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Esophageal Dysmotility and Gut Microbiome Alterations in Systemic Sclerosis

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Abstract

Background and Aims: Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by widespread fibrosis and vascular abnormalities that affect multiple organs, including the gastrointestinal tract. Esophageal dysmotility (ED), a common complication of SSc, significantly impairs patients' quality of life and contributes to morbidity and mortality. Concurrently, alterations in gut microbiota composition referred to as dysbiosis, have been observed in SSc patients. This review aims to synthesize current literature on the relationship between ED and gut microbiome alterations in SSc, exploring potential pathophysiological links and therapeutic implications. **Methods:** A comprehensive literature search was conducted across multiple databases, including PubMed, Scopus, and Web of Science, using keywords such as "systemic sclerosis," "esophageal dysmotility," "gut microbiota," and "dysbiosis." Studies examining gut microbiome composition and function in SSc patients with ED were included. This review prioritizes human studies employing high-resolution manometry (HRM), esophageal transit studies, 16S rRNA gene sequencing, metagenomics, and metabolomics. Studies were assessed for methodological quality and potential biases. Extracted data included the prevalence of ED and specific patterns of dysbiosis observed in SSc patients. **Results:** A high prevalence of ED was reported among SSc patients, ranging from 50% to 90% across different studies. The severity of ED varied, spanning from ineffective esophageal motility to complete absence of contractility. Multiple studies iden-

tified significant alterations in the gut microbiome of SSc patients compared to healthy controls. These alterations included a decreased abundance of beneficial bacteria such as *Faecalibacterium*, *Clostridium*, and *Bacteroides*, alongside an increased prevalence of potentially pathogenic bacteria like *Fusobacterium*, *Prevotella*, and *Erwinia*. The specific composition of gut microbiota varied across studies, likely influenced by factors such as SSc subtype (limited vs. diffuse cutaneous SSc), disease duration, and treatment regimens. Several studies investigated the correlation between gut microbiome alterations and specific gastrointestinal symptoms, including dysphagia. However, the causal relationship between gut dysbiosis and ED remains uncertain. Some evidence suggests that dysbiosis may contribute to inflammation and fibrosis in the esophagus, exacerbating ED, while other findings propose that ED may induce secondary changes in gut microbiota due to altered motility and nutrient absorption. **Conclusion:** This review underscores the strong association between ED and gut microbiome alterations in SSc. The high prevalence of ED and the consistent findings of dysbiosis suggest a complex interplay between these two factors. However, further research is necessary to elucidate the precise mechanisms underlying their relationship, particularly whether dysbiosis is a cause, consequence, or contributing factor to ED. Future studies should prioritize longitudinal investigations, mechanistic studies exploring interactions between gut microbiota, immune responses, and esophageal tissue, and well-designed clinical trials assessing microbiome-targeted therapies for ED in SSc.

Keywords

Systemic Sclerosis, Esophageal Dysmotility, Gut Microbiota, Dysbiosis

1. Introduction

1.1. Background on Systemic Sclerosis (SSc)

Systemic sclerosis (SSc) is a chronic autoimmune connective tissue disorder, primarily affecting the skin and the gastrointestinal tract. Its pathology is driven by immune dysregulation and vascular injury, leading to its characteristic fibrosis. The abnormal activation of platelets and T cells, as well as impaired vascular repair mechanisms, leads to endothelial damage and tissue hypoxia [1]. Abnormally active fibroblasts trigger the overproduction of collagen and extracellular matrix proteins, leading to the accumulation of connective tissue in affected systems [2]. SSc affects multiple organ systems, leading to fibrosis in the pulmonary, renal, and cardiac systems. The gastrointestinal (GI) system is the most frequently affected system, with a prevalence of 90%, primarily impacting the esophagus [2]. The lower two-thirds of the esophagus, primarily composed of smooth muscle, is particularly susceptible to SSc because of its autonomic regulation and microvascular perfusion [3]. Recognizing gastrointestinal manifestations, especially esophageal dysfunction, is essential for reducing the morbidity and severity of systemic scle-

rosis and for improving long-term outcomes.

1.2. Importance of Esophageal Dysmotility (ED) in SSc

Esophageal dysmotility (ED) is one of the most common gastrointestinal manifestations in SSc [2]. The severity of ED varies significantly, with primary abnormalities being impaired peristalsis, and progression of the disease can lead to aperistalsis. Endothelial abnormalities severely impact the vasculature of smooth muscle, as minimal changes in these vessels cause tissue ischemia [3]. Impaired esophageal function and accumulation of connective tissue, leading to the narrowing of the esophagus, contribute to other complications. Lower esophageal sphincter hypotonia is a common form of ED in SSc and contributes to gastroesophageal reflux disease (GERD), which can cause strictures and conditions such as reflux esophagitis and Barrett's esophagus [4]. Strictures, formed from acid exposure, result in dysphagia and malnutrition due to the obstruction of food passage [4]. By using diagnostic modalities in a timely manner, long-term complications with ED are able to be prevented with adequate treatment. High-resolution manometry is the standard and most effective method for diagnosing ED, as it precisely identifies peristaltic and sphincter abnormalities [5]. Barium esophagrams and endoscopies are supplemental techniques for structural and anatomical information [5]. Early detection of systemic sclerosis using these methods can mitigate the long-term effects, especially those seen in esophageal dysmotility.

