophageal reflux disease (GERD), Barrett's esophagus, and treatment with proton pump inhibitors.^{34,35} Espinoza *et al.* described the esophagus microbiota in patients with SSc, concluding that the samples from SSc patients were less abundant in species such as *Lactobacillus*, *Bacillus*, and *Rhodococcus*.³⁶

Patients with SSc may experience nausea, vomiting, early satiety, heartburn, bloating, and abdominal pain due to gastroesophageal dysmotility.^{4,26} It has been shown that infection with *Helicobacter pylori* (*H. pylori*) is frequent and could be a risk factor for the appearance of certain digestive symptoms in SSc.³⁷ *H. pylori* is a Gram-negative bacterium that commonly infects the gastric mucosa through virulence factors, triggering and maintaining an inflammatory response and eventually promoting the development

of cross-reactive antibodies against bacterial proteins by molecular mimicry.³⁸ Several studies (presented in Table 1) have revealed an increased prevalence of *H. pylori* infection in SSc patients, indicating possible links between certain clinical features (including digestive symptoms) and *H. pylori* infection.³⁹ Furthermore, a relationship between *H. pylori* infection and the severity of skin involvement has been suggested despite the fact that no link has been found with the peripheral vascular damage.⁴⁰

MICROBIOTA CHANGES IN THE LOWER DIGESTIVE TRACT

Small bowel involvement has been linked to pseudo-obstruction and small intestinal bacterial overgrowth (SIBO) in SSc. Patients may experience nausea, emesis, bloating, abdominal pain or distension, diarrhea, and malabsorption, the latter leading to weight loss and various nutrient deficiencies.²⁶ The most important defensive system

against SIBO is the integrity of the intestinal motor activity. There are several studies which showed that the SSc-related fibrosis of the bowel smooth muscle (impacting its functionality) and vasculopathy may promote bacterial overgrowth.^{46,47}

The prevalence of SIBO in SSc was analyzed in many studies, as seen in Table 2, its prevalence spanning between 13% and 65%, with higher values in Western areas compared to Asian countries.⁴⁹ Patients with SIBO complain more frequently of abdominal pain/discomfort, bloating, diarrhea or constipation compared to healthy controls (HC).⁵⁰ Furthermore, patients with SIBO have higher levels of fecal calprotectin (a bowel inflammatory marker).⁵⁰ Approximately 10% of SSc patients can develop malnutrition,⁵¹ with lower levels of serum albumin and vitamin B12 and reduced quality of life.^{49,51}

Regarding the microbiota composition in SSc and SIBO patients, a study published in 2019 reported an abundance of *Odoribacter*, *Bilophila* and *Lachnospira* species, finding

TABLE 1. The relationship between SSc and *H. pylori* infection

Study	Patients	Evaluation	Results
Yamaguchi <i>et al.</i> , 2008 ⁴¹	64 patients	Upper gastrointestinal endoscopy Anti- <i>H. pylori</i> IgG antibodies (serum samples)	29 of 64 participants were diagnosed with esophagitis. 37 patients (57.8%) were found positive for <i>H. pylori</i> infection of which 10 had reflux esophagitis. The prevalence of reflux esophagitis was lower than in <i>H. pylori</i> negative patients.
Radić <i>et al.</i> , 2013 ⁴⁰	42 patients (2 with lcSSc and 40 with dcSSc)	Upper gastrointestinal endoscopy and rapid urease test	The prevalence of <i>H. pylori</i> infection was 62% (26 positive patients, 1 with lcSSc and 25 with dcSSc) with significant differences in the digestive involvement between positive and negative patients. The study described a possible relation between <i>H. pylori</i> infection status and skin involvement, positive patients having more severe mRSS score. Furthermore, <i>H. pylori</i> positive SSc patients had a more severe lung and heart involvement.
Ram <i>et al.</i> , 2013 ⁴²	79 SSc patients (from a total of 1,290 subjects with various autoimmune diseases)	Anti- <i>H. pylori</i> IgG antibodies	The authors found a 55.7% prevalence in SSc patients.
Bilgin <i>et al.</i> , 2015 ⁴³	30 SSc patients (18 with lcSSc and 12 with dcSSc) <i>versus</i> 30 HC	Anti- <i>H. pylori</i> IgG and IgM antibodies	73.3% of SSc patients were positive (72.2% with lcSSc and 75% with dcSSc), whereas only 46.6% from the control group had positive IgG antibodies.
Balaji <i>et al.</i> , 2017 ⁴⁴	55 SSc patients (23 with lcSSc and 32 with dcSSc) <i>versus</i> 25 HC	Anti- <i>H. pylori</i> IgG antibodies	61.8% of SSc patients were found to be positive compared to 24% in the HC group. Anti- <i>H. pylori</i> antibody levels were higher in SSc patients with digestive symptoms, yet did not differ according to disease phenotype.
Efthymiou <i>et al.</i> , 2020 ⁴⁵	91 patients (41 with dcSSc and 50 with lcSSc) <i>versus</i> 59 HC	Anti- <i>H. pylori</i> antigen-specific antibody testing	67% (68.3% in dcSSc patients and 66% in lcSSc patients) compared with 76.3% in HC.

