Small intestinal bacterial overgrowth in systemic sclerosis

Isabelle Marie¹, Philippe Ducrotte², Philippe Denis³, Jean-François Menard⁴ and Hervé Levesque¹

Objectives. The aims of this study were to: (i) determine the prevalence of small intestinal bacterial overgrowth (SIBO) in unselected patients with SSc; (ii) assess both clinical presentation and outcome of SIBO; and (iii) make predictions about which SSc patients are at risk for SIBO.

Methods. Fifty-one consecutive patients with SSc underwent glucose hydrogen and methane (H₂/CH₄) breath test. All SSc patients also completed a questionnaire for intestinal symptoms, and a global symptomatic score (GSS) was calculated. SSc patients with SIBO were given rotating courses of antibiotics (norfloxacin/metronidazole) for 3 months; glucose H₂/CH₄ breath test was performed at 3-month follow-up.

Results. The prevalence of SIBO was 43.1% in our SSc patients. After logistic regression, we identified the following risk factors for SIBO: presence of diarrhoea and constipation. Interestingly, we observed a marked correlation between values of GSS of digestive symptoms (P < 0.05) and the presence of SIBO (P = 10⁻⁵). Indeed, both sensitivity and specificity of GSS > 5 to predict SIBO were as high as 0.909 and 0.862, respectively. Finally, eradication of SIBO was obtained in 52.4% of the SSc patients with a significant improvement of intestinal symptoms.

Conclusion. Our study underscores that SIBO often occurs in SSc patients. We further suggest that GSS may be systematically performed in the subgroup of SSc patients exhibiting GSS > 5. Patients with SIBO, using glucose hydrogen and methane breath test, in fact, represents a simple, non-invasive and reproducible method to depict SIBO [14, 24–30].

Patients and methods

Patients

From January 2006 to June 2007, 51 consecutive patients with a definite diagnosis of SSc were included in the study. The criteria for the diagnosis of SSc were based on the ACR criteria [31]. Ethical approval was obtained from the local ethical committee (CERNI for the CCP de Haute Normandie), and informed consent was obtained from all patients.

The study cohort consisted of 10 men and 41 women with a median age of 54 (range: 23–82) years; the median duration of the disease, considered to have existed from the onset of the first non-RP clinical manifestations, was 4 (range: 1–37) years. Patients were grouped according to the criteria of Leroy et al. [32]: 25 (49%) patients had dcSSc and 26 (51%) had lcSSc. In these 51 SSc patients, the median Scleroderma Health Assessment Questionnaire (SHAQ) score [33] was 0.2 (range: 0–2.55). No patient with SSc had other CTDs or a history of liver or digestive diseases, diabetes mellitus, gastric surgery or vagotomy. Moreover, no patient received NSAIDs. Eleven SSc patients received immunosuppressive drugs, i.e. low-dose steroid regimen (<10 mg daily) (n = 11), MTX (n = 1), AZA (n = 2) and mycophenolate mofetil (n = 2).

SSc patients had pulmonary involvement as follows: interstitial lung disease (ILD) (n = 20; 39.2%) and pulmonary arterial hypertension (PAH) (n = 6; 11.8%), and 31 SSc patients had digital pitting scars (60.8%).

All patients had undergone oesophageal manometry. Hurwitz’s criteria for the degree of oesophageal involvement on manometry are as follows: normal oesophageal motility (Stage I); uncoordinated peristalsis with normal pressure wave amplitude (Stage II); peristalsis with normal low-pressure wave amplitude (Stage III); and both aperistalsis and decreased low-oesophageal sphincter pressure (Stage IV) [5, 6]. According to Hurwitz’s criteria, 28 patients had severe oesophageal motor impairment (Stage IV) and 23 had normal/mild/moderate oesophageal motor impairment (Stages I/II/III). Also, all patients had undergone gastroscopy; gastroscopy revealed the following mucosal damage: oesophagitis (n = 16), Barrett’s oesophagus (n = 3) and watermelon stomach (n = 3).

References

¹Department of Internal Medicine, ²Department of Gastroenterology, ³Department of Digestive Physiology and ⁴Department of Biostatistics, Rouen University Hospital, Rouen Cedex, France.

Submitted 23 March 2009; revised version accepted 30 June 2009.