1.3. Gut Microbiota and Dysbiosis in SSc

Dysbiosis, an imbalance in the gut microbiome, has a significant role in the pathogenesis of systemic sclerosis. The immune dysregulation of SSc is a strong contributing factor to the prevalence of dysbiosis, as the gut microbiome environment is significantly altered. The dysbiosis observed in SSc is a depletion of beneficial bacteria and overgrowth of harmful bacteria. Specific bacterial genus alterations are seen with certain symptoms, such as patients with severe constipation having an abnormal increase in *Parabacteroides* [6]. Nguyen *et al.* (2023) observed that commensal genera such as *Clostridia* were decreased and pathobiont genera such as *Enterococcus* and *Klebsiella* were increased in patients with severe GI symptoms with SSc [7]. Furthermore, an increase in pro-inflammatory bacterial species exacerbates fibrosis and leads to aperistalsis in the GI tract. Changes in the gut microbiome can lead to malnutrition because of abnormal activity of key metabolic pathways [6]. The relationship between dysbiosis and systemic sclerosis demonstrates the multisystem involvement in systemic sclerosis' pathogenesis and effects on the body.

1.4. Aim of the Review

Esophageal dysfunction in SSc is a prominent indication of gastrointestinal involvement, and existing literature has demonstrated its association with gut microbiome changes. While esophageal dysmotility and gut microbiome changes are

well-documented features of SSc, their relationship remains unclear. This review aims to synthesize evidence on the relationship between gut microbiome alterations and ED in SSc, identify gaps in literature, and emphasize potential therapeutic strategies targeting the microbiome.

2. Methods

2.1. Literature Search Strategy

In order to yield a comprehensive literature search, multiple databases were searched using key search terms, such as Systemic sclerosis," "esophageal dysmotility," "gut microbiome," "dysbiosis," "high-resolution manometry," "16S rRNA sequencing," "metagenomics," "metabolomics". These databases included PubMed, Scopus and Web of Science. The search was filtered to include studies published from the early 2000s through 2025, with most papers falling between 2005 and 2025; one key study from 2001 was included due to its valuable insights.

2.2. Inclusion Criteria

This review focused on studies investigating the composition and function of the gut microbiome in patients with systemic sclerosis (SSc) who experience esophageal dysmotility (ED). Priority was given to human studies that utilized advanced diagnostic and analytical techniques, including high-resolution manometry (HRM) to assess esophageal function, esophageal transit studies to evaluate motility, and microbiome profiling methods such as 16S rRNA gene sequencing, metagenomics, and metabolomics. These methodologies provide a comprehensive understanding of the interplay between microbial communities and gastrointestinal dysfunction in SSc.

2.3. Quality Assessment

The studies included in review were assessed for methodological quality by evaluating study design, sample size, risk of bias (randomization, blinding, confounders), clarity of outcome measures, appropriateness of statistical analysis, transparency in reporting, and applicability to the research question. Additionally, any potential biases such as selection bias, publication bias, and limitations related to sample size and study design were considered during study selection.

2.4. Data Extraction

Data on the prevalence and severity of esophageal dysmotility in systemic sclerosis (SSc) patients were extracted, with a focus on findings from high-resolution manometry (HRM). These studies revealed common motility disorders, such as ineffective esophageal motility and absent peristalsis, though the severity and prevalence varied widely across patients, highlighting the diverse ways esophageal involvement manifests in SSc. Patterns of gut dysbiosis in SSc patients were also identified, with significant changes in bacterial diversity and composition. These included a reduction in beneficial bacteria and an increase in potentially patho-

genic species. Notably, correlations were documented between these gut microbiome alterations and esophageal symptoms like dysphagia and reflux, suggesting a potential link between microbial imbalances and esophageal dysfunction in SSc. The review incorporated a wide range of studies, and the total number of papers analyzed was recorded. A PRISMA flowchart was created to transparently outline the study selection process, ensuring a systematic and thorough approach to exploring these complex relationships [8]. (**Figure 1**)

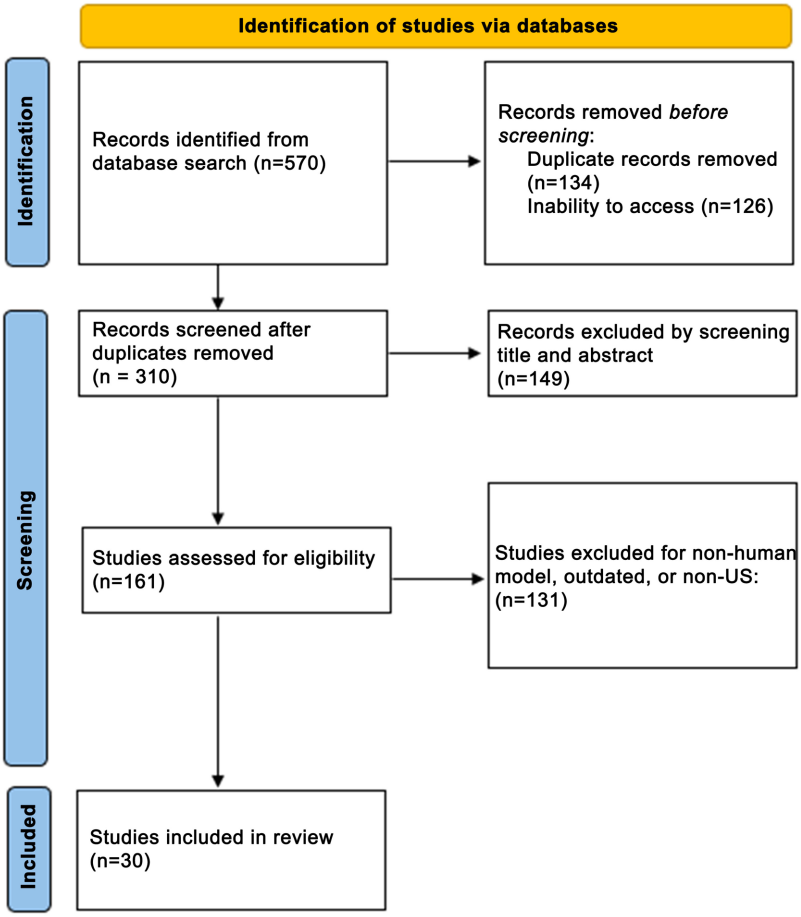

Figure 1. PRISMA flowchart of study selection process.