TABLE 2. The investigation of SIBO in SSc patients

Study	Patients	Evaluation	Results
Parodi <i>et al.</i> , 2008 ⁵³	55 patients (18 with dcSSc and 37 with lcSSc) <i>versus</i> 60 HC	Lactulose breath test	54.5% tested positive (30/55 compared to 4/60 positive HC).
Marie <i>et al.</i> , 2009 ⁴⁹	51 patients (25 with dcSSc and 26 with lcSSc)	Glucose hydrogen and methane breath test	43.1% tested positive. Among the 22 patients with SIBO, 11 also exhibited abnormal small bowel manometry.
Fynne <i>et al.</i> , 2011 ⁵⁴	15 patients with dcSSc	Hydrogen breath test	3 patients tested positive according to the breath test.
Gemignani <i>et al.</i> , 2013 ⁵⁵	50 patients (18 with dcSSc and 32 with lcSSc) <i>versus</i> 60 HC	Glucose breath test	18% from the SSc group and 5% from the HC group were diagnosed with SIBO.
Savarino <i>et al.</i> , 2013 ⁵⁶	99 patients (31 with dcSSc and 68 with lcSSc) <i>versus</i> 60 HC	Lactulose breath test	In the SSc group, 46% tested positive compared to 5% of controls.
Tauber <i>et al.</i> , 2014 ⁵⁷	38 patients (18 with dcSSc and 20 with lcSSc)	Glucose hydrogen and methane breath test	37% tested positive at the breath test, 37% also exhibiting gastrointestinal involvement.
Soukup <i>et al.</i> , 2014 ⁵⁸	37 patients	Hydrogen breath test	37.8% tested positive.
Marie <i>et al.</i> , 2015 ⁵⁹	125 patients (43 with dcSSc and 82 with lcSSc)	Glucose hydrogen and methane breath test and fecal calprotectin	46.2% tested positive. Patients with higher levels of fecal calprotectin experienced more severe gastrointestinal symptoms.
Adarsh <i>et al.</i> , 2017 ⁶⁰	50 patients (34 with lcSSc and 16 with dcSSc), of which 37 underwent a lactulose breath test	Lactulose breath test	21% of the 37 participants who underwent lactulose breath test were positive.
Cruz-Dominguez <i>et al.</i> , 2017 ⁶¹	68 patients (41 with lcSSc and 27 with dcSSc)	Glucose/lactulose hydrogen breath test	64.7% tested positive, the breath test being linked to the severity of symptoms.
Sawadpanich <i>et al.</i> , 2019 ⁶²	89 patients with non-digestive symptoms (65 with dcSSc and 24 lcSSc)	Glucose hydrogen and methane breath test	12 patients tested positive for SIBO (the only statistically significant correlation was between disease duration and SIBO)
Polkowska-Pruszyńska <i>et al.</i> , 2020 ⁵⁰	40 patients (6 with dcSSc and 33 with lcSSc) <i>versus</i> 39 HC	Lactulose hydrogen breath test	47.5% tested positive compared to only 12.8% in HC. Fecal calprotectin levels were higher in the study group, particularly in the SSc – SIBO patients.
García-Collinot <i>et al.</i> , 2020 ⁶³	74 patients (43 with lcSSc and 32 with dcSSc)	Lactulose hydrogen breath test	Results showed a positivity rate of 64.9%.

