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Systematic Review and Meta-analysis

Small Intestinal Bacterial Overgrowth Complicating Gastrointestinal Manifestations of Systemic Sclerosis: A Systematic Review and Meta-analysis

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Background/Aims
Systemic sclerosis (SSc) often is complicated by small intestinal bacterial overgrowth (SIBO). A systematic review and meta-analysis thus examined the prevalence of SIBO in SSc (SSc-subtypes), identify risk factors for SIBO in SSc and the effects of concomitant SIBO on gastrointestinal symptoms in SSc.

Methods
We searched electronic databases until January-2022 for studies providing prevalence rates of SIBO in SSc. The prevalence rates, odds ratio (OR) and 95% confidence intervals (CI) of SIBO in SSc and controls were calculated.

Results
The final dataset comprised 28 studies with 1112 SSc-patients and 335 controls. SIBO prevalence in SSc-patients was 39.9% (95% CI, 33.1-47.1; $P = 0.006$), with considerable heterogeneity, ($I^2 = 76.00\%$, $P < 0.001$). As compared to controls, there was a 10-fold increased SIBO prevalence in SSc-patients (OR, 9.6; 95% CI, 5.6-16.5; $P < 0.001$). The prevalence of SIBO was not different in limited cutaneous SSc as compared to diffuse cutaneous SSc (OR, 1.01; 95% CI, 0.46-2.20; $P = 0.978$). Diarrhea (OR, 5.9; 95% CI, 2.9-16.0; $P = 0.001$) and the association between SIBO in SSc and proton pump inhibitor use (OR, 2.3; 95% CI, 0.8-6.4; $P = 0.105$) failed statistical significance. Rifaximin was significantly more effective as compared to rotating antibiotic in eradicating SIBO in SSc-patients (77.8% [95% CI, 64.4-87.9]) vs 44.8% [95% CI, 31.7-58.4]; $P < 0.05$).

Conclusions
There is a 10-fold increased prevalence of SIBO in SSc, with similar SIBO prevalence rates in SSc-subtypes. Antimicrobial therapy of SIBO-positive SSc-patients with diarrhea should be considered. However, the results must be interpreted with caution due to substantial unexplained heterogeneity in the prevalence studies, and the low sensitivity and specificity of the diagnostic tests suggesting that the reliability of the evidence may be low.
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Key Words
Bacterial overgrowth; Breath tests; Limited scleroderma; Prevalence; Small intestinal bacterial overgrowth; Systemic sclerosis

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Introduction

The autoimmune disease systemic sclerosis (SSc) affects multiple organ systems, including the pulmonary, cardiac, renal and gastrointestinal (GI) systems and is characterized by abnormalities of the microvasculature with increased deposition of matrix proteins and collagen into the connective tissues, with subsequent fibrosis of skin and internal organs.[1] SSc can be categorized into 2 major groups reflecting the extent of skin involvement; those with proximal involvement are addressed as diffuse cutaneous systemic sclerosis (dcSSc), whereas those with skin involvement mainly affecting the distal limbs (elbows or knees), with or without involvement of face and neck, are addressed as limited cutaneous systemic sclerosis (lcSSc).[2]

Most patients with SSc (~90%) develop GI manifestations and may present with a variety of symptoms ranging from dry mouth, dysphagia to fecal incontinence.[3] Most relevant small intestinal manifestations in SSc include small intestinal bacterial overgrowth (SIBO), pseudo-obstruction, malabsorption, and pneumatosis cystoides intestinalis.[4] SIBO is a disorder, associated with a variety of symptoms, when $\geq 10^5$ colony forming units per millilitre (CFU/mL) of bacteria (typically found in the colon) are found in culture of jejunal aspirates. However, concentrations $\geq 10^5$ CFU/mL are mostly seen initial studies investigating SIBO in patients with post-surgical anatomy, eg, stagnant loop syndrome. Healthy adults may have counts between 0 and 10^3 CFU/mL[5,6] and more recently a bacterial concentration of $\geq 10^3$ CFU/mL is considered as the cut off criteria for diagnosing SIBO.[7] Traditionally, culture-based approach is the gold standard for the diagnosis of SIBO.[8] However, besides being invasive, culture-based techniques for diagnosing SIBO have several limitations[6] and are infrequently used in the standard clinical practice. As a consequence, breath tests (BT) have been developed. However, when culture-based methods are used as a standard, which as outlined above are clearly suboptimal tests for diagnosing SIBO, BT show poor sensitivity and limited specificity and have several methodological problems for SIBO diagnosis.[9] All this has questioned their suitability as diagnostic tests in the clinical setting.[10,11] Thus, one of the fundamental problems in diagnosing SIBO is the lack of validated and universally accepted diagnostic tests.

In SSc, intestinal hypomotility caused by the vasculopathy, smooth muscles atrophy, and subsequent fibrosis leading to small bowel stasis causes bacterial colonization and ultimately leading to SIBO. Thus, although SIBO can be considered a complication of SSc, SIBO potentially aggravates the clinical manifestation of SSc. The rates of SIBO prevalence in SSc and SSc-subtypes as well as the role of potential risk modifiers for SIBO such as treatment with proton pump inhibitors (PPI) therapy in the setting of SSc are uncertain.[12] Moreover, the link between SIBO and GI symptoms in SSc is incompletely characterized and the efficacy of antibiotic therapy on elimination of SIBO and symptoms in SSc is poorly defined.

Against this background we performed a systematic review and meta-analysis (SRMA). As a primary endpoint of this systematic review and meta-analysis we aim to (1) determine the prevalence rates of SIBO in patients with SSc (and SSc-subtypes) and controls. The secondary endpoints are to (2) assess the role of diagnostic approach on differences in SIBO prevalence rates comparing various geographic regions, (3) explore the underlying risk modifiers for the occurrence of SIBO in SSc, and (4) analyze response to therapy (antimicrobial and octreotide) in relation to symptoms in SIBO positive patients with SSc.

Methods

Protocol and Registration

This SRMA was conducted in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis" statement (PRISMA).[13,14] Compliant with existing standards the study-protocol for this SRMA has been registered (PROSPERO, CRD42021274206).