3. Results

3.1. Prevalence of Esophageal Dysmotility in SSc

Esophageal dysmotility is a common complication associated with systemic sclerosis, occurring with the diagnosis in 50% to 90% of patients, depending on diagnostic strategy and disease subtype [9] [10]. Roman *et al.* (2011) utilized high-resolution manometry (HRM), which uses pressure sensors that record pressure change throughout the esophagus, providing a more accurate diagnostic tool for assessing esophageal motility and function compared to conventional methods [11]. Using HRM, it was found that esophageal body dysmotility was present in 67.3% of SSc patients, with over half of these patients having hypotensive esoph-

agogastric junctions caused by lower esophageal sphincter dysfunction. Findings of Roman *et al.* (2011) highlight the lack of sensitivity to detect the complete presence of esophageal involvement in these patients in conventional diagnostic methods, especially in early cases where symptoms may not be present. Additionally, Roman *et al.* (2011) found a significant influence of severe motility abnormalities in patients with diffuse cutaneous SSc (dcSSc) and positive anti-Scl70 antibodies [11]. These findings suggest that the presence of serological markers may serve as predictors for more severe gastrointestinal involvement and symptom progression in SSc, allowing for expedited categorization of high-risk patients, regardless of symptom presentation, as well as a predictor of a higher-risk subgroup for developing esophageal dysfunction. Prioritizing diagnostic sensitivity is critical to ensuring that disease progression does not go unnoticed in patients without esophageal symptoms. Collectively, this data emphasizes the importance of routine and specific screening tools for essential clinical intervention.

The severity of SSc esophageal dysmotility ranges across a wide spectrum, from weak, mild motility to complete loss of normal motility and incompetence of the lower esophageal sphincter. Based on the severity of dysmotility, motor abnormalities may produce significant impairment of bolus transit, with dangers of gastroesophageal reflux, malnutrition, and aspiration. Findings from Marie *et al.* (2001) report a significant number of patients with abnormal HRM findings, despite a lack of symptoms, emphasizing the idea that esophageal involvement may extend subclinically [10]. The range of dysmotility presentations creates a clinical blind spot, especially in asymptomatic patients in the absence of screening guidelines. According to Gyger and Baron (2015), there remains a large discrepancy between gastrointestinal symptoms and measurable esophageal dysfunction, yet again emphasizing the importance of regular surveillance [9]. Given this discrepancy, sole reliance on symptoms reported by the patient may lead to inappropriate delay in treatment and intervention. It is critical that standardized screening methods are introduced, separate from patient-reported symptoms. By employing early detection methods, timely diagnosis and interventions can be achieved, significantly reducing the risk of downstream complications from undiagnosed esophageal complications.

3.2. Gut Microbiome Alterations in SSc

Patients with systemic sclerosis (SSc) exhibit clinically significant changes in the composition of the gut microbiome, particularly in the loss of beneficial anti-inflammatory bacteria that are present in healthy individuals. Multiple studies report a significant decrease in *Faecalibacterium prausnitzii*, a bacterium playing an essential role in producing abundant short-chain fatty acids and maintaining mucosal barrier integrity and modulating immune responses [12] [13]. Without F. prausnitzii balancing intestinal homeostasis, an environment more prone to inflammation and fibrosis is formed. Similarly, depletions have been found in the Clostridium species, which play an essential role in the activation of regulatory T

cells and anti-inflammatory signaling. The loss of Clostridium species can impair the immunological tolerance mechanisms of the gut and can play a role in immune dysregulation at both the systemic and local levels in SSc. Furthermore, the Bacteroides species involved in bile acid metabolism and epithelial tissue repair function decline markedly in patients with systemic sclerosis (SSc), potentially interfering with gut-liver communication and nutrient absorption [14]. These changes in general indicate that SSc is linked with a microbiome lacking key regulatory organisms, which can compromise the gut barrier integrity and predispose to immune-mediated tissue injury. The consistent loss of these beneficial microbes highlights the importance of investigating microbiome reconstitution therapies as a potential supplemental therapy in the management of gastrointestinal symptoms in SSc. Clinical monitoring of the gut microbiota and necessary restoration of healthy microbiome balance could offer a non-invasive strategy to improve immune regulation in impacted patients, preserving critical immune homeostasis and intestinal wall integrity. Further randomized controlled trials are necessary in order to determine the long-term effects and safety of such interventions. There are key factors regarding delivery method and patient selection that need to be accounted for.

