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ORIGINAL PAPERS

Link between Imbalanced Gut Microbiome and Systemic Sclerosis

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Abstract. Recent research suggests that the intestinal microbiota influences the development and function of the immune system, may also play a role in the pathogenesis of autoimmune diseases. **Systemic sclerosis,** also known as scleroderma (SD), is a rare disease. Scleroderma is an immune-mediated systemic autoimmune disease, of unknown etiology, with high morbidity and mortality. The link between the disease and the imbalance of the intestinal microbiota suggested that it would contribute to the development of SD, which is characterized by immune disorder, vasculopathy, organ fibrosis. Gastrointestinal dysfunction affects 90% of patients with SD and is a leading cause of morbidity and mortality in these patients. Emerging evidence suggests that there are changes in the intestinal microbiota in SD, further laboratory and clinical studies are needed to establish the mechanism by which these changes perpetuate inflammation and fibrosis in SD. Although several studies have shown that the intestinal microbiota of patients with SD is abnormal compared to that of seemingly healthy people, it remains unclear whether changes in the intestinal microbiota are the result of the disease or the initial causes. Therapeutic studies are needed to investigate whether dietary interventions or fecal transplantation can restore intestinal microbial balance and improve health outcomes. Interventional studies aimed at addressing / correcting these disorders, either by dietary modification, pro / prebiotic supplementation or fecal transplantation, may lead to improved outcomes for patients with SD. It is necessary to further investigate the potential pathophysiological role of dysbiosis of the intestinal microbiota in triggering SD, we will discuss natural remedies for modulating the microbiota in SD.

Keywords: *microbiome, dysbiosis, scleroderma, natural remedies*
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Systemic sclerosis, also known as scleroderma (SD) is a rare disease. Scleroderma is a heterogeneous chronic multisystem disease of unknown etiology. Multiple genes are implicated in SD susceptibility, and the genetic architecture, dominated by the HLA locus, shows considerable overlap with other autoimmune diseases. Scleroderma is actually a collection of several autoimmune diseases that are characterized by hardened patches of skin and connective tissue. Approximately 80% of patients are females, and one-half present before

the age of 40. Some studies suggest a higher incidence and severity of disease in black females than in whites. Despite extensive investigations, the key pathogenic links between these disease hallmarks remain obscure, as well as the etiology underlying the beginning of this complex disorder. Scleroderma is an immune-mediated systemic autoimmune disease with unknown etiology, which has high morbidity and mortality. Scleroderma is a disease characterized by immunological abnormalities, vascular lesions, and extensive fibrosis. Scleroderma is due to an abnormal immune response of the body against substances and tissues normally present in the body) and is characterized by skin thickening - a process known as fibrosis (1-3).

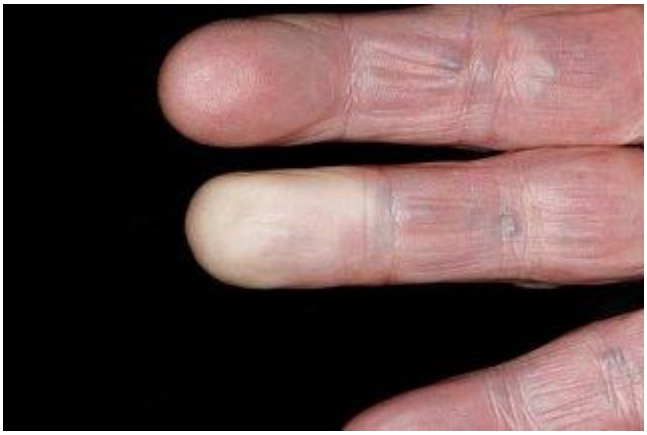

Fig. 1 The skin may turn white or a lighter colour as blood flow is restricted.

Immunologic abnormalities are suggested by the presence of characteristic autoantibodies such as antinuclear, anticentromere, and anti-Scl-70 antibodies. In addition to skin, the most commonly affected organs are lung and kidney. Localized SD generally affects only the skin, however in some people it can spread to muscles, joints, and bones. Systemic SD is the more serious form. It can affect the skin and muscles, and can also impact your lungs, kidneys, and heart as well as your digestive system. While in some types of SD skin hardening is confined to head, face and feet, in more severe cases it affects internal organs such as kidneys, heart, lungs and intestine. Scleroderma has the highest cause specific mortality of all of the connective tissue diseases, and the majority of patients with SD suffer from serious gastrointestinal tract (GI) symptoms. Gastrointestinal tract dysfunction affects 90% of scleroderma patients and is a leading cause of morbidity and mortality in these patients (4-6).

Recent evidence suggests that there is a link between the gut microbial community and immune-mediated disorders. Our evolving understanding of how gut microbiota immune function and homeostasis has many investigators to

explore the potentially pathogenic role of gut microbiota in autoimmune diseases. Scleroderma patients appear to have a characteristic microbiome composition. The gastrointestinal tract is the most common internal organ manifestation, which contributes to significant morbidity and mortality in patients with SD (7).