Search Strategy

Available electronic databases, (MEDLINE [Ovid], EM-

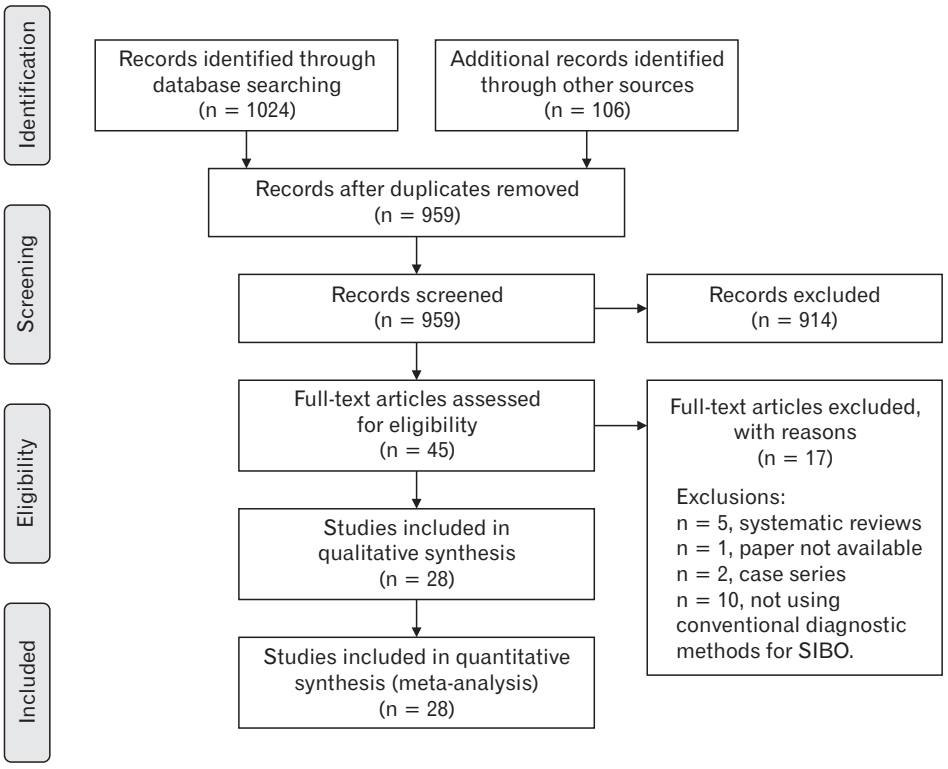

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.

BASE, PUBMED, SCOPUS, Web of Science, and the COCHRANE Library), were searched from initiation (1966) until Jan 2022 for all studies evaluating the link between SIBO and SSc (and/or lcSSc/dcSSc). For the detailed search strategy please see the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram (Fig. 1). With the expert support from our librarian the literature search was conducted. The search strategy utilized for the MEDLINE and EMBASE data bases is depicted (Supplementary Fig. 1A and 1B). For the initial search no restrictions in relation to languages were used. Subsequently, an advanced search step was used to identify "grey" literature with search engines such as Google or Google Scholar, and as a further step "Snowball" method was applied to find relevant articles.

Selection of Studies

Independently titles and abstracts were screened and publications with relevant information in relation to the research question (link between SIBO and SSc and/or lcSSc/dcSSc) were further assessed. Full texts of the relevant articles were subsequently assessed. Case-control studies, prevalence studies recruiting random (unselected) study subjects and controls meeting standardized diagnostic criteria for SSc and SIBO were included. For diagnosis of SSc the diagnostic standards of the updated American College of Rheumatology and the European League Against Rheumatism 2013 criteria or the former ACR 1980 diagnostic criteria[15-18] were used. Studies without original data or including diverse populations of autoimmune disease or mixed connective tissue disorders without detailed extractable information on SSc, or without validated methods for the diagnosis of SIBO in SSc were excluded, as outlined in Supplementary Table 1. Information in relation to antimicrobial and/or PPI therapy were taken from the identified studies. Conference abstracts were also included if the required data were reported. The control group comprised of healthy subjects without symptoms or patients undergoing investigations for chronic or relapsing unexplained GI symptoms (patient controls). Table 1 summarizes eligibility criteria for study inclusion and studies that were not included are shown in Supplementary Table 1. Any disagreements between reviewers were jointly resolved by review of the original publication.

Data Extraction and Quality Assessment

Two authors (V.P. and K.V) extracted independently the data and entered the data into a spreadsheet (Microsoft Excel, 2010 Professional edition; Microsoft Corp, Redmond, Washington, USA). For the purpose of this study, the following information was retrieved: year of publication, name of authors, design of the study,

Table 1. Eligibility Criteria for the Studies Included in Systematic Review and Meta-analysis

Eligibility criteria
• Prevalence or case-control studies, published as full papers in peer reviewed journals or conference abstracts.
• Adults and children with a presumed diagnosis of Systemic sclerosis based on meeting specific diagnostic criteria[a].
• Non SSc control group, referred to as 'controls' included "healthy asymptomatic controls" as well as "patient controls" including subjects undergoing evaluation for unexplained gastrointestinal "syndromes" (eg, dyspepsia, abdominal pain, and diarrhea).
• Studies reporting on efficacy data after antibiotic treatment of SIBO in SSc-patients were also included.
• Clinically validated methods to diagnose SIBO[b].
• Participants not specially selected.

[a]American College of Rheumatology/European League Against Rheumatism criteria[15-18] or formerly known as the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee.
[b]Lactulose breath test, glucose breath test, or jejunal aspirate and culture (or any combination of these).
SSc, systemic sclerosis; SIBO, small intestinal bacterial overgrowth.

geographic region (country), type of controls, diagnostic methods for SIBO including details of tests (substrate used, cutoff values for SIBO diagnosis), age, gender, PPI use, fecal calprotectin (FC), and co-morbidities including prior surgery. Furthermore, the diagnostic criteria for SSc and subtypes, the treatment for SIBO in SSc-patients (antimicrobial compounds or other treatment modalities including octreotide) and response to treatment were recorded. We also captured the prevalence of subjects (both SSc-patients and controls) who had methane positivity on breath test or intestinal methanogen overgrowth.