Specific microbial patterns have been marked in patients presenting with SSc. In individuals with diagnosed systemic sclerosis, an elevated abundance of genus-level identified bacteria was determined. Volkmann *et al.* (2016) reported that patients classified under mild SSc gastrointestinal (GI) symptoms possess elevated levels of *Bacteroides fragilis*, a bacterium often regarded as a common component of the colon's cecum and sigmoid [12]. As this direct species is a common inhabitant of the GI tract, it is more evident to consider the *Fusobacterium* genus. Patrone *et al.* (2017) investigated fecal microbiota composition in systemic sclerosis (SSc) patients with and without gastrointestinal involvement [16]. *Fusobacterium*, *Prevotella*, or *Erwinia* were not found to have a significant increase in SSc patients compared to healthy controls [15]. Compared with other studies, there were increased levels of pathobiont bacteria, such as *Fusobacterium*, compared to healthy controls. Studies vary; however, recent work continues to identify distinct microbial signatures in systemic sclerosis (SSc) patients' gut microbiota, including the enhancement or enrichment of pro-inflammatory bacterial taxa such as *Fusobacterium*, *Prevotella*, and *Erwinia*. In a 2023 narrative review of rheumatic and musculoskeletal diseases (RMDs), Bixio *et al.* (2023) reported that SSc patients consistently demonstrated an increase in these genera among other taxa, such as *Ruminococcus*, *Akkermansia*, and γ-Proteobacteria [17]. These bacteria are known to interact with mucosal immune pathways and may promote inflammation. Supporting these findings, Volkmann *et al.* (2016) performed a 16S rRNA sequence of colonic mucosal samples and identified the increased abundance of *Fusobacterium* and *Prevotella* in SSc compared with controls [12]. Therefore, a dysbiotic microbial profile enriched in inflammatory taxa may contribute to chronic inflammation and the progression of SSc. The role of systemic sclerosis (SSc) sub-

types, disease duration, and treatment regimens influences intestinal microbial composition to delineate causality and disease heterogeneity in SSc-associated dysbiosis. Andréasson *et al.* (2016) provided a comprehensive analysis assessing these factors with gut microbiota composition [18]. From the comprehensive analysis, SSc's subtype did not statistically influence gut microbiota composition. Dysbiosis was prevalent in both patients with limited cutaneous SSc (lccSSc) and diffuse cutaneous SSc (dcSSc), with no significant difference ($p = 0.611$) [18]. This finding holds how dysbiosis is understood in SSc disease heterogeneity. Though the previous implications that dcSSc is more aggressively associated with visceral and GI complications, dysbiosis is not primarily exclusive to severe SSc. Safely, it can appear as a core pathophysiological feature of SSc. Similarly, the degree of intestinal dysbiosis did not correlate with skin fibrosis as assessed on the Rodnan skin score (mRSS) ($p = 0.659$), indicating that external fibrotic manifestations are not predictive of microbial imbalance in the gut alone. Integrating microbiome profiling can create more complete diagnostic value. Anticipations for chronic immune dysregulation and GI involvement in SSc over time can progressively worsen with dysbiosis. However, the study found no correlation between disease duration and dysbiosis, as dysbiosis was common in patients with early systemic sclerosis too: 72% - 73% of patients in the early disease stage already exhibited altered microbial composition [18]. Scientists can argue that dysbiosis may emerge early in the disease and not accumulate over time. Andréasson further examined how immunosuppressive therapy, glucocorticoid use, and proton pump inhibitor (PPI) therapy influenced microbial composition [18]. The degree of dysbiosis did not correlate with glucocorticoid usage ($p = 0.139$) [18]. However, patients using PPIs had significantly greater dysbiosis than those without ($p = 0.002$). The author cautions that PPI use in this context may reflect more severe GI symptoms rather than being a direct cause of dysbiosis, as regular use of PPI is a nonspecific marker of GI SSc.

Beyond these, dysbiosis was more severe in patients with certain inflammatory and fibrotic manifestations, suggesting that organ involvement and systemic inflammation have a more significant role in microbiota alterations than disease classification.

Future studies and longitudinal cohort studies are needed to help solve the relationship and establish causality or treatment options. It can investigate microbiota-targeted therapies that can yield different responses based on SSc subtype and organ involvement. (Table 1)

Table 1. Common gut microbial alterations in systemic sclerosis (SSc) and their functional roles.

Bacterial Genus/Species	Observed Trend in SSc	Physiological Role	Implication in SSc
Faecalibacterium prausnitzii	Decreased	Produces SCFAs, maintains mucosal integrity, anti-inflammatory	Loss leads to gut barrier dysfunction and inflammation
Clostridium spp.	Decreased	Induces regulatory T cells and immunotolerance	Immune dysregulation and increased fibrosis risk

Continued

Bacteroides spp.	Decreased	Bile acid metabolism, epithelial repair	Nutrient malabsorption, impaired barrier repair
Fusobacterium spp.	Increased	Pro-inflammatory interactions	Promotes mucosal inflammation
Prevotella spp.	Increased	Mucosal immune modulation	Associated with chronic inflammation
Erwinia spp.	Increased	Rare gut colonizer; unclear role	Possibly pathogenic in dysbiosis context
Desulfovibrio spp.	Increased	Amino acid metabolism, hydrogen sulfide production	Linked to inflammatory metabolites and fibrosis
Akkermansia spp.	Increased	Mucus layer degradation	May promote mucosal barrier erosion

3.3. Correlation between Dysbiosis and Gastrointestinal Symptoms

Bodies of evidence support the consistent association between gut microbiota dysbiosis and esophageal dysfunction (ED)-related symptoms such as gastroesophageal reflux disease (GERD) and dysphagia. Vaia *et al.* (2024) presented a review on pediatric leukodystrophies, stating GERD and dysphagia were amongst the most frequently observed GI manifestations: 22.1% and 37.1% of their cohort were affected, respectively [19]. Emphasis on these symptoms arose from the bidirectional relationship between GI dysfunction and gut dysbiosis, where microbial imbalance influences impaired motility and esophageal clearance. Alterations in gut microbiota composition also affect GI motility through short-chain fatty acid production and microbial signaling, disrupting mucosal layers and increasing inflammation susceptibility.

