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Small Intestinal Bacterial Overgrowth in Patients Suffering From Scleroderma: Clinical Effectiveness of Its Eradication

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OBJECTIVES: After the skin, the gastrointestinal tract is the second most common target of systemic sclerosis (SSc).

AIM: Our aims were to investigate orocecal transit time (OCTT) and the presence of small intestinal bacterial overgrowth (SIBO) in SSc as a cause of intestinal symptoms.

METHODS: Fifty-five SSc patients and 60 healthy controls, sex and age matched, entered the study. Enrolled subjects completed a questionnaire for intestinal symptoms and a global symptomatic score (GSS) was calculated. OCTT and the presence of SIBO were assessed by a lactulose breath test (LBT). Patients with SIBO were treated with rifaximin 1,200 mg/day for 10 days. Finally, a second questionnaire and LBT were performed 1 month after the end of therapy.

RESULTS: The prevalence of SIBO was higher in SSc patients compared with controls (30/54 *vs* 4/60, respectively, $P < 0.001$). OCTT was significantly slower in SSc patients compared with controls (150 min, 25–75th percentile 142.5–165 *vs* 105 min, 25–75th percentile 90–135, respectively, $P < 0.001$). In patients with SIBO, the median GSS score was 8 (25–75th percentile 3.25–10.75). Eradication of SIBO was achieved in 73.3% of patients, with a significant reduction of symptoms in 72.7% of them (GSS score 2, 25–75th percentile 1–3, $P < 0.05$).

CONCLUSIONS: These data suggest that SIBO occurs more frequently in SSc patients than in controls. Intestinal symptoms in these patients may be related to this syndrome and its eradication seems useful to improve clinical features. OCTT is significantly delayed in SSc patients, suggesting an impairment of intestinal motility, a further risk factor for the development of SIBO.

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INTRODUCTION

Systemic sclerosis (SSc) is a clinically heterogeneous and generalized disease, characterized by increasing thickness of the connective tissue of the skin and internal organs such as the gastrointestinal tract, lungs, kidneys, and heart (1, 2). The pathophysiology of SSc is based on disturbances of the immune system, alterations of the microvasculature, and massive deposition of collagen and other extracellular matrix proteins in the connective tissues (3, 4). Gastrointestinal manifestations of SSc are frequent (70–95%) (5) and greatly decrease the quality of life of these patients (6, 7).

Following the esophagus, the small intestine is the most common gastrointestinal target involved in SSc: pseudo-obstruction, malabsorption, and pneumatosis cystoides intestinalis are the most relevant clinical manifestations (8). Moreover, SSc patients may suffer from small bowel dysmotility detected by duodenal manometry, which was able to demonstrate a decrease in duodenal contraction amplitude and frequency in these patients (8–10).

The pathogenesis of these alterations has been related primarily to a neurogenic degeneration and then to a smooth muscle dysfunction due to atrophy and fibrosis of connective tissue. Moreover, functional antibodies, specifically inhibiting M_3-muscarinic receptor-mediated enteric cholinergic neurotransmission, may provide a pathogenic mechanism for the gastrointestinal dysfunction seen in patients with scleroderma (11, 12).

Frequently, the impairment of small bowel motility results in intestinal symptoms such as nausea, vomiting, bloating, distension, anorexia, abdominal pain, or even an overt malabsorption syndrome (8, 10).

* A.P. and M.S. contributed equally to this work.

Malabsorption may be caused by small intestinal bacterial overgrowth (SIBO) in up to 50% of SSc patients, because of intestinal stasis and also of intestinal diverticula or sacculation (8, 10). SIBO is defined as an unexpected microbial concentration ($>10^5$ CFU /mL) in the jejunal aspirate culture and is caused by numerous predisposing diseases, including the reduction of gastric acid secretion, intestinal motor and anatomic abnormalities, and immune function impairment (13–15). Although the gold standard analysis for the diagnosis of SIBO is the jejunal aspirate culture, this is a complex and invasive technique for routine use. In clinical practice, glucose and lactulose H_2/CH_4 breath tests (GBT and LBT) represent noninvasive and cheap valid diagnostic tools (16–20). SIBO shows a clinical spectrum varying from a completely asymptomatic status to severe malabsorption syndrome characterized by steatorrhea, multiple nutritional deficiencies, and weight loss (15, 18). In clinical practice, SIBO may determine unspecific intestinal symptoms such as meteorism, abdominal distension, flatulence, abdominal pain, and diarrhea, characterizing a picture similar to irritable bowel syndrome (IBS) (16–18).