Correspondence to: Isabelle Marie, Department of Internal Medicine, Rouen University Hospital, 76301 Rouen Cedex, France.

E-mail: isabelle.marie@chu-rouen.fr

© The Author 2009. Published by Oxford University Press on behalf of the British Society for Rheumatology. All rights reserved. For Permissions, please email: journals.permissions@oxfordjournals.org
Digestive symptoms

Before undergoing glucose H$_2$/CH$_4$ breath test, SSc patients were systematically interviewed, using a standardized questionnaire regarding the occurrence of small bowel symptoms, i.e. nausea, vomiting, abdominal pain/discomfort, bloating, diarrhoea, constipation, abdominal tenderness, dysuria, tenesmus, fever, general illness; each symptom carried a score from 0 (no symptoms) to 3 (severe).

A global symptomatic score (GSS), calculated as the sum of all symptom scores, was assigned to each patient (maximum score: 33), as described and validated previously [34, 35]. GSS of digestive symptoms was compared between SSc patients with SIBO and patients without.

Biochemical tests

SSc patients underwent biochemical tests, i.e. serum total protein (grams per decilitre), serum albumin (grams per decilitre), ferritin (micrograms per litre), plasmatic folic acid (nanomoles per litre) and vitamin B12 (picomoles per litre), haemoglobin level (grams per decilitre), ESR (millimetres per first hour). Laboratory findings were compared between SSc patients with SIBO and patients without.

Glucose H$_2$/CH$_4$ breath test

All SSc patients were receiving proton pump inhibitors and prokinetics (domperidone) before entering the study. None of the patients was allowed to take antibiotics, probiotics during the 4 weeks before the test.

Patients were instructed to avoid foods that likely generate hydrogen for the 3 days before the test. The day preceding the examination, all patients had low-carbohydrate meals, i.e. preparation based on non-seasoned boiled rice and meat cooked on a hot place or boiled fish and non-carbonated water. After a 12-h fasting, breath testing started after thorough mouth washing with 40ml of 1% chlorhexidine solution, in order to eliminate oral bacteria.

SSc patients underwent an initial breath test under standard conditions. H$_2$/CH$_4$ excretion was measured using glucose breath test. H$_2$/CH$_4$ breath concentration was expressed in parts per million (p.p.m.); it was measured by gas chromatography (Quintrom Microlizer analyzer model DPplus, Milwaukee, WI, USA) in basal conditions and every 15 min for at least 3 h after the administration of an oral loading dose of glucose (50 g in 250 ml of sterile water). Alveolar air samples were collected and connected to a bag for the collection of air coming from the respiratory dead space [24–26, 28].

For SSc patients, both baseline and peak values for H$_2$/CH$_4$ were recorded and their total excretion of either H$_2$/CH$_4$ was characterized by pulmonary arterial systolic pressure ≥40 mmHg at rest on echocardiography (confirmed by right heart catheterization); (vi) findings of oesophageal manometry according to Hurwitz’s criteria were as follows: (a) patients with severe oesophageal motor impairment (Stage IV) and (b) patients without (Stages I/II/III); and (vii) antibody status.

Outcome of SIBO in SSc patients

SSc patients with SIBO were given antibiotics intermittently (7 days/month) and in rotation, during 3 consecutive months; the used regimens were norfloxacin (400 mg twice daily) and metronidazole (250 mg three times daily).

One month after the end of this 3-month course of rotating antibiotic therapy, these SSc patients with SIBO underwent glucose H$_2$/CH$_4$ breath test in order to determine eradication of SIBO and gastrointestinal symptoms.

After glucose H$_2$/CH$_4$ breath test, in the subgroup of SSc patients with persistent SIBO, this rotating antibiotic regimen was re-instituted for 3 additional months; 1 month after the end of antibiotic therapy, these patients further underwent glucose H$_2$/CH$_4$ breath test in order to determine disappearance of SIBO.

Statistical analysis

For group comparison involving binary data, we used either the chi-square test or Fisher’s exact test, depending on the cells expected to count. Comparisons involving continuous data were performed using the Mann–Whitney U-test. The results were regarded as significant when the P-value was <0.05.

Moreover, we performed logistic regression to identify the predictive factors of SIBO. These results are reported as odds ratio (OR) and 95% CI; the used level of significance was P < 0.05 in all performed tests.