Esophageal inflammation and fibrosis are likely due to dysbiosis. Dysbiosis is increasingly recognized as being a meaningful contributor to esophageal inflammation and possibly fibrosis, shifting the pathogenesis model for purely acid-mediated damage toward microbe-initiated immune activation. Dysbiosis is increasingly recognized as being a meaningful contributor to esophageal inflammation and also to possible fibrosis, thereby shifting the pathogenesis model from purely acid-mediated damage toward microbe-initiated immune activation. D'Souza *et al.* (2021) provide substantial evidence supporting this shift, as gram-negative bacterial products can activate TLR on esophageal endothelial cells [20]. This causes the inflammatory cascade downstream and mucosal damage (p. 2061). The authors describe lipopolysaccharide (LPS), a pro-inflammatory component of gram-negative bacteria, as being the cause of the specific activation of Toll-like receptor 4 (TLR-4). This receptor will initiate NF-κB signaling, triggering cytokines like IL-8 and IL-1β, promoting leukocyte infiltration and epithelial disruption. The processes promote smooth muscle relaxation, compromise esophageal integrity, and promote chronic inflammation [20]. Furthermore, dysbiosis can precede inflammation. The composition of the microbiota can play a major role in downstream events. Bellocchi *et al.* (2018) support these findings within systemic sclerosis, noting Desulfovibrio, a genus improved within dysbiosis, is associated with inflammatory metabolites correlating with GI symptom severity and fibrosis [21].

The genus associated itself with alpha-N-phenylactetyl-L-glutamine, as well as 2,4-dinitrobenzenesulfonic acid, compounds involved in amino acid metabolism, also known to be mucosal irritants or inflammatory inducers [21]. These results suggest a bidirectional feedback loop in which microbial imbalance improves mucosal damage, and damaged tissue further selects for pro-inflammatory microbiota, as well. This persistent immune activation may ease the shift from inflammation toward fibrosis, especially in conditions featuring connective tissue issues, like SSc. Impaired esophageal motility alters gut microbiota composition through changes in transit time and nutrient absorption. Müller *et al.* (2018) present colonic transit time as a major factor in shaping microbiota ecosystems through the regulation and availability of nutrients and water and luminal washout [22]. Their findings pointed to prolonged exposure of bacteria, where in SSc patients or idiopathic ED, the slow transit promotes bacteria growth and anaerobic species proliferation. The alteration to fermentation patterns leads to small intestinal bacterial growth. Additionally, with delayed colonic transit, ingestible carbohydrates become more diminished, allowing bacteria to switch to protein fermentation, allowing for indole and p-cresol products to exist and harm gut health. Multiple animal models reinforce the conclusion that recolonization and, therefore, disturbances to upper GI motility initiate changes in microbial composition through the alteration of time, location, and nutrient subtypes to intestinal bacteria. The relationship between dysbiosis and esophageal dysfunction is complex and bidirectional. Through an analysis, dysbiosis is seen as a contributor to and consequence of esophageal dysfunction, as it creates a bidirectional cycle of motility impairment and microbial imbalance. Such conclusions can vary between subtypes. The immune dysregulation or motility loss can predispose patients to dysbiosis by disrupting gut physiology. Through highlights of *Desulfovibrio*, a pro-inflammatory bacterial genus overrepresented in patients with gastrointestinal symptoms, dysbiosis amplifies the inflammatory and fibrotic response that underlies ED. Bellocchi *et al.* (2018) caution against definitive claims and classifications of dysbiosis that act as a compounding factor in the pathogenesis and progression of ED-related symptoms [21]. Nonetheless, the bidirectional relationship between dysbiosis and gastrointestinal symptoms in SSc patients showcases a rationale for dysbiosis as a downstream effect on motility issues.

4. Discussion

4.1. Summary of Key Findings

Patients with SSc often experience ED, and studies show that this ED is linked to changes in the gut microbiome. The strongest association with this change is the loss of anti-inflammatory microbiota. The gut microbiome is vital in protecting mucosal barrier integrity and promoting regulatory immune responses. Thus, disrupting the microbiome can lead to disruption of gut-liver communication and immune dysregulation. Two specific bacteria linked to the association between SSc and ED are *F. prausnitzii* and the *Clostridium* species [12] [13]. *F. prausnitzii*

produces short-chain fatty acids and the interruption of this process leads to gut barrier disruption, and immune dysregulation. *Clostridium* species play a role in regulatory T cell activation and the decrease of these bacteria in SSc patients leads to the disruption of immunological tolerance.

Studies consistently show gut dysbiosis in SSc patients. Studies consistently show a depletion of anti-inflammatory bacteria. Volkmann *et al.* (2016) and Kim *et al.* (2019) show depletion of *Faecalibacterium prausnitzii* and Haussmann *et al.* (2024) show depletion of *Bacteroides* species [12]-[14]. The literature on the association between pro-inflammatory bacteria and SSc is weaker. Volkmann *et al.* (2016) and Bixio *et al.* (2023) found an association with the pro-inflammatory microbiota *Fusobacterium*, *Ruminococcus*, *Akkermansia*, *Prevotella*, *Erwinia* and *γ-Proteobacteria* [12] [17]. However, Patrone *et al.* (2017) did not find an increase in these pro-inflammatory bacteria in SSc patients [16].

