Probiotics for the treatment of systemic sclerosis-associated gastrointestinal bloating/distention

T.M. Frech¹, D. Khanna², P. Maranian², E.J. Frech³, A.D. Sawitzke¹, M.A. Murtaugh⁴

Objective. Treatment for gastrointestinal tract (GIT) disease in systemic sclerosis (SSc) is challenging as no immunosuppressive or anti-fibrotic therapy is available with clearly proven efficacy. Probiotics are viable, non-pathogenic microorganisms that are hypothesized to improve the composition of the intestinal microbiota from a potentially harmful composition to a composition that is beneficial to the host. Our hypothesis is that GIT symptoms in SSc patients with moderate bloating would improve with probiotic implementation.

Methods. Ten patients with a moderate-to-severe distention/bloating score (1.25–3.00) on the University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 (UCLA SCTC GIT 2.0), but otherwise stable organ disease not requiring any medication adjustment were recruited from the University of Utah Scleroderma Center. We compared the GIT 2.0 scores at baseline and after 2 months of use of Align (bifidobacterium infantis; 10⁹ CFU per capsule) or Culturelle (lactobacillus GG; 10⁹ CFU per capsule) using paired t-test and calculated effect size (ES).

Results. Significant improvement in total GIT 2.0 score (ES = 0.82), reflux (ES = 0.33), bloating/distention (ES = 1.76), and emotional scales (ES = 0.18) were reported after two months of daily probiotic use.

Conclusions. This pilot study suggests probiotics significantly improve the reflux, distention/bloating, and total GIT scales in SSc patients. As hypothesized, the largest effect was seen in distention/bloating scale. Probiotics may be useful for treatment of SSc-associated distention/bloating.

Introduction
The pathogenesis of systemic sclerosis (SSc) is thought to involve an appropriate genetic background, vascular injury and hypoxia, and excessive deposition of extracellular matrix proteins in skin, lungs, and other organs (1). Although there are several disease subsets, gastrointestinal tract (GIT) involvement occurs in approximately 90% of patients with SSc, and is characterised by varying degrees of inflammation, vascular damage, and fibrosis in both the upper and lower GIT (2). Major morbidity including profound motility issues possibly due to ischaemic neuropathy can result from this GIT involvement. Unfortunately, treatment for SSc is challenging and no immunosuppressive or anti-fibrotic therapy is currently effective for treatment of GIT disease. As such, for GIT disease a focus on symptomatic relief, with anti-reflux measures, rotating antibiotics, and pro-kinetics, is the standard of care (3).

Probiotics are viable, non-pathogenic microorganisms (bacteria or yeast) that are able to reach the intestines in sufficient numbers to confer benefit to the host (4). There is no consensus about the minimum number of microorganisms that must be ingested to obtain a beneficial effect, however, probiotics are generally regarded as safe, and have virtually no distinguishing characteristics from commensal organisms, which encompasses 400 to 500 different microbial species (5). To protect itself from uncontrolled inflammatory responses, the epithelium has developed mechanisms to limit direct contact with bacteria, restrain bacterial growth, and prevent bacterial dissemination into underlying tissue (6). Disruption of this barrier can lead to loss of immune tolerance to the microbiota and an inappropriate inflammatory response. Of interest, the microbiota instuct immune cells, guides their proper assembly, and contributes to the proper functioning of immunologic inductive sites (7). Probiotic species can confer

Competing interests: Dr D. Khanna developed the UCLA SCTC GIT instrument; the other co-authors have declared no competing interests.
The possible role of altered colonic microflora in the pathogenesis of GIT symptoms in SSc led us to exploration of probiotic therapy for symptomatic bloating in SSc. The hypothesis of probiotic use is to change the intestinal microbial milieu – improve the composition of the intestinal microbiota from a potentially harmful composition to a composition that is beneficial to the host. Furthermore, the ability of GIT microflora to modulate the immune system of both local and systemic levels makes their use in SSc of interest.

The University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 (GIT 2.0) is a validated, patient-reported tool to monitor GIT symptoms in SSc patients with at least moderate bloating/distention before and following the implementation of probiotics. Based on previous experience with other diseases where probiotics improved symptoms of distention/bloating, our hypothesis was that GIT symptoms in SSc patients with at least moderate bloating would improve with probiotic implementation.

**Patients and methods**

**Methods**

Patients were recruited from the University of Utah Scleroderma Clinic and consented during their routine clinic visit (IRB number 00038705). Inclusion criteria include adult patients (≥18 years) with a diagnosis of SSc (14). Ten patients with a moderate-to-severe distention/bloating score (1.25-3.00), but otherwise stable organ disease not requiring any medication adjustment, such as change in calcium channel blocker dose, immunosuppression, initiation of a prokinetic or antibiotic, or any other clinical intervention were offered either Align (bifidobacterium infantis; 10⁶ CFU per capsule) or Culturelle (lactobacillus GG; 10⁶ CFU per capsule) taken once a day. All patients completed a GIT 2.0 at baseline. This tool is available online at [http://uclasceroderma.researchcore.org](http://uclasceroderma.researchcore.org). After two months of probiotic initiation, GIT 2.0 was re-administered.