Results

Prevalence of SIBO

Of these 51 unselected patients with SSc, 22 (43.1%) patients were identified who fulfilled the criteria of SIBO.

Intestinal symptoms in SSc patients

SSc patients complained of the following signs: nausea (45.1%), vomiting (23.8%), abdominal pain/discomfort (54.9%), bloating (58.8%), diarrhoea (27.5%), constipation (27.5%), abdominal tenderness (27.5%) and tenesmus (5.9%). In our 51 SSc patients, the median value GSS of the digestive symptoms was 4 (range: 0–21).

Intestinal symptoms were further compared between SSc patients with and without SIBO (Table 1); the prevalence of the following symptoms was more common in patients with SIBO when compared with patients without: abdominal pain/discomfort (86.4% vs 31%), bloating (77.3% vs 44.8%), diarrhoea (50 vs 10.3%),

Comparison of SIBO and other systemic manifestations of SSc

We compared characteristics between two groups of SSc patients: (i) patients with SIBO at SIBO diagnosis; and (ii) patients without SIBO. The following parameters were compared between SSc patients with SIBO and patients without, i.e. (i) median age; (ii) median SSc duration; (iii) SSc subsets; (iv) median score of SHAQ; (v) prevalence of digital pitting scars, ILD and PAH characterized by pulmonary arterial systolic pressure ≥40 mmHg obtained by echocardiography; (vi) clinical symptoms; (vii) laboratory results.

Table 1. Clinical intestinal features of SSc patients with SIBO compared with those without

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>SIBO, n = 22</th>
<th>Absence of SIBO, n = 29</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>54.5</td>
<td>37.9</td>
<td>0.269</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18.2</td>
<td>3.4</td>
<td>0.152</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>86.4</td>
<td>31.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>bloating</td>
<td>77.3</td>
<td>44.8</td>
<td>0.0246</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>50.0</td>
<td>10.3</td>
<td>0.0034</td>
</tr>
<tr>
<td>Constipation</td>
<td>59.1</td>
<td>3.4</td>
<td>0.00001</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>54.5</td>
<td>6.9</td>
<td>0.0027</td>
</tr>
<tr>
<td>Fever</td>
<td>18.2</td>
<td>0.0</td>
<td>0.0292</td>
</tr>
<tr>
<td>Tenesmus</td>
<td>13.6</td>
<td>0.0</td>
<td>0.074</td>
</tr>
<tr>
<td>Global symptomatic score of digestive symptoms, median (range)</td>
<td>8.5 (3–21)</td>
<td>3 (0–10)</td>
<td>10$^{-6}$</td>
</tr>
</tbody>
</table>
constipation (59.1 vs 3.4%) and abdominal tenderness (54.5 vs 6.9%).

Furthermore, the median value GSS of digestive symptoms was significantly higher in SSC patients with SIBO than in those without (8 vs 5; \( P = 10^{-6} \)). We observed a marked correlation between value GSS of digestive symptoms \( \geq 5 \) and the presence of SIBO (\( P = 10^{-6} \)) as illustrated in the receiver operating characteristic (ROC) curve (Fig. 1); both sensitivity and specificity of GSS of digestive symptoms \( \geq 5 \) to predict SIBO were as high as 0.909 and 0.862, respectively. In our population, 19 SSC patients had GSS of digestive symptoms \( \geq 5 \).

**Small bowel motor impairment on manometry**

Among the 22 SSC patients with SIBO, 11 accepted to undergo 24-h ambulatory small bowel manometry, as described previously [7]. Small bowel manometry was abnormal in all 11 SSC patients. During fasting period, small bowel manometry demonstrated abnormalities of Phase III of motor migrating complex (MMC): (i) low duration (\( n = 3 \)), amplitude (\( n = 6 \)) and duodenal velocity (\( n = 4 \)); (ii) no spontaneous Phase III MMC (\( n = 4 \)); and (iii) bursts of uncoordinated hypercontractility (\( n = 2 \)).

The postprandial intestinal motility index was abnormal in 10 patients, because of duodenal and jejunal contractions of both decreased amplitude and frequency.

**Predictive factors of SIBO**

**General clinical data.** As illustrated in Table 2, there were significant differences between patients with and without SIBO with respect to median age (59.5 vs 50 years) and median SSC duration (7.5 vs 2 years). We failed to show any statistically significant difference between subsets of scleroderma for SIBO (\( P = 0.159 \)). However, SIBO tended to occur earlier in dcSSC patients than in lcSSC patients; the median duration of dcSSC was shorter before SIBO onset compared with that of lcSSC (6.5 vs 8.5 years).