For the quality assessment of prevalence studies, the Joanna Briggs Institute (JBI) critical appraisal tools[19] was utilized, while the Newcastle-Ottawa scale (NOS)[20] was used to assess the quality of case-control studies, further details in Supplementary Materials and Methods.

Data Analysis

The numbers of patients with SSc and the respective controls in the various cohorts were assessed as the first step. Subsequently, the pooled prevalence of SIBO in SSc (with or without a control group) was calculated. In separate steps, the pooled odds ratio (OR) and the respective 95% confidence intervals (CI) for the prevalence of SIBO in SSc-patients and controls were calculated. Standardized mean difference and 95% CI were used to estimate the difference between GI symptom scores in SSc-patients compared to controls. Other data (eg, total GI symptom score) were also recorded as mean and standard deviation, further details in Supplementary Materials and Methods. Subgroup analyses with stratification of data by diagnostic modalities, geographic region, SSc-subtype (lcSSc/dcSSc), the PPI-use, proportion of subjects with methane-positive SIBO in patients with SSc were performed. Finally, we calculated the proportion of SSc-patients with SIBO, who responded to antibiotic therapy with regards to normalisation of positive breath test and improvement in GI symptoms.

Furthermore, descriptive analysis was used to assess the link between SIBO and SSc utilizing the Comprehensive Meta-Analysis software (version 3.3.070; Biostat Inc, Englewood, NJ, USA). In the results section we also provide the observed (or unweighted) number of positive cases and total tested per study in addition to the weighted pooled estimates of the OR comparing treated with control groups. Subsequently we calculated ORs and pooled prevalence estimates of disease utilizing a random effects model.[21] This is intended to account for between-study variability and are reported such that an OR $>$ 1 favors responses in treated patients. The Supplementary Materials and Methods provide additional details of statistical analysis.

Results

Selection Outcome

Our search of the available literature (detailed in Fig. 1) identified 28 studies suitable for this systematic review and the subsequent meta-analysis. Eleven out of 28 studies[22-32] were case-control studies while 17[33-49] were prevalence studies. The specifics of these studies in relation to methodology for the diagnosis of SIBO and the characteristics of the patient cohorts are provided in Table 2 and Supplementary Tables 2 and 3.

Prevalence of Small Intestinal Bacterial Overgrowth in Systemic Sclerosis

Based upon 28 studies with 1112 SSc-patients the pooled prevalence for SIBO in SSc-patients was 39.9% (95% CI, 33.1-47.1) (Fig. 2). The primary analysis revealed considerable heterogeneity (I^2 = 76.00%, P < 0.001) while funnel plot inspection suggested potential asymmetry (Supplementary Fig. 2) and results of the Eg-

Table 2. Characteristics of the Studies Showing Mode of Diagnosis and Prevalence of Small Intestinal Bacterial Overgrowth in Systemic Sclerosis

No	Author	Study year	Region	Type of study	Patients with SSc (n)	Patients with SSc sub-type (n)		Criteria for SSc	Controls (n)	Type of control	Mode of diagnosis of SIBO	SIBO in SSc (n [%])	SIBO in SSc sub-types (n)		SIBO in controls (n)
						dcSSc	lcSSc						dcSSc	lcSSc	
1	Adarsh et al[48]	2017	India	Prevalence	37	16	34	ACR	NA	NA	GBT	7 (18.9)	NA	NA	NA
2	Bae et al[47]	2013	USA/France	Prevalence	55	24	27	ACR	NA	NA	LBT	21 (38.2)	NA	NA	NA
3	Brown et al[46a]	2008	UK	Prevalence	8	3	5	Not stated	NA	NA	GBT	8 (100.0)	3	5	NA
4	Chaudhary et al[45a,b]	2010	India	Prevalence	35	9	26	Not stated	NA	NA	BT	12 (34.3)	NA	NA	NA
5	Cobden et al[29]	1980	UK	Case control	20	NA	NA	Not stated	18	Not healthy	JAC	4 (20.0)	NA	NA	0
6	Cruz-Dominguez et al[44a,b]	2017	Mexica	Prevalence	68	27	41	ACR	NA	NA	GBT	44 (64.7)	NA	NA	NA
7	Di Ciaula et al[28a]	2008	Italy	Case control	38	4	34	ACR	60	NA	LBT	0 (0.0)	0	0	0
8	Fynne et al[43a]	2011	Denmark	Prevalence[c]	15	NA	NA	ACR	17	Healthy	GBT	3 (20.0)	NA	NA	NA
9	Garcia-Collinot et al[42a]	2019	Mexico	Prevalence	74	32	43	ACR/EULAR	NA	NA	LBT	40 (54.1)	18	22	NA
10	Gemignani et al[22]	2013	Italy	Case control	50	18	32	Not stated	60	Healthy	GBT	9 (18.0)	NA	NA	3
11	Gough et al[49a]	1995	UK	Prevalence	10	8	2	ARA	NA	NA	LBT	0 (0.0)	0	0	NA
12	Kaye et al[23] 1994	1994	UK	Case control	10	NA	NA	ARA	10	Healthy	JAC	4 (40.0)	NA	NA	0
13	Kaye et al[24] 1995	1995	UK	Case control	24	6	17	ACR	9	Healthy	JAC	8 (33.3)	2	6	0
14	Levin et al[41]	2021	Canada	Prevalence[c]	29	7	20	Not stated	20	Healthy	GBT	13 (44.8)	2	10	NA
15	Madrid et al[40] 2012[a,b]	2012	Chile	Prevalence	30	9	21	ARA	NA	NA	LBT	16 (53.3)	8	8	NA
16	Madrid et al[39] 2020[a,b]	2020	Chile	Prevalence	53	NA	NA	Not stated	37	NA	LBT	32 (60.3)	NA	NA	NA
17	Marie et al[37] 2009	2009	France	Prevalence	51	25	26	ACR	NA	NA	GBT	22 (43.1)	8	14	NA
18	Marie et al[38] 2015	2015	France	Prevalence	125	43	82	ACR/EULAR	NA	NA	GBT	44 (35.2)	NA	NA	NA
19	Owyang[32a]	1994	USA	Case control	5	NA	NA	ARA	6	Healthy	GBT	5 (100.0)	NA	NA	NA
20	Parodi et al[31]	2008	Italy	Case control	55	18	37	ARA	60	Healthy	LBT	30 (54.6)	NA	NA	4
21	Polkowska-Pruszy´nska et al[25]	2020	Poland	Case control	39	6	33	ACR/EULAR	39	Healthy	LBT	19 (48.7)	NA	NA	5
22	Savarino et al[26]	2013	Italy	Case control	99	31	68	ARA	60	Healthy	LBT	47 (47.5)	NA	NA	3
23	Sawadpanich et al[36]	2019	Thailand	Prevalence	89	65	24	ACR	NA	NA	GBT	12 (13.5)	9	3	NA
24	Shindo et al[27]	1998	Japan	Case control	12	12	0	ARA	19	Healthy	JAC	7 (58.3)	7	0	3
25	Soudah et al[35a]	1991	USA	Prevalence[c]	5	5	0	ARA	6	Healthy	GBT	5 (100.0)	5	0	NA
26	Tauber et al[34]	2014	France	Prevalence	37	14	23	Not stated	NA	NA	GBT	14 (37.8)	NA	NA	NA
27	Wegener et al[33a]	1994	Germany	Prevalence	14	6	7	ARA	NA	NA	GBT	3 (21.4)	NA	NA	NA
28	Zou et al[30]	2019	Canada	Case control	25	NA	NA	ACR/EULAR	20	Healthy	BT	13 (52.0)	NA	NA	NA