**Statistical analysis**

We compared GIT 2.0 scores at baseline and after two months of probiotic use using paired t-test and calculated effect size. Effect size (ES) is the ratio of observed change to a measure of variance (also known as signal to noise) and was chosen as it considered good practice when presenting empirical research findings (14, 15). For ES, the numerator is the mean change in GIT 2.0 to monitor GIT symptoms in SSc patients with at least moderate bloating/distention before and following the implementation of probiotics. Based on previous experience with other diseases where probiotics improved symptoms of distention/bloating, our hypothesis was that GIT symptoms in SSc patients with at least moderate bloating would improve with probiotic implementation.

**Results**

The majority of the participants in this study (9 of 10) were female and 8 had...
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Table II. Baseline and follow-up scores and the effect size of probiotic use on UCLA SCTC GIT 2.0 scores.

<table>
<thead>
<tr>
<th>GIT scales</th>
<th>Before Probiotic therapy</th>
<th>After 2 months of Probiotic therapy</th>
<th>Effect Size</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD (range)</td>
<td>Mean ± SD (range)</td>
<td></td>
</tr>
<tr>
<td>Total GIT score (0.0–3.0)</td>
<td>0.73 ± 0.35 (0.23–1.23)</td>
<td>0.43 ± 0.29** (0.11–0.93)</td>
<td>0.82</td>
</tr>
<tr>
<td>Reflux (0.0–3.0)</td>
<td>0.74 ± 0.56 (0.38–1.80)</td>
<td>0.64 ± 0.48* (0.00–1.5)</td>
<td>0.18</td>
</tr>
<tr>
<td>Bloating/distention (0.0–3.0)</td>
<td>2.15 ± 0.67 (1.25–3.00)</td>
<td>0.97 ± 0.77** (0.00–1.75)</td>
<td>1.76</td>
</tr>
<tr>
<td>Faecal soilage (0.0–3.0)</td>
<td>0.20 ± 0.42 (0.00–1.00)</td>
<td>0.10 ± 0.32 (0.00–1.00)</td>
<td>0.24</td>
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<tr>
<td>Diarrhoea (0.0–2.0)</td>
<td>0.20 ± 0.42 (0.00–1.00)</td>
<td>0.35 ± 0.53 (0.00–1.50)</td>
<td>0.36</td>
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<tr>
<td>Constipation (0.0–2.5)</td>
<td>0.72 ± 0.89 (0.00–2.00)</td>
<td>0.42 ± 0.55 (0.00–1.25)</td>
<td>0.34</td>
</tr>
<tr>
<td>Social (0.0–3.0)</td>
<td>0.30 ± 0.41 (0.00–0.83)</td>
<td>0.22 ± 0.42 (0.00–1.00)</td>
<td>0.20</td>
</tr>
<tr>
<td>Emotional (0.0–3.0)</td>
<td>0.59 ± 0.87 (0.00–2.110)</td>
<td>0.30 ± 0.57* (0.00–1.78)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*p<0.05  **p<0.01; Effect sizes interpretation: 0.20–0.49 as small, 0.50–0.79 as moderate and >0.80 as large.

limited cutaneous SSc subtype (ISSc). Mean disease duration was 7.1 years (range 2 to 18 years) defined by first non-Raynaud’s symptom. The mean modified Rodnan skin score (mRSS) was 9 (range 4–23). All patients were on anti-reflux therapy, 3 were on promotility agents, and 6 were on anti-depressants (Table I). No patients had a formal lactulose breath tests or jejunal culture or were on antibiotics for small intestinal bacterial overgrowth syndrome (SIBO). For skin, joint, or lung disease, 7 of these patients were on an immunosuppressant therapy. All patients were on a stable dose of a vasodilator for Raynaud phenomenon and/or pulmonary arterial hypertension. Baseline total GIT 2.0 scores ranged from 0.23 to 1.23 (Table II). Total and individual symptom scores reflect a range of GI symptom severity. All participants reported some degree of reflux and moderate-to-severe bloating/distention symptoms. At baseline, faecal soilage and diarrhoea were reported by two individuals; half of the participants reported constipation and social or emotional impact of GIT symptoms. Statistically significant improvement in total GIT score, and reflux, bloating/distention, and emotional scales were reported after two months of daily probiotic use (Table II). The largest improvement in symptoms was reported for bloating/distention (ES=1.76). Emotional and reflux scores had small effect sizes (ES=0.33 and 0.18, respectively).

Discussion

This study suggests that probiotics may have a role for treating symptoms of bloating and distention in SSc. Bloating is frequently described in SSc patients and can be a multi-factorial symptom that has a role for treating symptoms of distention, and emotional scales were generalised to a different clinic sample. Nonetheless, this pilot study suggests that probiotics significantly improve the reflux, distention/bloating, and total GIT scales in SSc patients and suggests that the study should be redone in a true control trial fashion. As hypothesized, the largest effect was seen in distention/bloating scale (effect size 1.76).

References