The prevalence of the systemic manifestations related to SSC was similar in patients with and without SIBO as follows: digital pitting scars (54.5 vs 65.5%), ILD (31.8 vs 44.8%) and PAH (13.6 vs 10.3%). Severe oesophageal motor disorders (Stage IV) was significantly more frequent in patients with SIBO than in those without (72.7 vs 41.4%) (Table 2); gastric and oesophageal mucosal involvement was also more common in patients with SIBO than in those without (52.4 vs 27.5%). Moreover, median value of SHAQ was significantly higher in patients with SIBO (0.325 vs 0.15).

Finally, immunosuppressive therapy did not differ between SSC patients with and without SIBO for low-dose steroid regimen (18.2 vs 24.1%), MTX (4.5 vs 0%), AZA (4.5 vs 3.4%) and mycophenolate mofetil (0 vs 6.9%).

**Laboratory findings.** As seen in Table 3, high rates of ESR were significantly more numerous in the group of SSC patients with SIBO (24 vs 8 mm/h). Patients with SIBO also had significantly more frequent lower median levels of serum total protein (65.5 vs 69 g/dl), serum albumin (39 vs 42 g/dl) and haemoglobin (12.5 vs 13.9 g/dl).

Autoantibody screen tests were similar in both SSC patients with and without SIBO (Table 3).

After logistic regression, significant risk factors for SIBO were: diarrhoea [OR: 11.043 (95% CI: 1.933, 63.091); \( P = 0.0009 \)] and constipation [OR: 48.537 (95% CI: 4.885, 482.186); \( P = 0.006 \)]. Interestingly, we further observed a marked correlation between GSS of digestive symptoms \( \geq 5 \) and the presence of SIBO (\( P = 10^{-6} \)); as shown in ROC curve (Fig. 1), both sensitivity and specificity of GSS of digestive symptoms \( \geq 5 \) to predict SIBO were as high as 0.82 and 0.86, respectively; predictive positive and negative values of GSS of digestive symptoms \( \geq 5 \) were 0.868 and 0.905, respectively.

**Follow-up of SSC patients with SIBO.** Rotating courses of antibiotic therapy for SIBO were well tolerated by all SSC patients.
and no side effects were reported during therapy. Twenty-one patients underwent systematic glucose H2/CH4 breath test at 3-month follow-up. Eradication of SIBO was achieved in 31.8% of the patients (n = 7/21).

Among the 14 remaining patients with persistent SIBO at glucose H2/CH4 breath test, rotating courses of alternative antibiotic therapy was re-instituted. Glucose H2/CH4 breath test was, once again, performed systematically after 3 months. In essence, we observed that 28.6% of these patients achieved eradication of SIBO (n = 4/14).

At 6-month follow-up, 11 (52.4%) of the 21 SSc patients with SIBO had eradication of SIBO; in these 11 patients, normalization of the glucose H2/CH4 breath test was associated with significant decrease of the GSS of digestive symptoms to 1.5 (range: 0–9), which corresponds to a significant decreased frequency of intestinal symptoms. As shown in Table 4, we found that eradicated SSc patients exhibited less commonly than non-eradicated SSc patients: diarrhoea (P = 0.004), abdominal pain (P = 0.008), bloating (P = 0.03), as well as abdominal tenderness (P = 0.06); in addition, median value of GSS of digestive symptoms was significantly lower in eradicated SSc patients compared with non-eradicated SSc patients (1.5 vs 8; P = 0.001).

### Discussion

SIBO is a severe condition in SSc patients. Nevertheless, previous studies of SIBO are rare and have included a small number of symptomatic SSc patients [16, 19–21, 23]. In a study of 24 SSc patients exhibiting malabsorption, one-third were found to have SIBO (>10^5 CFU/ml) in jejunal fluid [21]. In other symptomatic patients with advanced SSc, SIBO has been reported in 30–62% of the cases [16, 18–20, 23]. In another series, SSc patients were found to have SIBO, using lactulose breath test, in 55.5% of the cases [35].