These patients showed decreased populations of beneficial commensal flora and increased populations of proinflammatory species. Patients with SD have a distinct colonic microbiota, compared with healthy individuals, which could contribute to their immune dysfunction and symptoms. Patients with SD harbor a unique microbiome in their gut when compared to healthy individuals, which may contribute to patients' immune dysfunction. Changes in the intestinal microbiota have been associated with the pathogenesis of SD. We believe the gut microbiome is at the root of most autoimmune issues and probably just about all chronic illnesses. This suggests a link between SD and the gut microbiome, a finding that could open the door to discoveries of new microbiome-related therapeutic and diagnostic tools for SD (8,9).

The goal of this manuscript is to discuss the potential treatment options for gut disease in SD.

Since the gastrointestinal tract is one of the organs most involved, the goal of this study was to explore the composition of the intestinal microbiota in SD patients with (SD/GI+) and without gastrointestinal involvement (SD/GI-) in comparison to healthy controls. Furthermore, specific species seem to correlate with specific gastrointestinal symptoms. Studies have shown that deregulation of the natural body microbiome (communities of bacteria) can contribute to the development or progression of several diseases, including inflammatory disorders such as multiple sclerosis, psoriasis, and SD. Recent report have identified common perturbation in gut microbiota across different SD cohorts. Compared with healthy controls, patients with SD have decreased abundance of beneficial commensal genera (e.g. Faecalibacterium, Clostridium and Bacteroides) and increased abundance pf pathobiont genera (e.g. Fusobacterium, Prevotella and Erwinia). Certain genera may protect against (e.g. Bacteroides, Clostridium, and Lactobacillus), or conversely exacerbate (e.g. Fusobacterium and Prevotella) gastrointestinal symptoms in SD. These genera represent potential targets to avert or treat gastrointestinal dysfunction in SD.

Patients also showed relative increases in pathobionts. Researchers found an enrichment of bacteria species Erwinia and Trabulsiella in SD patients with the most severe symptoms, suggesting that not only are there differences in the microbiota composition between SD sclerosis patients and healthy controls, but these differences may contribute to clinical symptoms, notably, they found that SD patients surprisingly were also enriched in two bacteria species usually found in healthy individuals, Lactobacillus and Bifidobacterium, which are usually reduced in inflammatory diseases patients. Similar to the findings in inflammatory

disease states, scleroderma patients had decreased levels of commensal Clostridia, a class of Firmicutes that is established in early infancy and very important in the maintenance of gut homeostasis (10,11).

Emerging evidence suggests that alterations in gut microbiota exist in the SD disease state; however, future basic and clinical studies are needed to ascertain the mechanism by which these alterations perpetuate inflammation and fibrosis in SD.

Our study reveals microbial signatures of dysbiosis in the gut microbiota of SD patients that are associated with clinical evidence of gastrointestinal disease. Genetic analysis of skin samples revealed that several bacteria-related proteins were similar among samples, regardless of disease type or severity. In contrast, some proteins were more or less abundant compared to healthy controls, suggesting that the skin microbiome in SD patients may be changed.

Although several studies have shown that the gut microbiota of SD patients is abnormal compared to that of normal people, it remains unclear whether the changes in the gut microbiota are results of disease or initiating causes (10).

Current treatments to dispose of this disorder are limited. Therapeutic trials are also needed to investigate whether dietary interventions or fecal transplantation can restore the gut microbial balance and improve health outcomes in SD. The reduction in Th17 cell levels suggests and immunomodulatory effect of probiotics on SD (12).

This knowledge will allow design in the future potential new therapeutics against SD. Therapeutic trials are also needed to investigate whether dietary interventions or fecal transplantation can restore the gut microbial balance and improve health outcomes in SD. The team is continuing to study the role of the microbiome in SD in order to understand if the alterations observed are a cause or consequence of the disease.

Conclusion

Emerging evidence suggests that alterations in gut microbiota exist in the SD disease state; however, future basic and clinical studies are needed to ascertain the mechanism by which these alterations perpetuate inflammation and fibrosis in SD. Deregulation of the microorganisms that naturally populate the skin is associated with increased inflammation and disease duration in patients with SD. Microbiome dysbiosis is associated with disease duration and increased inflammatory gene expression, and suggests a potential link between the skin microbiome and immune activation. Interventional studies aimed at addressing/correcting these perturbations, either through dietary modification, pro/pre-biotic supplementation, or fecal transplantation, may lead to improved outcomes for patients with SD. More research is needed to further characterize the

gastrointestinal microbiota in SD and understand how microbiota perturbations can affect inflammation, fibrosis, and clinical outcomes.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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