HC – healthy controls

a considerably higher bacterial abundance and diversity compared to SSc patients without SIBO.⁵²

Colonic involvement is often asymptomatic, although some patients may exhibit diarrhea, constipation, tenesmus, painful defecation, and fecal incontinence. There are various studies, presented in Table 3, on patients with SSc with or without gastrointestinal involvement, which described their gut microbiota compared to HC and explored the potential relationship between gastrointestinal symptoms and dysbiosis in this respect.⁶⁴ The studies

performed on SSc patients' gut microbiota showed an increase in *Lactobacillus* expression, a commensal microbe whose role in gut peristalsis remains unknown. Moreover, recent research described a decrease in certain beneficial commensal genera (*Clostridium*, *Faecalibacterium*, and *Bacteroides*) and an increase in potentially pathobiont genera (*Fusobacterium*, *Prevotella*, *Ruminococcus*).^{65–71}

Volkman *et al.* analyzed the cecum and sigmoid mucosal lavage samples from SSc patients. The authors described the following changes: patients displayed an abun-

TABLE 3. The alteration of large bowel microbiota in SSc

Study	Evaluation	Patients	Increased*	Decreased*
Volkman et al., 2016 ⁶⁵	Cecum and sigmoid mucosal lavage samples	17 SSc versus HC	<i>Lactobacillus</i> <i>Bifidobacterium</i> <i>Fusobacterium</i> <i>Erwinia</i> <i>Ruminococcus</i> <i>Prevotella</i>	<i>Faecalibacterium</i> <i>Clostridium</i> <i>Rikenella</i> <i>Bacteroides fragilis</i>
Andrasson et al., 2016 ⁶⁶	Fecal samples	98 SSc versus HC	<i>Lactobacillus</i>	<i>Faecalibacterium prausnitzii</i> <i>Clostridiaceae</i>
Bosello et al., 2016 ⁶⁷	Fecal samples	66 SSc versus HC	<i>Lactobacillus</i> <i>Ruminococcus</i> <i>Roseburia</i> <i>Faecalibacterium</i>	<i>Clostridium</i> <i>Odoribacter</i> <i>Veillonella</i> <i>Prevotella</i>
Volkman et al., 2017 ⁶⁸	Fecal samples	17 SSc versus HC (Norway)	<i>Lactobacillus</i>	<i>Clostridium</i> <i>Bacteroides</i>
		17 SSc versus HC (USA)	<i>Lactobacillus</i> <i>Fusobacterium</i> <i>Erwinia</i> <i>Akkermansia</i> <i>Ruminococcus</i>	<i>Faecalibacterium</i> <i>Bacteroides</i>
Patrone et al., 2017 ⁶⁹	Fecal samples	18 SSc versus HC	<i>Blautia</i> <i>Lactobacillus</i> <i>Eubacterium</i> <i>Bacteroides</i> <i>Acinetobacter</i>	<i>Roseburia</i> <i>Clostridium</i> <i>Ruminococcus</i> <i>Streptococcus</i>
Bellocchi et al., 2018 ⁷⁰	Fecal samples	59 SSc versus HC	<i>Fonticella</i> <i>Parabacterioides</i> Unidentified members of the <i>Firmicutes</i> phylum <i>Butyrivibrio</i> <i>Desulfovibrio</i>	<i>Turicibacter</i> Unidentified members of the <i>Lachnospiraceae</i> family
Natalello et al., 2020 ⁷¹	Fecal samples	63 SSc versus HC	<i>Firmicutes</i> <i>Streptococcus</i> <i>Lactobacillus</i> <i>Blautia</i> <i>Ruminococcus</i> <i>Phascolarctobacterium</i>	<i>Sutterella</i> <i>Bacteroides</i> <i>Odoribacter</i> <i>Roseburia</i>

* relative to the control group; HC – healthy controls; USA – United States of America

dance of *Lactobacillus*, *Bifidobacterium*, *Fusobacterium*, *Erwinia*, *Ruminococcus*, and *Prevotella*, and a decrease in *Faecalibacterium*, *Clostridium*, *Rikenella*, and *Bacteroides fragilis*.⁶⁵ In 2017, Volkman et al. compared two independent SSc cohorts from Norway and the USA, providing evidence that gut microbiota varies between the two populations, the extent of dysbiosis being greater in the American cohort. It has been stated that an increased expression of species such as *Ruminococcus* or *Akkermansia* may contribute to the fibrotic process in scleroderma patients, yet further studies are needed to confirm this relationship.^{66,68}