[a]Indicates studies which only measured hydrogen (and not methane) during breath testing.
[b]Indicates studies published as conference abstract.
[c]SIBO was measured only in cases (systemic sclerosis [SSc]-patients) and not in controls, hence classified as prevalence studies.
[d]cSSc, diffuse cutaneous systemic sclerosis; lcSSc; limited cutaneous systemic sclerosis; SIBO, small intestinal bacterial overgrowth; ACR, American College of Rheumatology, ACR/EULAR, American College of Rheumatology & European League Against Rheumatism; ARA, American Rheumatism Association; NA, not available; GBT, glucose breath test; LBT, lactulose breath test; BT, breath test; JAC, jejunal aspirate and culture.

ger's test (Supplementary Table 4) did not suggest publication bias.

Nine out of 11 case-control studies in the final analysis included 347 adult SSc-patients and 335 controls.[22-29,31] The remaining 2 studies did not report SIBO prevalence in controls, and were not included in further analysis.[30,32] SIBO prevalence in SSc-patients was 7-fold higher at 36.9% (95% CI, 31.9-42.2) compared to 5.4% (95% CI, 3.2-8.3) in controls (Supplementary Table 4). In relation to the prevalence of SIBO, the pooled OR was significantly higher in SSc-patients as compared to controls (9.6; 95% CI, 5.6-16.5; $P < 0.001$; Fig. 3) without any measurable statistical heterogeneity noted in this analysis ($I^2 = 0,00\%$, $P = 0.798$).

Risk of Bias on the Small Intestinal Bacterial Overgrowth Prevalence and Selection Criteria for Controls

High-quality studies

The quality assessment of the studies is outlined in Supplementary Tables 5 and 6. Utilising the NOS, the majority (6/11, 54.5%) of the case-control studies were categorized as high-quality (NOS score of ≥ 6, Supplementary Table 5). With the JBI critical appraisal tool (Supplementary Table 6), 3 out of the 11 case-control studies had a low risk of bias, 4 had a moderate risk of bias and 4 had a high risk of bias. Furthermore, 6 out of 17 prevalence studies had low, 3 had moderate, and 8 had a high risk of bias.

Including all 16 high-quality studies, there was no significant difference for SIBO prevalence rates in SSc-patients (37.4%; 95% CI, 29.8-45.8; Supplementary Fig. 3). In addition, the analysis revealed considerable heterogeneity ($I^2 = 77.40\%$, $P < 0.001$).

Healthy asymptomatic controls

Healthy subjects as controls were included in 8 out of the 9, case-control studies Table 2. Subgroup analysis with studies that included healthy controls, the odds for SIBO prevalence in SSc-patients as compared to controls remained unchanged, (OR, 9.6; 95% CI, 5.5-16.6; $P < 0.001$, data not shown) without any measurable statistical heterogeneity seen in this analysis ($I^2 = 0.00\%$, $P < 0.001$).

Effects of Diagnostic Tests for Small Intestinal Bacterial Overgrowth (Breath-tests Versus Small Bowel Aspirate and Culture)

Twenty-four studies utilized BT (13 glucose breath test [GBT], 9 lactulose breath test [LBT], and 2 BT without specified substrates) and 4 studies (all case-control studies) utilized jejunal aspirate and culture to diagnose SIBO. When BT were used to diagnose SIBO, the pooled prevalence rate of SIBO in SSc-patients was 44.4% (95% CI, 38.0-51.1; Supplementary Fig. 4), considerable heterogeneity was noted in this analysis ($I^2 = 78.45\%$, $P < 0.001$). In addition, the funnel plot suggested overall asymmetry (Supplementary Fig. 5), while results of the Egger's test did not suggest publication bias, (Supplementary Table 4). Utilizing LBT as compared to GBT, SIBO prevalence in SSc-patients was numerically higher 48.2% (95% CI, 39.8-56.8) vs 36.8% (95% CI, 25.5-49.8) (Supplementary Fig. 4.) Again, the analyses demonstrated substantial heterogeneity for studies utilizing both GBT ($I^2 = 82.42\%$, $P < 0.001$) and LBT ($I^2 = 60.68\%$, $P = 0.009$). With jejunal aspirate and culture as diagnostic modality, the pooled SIBO prevalence rates for SSc-patients was 36.2% (95% CI, 22.5-52.5) comparable to that utilizing GBT with moderate heterogeneity seen in the analysis ($I^2 = 35.7\%$, $P = 0.198$).