Our series is, to the best of our knowledge, the first to evaluate SSc patients who were not selected according to their clinical digestive presentation. In this instance, we observed a high frequency (43.1%) of SIBO. We considered a sample of 51 consecutive SSc patients without any prior selection based on clinical presentation, which tends to be representative of the entire SSc population. Our findings underscore that SIBO is prevalent in the whole population of SSc patients.

Our series is, to the best of our knowledge, the first to evaluate SSc patients who were not selected according to their clinical digestive presentation. In this instance, we observed a high frequency (43.1%) of SIBO. We considered a sample of 51 consecutive SSc patients without any prior selection based on clinical presentation, which tends to be representative of the entire SSc population. Our findings underscore that SIBO is prevalent in the whole population of SSc patients.

Moreover, although aspiration and direct culture of jejunal contents are considered by many as the gold standards for SIBO diagnosis, those methods have several limitations such as the potential for contamination by oropharyngeal bacteria during intubation, and the fact that SIBO may be missed by a single aspiration. Overall, the reproducibility of jejunal aspiration and culture has been reported to be 38%. In addition, intubation methods may be regarded as cumbersome and invasive for patients with non-specific symptoms or for those who may require repeated testing. For this reason, a variety of non-invasive diagnostic tests have been devised for SIBO diagnosis in routine clinical practice [36, 37]. Breath tests were used, as they are sensitive, non-invasive and reproducible methods to identify patients with SIBO; the glucose breath test has, in fact, been shown to have a sensitivity of 90% [24–30]. Our data confirm previous authors’ results, as glucose H2/CH4 breath test accurately disclosed SIBO. Nevertheless, glucose breath test has some limitations in patients with SIBO, especially an inability to evaluate SIBO-related antibiotic sensitivity/resistance.

Furthermore, our study underlines the pathogenic role of SIBO in the development of intestinal symptoms in SSc patients. In essence, we have found that SIBO is associated with a greater prevalence of diarrhoea, abdominal pain and gas-related symptoms (bloating and abdominal tenderness).

The second main finding in the present series was that we observed a marked correlation between values of GSS of digestive symptoms ≥ 5 and the presence of SIBO (P = 10^-6). Interestingly, we found that higher values were markedly predictive factors of SIBO, with a sensitivity of 0.90 and a specificity of 0.86; both predictive positive and negative values of global symptomatic score of digestive symptoms ≥ 5 were 0.868 and 0.905, respectively. Our findings therefore indicate that SIBO should be considered in SSc patients exhibiting values of GSS of digestive symptoms ≥ 5; we suggest that GSS of digestive symptoms ≥ 5 should be performed in patients to depict SIBO.

Moreover, in SSc patients with SIBO, it is observed that the overgrowth of the flora competes with the hosts for nutrients, and may cause fat malabsorption [18, 38, 39]. In this instance, we have found that SSc patients with SIBO had lower levels of serum albumin and serum total protein, and both vitamin B12 and ferritin blood levels, which were probably related to underlying SIBO-associated malabsorption. We suggest that biochemical tests (serum total protein and serum albumin, blood ferritin, vitamin B12 and folic acid) may be helpful to detect subclinical SIBO-related malabsorption in SSc patients.

The pathological mechanisms of small intestinal dysmotility in SSc remain unknown. It has been postulated that impairment of the small bowel in SSc may result from progressive histological lesions similar to those found in the skin [7–9, 12, 13], Sjögren [12, 13] has proposed the following steps for the occurrence of sclerodermatous involvement: (i) vascular damage (Grade 0); (ii) neurogenic involvement (Grade 1); and (iii) myogenic involvement (Grade 2) with replacement of normal smooth muscle by collagenous fibrosis and atrophy of muscle fibers within the circular muscle layer. It is possible to classify intestinal motor disorders, as either myogenic (hypomotility) or neurogenic (abnormally propagated phasic contractions and failure of fed pattern response development); the myogenic abnormalities are characterized by low-amplitude intestinal contractions [7, 9, 12, 13].