Regarding gastrointestinal involvement, it has been shown that patients with none to mild gastrointestinal tract involvement had increased abundance of *Bacteroides fragilis* and *Clostridium*, while patients with moderate to severe gastrointestinal symptoms had an increase of *Prevotella* and *Fusobacterium* species.⁷² Patrone et al. conducted a study comparing HC to SSc patients with/without gastrointestinal involvement.⁶⁹ The results showed that the diversity and richness of the gut microbiota varied significantly between controls and SSc patients with gastrointestinal involvement, albeit there were no differences between healthy individuals and SSc patients with-

out digestive involvement. The group without gastrointestinal symptoms had a lower level of *Blautia*, *Dorea*, and *Bacteroides* compared with the other patients. *Dorea* is a gas-producing bacterium, and its high levels could explain the abdominal bloating experienced by SSc patients with gastrointestinal involvement.⁶⁹ Bellocchi *et al.* conducted a study on 59 subjects diagnosed with SSc, suggesting a possible connection between treatment and the gut microbiota profile in these patients.⁷⁰

CONCLUSIONS

SSc is an autoimmune disease with a complex pathogenesis and a wide range of symptoms derived from multiple organ involvement. Recent studies indicate an interrelationship between the activation of the immune system and the disturbance of gastrointestinal tract microbiota in various immune-inflammatory diseases including SSc. Moreover, the reported data indicate an association between dysbiosis and gastrointestinal as well as non-digestive manifestations in SSc patients. Further research is needed to elucidate the dynamics between digestive microbiota and SSc progress (pertaining to both gastrointestinal and non-digestive manifestations), focusing on the development of strategies to improve clinical outcomes and quality of life in these patients.

CONFLICT OF INTEREST

Nothing to disclose.