Four case-control studies utilizing jejunal aspirate, used a cut off ≥ 10^5 CFU/mL of bacteria for SIBO diagnosis. In these studies, the prevalence of SIBO in SSc-patients was 34.8% (95% CI, 23.3-46.3) as compared to 5.4% (95% CI, 1.1-14.8) in controls. Furthermore, the odds for SIBO prevalence in SSc-patients was 9.0 (95% CI, 2.7-30.4; $P < 0.001$; Fig. 3) compared to controls, without any measurable statistical heterogeneity in the analysis ($I^2 = 0.00\%$, $P = 0.985$).

Utilizing jejunal aspirate and culture (all in case-control studies), the OR for SIBO in SSc-patients compared with controls was 9.0 (95% CI, 2.7-30.4; $P < 0.001$). Again, there was no measurable statistical heterogeneity noted in the analysis, ($I^2 = 0.00\%$, $P = 0.985$).

Prevalence Rates of Small Intestinal Bacterial Overgrowth in Systemic Sclerosis-subtypes

Nine studies analysed the prevalence rates of SIBO in SSc-subtypes (Table 2). The odds of SIBO prevalence was not different in lcSSc as compared to dcSSc (OR, 1.01; 95% CI, 0.46-2.20; $P = 0.978$) (Supplementary Fig. 6), with moderate heterogeneity noted for this analysis ($I^2 = 41.20\%$, $P = 0.153$).

Risk Factors for Small Intestinal Bacterial Overgrowth in Systemic Sclerosis

Link between proton pump inhibitors use and small intestinal bacterial overgrowth in systemic sclerosis-patients

Five studies analyzed the effects of PPI on the prevalence of

SIBO in SSc-patients, (Supplementary Table 7). The prevalence of SIBO in 98/228 (43%; 95% CI, 36.5-49.6) SSc-patients on PPI was significantly higher as compared to 27/94 (28.7%; 95% CI, 19.8-28.9) in SSc-patients not on a PPI. PPI use in SIBO positive, SSc-patients was numerically higher than SIBO positive SSc-patients not on a PPI (OR, 2.3; 95% CI, 0.8-6.4; $P = 0.105$) (Supplementary Fig. 7), with moderate heterogeneity in the analysis, ($I^2 = 57.60\%$, $P = 0.060$).

Effect of disease duration on small intestinal bacterial overgrowth in systemic sclerosis-patients

Three studies explored the association between SIBO and disease duration in SSc-patients.[34,36,37] All 3 found statistically significantly association between disease duration and SIBO prevalence in SSc-patients.[34,36,37]

Link between small intestinal bacterial overgrowth prevalence in systemic sclerosis-patients and autoantibodies and biochemical markers for malnutrition and inflammation

Three studies evaluated the potential link between SIBO in SSc-patients and markers of inflammation and markers of malnutrition (Supplementary Table 8).[34,36,37] Two studies found no significant association between prevalence of SIBO in SSc-patients and biochemical-markers of inflammation (erythrocyte sedimentation rate, C-reactive protein, leucocyte counts, serum concentrations of total protein, albumin, vitamin B12, serum ferritin, folic acid, or Vitamin D).[34,36] In contrast, Marie et al,[37] found that the SIBO positive SSc-patients in their study had significantly greater erythrocyte sedimentation rate, reduced serum total protein, albumin, and haemoglobin, and no differences in Vitamin B12, ferritin, and folic acid. Autoantibody screen tests (anti-Centromere antibody and anti-Scl 70 antibody)[34,36,37,41] were similar in both SSc-patients with and without SIBO, except for one study,[34] where only anti-Scl 70 was significantly associated with SIBO positivity in SSc.

Finally, all 3 studies found no association between other systemic manifestation of scleroderma (interstitial lung disease, digital ulceration, Raynaud's phenomenon, and pulmonary arterial hypertension)[34,36,37,42] and SIBO, except 1 study[34] found significantly increased pulmonary arterial hypertension but not interstitial lung disease in SIBO positive SSc-patients. Two studies[25,38] found significantly higher FC levels (> 200 μg/g) in SIBO positive SSc-patients as compared to SIBO negative SSc-patients (Supplementary Table 2).

Link between small intestinal bacterial overgrowth in systemic sclerosis and gastrointestinal symptoms

Four studies reported on total GI symptoms, using different symptom assessment scales (Supplementary Table 9). Overall, the total GI symptom score in SSc-patients, with and without SIBO were not different (standardized mean difference, 0.28; 95% CI, −0.05-0.61; $P = 0.090$) (Supplementary Fig. 8) with minimal heterogeneity ($I^2 = 12.50\%$, $P = 0.330$). Analysing symptoms individually, the odds of diarrhea prevalence (reported in 7 studies) was significantly higher in SIBO-positive SSc-patients (OR, 5.9; 95% CI, 2.9-16.0; $P = 0.001$) (Supplementary Fig. 9) with moderate heterogeneity ($I^2 = 44.40\%$, $P = 0.126$) in the analysis.[23,24,29,33,36,37,44] Further subgroup analysis regarding other GI symptoms could not be performed, however the descriptive results are summarized below.

Although numerically higher, we found no significant increase in the prevalence of constipation in SSc-patients with SIBO as compared to those without SIBO (OR, 2.6; 95% CI, 3.3-20.6; $P = 0.355$) (Supplementary Fig. 10). This data was reported in 3 studies.[36,37,44] There was substantial heterogeneity noted in the analysis ($I^2 = 82.00\%$, $P = 0.001$). Although data could be extracted from only limited studies, SSc-patients who were SIBO positive as compared to those who were SIBO negative, there was significant difference in prevalence of symptoms like bloating[37,44] (84.8% [95% CI, 73.9-92.4] vs 60.4% [95% CI, 46.0-73.5]), dyspepsia[29,36] (63.2% [95% CI, 38.3-83.7] vs 22.2% [95% CI, 14.1-32.2]), and abdominal pain[37] (86.4% [95% CI, 65.1-97.1] vs 31% [95% CI, 15.2-50.8]) but no significant difference was noted in regard to prevalence of dysphagia[36] (66.7% [95% CI, 34.8-90.1] vs 37.7% [95% CI, 26.8-49.4]) and weight loss[24,29] (53.3% [95% CI, 16.5-78.7] vs 13.8% [95% CI, 3.8-31.6]).