In the present series, 11 SSc patients with SIBO accepted to undergo 24-h small bowel manometry; for ethical reasons, because small bowel manometry is an invasive test, it was not carried out in the group of non-SIBO patients (who exhibited neither malabsorption nor intestinal pseudo-obstruction). Interestingly, these 11 patients had abnormal small bowel manometry. Indeed, we observed patterns of myogenic dysfunction in 10 (90.9%) of these 11 patients; our findings may explain the onset of SIBO in these later SSc patients with Phase III MMC abnormalities, as disruption of MMC appears to be the main factor leading to SIBO [40, 41]. Moreover, in the intact intestine, SIBO is prevented by the action of gastric acid [40, 41]. There have been previous reports of increased gastric bacterial counts and duodenal bacterial overgrowth in proton pump inhibitor (PPI)-treated patients [19, 38]. In this instance, SSc patients received PPIs to treat severe gastro-oesophageal reflux disease, which may have also contributed to SIBO onset.

From a practical point of view, knowledge of predictive factors of SIBO appears essential in order to improve the management of SSc patients. Kayes et al. [21] have demonstrated that 75% of the

### Table 4. Intestinal features of SSc patients with eradicated SIBO compared with non-eradicated SIBO

<table>
<thead>
<tr>
<th>Clinical parameters, %</th>
<th>Eradicated SSc patients, n = 11</th>
<th>Non-eradicated SSc patients, n = 10</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>9.1</td>
<td>30</td>
<td>0.31</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>20</td>
<td>0.21</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>27.2</td>
<td>90</td>
<td>0.008</td>
</tr>
<tr>
<td>Bloating</td>
<td>18.1</td>
<td>70</td>
<td>0.03</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>60</td>
<td>0.004</td>
</tr>
<tr>
<td>Constipation</td>
<td>45.5</td>
<td>60</td>
<td>0.67</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>9.1</td>
<td>50</td>
<td>0.06</td>
</tr>
<tr>
<td>Global symptomatic score of digestive symptoms, median (range)</td>
<td>1.5 (0–9)</td>
<td>8 (5–23)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
patients with SIBO were in the lcSSc group. Our series reveals that the prevalence of SIBO tended to be higher in patients with lcSSc than in dcSSc, although not significantly so; our findings interestingly underline that the ‘benign’ nature of the lcSSc subset is questionable. On the other hand, our study suggests that SIBO tends to occur earlier in dcSSc compared with lcSSc (6.5 vs 8.5 years). In the present study, we found that none of the SSc systemic manifestations could be considered as predictive factors for SIBO, i.e. pitting scars, PAH and ILD. We have observed that severe oesophageal motor impairment may be considered as a factor associated with SIBO onset; our data suggest that these patients with SIBO had severe motor impairment involving both oesophagus and small intestine; in addition, oesophageal and gastric mucosal involvement was more often found in the group of SSc patients with SIBO.

Optimal therapy for management of SIBO remains unclear in SSc patients [36, 37, 42–44]. Indeed, we failed to find randomized and controlled studies evaluating therapy in SSc patients with SIBO. In SSc patients with SIBO, care should be taken to avoid drugs that interfere with gut motility (e.g. anti-cholinergics). Empiric courses with repeated rotating courses of antibiotics are still the standard approach along with dietary measures and vitamin supplements [17, 36, 37]. Antibiotics have been proven to be effective in non-SSc patients with SIBO [36, 37, 42]: amoxicillin-clavulanic acid (500 mg 3 times/day), ciprofloxacin (250 mg 2 times/day), norfloxacin (400 mg 2 times/day), metronidazole (250 mg 3 times/day), neomycin (500 mg. 4 times/day), trimethoprim–sulfamethoxazole (one double-strength tablet, 250 mg 2 times/day), rifampicin (1200 mg 2 times/day) [17]. There are no trials regarding the efficacy of these antibiotic regimens in SSc. In our study, SSc patients with SIBO were given antibiotics intermittently (7 days/month), and in rotation; the used regimens were metronidazole (250 mg 3 times/day) and norfloxacin (400 mg 2 times/day). We used such rotating antibiotic regimens to prevent the development of resistance [17, 36, 37, 40, 41]. With such an antibiotic regimen, at 3- and 6-month follow-up, glucose breath test was found negative in 31.8 and 52.4% of the SSc patients, respectively. In these eradicated SSc patients, antibiotic therapy for SIBO was able to improve intestinal symptoms in SSc patients, respectively. In these eradicated SSc patients, antibiotic therapy for SIBO was able to improve intestinal symptoms in SSc patients, respectively. In these eradicated SSc patients, antibiotic therapy for SIBO was able to improve intestinal symptoms in SSc patients, respectively.