REFERENCES

- McMahan ZH, Hummers LK. Gastrointestinal involvement in systemic sclerosis: diagnosis and management. *Curr Opin Rheumatol.* 2018;30:533-540.
- Denaxas K, Ladas SD, Karamanolis GP. Evaluation and management of esophageal manifestations in systemic sclerosis. *Ann Gastroenterol.* 2018;31:1-6.
- Tétrault MP, Kahrilas P. GI Manifestations With a Focus on the Esophagus: Recent Progress in Understanding Pathogenesis. *Curr Rheumatol Rep.* 2019;21:42.
- Miller JB, Gandhi N, Clarke J, McMahan Z. Gastrointestinal Involvement in Systemic Sclerosis: An Update. *J Clin Rheumatol.* 2018;24:328-337.
- Schmeiser T, Saar P, Jin D, et al. Profile of gastrointestinal involvement in patients with systemic sclerosis. *Rheumatol Int.* 2012;32:2471-2478.
- Ferrelli C, Gasparini G, Parodi A, Cozzani E, Rongioletti F, Atzori L. Cutaneous Manifestations of Scleroderma and Scleroderma-Like Disorders: a Comprehensive Review. *Clinic Rev Allerg Immunol.* 2017;53:306-336.
- Anton E. Current management of the gastrointestinal complications of systemic sclerosis. *Nat Rev Gastroenterol Hepatol.* 2016;13:461-472.
- Lynch S, Pedersen O. The Human Intestinal Microbiome in Health and Disease. *N Engl J Med.* 2016;375:2369-2379.
- Vogelzang A, Guerrini MM, Minato N, Fagarasan S. Microbiota – an amplifier of autoimmunity. *Curr Opin Immunol.* 2018;55:15-21.
- Tallota R, Atzeni F, Ditto MC, Gerardi MC, Sarzi-Putini P. The Microbiome in Connective Tissue Diseases and Vasculitides: An Update Narrative Review. *J Immunol Res.* 2017; 2017:6836498.
- Tong Y, Marion T, Schett G, Luo Y, Liu Y. Microbiota and metabolites in rheumatic diseases. *Autoimmun Rev.* 2020;19:102530.
- König MF. The microbiome in autoimmune rheumatic disease. *Best Pract Res Clin Rheumatol.* 2020;34:101473.
- Asano Y. The Pathogenesis of Systemic Sclerosis: An Understanding Based on a Common Pathologic Cascade across Multiple Organs and Additional Organ-Specific Pathologies. *J Clin Med.* 2020;9:2687.
- Frantz C, Avouac J, Distler O, et al. Impaired quality of life in systemic sclerosis and patient perception of the disease: A large international survey. *Semin Arthritis Rheum.* 2016;46:115-123.
- Smirani R, Poursac N, Naveau A, Schaeveverbeke T, Devillard R, Truchetet ME. Orofacial consequences of systemic sclerosis: A systematic review. *J Scleroderma Relat Disord.* 2018;3:88-90.
- Hadj Said M, Foletti J, Graillon N, Guyot L, Chossegros C. Orofacial manifestations of scleroderma. A literature review. *Rev Stomatol Chir Maxillofac Chir Orale.* 2016;117:322-326.
- Jung S, Martin T, Schmittbuhl M, Huck O. The spectrum of orofacial manifestations in systemic sclerosis: a challenging management. *Oral Dis.* 2017;23:424-439.
- Gomes da Silva G, Maymone de Melo M, Leão J, et al. Oral features of systemic sclerosis: A case control study. *Oral Dis.* 2019;25:1995-2002.
- Baron M, Hudson M, Tatibouet S, et al. The Canadian systemic sclerosis oral health study: orofacial manifestations and oral health-related quality of life in systemic sclerosis compared with the general population. *Rheumatology (Oxford).* 2014;53:1386-1394.
- Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. *Lancet.* 2005;366:1809-1820.
- Isola G, Williams RC, Lo Gullo A, et al. Risk association between scleroderma disease characteristics, periodontitis, and tooth loss. *Clin Rheumatol.* 2017;36:2733-2741.
- Cheng Z, Meade J, Mankia K, Emery P, Devine DA. Periodontal disease and periodontal bacteria as triggers for rheumatoid arthritis. *Best Pract Res Clin Rheumatol.* 2017;31:1-12.
- Kobak S, Oskel F, Aksu K, Kabasakal Y. The frequency of sicca symptoms and Sjogren's syndrome in patients with systemic sclerosis. *Int J Rheum Dis.* 2013;16:88-92.
- Denaxas K, Ladas SD, Karamanolis GP. Evaluation and management of esophageal manifestations in systemic sclerosis. *Ann Gastroenterol.* 2018;31:165-170.
- Roberts CGP, Hummers LK, Ravich WJ, Wigley FM, Hutchins GM. A case-control study of the pathology of oesophageal disease in systemic sclerosis (scleroderma). *Gut.* 2006;55:1697-1703.
- Kumar S, Singh J, Rattan S, DiMarino A, Cohen S, Jimenez S. Review article: pathogenesis and clinical manifestations of gastrointestinal involvement in systemic sclerosis. *Aliment Pharmacol Ther.* 2017;45:883-898.
- Lee JS, Kim HS, Moon JR, et al. Esophageal involvement and Determinants of Perception of Esophageal Symptoms Among South Koreans With Systemic Sclerosis. *J Neurogastroenterol Motil.* 2020;26:477-485.
- Arana-Guajardo AC, Barrera-Torres G, Villarreal-Alarcón MÁ, Vega-Morales D, Esquivel-Valerio JA. Esophageal symptoms and their lack of association with high-resolution manometry in systemic sclerosis patients. *Reumatol Clin.* 2017;15:165-169.
- Crowell MD, Umar SB, Griffing LW, DiBase JK, Lacy BE, Vela MF. Esophageal Motor Abnormalities in Patients With Scleroderma: Heterogeneity, Risk Factors, and Effects on Quality of Life. *Clin Gastroenterol Hepatol.* 2017;15:207-213.
- De Carlan M, Lescoat A, Brochard C, et al. Association between clinical manifestations of systemic sclerosis and esophageal dysmotility assessed by high-resolution manometry. *J Scleroderma Relat Disord.* 2017;2:50-56.
- Nicola S, Rolla G, Bucca C, et al. Gastric Juice Expression of Th-17 and T-Reg Related Cytokines in Scleroderma Esophageal Involvement. *Cells.* 2020;19:2106.
- 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.* 2020;116:517-521.
- Petcu A, Ghib LJ, Grad SM, et al. Upper gastrointestinal involvement in systemic sclerosis: Findings in a real-life setting. *Exp Ther Med.* 2019;18:5095-5100.
- Grusell NE, Dahlén G, Ruth M, et al. Bacterial flora of the human oral cavity, and the upper and lower esophagus. *Dis Esophagus.* 2012;53:650-656.
- D'Souza SM, Cundra LB, Yoo BS, Parekh PJ, Johnson DA. Microbiome and Gastroesophageal Disease: Pathogenesis and Implications for Therapy. *Ann Clin Gastroenterol Hepatol.* 2020;4:020-033.