Treatment With Antibiotics of Small Intestinal Bacterial Overgrowth Positive Systemic Sclerosis-patients

Nine studies with 158 SIBO positive SSc-patients reported response to antibiotic treatment (Supplementary Table 10). There was significant symptom improvement reported by 60.4% (95% CI, 49.9-70.2) of these patients. Fifty-six percent (95% CI, 47.8-64.9) of SSc-patients treated with antibiotics had normalization of BT after treatment with antibiotics. Rifaximin[22,25,31] was almost twice as effective as compared to rotating antibiotic therapy[34,37,38] (77.8% [95% CI, 64.4-87.9] vs 44.8% [95% CI, 31.7-58.4]) in achieving normalization of the BT after treatment. Only 4 studies reported

SIBO in patients with SSc

Study name	Event rate	Lower limit	Upper limit	Z-value	*P*-value
Adarsh et al	0.189	0.093	0.347	−3.467	0.001
Bae et al	0.382	0.264	0.516	−1.736	0.083
Brown et al	0.944	0.495	0.997	1.947	0.052
Chaudhary et al	0.343	0.206	0.512	−1.827	0.068
Cobden et al	0.200	0.077	0.428	−2.480	0.013
Cruz-Dominguez et al	0.647	0.527	0.751	2.389	0.017
Di Caula et al	0.013	0.001	0.175	−3.052	0.002
Fynne et al	0.200	0.066	0.470	−2.148	0.032
Garcla-Collinot et al	0.541	0.427	0.650	0.697	0.486
Gemignani et al	0.180	0.096	0.311	−4.119	<0.001
Gough et al	0.045	0.003	0.448	−2.103	0.035
Kaye et al 1994	0.400	0.158	0.703	−0.628	0.530
Kaye et al 1995	0.333	0.176	0.539	−1.601	0.109
Levin et al	0.448	0.281	0.628	−0.556	0.578
Madrid et al 2012	0.533	0.358	0.701	0.365	0.715
Madrid et al 2020	0.604	0.468	0.725	1.500	0.134
Marie I et al 2009	0.431	0.304	0.569	−0.977	0.329
Marie I et al 2015	0.352	0.273	0.439	−3.259	0.001
Owyang	0.917	0.378	0.995	1.623	0.105
Parodi et al	0.545	0.414	0.671	0.673	0.501
Polkowska-Pruszy'nska et al	0.487	0.336	0.640	−0.160	0.873
Savarino et al	0.475	0.379	0.573	−0.502	0.615
Sawadpanich et al	0.135	0.078	0.223	−5.990	<0.001
Shindo et al	0.583	0.308	0.815	0.575	0.566
Soudah et al	0.917	0.378	0.995	1.623	0.105
Tauber et al	0.378	0.239	0.542	−1.465	0.143
Wegener et al	0.214	0.071	0.494	−1.995	0.046
Zou et al	0.520	0.331	0.704	0.200	0.842
	0.399	0.331	0.471	−2.736	0.006

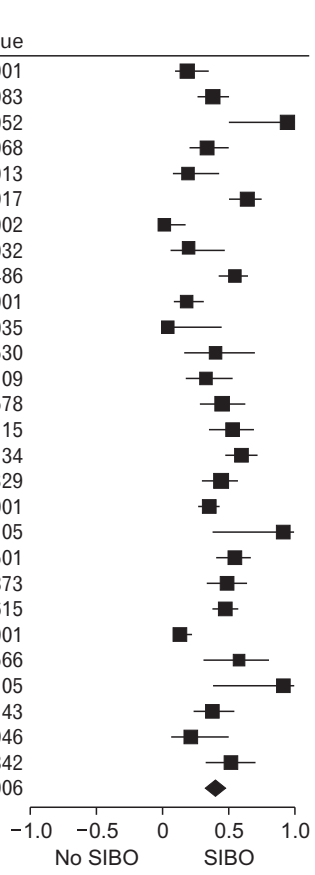

Figure 2. Forest plot of studies showing prevalence of small intestinal bacterial overgrowth in systemic sclerosis-patients (39.9% [95% CI, 33.1-47.1]; I^2 = 76.00%; $P < 0.001$).

SIBO in SSc patients compared to controls

Group by Type of test	Study name	Odds ratio	Lower limit	Upper limit	Z-value	*P*-value
GBT	Gemignani et al	4.171	1.063	16.362	2.048	0.041
GBT		4.171	1.063	16.362	2.048	0.041
JAC	Cobden et al	10.091	0.504	201.907	1.512	0.130
JAC	Kaye et al 1994	14.538	0.667	316.694	1.703	0.089
JAC	Kaye et al 1995	9.788	0.506	189.219	1.510	0.131
JAC	Shindo et al	7.467	1.385	40.245	2.339	0.019
JAC		9.093	2.712	30.489	3.576	<0.001
LBT	Parodi et al	16.800	5.347	52.785	4.830	<0.001
LBT	Polkowska-Pruszy'nska et al	6.460	2.088	19.986	3.238	0.001
LBT	Savarino et al	17.173	5.039	58.528	4.545	<0.001
LBT		12.052	6.153	23.609	7.256	<0.001
Overall		9.656	5.627	16.568	8.232	<0.001

