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

T.M. Frech[1], D. Khanna[2], P. Maranian[2], E.J. Frech[3], A.D. Sawitzke[1], M.A. Murtaugh[4]

[1]Division of Rheumatology, [4]Division of Epidemiology, Department of Internal Medicine, University of Utah, Salt Lake City, UT, USA;
[2]Division of Rheumatology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA;
[3]Mountain West Gastroenterology, Salt Lake City, UT, USA.

Tracy M. Frech, MD, MS
Dinesh Khanna, MD, MS
Paul Maranian, MS
Edward J. Frech, MD
Allen D. Sawitzke, MD
Maureen A. Murtaugh, PhD, RD

Please address correspondence and reprint requests to:
Tracy Frech, MD, MS,
4B200 SOM, 30 N 1900 E,
Salt Lake City, UT 84132, USA.
E-mail: tracy.frech@hsc.utah.edu

Received on January 7, 2011; accepted in revised form on March 9, 2011.

Clin Exp Rheumatol 2011; 29 (Suppl. 65): S22-S25.

Key words: Systemic sclerosis, gastrointestinal involvement, UCLA SCTC GIT 2.0, bloating/distention, probiotics

Competing interests: Dr D. Khanna developed the UCLA SCTC GIT instrument; the other co-authors have declared no competing interests.

ABSTRACT

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, nonpathogenic 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; 10^9 CFU per capsule) or Culturelle (lactobacillus GG; 10^9 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, nonpathogenic 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 instruct immune cells, guides their proper assembly, and contributes to the proper functioning of immunologic inductive sites (7). Probiotic species can confer

benefit to the host by suppressing the release of pro-inflammatory cytokines by T cells (8). Higher counts of certain intestinal microbiota correlate to markers of inflammation and vascular disease (9). The potential role of the intestinal microflora in modulating immune responses has led to an interest in using probiotics as preventive and therapeutic interventions in other inflammatory conditions, such as rheumatoid arthritis (10). Additionally, probiotics have been suggested to decrease bloating and distention in irritable bowel syndrome (IBS), in which abnormal gastrointestinal motor functions, visceral hypersensitivity, intra-luminal changes, psychosocial factors, and mucosal immune activation, are thought to be modulated (11).

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 microbiota 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 outcome measure to assess health related quality of life (HRQOL) and GIT severity in SSc (12, 13). This 34-item instrument has seven scales: reflux, distention/bloating, diarrhoea, faecal soilage, constipation, emotional well-being, and social functioning and a total GI score. All scales are scored from 0.0 (better HRQOL) to 3.0 (worse HRQOL) except diarrhoea and constipation scales that ranges from 0.0-2.0 and 0.0–2.5, respectively. The total GI score is the average of 6 of 7 scales (excludes constipation) and total GI score are scored from 0.0 (better HRQOL) to 3.0 (worse HRQOL). Each scale is further divided into 3 groups by severity – none-to-mild, moderate, and severe-to-very severe.

Herein we describe the use of the 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.

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; 10^9 CFU per capsule) or Culturelle (lactobacillus GG; 10^9 CFU per capsule) taken once a day. All patients completed a GIT 2.0 at baseline. This tool is available online at http://uclascleroderma.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 the UCLA SCTC GIT 2.0 scales from baseline to 2 months and the denominator is the standard deviation of scales at baseline. ES were interpreted as follows: 0.20–0.49 as small, 0.50–0.79 as moderate and >0.80 as large. All analyses were performed using STATA 10.2.

Results

The majority of the participants in this study (9 of 10) were female and 8 had

Table I. Participant characteristics.

Patient no.	1	2	3	4	5	6	7	8	9	10
Age	72	62	35	63	24	65	50	39	64	43
Gender	F	F	F	F	M	F	F	F	F	F
mRSS	8	6	23	12	6	8	4	8	9	6
Disease duration (years)	6	7	3	12	5	18	11	4	3	2
PPI	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pro-motility therapy: Domperidone	No	No	Yes	No	No	No	Yes	No	Yes	No
Anti-depressant: SSRI	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Vasodilator: CaCB and/or phosphodiesterase inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Immunosuppression: Cyclosphosphamide, Mycophenolate Mofetil, or Methotrexate	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No

F: female; M: male; mRSS: modified Rodnan skin score; PPI: proton pump inhibitor; SSRI: selective serotonin uptake inhibitor; CaCB: calcium channel blocker.

Table II. Baseline and follow-up scores and the effect size of probiotic use on UCLA SCTC GIT 2.0 scores.