36. Espinoza M, Mehta BK, Wang Y, et al. Characterization of the Esophageal Microbiome in Patients with Systemic Sclerosis (SSc). *Arthritis Rheumatol*. 2018;Suppl70.
37. Hong BY, Giang R, Mbuagbaw L, Larche M, Thabane L. Factors associated with development of gastrointestinal problems in patients with scleroderma: a systematic review. *Syst Rev*. 2015;4:188.
38. Radić M. Role of *Helicobacter pylori* infection in autoimmune systemic rheumatic diseases. *World J Gastroenterol*. 2014;20:12839-12846.
39. Yong W, Upala S, Sanguankee A. *Helicobacter pylori* infection in systemic sclerosis: a systematic review and meta-analysis of observational studies. *Clin Exp Rheumatol*. 2018;36(Suppl113): S168-S174.
40. Radić M, Kaliterna MD, Bonacin D, et al. Is *Helicobacter pylori* infection a risk factor for disease severity in systemic sclerosis? *Rheumatol Int*. 2013;33:2943-2948.
41. Yamaguchi K, Iwakiri R, Hara M, et al. Reflux Esophagitis and *Helicobacter pylori* Infection in Patients with Scleroderma. *Inter Med*. 2008;47:1555-1559.
42. Ram M, Barzilai O, Shapira Y, et al. *Helicobacter pylori* serology in autoimmune diseases: fact or fiction? *Clin Chem Lab Med*. 2013;51:1075-1082.
43. Bilgin H, Kocabaş H, Keşli R. The prevalence of infectious agents in patients with systemic sclerosis. *Turk J Med Sci*. 2015;45:1192-1197.
44. Balaji C, Bhuvanesh M, Saranya C, Ramesh R, Saravanan M, Rajeswari S. *Helicobacter Pylori* infection in Systemic Sclerosis and Its Association with Upper Gastrointestinal Dysfunction. *Indian J Rheumatol*. 2017;12:204-208.
45. Efthymiou G, Liaskos C, Siamopoulou T, et al. Antigen-specific humoral responses against *Helicobacter pylori* in patients with systemic sclerosis. *Immunol Res*. 2020;68:39-47.
46. Quigley EM. Small Intestinal Dysmotility, Its Role in Irritable Bowel Syndrome and Small Intestinal Bacterial Overgrowth: Assessment and Management. *Front Gastrointest Res Basel Karger*. 2014;33:55-64.
47. Rawn S, Pitman N, Beattie K, Bazzaz A, Larche M. Small Intestinal Bacterial Overgrowth in Patients with Systemic Sclerosis. *Indian J Rheumatol*. 2017;12:S167-S170.
48. Feng X, Li XQ, Jiang Z. Prevalence and predictors of small intestinal bacterial overgrowth in systemic sclerosis: a systematic review and meta-analysis. *Clin Rheumatol*. 2021 January. [Epub ahead of print]
49. Marie I, Ducrotte P, Denis P, Menard JF, Levesque H. Small Intestinal bacterial overgrowth in systemic sclerosis. *Rheumatology*. 2009;48:1314-1319.
50. Polkowska-Pruszyńska B, Gerkowicz A, Rawicz-Pruszyński K, Krasowska D. The Role of Fecal Calprotectin in Patients with Systemic Sclerosis and Small Intestinal Bacterial Overgrowth (SIBO). *Diagnostics*. 2020;10:587.
51. Preis E, Franz K, Siegert E, et al. The impact of malnutrition on quality of life in patients with systemic sclerosis. *Eur J Clin Nutr*. 2018;72:504-510.
52. Zou H, De Palma G, Bercik P, Verdu E, Beattie K, Larche M. Distinct Characteristics of the Gut Microbiome of Patients with Systemic Sclerosis and Small Intestinal Bacterial Overgrowth [abstract]. *Arthritis Rheumatol*. 2019;71(suppl10).
53. Parodi A, Sessarego M, Greco A, et al. Small Intestinal Bacterial Overgrowth in Patients Suffering From Scleroderma: Clinical Effectiveness of Its Eradication. *Am J Gastroenterol*. 2008;103: 1257-1262.
54. Fynne L, Worsøe J, Gregersen T, Schallageter V, Laurberg S, Krogh K. Gastrointestinal transit in patients with systemic sclerosis. *Scand J Gastroenterol*. 2011;46:1187-1193.