4.2. Pathophysiological Interplay

The relationship between gut microbial changes and ED in SSc is a complex, bi-directional process, where microbial imbalance both contributes to and results from impaired gastrointestinal motility. On the one hand, the increase in pro-inflammatory bacteria leads to the release of the gram negative microbial product lipopolysaccharide (LPS), which activates Toll-like receptor 4 (TLR-4) and downstream NF-κB signaling (D'Souza *et al.*, 2021, pp. 2061-2062) [20]. This cascade promotes pro-inflammatory cytokine production, mucosal inflammation, and muscle dysfunction. On the other hand, depletion of anti-inflammatory microbiota impairs the activation of regulatory T cells, leading to the reduction of anti-inflammatory cytokines such as IL-10 and TGF-β, contributing to immune dysregulation (Lu *et al.*, 2017) [23]. In the reverse direction, impaired motility associated with ED alters transit time and nutrient availability in the gut, which promotes further overgrowth of pro-inflammatory microbes. An example of this is *Desulfovibrio* overgrowth as a result of inflammation which further increases inflammation by modulating amino acid metabolism [21]. This reciprocal feedback loop amplifies dysbiosis and leads to further worsening of ED in SSc patients.

The hallmark of systemic sclerosis is organ fibrosis, and gut dysbiosis plays a role in this process. As highlighted above, immune dysregulation is a key mediator of inflammation which then leads to fibrosis. Another mechanism that contributes to fibrosis is the modulation of short chain fatty acids (SCFA). Butyrate is a SCFA that is crucial for providing an energy source for intestinal epithelial cells, and also its immunomodulatory and anti-inflammatory effects. *Desulfovibrio*, a bacteria linked to SSc, promotes fibrosis by affecting amino acid metabolism and forming heterodimers with Butyrate [21]. Another mechanism shown to cause fibrosis is the metabolite products produced by bacteria amplified in dysbiosis, such as *Ruminococcus*. One byproduct that plays a role in fibrosis is trimethylamine N-oxide (TMAO). Jang *et al.* (2024) demonstrated that TMAO leads to a dose-dependent activation of protein kinase R-like endoplasmic reticulum kinase

(PERK) in human fibroblasts [24]. The gut microbial metabolite trimethylamine N-oxide is linked to specific complications of systemic sclerosis [25]. Finally, the mechanism that underlies all of the systemic effects in systemic sclerosis is increased intestinal permeability. The breakdown of the intestinal epithelial cells as a result of dysbiosis is what leads to systemic circulation of these toxins such as LPS, leading to systemic inflammation [18].

ED is a common manifestation of SSc. Unfortunately, there is insufficient research identifying the mechanism such that dysbiosis is linked to ED in SSc. However, research has been done to establish the relationship between dysbiosis and ED in the context of other GI pathologies such as IBS [26]. Evidence exists showing two proposed mechanisms of how dysbiosis contributes to ED: the indirect and direct pathway. The indirect pathway is an immune-mediated pathway in that chronic immune responses to microbiota, such as the COX-2 and NF-κB pathway, disrupt muscle function, which is regulated by T cells. This can theoretically be applied to SSc in which evidence exists to show the NF-κB and T cell-mediated pathway of inflammation due to dysbiosis [20]. The other mechanism by which dysbiosis leads to ED is through the direct pathway in which bacterial metabolites directly affect the esophageal enteric nerves. For example, SCFAs cause smooth muscle and myenteric neuron activation [27]. However, there are no studies to show that SCFAs are present in the esophagus in SSc.

Often, patients with scleroderma require medical therapy. One of the questions is how does the therapy used to treat SSc affect gut microbiota? Andréasson *et al.*, 2016 specifically looked at the following commonly used medications in SSc patients to determine its effects on gut microbiota: immunosuppressive therapy, glucocorticoids, and PPIs [18]. What he found was no difference in dysbiosis between patients on and not on glucocorticoids and immunosuppressive therapy, however, a significant difference in patients on PPI therapy. However, PPI therapy is commonly used to treat GI symptoms such as GERD which is commonly found in ED patients, so likely it is more correlation rather than causation. (**Table 2**)

Table 2. Pathogenic pathways linking gut dysbiosis to esophageal dysmotility in systemic sclerosis.

Mechanism	Mediating Factors	Outcome	Reference/Context
Immune-mediated inflammation (Indirect)	LPS → TLR-4 → NF-κB → cytokines (IL-8, IL-1β)	Smooth muscle dysfunction, esophageal fibrosis	D'Souza *et al.*, 2021; Lu *et al.*, 2017
Loss of anti-inflammatory signaling	↓ *Clostridium* spp. → ↓ Tregs → ↓ IL-10, TGF-β	Loss of immune tolerance, promotes fibrosis	Lu *et al.*, 2017
SCFA depletion (Direct)	↓ *F. prausnitzii* → ↓ butyrate	Disrupted motility signaling, epithelial damage	Volkmann *et al.*, 2016
Altered fermentation via slow transit	ED → increased transit time → ↑ anaerobic fermentation	Promotes pathogenic bacterial overgrowth	Müller *et al.*, 2018
Pro-inflammatory metabolite production	↑ Desulfovibrio → ↑ inflammatory amino acid metabolites	Promotes fibrosis, inflammation	Bellocchi *et al.*, 2018
Fibrosis-triggering microbial byproducts	↑ Ruminococcus → ↑ TMAO → ↑ PERK activation in fibroblasts	Esophageal fibrosis	Jang *et al.*, 2024

4.3. Gaps in Current Research

The microbiome is a field of research that is extremely complex and a hot topic. In regards to this review, the main problem occurs in determining causation. Although there are proven microbiota pattern associations seen in SSc and ED, in many cases, it is hard to tell if this is a result or the cause of the disease [13]. SSc inherently damages organs such as the skin and gut, so it is unclear if these microbiome changes are a cause of the disease or a result of vulnerability to dysbiosis. Another flaw, as it relates to SSc, is that many patients are put on antibiotic therapy early in the disease course, which can affect the gut microbiota as well. In order to get a better understanding of the relationship between dysbiosis and SSc, longitudinal studies are needed to see how the microbiota changes over time.