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

*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 (lSSc). 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 pro-motility 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's 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 of upper or lower GIT dysfunction. Immune modulation and anti-inflammatory effect also may result from probiotic use (10). As such, probiotics for bloating in SSc, where concurrent reflux, SIBO, and/or constipation may be present concurrently, is a rational intervention.

The 10 SSc patients reported in this study did not have any complications with probiotic use, although one patient developed diarrhoea. It is important to highlight that although probiotics appear to be generally safe in an outpatient setting, the situation may be different in immunocompromised, hospitalised patients who may be at a greater risk of developing probiotic sepsis (16).

Our study is limited in that is a descriptive report conducted on a relatively short time period (two months of therapy), in a low number of patients. The design precludes disease subsetting, treatment subsetting (presence or absence of prokinetic or immunosuppression), or description of probiotic type superiority. It is important to highlight that probiotics are available in a variety of formulations, are not currently regulated, and only few randomised controlled trials exist investigating their efficacy in different GIT disorders. Additionally, we were trying to identify a subset of patients for use of probiotics, thus patients were pre-selected for moderate-to-severe bloating scores. Thus, probiotics effect on GIT 2.0 scores when other interventions are made (such as initiation of GERD therapy or prokinetics) cannot be determined from this study. Also, we did not determine the cause of bloating/ distention that can range from gastroparesis, SIBO, coexisting irritable bowel syndrome, or adverse effects of medications. Third, the GIT 2.0 is not measured against radiologic tests such as endoscopy, esophageal manometry, and breath testing since it is designed to minimise expensive diagnostic procedures. Fourth, the effect size is influenced by the variability in the specific sample and cannot be generalised to a different clinic sample. Nonetheless, this pilot study suggests 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

1. HUNZELMANN N, KRIEG T: Scleroderma: From pathophysiology to novel therapeutic approaches. *Exp Dermatol* 2010; 19: 393-400.
2. LOCK G, HOLSTEGE A, LANG B, SCHOLMERICH J: Gastrointestinal manifestations of progressive systemic sclerosis. *Am J Gastroenterol* 1997; 92: 763-71.
3. KHANNA D, DENTON CP: Evidence-based management of rapidly progressing systemic sclerosis. *Best Pract Res Clin Rheumatol* 2010; 24: 387-400.

4. BOIRIVANT M, STROBER W: The mechanism of action of probiotics. *Curr Opin Gastroenterol* 2007; 23: 679-92.
5. LAKHAN SE, KIRCHGESSNER A: Gut inflammation in chronic fatigue syndrome. *Nutr Metab* (Lond) 2010; 7: 79.
6. OHLAND CL, MACNAUGHTON WK: Probiotic bacteria and intestinal epithelial barrier function. *Am J Physiol Gastrointest Liver Physiol* 298: G807-19.
7. GARRETT WS, GORDON JI, GLIMCHER LH: Homeostasis and inflammation in the intestine. *Cell* 2010; 140: 859-70.
8. SUTAS Y, HURME M, ISOLAURI E: Down-regulation of anti-cd3 antibody-induced il-4 production by bovine caseins hydrolysed with lactobacillus gg-derived enzymes. *Scand J Immunol* 1996; 43: 687-9.
9. MIKELSAAR M, STSEPETOVA J, HUTT P *et al*.: Intestinal lactobacillus sp. Is associated with some cellular and metabolic characteristics of blood in elderly people. *Anaerobe* 2010; 16: 240-6.
10. MANDEL DR, EICHAS K, HOLMES J: Bacillus coagulans: A viable adjunct therapy for relieving symptoms of rheumatoid arthritis according to a randomized, controlled trial. *BMC Complement Altern Med* 2010; 10: 1.
11. DROUAULT-HOLOWACZ S, BIEUVELET S, BURCKEL A, CAZAUBIEL M, DRAY X, MARTEAU P: A double blind randomized controlled trial of a probiotic combination in 100 patients with irritable bowel syndrome. *Gastroenterol Clin Biol* 2008; 32: 147-52.
12. KHANNA D, HAYS RD, MARANIAN P *et al*.: Reliability and validity of the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. *Arthritis Rheum* 2009; 61: 1257-63.
13. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the american rheumatism association diagnostic and therapeutic criteria committee. *Arthritis Rheum* 1980; 23: 581-90.
14. HAYES, RD: Reliability and validity (including responsiveness). *In*: FAYERS P HR (Ed.) Assessing quality of life in clinical trials. New York: Oxford, 2005: pp. 25-39.
15. VERNA EC, LUCAK S: Use of probiotics in gastrointestinal disorders: What to recommend? *Therap Adv Gastroenterol* 2010; 3: 307-19.