Although SIBO has been shown to play a relevant role in favoring the development of malabsorption syndrome in SSc, its influence on the intestinal symptoms of these patients is far from clear, and there are still few data dealing with the outcomes after eradication therapy in an adequate cohort of SSc patients.

AIMS

The aim of this study was to assess the prevalence of SIBO in SSc patients and to evaluate its role in the development of intestinal symptoms and the clinical effectiveness of its eradication.

METHODS

The study was approved by our local ethical committee and each subject gave his/her consent to take part in it.

In this prospective study, we enrolled 55 consecutive patients (50 women, 5 men; mean age 59 ±11) suffering from SSc and referring to our unit of clinical immunology for follow-up visit. Those patients were sent for breath testing for SIBO independently of gastrointestinal complaining. Diagnosis of SSc was based on literature criteria (21–24). Eighteen out of 55 patients were affected by diffuse SSc and the remaining ones by limited SSc (21).

Sixty healthy volunteers, sex and age matched (48 women, 12 men; mean age 51 ± 11), without any gastrointestinal disorder and with negative symptoms as per a questionnaire, were selected as controls.

The severity of disease was assessed by Eustar severity score (25), which ranges from a score of 0 (normal) to a score of 4 (terminal). Patients were subdivided according to this classification, that is, 1 (N = 28), 2 (N = 24), 3 (N = 2), and 4 (no patients).

Patients and controls underwent stool examination, laboratory analyses, and LBT in order to determine the presence of SIBO and to estimate the orocecal transit time (OCTT) (16–20). Moreover, patients completed an interview questionnaire taking into account 11 variables (diarrhea, upper and lower abdominal pain/discomfort, bloating, abdominal tenderness, nausea, emesis, dysuria, tenesmus, fever, general illness), each carrying a score from 0 (no symptoms) to 3 (severe). A global symptomatic score (GSS) (26), calculated as the sum of all symptom scores, was assigned to each patient (maximum score 33). It was aimed at assessing the effect of antibiotic therapy for SIBO on the overall severity of the various symptoms. A 50% decrease in GSS score from baseline after treatment was considered as a significant reduction in symptoms.

Patients positive for SIBO received rifaximin therapy (400 mg t.i.d.) for 10 days, and 1 month after the end of antibiotic treatment, they underwent a second LBT in order to determine eradication of SIBO and completed a second symptom questionnaire.

LBT

All enrolled patients were taking proton pump inhibitors before entering the study. However, none of them was allowed to take antibiotics, probiotics, and antisecretory drugs during the 2 wk before the test. After a 12 h fasting, H_2/CH_4 breath concentration, in parts per million (ppm), was measured by gas chromatography (Quintron MicroLizer^{TM} model DP plus, Milwaukee, WI) in basal conditions and every 15 min for at least 4 h after the administration of an oral loading dose of lactulose (10 g in 120 mL of water). Alveolar air samples were collected in a 750-mL bag equipped with a ”T” having a nozzle and connected to a bag for the collection of air coming from the respiratory dead space (20).

All subjects were studied after an overnight fasting, having been instructed to avoid foods likely to generate hydrogen for the 24 h before the test. The day preceding the examination, all subjects had a preparation diet based on nonseasoned boiled rice and meat cooked on a hot plate or boiled fish; and no gas water. Breath testing started between 08:30 h and 09:30 h, after thorough mouth washing with 40 mL of 1% chlorhexidine solution. Smoking and physical exercise were not allowed for 1 h prior to and throughout the test. The test was considered positive for SIBO if two or more distinct peaks of H_2/CH_4 excretion (>10 ppm compared to the basal value) were present. SIBO eradication was defined as the disappearance of the double-peak profile.