There are unfortunately methodological challenges that make studying gut microbiota difficult [13]. Firstly, disease therapies can affect the gut microbiome, so it is often hard to standardize studies as patients are on different therapies and it is difficult to assess if dysbiosis is a result of therapy or the cause of the disease itself. Secondly, current studies use 16S rRNA sequencing which identifies bacteria on the genus level and not the species level; however, different bacterial strains can act differently, creating another confounding variable. Finally, in order to fully assess causality between dysbiosis and SSc, longitudinal studies are needed, starting early in the disease course. Unfortunately, enrolling early-stage or preclinical SSc patients is extremely challenging and a barrier to performing these longitudinal studies, often because patients are diagnosed later in their disease course [28].

5. Future Directions

Further research can aid in closing some of the critical gaps by investigating the relationship between esophageal dysmotility and alterations in gut microbiome in systemic sclerosis. Volkmann *et al.* longitudinal study assessed changes in the microbiome composition through stool samples of the lower gastrointestinal tract of SSc patients with gastrointestinal symptoms. Over the course of the year, they demonstrated relative stability of genera abundance with SSc patients and gastrointestinal symptoms [29]. This is a starting point for understanding the relationship between ED and microbiome alterations in SSc, yet further longitudinal studies are needed to evaluate the trends focusing on the upper gastrointestinal tract microbiome alterations over a longer period of time. The Volkman *et al.* study additionally included 19 participants which decreases the external validity when compared to the general SSc patient. Concurrently, different modalities to obtain the microbiome directly from the esophagus need to be investigated.

Moreover, the technology available to study microbiome is a continuously evolving field of medicine. A multi-omics approach is required to fully understand the interactions between dysbiosis and ED due to the complex relationships between the different bacterial species itself and concurrent interactions with the host. Filrado *et al.* analyzed the advancements and setbacks in current microbiome research, implying that a multi-omic approach is necessary to understand a microbe

in a multifaceted view. Metagenomics by sequencing the 16s rRNA gene via Next Generation Sequencing (NGS) or whole genome sequencing is currently one of the leading tools to identify different variations of a species, which is a current advantage in the understanding of microbiomes. Sequencing hypervariable regions of the 16S rRNA gene via NGS enables identification of bacterial species by analyzing many short DNA fragments, though it is limited by the use of narrow markers that cannot capture variability within species or outside the targeted regions. These hypervariable regions represent only a small portion of the bacterial genome, preventing a comprehensive view of microbial complexity. In contrast, whole-genome shotgun metagenomics assembles all sequenced DNA fragments to analyze the full genome, including virulence and other functional factors, but it is significantly more expensive and requires more complex analysis [30]. Combining both methods offers a more in-depth and accurate understanding of the bacterial species being studied. Additionally, a multi-omics approach integrates not just the genome but also the microbial structural composition and all the contents that allow the microbe to function such as signaling molecules, metabolic process, proteins, and toxins thus creating a multifaceted understanding of a microbiome [30]. Furthermore, immune profiling should be evaluated to further understand how the microbiome subsequently interacts with the host.

Additional studies should be performed to analyze different microbiome-targeted therapies for systemic sclerosis patients with esophageal dysmotility either at the time of diagnosis for prevention or after the onset to help mitigate symptoms and restore the microbiome. These microbiome-targeted therapies can give rise to personalized medicine that can manipulate a targeted microbiome for different SSc patients. The ultimate goal is to increase beneficial bacteria, such as *Faecalibacterium*, *Clostridium*, and *Bacteroides*, while decreasing the harmful bacteria like *Fusobacterium*, *Prevotella*, and *Erwinia*.

Certain microbiota-targeted therapies such as prebiotic and probiotic should be studied individually to gather information on whether they are beneficial for SSc patients. Prebiotics contain nutrients which can be digested by the bacteria in the gastrointestinal tract and help promote a healthy microbiome. Research should first evaluate which prebiotic components are most beneficial for *Faecalibacterium*, *Clostridium*, and *Bacteroides* species then perform clinical trials to evaluate if those prebiotics would improve ED symptoms in SSc. Additionally, although probiotics have been shown to help other autoimmune conditions, they have failed to improve gastrointestinal symptoms in SSc patients in two randomized controlled trials [14]. As with prebiotics, further research into probiotics should evaluate how to introduce bacterial species that are known to improve outcomes in SSc patients and assess potential improvement with ED. Lastly, once research conclusions have determined the efficacy in regards of prebiotic and probiotic, further randomized trials should analyze if the use of either a prebiotic, probiotic, or a combination would improve ED symptoms in SSc patients compared to a control. Limitations when studying the effects of prebiotics and probiotics on the microbiome are the diversity of the microbiome between people and how it would po-

tentially have to be a tailored form of medicine, different for each patient.