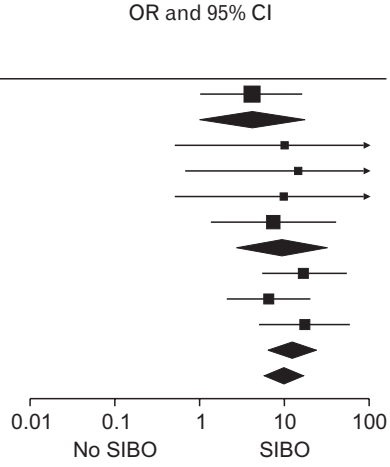

Figure 3. Forest plot of studies showing prevalence of small intestinal bacterial overgrowth (SIBO) in systemic sclerosis-patients and controls, stratified according to mode of diagnosis of SIBO (OR, 9.6; 95% CI, 5.6-16.5; $P < 0.001$), ($I^2 = 0.00\%$, $P = 0.798$). The odds ratio for SIBO in SSc-patients compared to controls utilizing jejunal aspirate and culture (JAC) is 9.0 (95% CI, 2.7-30.4; $P < 0.001$), ($I^2 = 0.00\%$, $P = 0.985$), utilizing lactulose breath test (LBT) is 12.0 (95% CI, 6.1-23.6; $P < 0.001$), ($I^2 = 0.00\%$, $P = 0.404$), utilizing glucose breath test (GBT) is 4.1 (95% CI, 1.0-16.3; $P = 0.041$), ($I^2 = 0.00\%$, $P > 0.999$).

on antibiotic related adverse events, in 2 out of 4 studies,[31,37] none of the patients developed any side effects. In one study,[34] 1 patient treated with rotating antibiotic developed pseudomembranous colitis, leading to antibiotic discontinuation while in another study[42] 12/26 (46.1%) patient reported mild GI symptoms.

Two studies evaluated the efficacy of antimicrobial therapy on SIBO in SSc-patients on FC.[25,38] One study[38] found a statistically significant reduction in FC post SIBO eradication with antibiotic therapy while in the other study[25] the reduction in mean FC levels failed statistical significance.

Influence of Geographic Factors on Small Intestinal Bacterial Overgrowth in Systemic Sclerosis-patients and Controls

Subgroup analysis stratified according to geographic regions, revealed the highest SIBO prevalence in SSc-patients in the USA (54.9% [95% CI, 49.5-60.2]), followed by the studies conducted in Europe at 36.1% (95% CI, 32.2-40.1) and lowest in studies from Asian countries 22% (95% CI, 16-28.8) (Supplementary Table 11). Moderate heterogeneity among the studies included in these analyses was found ($I^2 = 46.32\%$, $P = 0.061$).

Discussion

Twenty-eight published peer-reviewed studies (11 case-control and 17 prevalence) with 1112 SSc-patients and 335 controls from 13 countries were included in this systematic review and meta-analysis. With more than 1000 SSc-patients this is the thus far largest pooled analysis of case-control and prevalence studies focussing on the association between SIBO and SSc (and SSc sub-types) and potential risk modifiers for SIBO in SSc. Overall, the data reveal a strong link between SIBO and SSc with a 10-fold increased prevalence of SIBO in SSc-patients as compared to controls (OR, 9.6; 95% CI, 5.6-16.5). Conversely, no significant difference in SIBO prevalence rates between different SSc sub-types, namely lcSSc and dsSSc was found. Furthermore, antibiotic treatment targeting SIBO in SSc significantly improved symptoms suggesting that concomitant SIBO in SSc-patients aggravates GI symptoms.

Previous work by Grace et al,[50] found diarrhea as the most common symptom in SIBO, which was followed by abdominal pain and bloating as the next most frequent symptoms. Notably, the symptom diarrhea was closely associated (OR, 5.9; 95% CI, 16.0-2.9; $P = 0.001$) with SIBO in SSc-patients. Furthermore, GI symptoms like bloating, dyspepsia and abdominal pain were also significantly increased in SSc-patients with SIBO. On the other hand, the total GI symptom score and symptoms like weight loss, constipation, and dysphagia were not significantly increased in SIBO positive SSc-patients. Nevertheless, SIBO symptoms frequently overlap with symptoms observed in other GI conditions and are regarded as poor predictors for bacterial overgrowth. Other serious but less frequent clinical manifestations of SIBO are nutrient malabsorption,[51] indicated by deficiencies of fat-soluble vitamins, vitamin B12, folate and iron, and ultimately weight loss. Studies focussing on the associations between inflammatory markers, nutritional markers and SIBO positive SSc-patients were inconclusive. Autoantibody screen tests (anti-Centromere antibody and anti-Scl 70 antibody) were not increased in SIBO positive SSc-patients compared to those without SIBO. This suggests that SIBO is not directly linked to the underlying immune process of SSc. On the other hand, FC was significantly increased in SIBO positive SSc-patients consistent with the concept that SIBO can result in mucosal inflammation.[52] Interestingly, SIBO was not associated with other systemic manifestations of SSc.

We observed substantial heterogeneity and recurrent potential for publication bias among studies that were available for the primary and most secondary analyses. We thus performed a separate analysis according to study design. While prevalence studies yielded a high heterogeneity score, no measurable heterogeneity was found for case-control studies.

Furthermore, separate analysis stratified by type of diagnostic test used were conducted. This revealed numerically higher prevalence of SIBO when LBT was used for SIBO diagnosis instead of studies utilizing GBT or culture-based methods. Nevertheless, at least moderate heterogeneity was found for each subgroup analysis. Similar, subgroup analysis for cases-control studies was not possible due to the small number of studies utilizing different diagnostic modalities for SIBO diagnosis.

To explore heterogeneity of the primary analysis, we did an additional sensitivity analysis, by restricting the analysis only to only "high-quality" studies based upon NOS and the JBI appraisal tool. However, among the studies meeting this criterion, heterogeneity was also high and the potential for bias remained. Given this, the high heterogeneity scores and the obvious high risk of bias is most likely explained by extraneous but unreported features of the prevalence studies included in this systematic review and meta-analysis. It is noteworthy, that most prevalence studies included in these meta-analyses were based upon retrospective audits, of frequently poorly characterized study cohorts, with insufficient information regarding selection criteria or potential confounders (eg, PPI-use, previous antibiotic therapies, or probiotic use). This potentially could explain

the increased SIBO prevalence in SSc-patients when prevalence studies are compared to case-control studies. Furthermore, 8 out of the 9 case-control studies used healthy (asymptomatic) subjects as controls, minimizing the risk of bias.