OCTT is defined as the time the lactulose bolus reaches the cecum. We have considered, as OCTT measurement, the beginning of the first peak rising branch in SIBO-negative subjects and the second peak rising branch in SIBO-positive ones (20).

Statistical analysis of data was carried out by SPSS software, version 12 for Windows (SPSS Inc., Chicago, IL). The quantitative variables were expressed as median and interquartile range, and the Mann-Whitney Test was used to

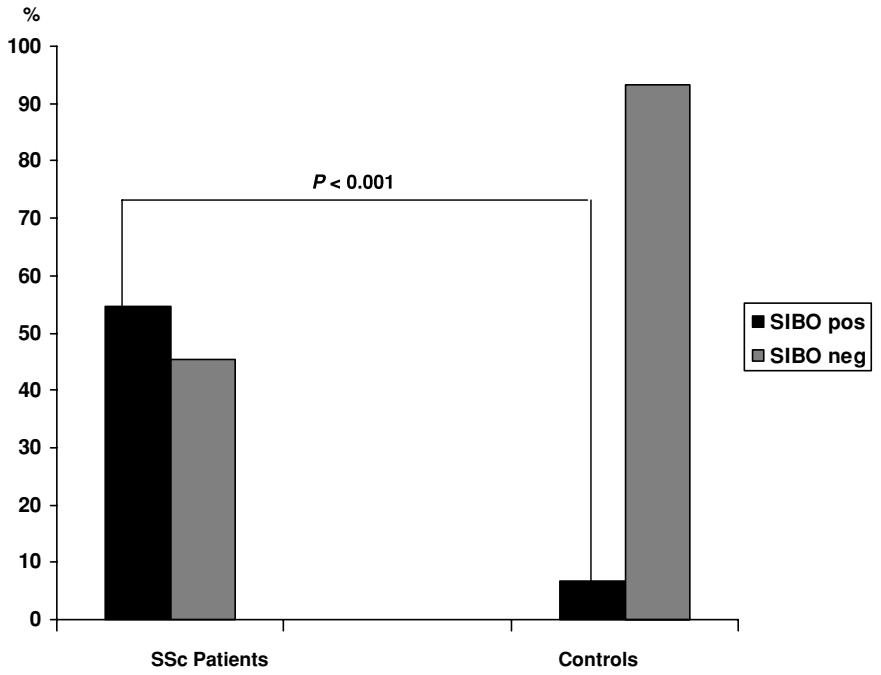

Figure 1. Prevalence of SIBO in SSc patients and controls.

compare data between patients and controls. The χ^2 test was performed to evaluate SIBO prevalence in all studied groups.

RESULTS

Laboratory analyses and stool examinations were normal in all patients and controls. The LBT and antibiotic therapy for SIBO were well tolerated by all patients and no side effects were reported during treatment.

A significantly greater prevalence of SIBO was found in patients with SSc compared to controls (30/55 *vs* 4/60, respectively, $P < 0.001$) (Fig. 1). The prevalence of SIBO was not statistically different among Eustar severity score groups or between diffuse and limited SSc patients.

The OCTT recorded was significantly longer in the SSc patients compared with that for healthy controls (165 min, 25–75th percentile 150–180 and 105 min, 25–75th percentile 90–135, respectively, $P < 0.001$).