Moreover, the use of fecal microbiota transplantation, which introduces a donor's microbiome to correct the recipient's dysbiosis, should also be studied in a research capacity to determine its benefits for SSc patients. Emerging research has presented the fact that fecal microbiota transplantation has been beneficial in some autoimmune conditions but other research has found there is not an associated improvement in lower gastrointestinal symptoms with a small subset of SSc patients [14]. The research compiled has been evaluating the generality of SSc symptoms, so further studies are needed to determine if fecal microbiota transplantation would improve specific ED symptoms. Additional research is required to compare the different microbiome-targeted therapies and conclude whether or not they have a benefit for SSc patients with ED. Furthermore, if a conclusion has been made with regards to pathogenic bacterial overgrowth, randomized control trials should investigate whether an antibiotic decontamination protocol is more beneficial and creates better outcomes for system sclerosis patients on top of a microbiome targeted therapy research.

Lastly, diet plays a large role in the gut microbiome. Diet not only has an effect on the microbiome but can perpetuate illness in humans. Haussmann *et al.* reviewed the current understanding of the gastrointestinal microbiome in SSc patients. In regards to the role diet plays, some studies have shown different diets such as Mediterranean diet, low-fat diet, or low carbohydrate diet have improved the microbial diversity in participants or decreased symptoms in other autoimmune diseases Cross-sectional research on the Mediterranean diet with a sample size of 387 has found that the effect of diet on SSc symptoms improves patients' perception of Raynaud's symptoms, digital ulcers, and depression. Additionally, a prospective observational study with a sample size of 69 of a low-carbohydrate diet found that the effect of diet on SSc symptoms improved small intestinal bacterial overgrowth such as bloating, nausea, and loose stools. [14]. Currently research on diets is very broad and needs to be refined to look at the cause and effect on very specific criteria, in this case, if a known anti-inflammatory diet vs a control diet improves ED in SSc patients. Future randomized controlled research or longitudinal studies should compare diets to evaluate how they can promote the beneficial bacteria, *Faecalibacterium*, *Clostridium*, and *Bacteroides*, and decrease the microbiome-host interactions which can potentially lead to inflammation and promote esophageal dysmotility.

It is crucial for future studies to include a sample size that maximizes external validity. This is a stepping stone to understanding how dysbiosis can lead to ED. Future research and studies are required to determine not only what alterations in the microbiome cause esophageal dysmotility in systemic sclerosis patients but also how it can be mitigated or prevented in future patients.

6. Conclusions

Esophageal dysmotility is a common and significant complication of SSc. It has a frequent co-occurrence with gut microbiota alterations, and this points to a po-

tentially important relationship. Specific microbial signatures, such as reduced *Faecalibacterium* and increased *Fusobacterium* and *Prevotella*, further support this relation [13]. These microbial changes can influence esophageal function through pathways such as immune activation, inflammation, and disruption of neuromuscular signaling. At the same time, impaired motility may contribute to dysbiosis by altering transit time and nutrient absorption. While ED and dysbiosis are researched extensively in SSc, their relationship is not yet clearly understood.

Understanding the relationship between ED and dysbiosis is therefore important not only for understanding disease pathogenesis, but also for identifying patients at risk of early gastrointestinal involvement. Casual pathways, however, remain unknown, and findings across studies are often limited by small sample sizes, methodological variability, and lack of longitudinal follow-up. To address these gaps, future research should prioritize longitudinal designs that use high-resolution manometry, microbial sequencing, and immune profiling.

Integrating microbiome-targeted therapies can create new opportunities to address and alleviate esophageal symptoms and modify disease progression. Therapies including probiotics, dietary interventions, and fecal microbiota transplantation show effectiveness in reducing inflammation and restoring microbial balance [31]. These approaches can address dysbiosis, enhance mucosal healing, and improve motility caused by tissue damage in SSc. However, using these new strategies requires collaboration across different specialties. A collaboration involving gastroenterologists, immunologists, and microbiologists will be critical to developing new diagnostic tools and therapeutic protocols. A deeper understanding of the gut-esophagus axis can ultimately lead to additional opportunities for earlier intervention and personalized care for individuals living with SSc.

Conflict of Interest Statement

The authors of this manuscript declare that they have no conflicts of interest that are directly or indirectly related to the work submitted for publication. Specifically:

1) Financial Interests: None of the authors has received any financial compensation, funding, grants, or other monetary support that could be perceived as influencing the research, analysis, or conclusions presented in this work.

2) Professional Relationships: The authors have no employment, consultancy, board membership, or other professional relationships with organizations that could be perceived as influencing the work presented here.

3) Intellectual Property: The authors declare no patents, copyrights, or other intellectual property rights that could be affected by or affect the publication of this work.

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This review systematically identifies critical gaps in the current literature concerning the intricate relationship between esophageal dysmotility (ED) and gut microbiome alterations in systemic sclerosis (SSc). SSc, a complex autoimmune disease, is characterized by a triad of features: fibrosis, vascular abnormalities, and multi-organ involvement. A significant proportion of SSc patients experience ED and broader gastrointestinal (GI) dysfunction, significantly impacting their quality of life. The growing body of research increasingly highlights the crucial role of the gut microbiome in SSc pathogenesis. However, the precise mechanisms by which gut dysbiosis contributes to the development and progression of ED remain poorly understood. This comprehensive review will meticulously analyze the existing literature, highlighting key findings, identifying areas of consensus and discrepancy, and ultimately pinpointing crucial research gaps that demand further investigation to advance our understanding of this complex interplay.

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