55. Gemignani L, Savarino V, Ghio M, et al. Lactulose Breath Test to Assess Oro-cecal Transit Delay and Estimate Esophageal Dysmotility in Scleroderma Patients. *Semin Arthritis Rheum*. 2013;42:522-529.
56. Savarino E, Mei F, Parodi A, et al. Gastrointestinal motility disorder assessment in systemic sclerosis. *Rheumatology*. 2013;52:1095-1100.
57. Tauber M, Avouac J, Benahmed A, et al. Prevalence and predictors of small intestinal bacterial overgrowth in systemic sclerosis patients with gastrointestinal symptoms. *Clin Exp Rheumatol*. 2014;32:S82-S87.
58. Soukup T, Cyran J, Kopacova M, Tachei I, Bures J. Small intestinal bacterial overgrowth in patients with systemic sclerosis, clinical data relevance [abstract]. *Clin and Exp Rheumatol*. 2014;32:S132.
59. Marie I, Leroi A, Menard J, Levesque H, Quillard P, Ducrotte P. Fecal calprotectin in systemic sclerosis and review of the literature. *Autoimmun Rev*. 2015;14:547-554.
60. Adarsh M, Sharma S, Sinha S, et al. Gastrointestinal Dysmotility and Infections in Systemic Sclerosis – An Indian Scenario. *Curr Rheumatol Rev*. 2017;13.
61. Cruz-Dominguez M, Garcia-Collinot G, Madrigal-Santillan E, et al. Small intestinal bacterial overgrowth in relation to gastrointestinal symptoms in systemic sclerosis [abstract]. *Ann Rheum Dis*. 2017;103:1282.
62. Sawadpanich K, Soison P, Chunlertrith K, et al. Prevalence and associated factors of small intestinal bacterial overgrowth among systemic sclerosis patients. *Int J Rheum Dis*. 2019;22:695-699.
63. Garcia-Collinot G, Madrigal-Santillán EO, Martínez-Benzomo MA, et al. Effectiveness of *Saccharomyces boulardii* and Metronidazole for Small Intestinal Bacterial Overgrowth in Systemic Sclerosis. *Dig Dis Sci*. 2020;65:1134-1143.
64. Zhang X, Chen Bd, Zhao Ld, Li H. The Gut Microbiota: Emerging Evidence in Autoimmune Diseases. *Trends Mol Med*. 2020;26:862-873.
65. Volkmann E, Chang Y, Barroso N, et al. Association of Systemic Sclerosis With a Unique Colonic Microbial Consortium. *Arthritis Rheumatol*. 2016;68:1483-1492.
66. Andrnasson K, Alrawi Z, Persson A, Jonsson G, Marsal J. Intestinal dysbiosis is common in systemic sclerosis and associated with gastrointestinal and extraintestinal features of disease. *Arthritis Res Ther*. 2016;18:278.
67. Bosello S, Paroni Sterbini F, Natalello G, et al. The intestinal involvement in systemic sclerosis is characterized by a peculiar gut microbiota [abstract]. *Arthritis Rheumatol*. 2016;68.
68. Volkmann E, Hoffman-Vold A, Chang Y, et al. Systemic sclerosis is associated with alterations in gastrointestinal microbiota in two independent cohorts. *BMJ Open Gastroenterol*. 2017;4: e000134.
69. Patrone V, Puglisi E, Cardinali M, et al. Gut microbiota profile in systemic sclerosis patients with and without clinical evidence of gastrointestinal involvement. *Sci Rep*. 2017;7:14874.
70. Bellocchi C, Fernandez-Ochoa A, Montanelli G, et al. Microbial and metabolic multi-omic correlations in systemic sclerosis patients. *Ann N Y Acad Sci*. 2018;1421:97-109.
71. Natalello G, Bosello S, Paroni Sterbini F, et al. Gut microbiota analysis in systemic sclerosis according to disease characteristics and nutritional status. *Clin Exp Rheumatol*. 2020;38(Suppl. 125).
72. Bellocchi C, Volkmann ER. Update on the Gastrointestinal Microbiome in Systemic Sclerosis. *Curr Rheumatol Rep*. 2018;20:49.