SSc patients with SIBO complained more frequently of diarrhea compared to patients without SIBO; however, the prevalence of the other symptoms was not different between the two groups (Fig. 2). The median GSS score was higher in patients positive for SIBO (8, 25–75th percentile 3.25–10.75)

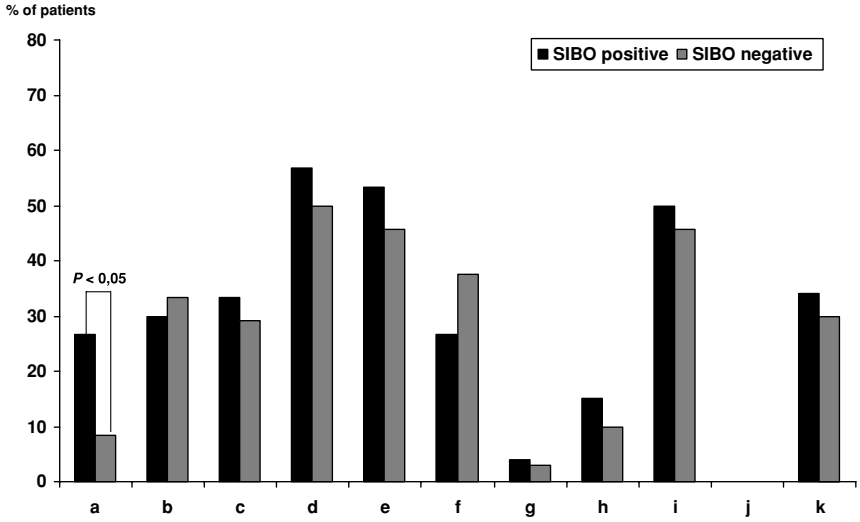

Figure 2. Prevalence of symptoms in SSc patients with and without SIBO. (a) Diarrhea, (b) upper and (c) lower abdominal pain, (d) bloating, (e) abdominal tenderness, (f) nausea, (g) emesis, (h) dysuria, (i) tenesmus, (j) fever, and (k) general illness.

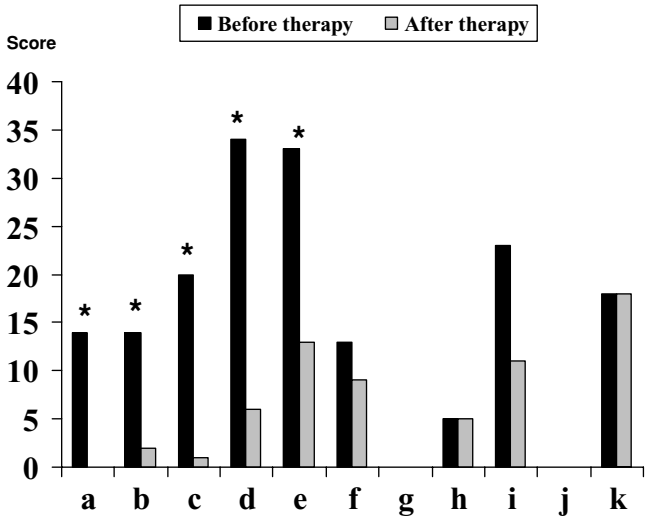

Figure 3. Symptom assessment before and after therapy in eradicated patients. (a) Diarrhea, (b) upper and (c) lower abdominal pain, (d) bloating, (e) abdominal tenderness, (f) nausea, (g) emesis, (h) dysuria, (i) tenesmus, (j) fever, and (k) general illness. Statistical significance (∗) $P < 0.05$ is also shown.