The lack of data on methane positivity during BT in patients with SSc is one of the limitations of this meta-analysis. Only 3 studies reported methane positivity (in addition to hydrogen) during breath testing to diagnose SIBO in SSc. Methane, produced by Archaea (and not bacteria), is believed to slow intestinal transit and is often associated with constipation.[53-55] The importance of breath methane measurements in subjects with suspected intestinal dysbiosis, is emphasized by the guideline of the American College of Gastroenterology for SIBO.[56] Indeed, the term, intestinal methanogen overgrowth has been coined to highlight the distinct importance of methane production by methanogens (Archaea) as compared to hydrogen positive SIBO caused by bacteria. Consequently, failure to measure methane, will result in an underestimation of the SIBO prevalence and is likely to influence the outcomes this meta-analysis.

SSc-patients frequently have severe motility disturbance of the esophagus, manifesting with heartburn, dysphagia, and regurgitation[57] requiring treatment with PPI. A meta-analysis published by Su et al[58] found that treatment with PPI and the subsequent chronic gastric acid suppression is linked with a moderate increase of SIBO in a variety of GI disease conditions (OR, 1.7; 95% CI, 1.2-2.4). However, a recent study showed that, PPI was not associated with an increased rate of SIBO, although modest changes were seen in the small intestinal microbiome in PPI users, including a notable reduction in relative abundance of the family Clostridiaceae.[59] Thus, the effect of PPI on the small intestinal microbiome remains inconclusive. In the current systematic review and meta-analysis, although limited by a small sample size, PPI use was numerically (but not significantly) higher in SIBO positive SSc-patients (OR, 2.3; 95% CI, 0.8-6.4; $P = 0.105$). However, it is important to note that SSc-patients with more severe GI symptoms, who are more likely to have SIBO are often treated with PPI, thus the true link between SIBO in SSc-patients and PPI use remains to be explored.

Increased duration of disease was significantly related with an increased SIBO prevalence rates in SSc-patients, suggesting that SIBO is potentially the consequence (and not the cause) from the worsening global GI dysmotility seen with disease progression, resulting in subsequent stasis of luminal contents promoting bacterial overgrowth in SSc.

This systematic review and meta-analysis revealed that a short course of antibiotic therapy or octreotide treatment were effective in treating SIBO in SSc-patients. In more than 60% of SSc-patients, antibiotic therapy resulted in a significant symptom improvement and in more than 60% of SSc-patients in normalization of breath tests. Overall, it appears that rifaximin was potentially twice as effective as rotating antibiotics for SIBO treatment in SSc, while our analysis could not account for potential confounders. Antibiotic therapy was well tolerated and only a small proportion of patients developed mild GI symptoms. Moreover, there was reduction in FC after SIBO eradication with antibiotic therapy in SSc-patients. Similarly, although only limited data is available,[32,35] treatment of SIBO in SSc with octreotide, exerting a prokinetic effect,[32] improved abdominal symptoms significantly and normalized hydrogen breath tests. Thus, antimicrobial therapy may be an effective therapeutic option to improve GI symptoms in SSc, similar to that reported for treating small intestinal dysbiosis and symptoms in FGIDs[60] and IBD.[61] Furthermore, only 1 open-label study reported on the efficacy of probiotics in treating SIBO in SSc-patients and found *Saccharomyces boulardii* monotherapy or in combination with metronidazole was well tolerated and effective in improving GI outcomes in SIBO positive SSc-patients.[42] This points towards a potential role of small intestinal dysbiosis as a relevant pathophysiological factor for digestive symptoms in a subgroup of SSc-patients.

Subgroup analysis for different countries and regions of the world, found the increased SIBO prevalence rates in the US, followed by the European countries and the lowest rates were from the Asian countries. In all these countries a combination of BT and/or small bowel aspirate and culture was used for SIBO diagnosis. It can be speculated that this variation in SIBO prevalence is caused by environmental factors such as diet or the background risk of GI infections.

The only earlier meta-analysis[12] incorporated 14 studies as compared to 28 studies used for the primary analysis for this meta-analysis. This increased number of studies enabled detailed analyses of subgroups of the included studies and allowed to explore the heterogeneity inherent to these studies. The larger sample size also enabled additional analyses in relation to other predictors or risk factors for SIBO in SSc including PPI use, antibiotic therapy and octreotide, environmental factors like geographic region or the role of potential biomarkers such as FC, markers of inflammation and markers of malnutrition for SIBO in SSc. Furthermore, we assessed the impact of SIBO on GI symptoms and other systemic manifestations of SSc. Nevertheless, there are limitations of this systematic review and meta-analysis. The diagnosis of SIBO is always fraught by the absence of an appropriately validated and clinically accepted diagnostic tests. Furthermore, the various case-control studies included "healthy asymptomatic subjects" as well as diverse

patient cohorts as controls. In addition, small sample sizes (eg, < 50 subjects per group) in some of the studies limited the statistical power of some of the sub-group analyses.

Collectively, this systematic review and meta-analysis observes an increased prevalence of SIBO in SSc-patients as compared to controls. However, there was no difference in SIBO prevalence between lcSSc and dcSSc. Diarrhea is strongly associated with SIBO in SSc-patients, while the risk of SIBO increases with longer disease duration and PPI use. While the data are limited, FC is increased in SIBO positive SSc-patients, but the role of other markers of inflammation and malnutrition, remains uncertain. Antibiotic treatment (or treatment with octreotide) of SIBO (predominantly rifaximin) in SSc-patients and/or octreotide results in a significant symptom improvement and in a significant proportion of patient's the BT are normalized. On the other hand, moderate heterogeneity was found by the comparative analysis in addition to risk of bias. Furthermore, there is substantial "clinical heterogeneity," which is most likely due to the absence of uniform criteria for selection of cases, a consequence of potential confounders and lack of validated tests to diagnose SIBO. Based upon this, the overall reliability of the evidence available must be considered low, and the results need to be interpreted with caution.

Supplementary Materials

Note: To access the supplementary materials and methods, tables, and figures mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm22168.

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