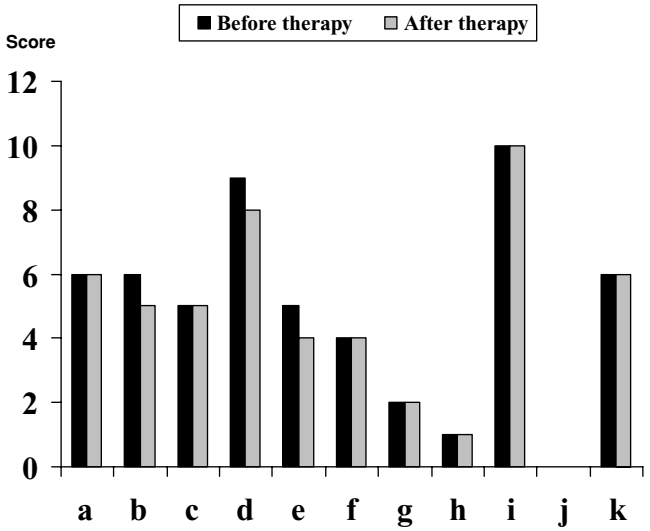

Figure 4. Symptom assessment before and after therapy in not eradicated patients. (a) Diarrhea, (b) upper and (c) lower abdominal pain, (d) bloating, (e) abdominal tenderness, (f) nausea, (g) emesis, (h) dysuria, (i) tenesmus, (j) fever, and (k) general illness.

than in the negative ones (6, 25–75th percentile 3.75–9), without a significant statistical difference.

Eradication of SIBO was achieved in 22/30 patients (73.3%), and this was associated with a significant decrease in the median GSS score from 8 to 2 (25th–75th percentile 1–3, $P < 0.05$), which corresponded to a significant reduction in symptoms in 72.7% of them. SIBO eradication provided a significant improvement in diarrhea, upper and lower abdominal pain/discomfort, bloating, and abdominal tenderness, as shown in Figure 3. Not eradicated patients did not show significant reduction of any single symptom or median GSS score (7, 25–75th percentile 3–8, $P > 0.05$) or both (Fig. 4). The comparison among the median LBT readings over time in SSc patients before and after rifaximin therapy are showed in Figure 5.

Ten out of 55 patients had a prevalent methanogenic flora and, among them, 4 had an LBT positive for SIBO. None of them complained of diarrhea, while two patients (one SIBO-positive) reported constipation. The other clinical features were similar to those of H_2 producer patients.

DISCUSSION

This study underlines the pathogenetic role of SIBO in the development of intestinal symptoms and the clinical effectiveness of its eradication in SSc patients. To the best of our knowledge, this is the first study that demonstrates a delayed OCTT, a greater risk of SIBO, and an associated greater risk of diarrhea and gas-related symptoms, in quite a great and homogeneous series of patients with such a low prevalence of disease. In SSc, the small bowel and colon involvement is less common than the esophageal one (8). The impairment of gastrointestinal motor functions may explain the development in SSc patients of gastroparesis and constipation and even life-threatening complications such as chronic pseudo-obstruction or pneumatosis cystoides intestinalis (27). Also, SIBO and its related malabsorption syndrome are well known complications of severe SSc involving the small bowel (8, 9, 28).

Moreover, manometric and electrophysiological studies brought evidence of a neuropathy of the enteric nervous system in the early stages of the disease, resulting in disturbances of the digestive and interdigestive peristalsis (9, 27).

In this study, we enrolled SSc patients ranging from mild to moderate Eustar severity score. The OCTT was significantly delayed in our patients compared to healthy controls, and this highlights the presence of intestinal motility

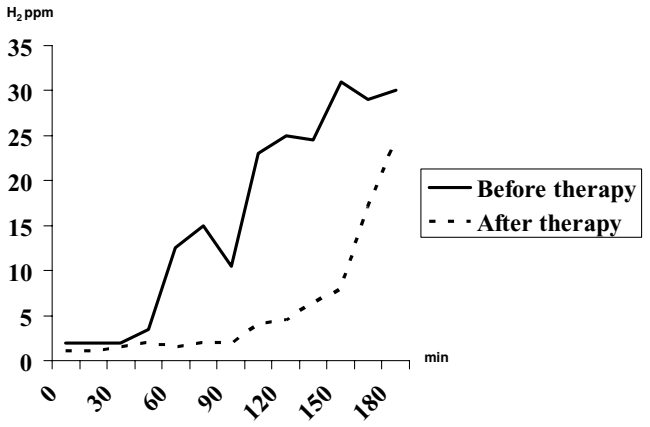

Figure 5. Median H_2 concentration readings before and after therapy in SIBO-positive patients. The disappearance of the double-peak profile demonstrates the efficacy of rifaximin in eradicating SIBO.

disturbances, confirming that in low severity stages of the disease as well, there is an involvement of the gastrointestinal tract.

Moreover, the prevalence of SIBO was significantly higher in SSc patients than in controls. More than 55% of these patients had an LBT positive for SIBO, suggesting that, in these patients, intestinal motility disorders are able to determine impairment of intestinal clearance, which is one of the most important protective mechanisms against the bacterial overgrowth.

Antibiotic therapy with rifaximin was safe and useful to achieve eradication of SIBO in 73.3% of treated SSc patients. Furthermore, antibiotic therapy for SIBO was able to significantly improve intestinal symptoms in eradicated SSc patients compared to not eradicated ones. We obtained a complete resolution of diarrhea in all eradicated patients, and the normalization of LBTs after antibiotic therapy provided a significant improvement in abdominal pain, bloating, and abdominal tenderness compared with subjects who maintained an altered breath test (BT), suggesting that intestinal symptoms in these patients are related to increased gas production in the small bowel. These findings confirm that SIBO may play a significant role in the development of intestinal symptoms in SSc.

Despite a good specificity, LBT has a suboptimal sensitivity in SIBO diagnosis; thus, the real prevalence of SIBO in our patients might have been underestimated. In our opinion, this could explain why all intestinal symptoms but diarrhea were quite comparable between SIBO-positive and SIBO-negative SSc patients. Finally, while diarrhea is a clear SIBO-dependent symptom, abdominal pain and meteorism also could be based on different pathophysiological mechanisms such as the impairment of intestinal motility.

Although in our study SIBO did not cause an overt malabsorption syndrome, these data demonstrate that this condition should be investigated and treated in SSc, independent of its severity stage, in order to improve clinical features and quality of life of these patients.

This study has several limitations. We used a diagnostic tool for SIBO detection, which is associated with lower rates of accuracy than jejunal culture (29, 30). However, upper gut juice culture is invasive and difficult to perform in routine clinical practice. Conversely, LBT is a noninvasive, inexpensive, and well-tolerated technique, which has been shown to assess, with sufficient accuracy, the presence of bacterial contamination in the small intestine, and it is also able to evaluate bowel transit time, although indirectly (16–20). Moreover, we measured both hydrogen and methane in order to improve the sensitivity of BTs in patients presenting methanogenic microflora (31).

These data demonstrate that SIBO occurs more frequently in SSc patients than in normal subjects. Intestinal symptoms in these patients may be related to this syndrome. Therapy with rifaximin is safe and useful for eradication of SIBO and for improvement of clinical features. OCTT is significantly delayed in SSc patients and this suggests impairment of intestinal motility, which represents a risk factor for the development of SIBO.

Our data suggest that SIBO should also be detected and treated in patients with low grade severity SSc, in order to improve the quality of life of these patients, who often complain of frustrating intestinal symptoms, otherwise difficult to diagnose and cure.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Systemic sclerosis (SSc) gastrointestinal manifestations greatly decrease the quality of life of these patients.
- SSc patients complain of frustrating intestinal symptoms otherwise difficult to diagnose and cure.
- There are still few data dealing with small bowel SSc involvement.

What Is New Here

- Small intestinal bacterial overgrowth (SIBO) contributes to intestinal symptoms in SSc patients.
- SIBO eradication provides a significant improvement of intestinal symptoms in SSc patients.
- The lactulose breath test is a valid, cheap, and noninvasive tool useful in SSc management.

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CONFLICT OF INTEREST

Guarantor of the article: Massimo Ghio, M.D., Ph.D.
Specific author contributions: Massimo Ghio and Andrea Parodi designed the study and were involved in discussing and writing the paper; Marta Sessarego, Marco Bazzica, and Alfredo Greco performed clinical evaluations and breath tests; Gilberto Filaci, Maurizio Setti, and Edoardo Savarino performed analysis and/or interpretation of data; Francesco Indiveri and Vincenzo Savarino were involved in the revision of the manuscript and the approval of the final version of the manuscript.
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