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The efficacy of dietary intervention on gastrointestinal involvement in systemic sclerosis: A systemic literature review

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Abstract

Background: Gastrointestinal involvement in systemic sclerosis is common and a major cause of disease-related morbidity. Patients increasingly enquire about dietary modifications that may help with gastrointestinal symptoms and many clinical practice reviews and treatment guidelines make specific reference to dietary modifications in the management of gastrointestinal involvement in systemic sclerosis. We report the findings of a systematic literature review designed to evaluate the evidence to support dietary modification in the management of gastrointestinal symptoms of systemic sclerosis.

Methods: A systematic literature review protocol was developed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered with the International prospective register of systematic reviews (CRD42018103549). Standardised searches of EMBASE and MEDLINE were undertaken to identify studies reporting the outcome of dietary modification in the management of gastrointestinal symptoms of systemic sclerosis. Wide heterogeneity in study design, interventions and study outcomes necessitated a qualitative data synthesis.

Results: Our standardised searches identified 1032 articles, of which 3 were deemed eligible for full data extraction. These studies were small (mean 19 subjects per study), single centre, short-term (mean 6 week duration) open-label non-randomised studies examining the role of probiotics, low-fermentable oligo-saccharides, disaccharides, monosaccharides, and polyol (low-FODMAP) diet and highly individualised medical nutrition therapy counselling respectively. Improvements in patient-reported outcome assessment of gastrointestinal symptoms were reported after intervention with probiotic therapy and low-FODMAP diet but not following tailored dietary and nutritional counselling. The Risk of Bias Assessment Tool for Nonrandomized Studies identified high risk-of-bias for confounding variables and blinding of assessors in each of the three studies evaluated.

Conclusions: The evidence-base to support dietary modification for gastrointestinal involvement in systemic sclerosis is currently limited and clinical practice guidelines should take a measured approach to such recommendations. The recent emergence of large patient registries could facilitate the capture vital

practice-based evidence regarding the efficacy of dietary modification in the management of gastrointestinal involvement in systemic sclerosis to inform future clinical practice guidelines.

Keywords: Systemic Sclerosis, Scleroderma, Dietary modification, gastrointestinal, Systematic Literature Review

Abbreviations

Low-FODMAP, low-fermentable oligo-saccharides, disaccharides, monosaccharides, and polyol diet

GIT, gastrointestinal tract

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO, International prospective register of systematic reviews

RoBANS, Risk of Bias Assessment Tool for Nonrandomized Studies

SSc, systemic sclerosis

SCTC, Scleroderma Clinical Trials Consortium

Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune disease characterised by aberrant tissue remodelling with fibrosis occurring in multiple organs including the skin, lungs and gastrointestinal (GI) tract [1]. Fibrosis and smooth muscle atrophy within the GI tract results in sphincter disturbance (gastro-oesophageal reflux disease, GORD and ano-rectal dysfunction) and delayed GI transit (dysphagia, gastroparesis, small intestinal bacterial overgrowth, constipation). GI symptoms of SSc are very common and a major cause of disease-related morbidity [2-4]. A number of reviews and clinical practice guidelines stress the importance of dietary and lifestyle modifications in managing GI disease. These range from supplemental calories, alteration of fibre intake, probiotics, vitamin supplementation or changes to the timing, frequency, size or composition (exclusion and inclusion of particular food stuffs) of meals [5-7]. Many patients make enquires to their healthcare practitioners about dietary modifications that might help them symptomatically. Interest in this field has been bolstered by recent work that has identified characteristic intestinal microbiome signatures in SSc. Speculation has mounted concerning the potential role of dietary modification and probiotics to modify the GI tract microbiota in an attempt to improve GI symptoms and augment pathological drivers of the disease [8].

The principal objective of this systematic literature review is to identify and critically appraise the current evidence concerning the efficacy of dietary modifications on GI symptoms in SSc. Where applicable, limitations of existing research and knowledge gaps shall be highlighted alongside suggestions for future research.

METHODS AND ANALYSIS

Protocol development and review registration

A study protocol was developed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) guidelines [9] and registered in the International Prospective Register of Systematic Reviews (Registration: PROSPERO CRD42018103549).

Eligibility criteria

Studies reporting the impact of dietary intervention (of any form) on gastrointestinal symptoms in SSc were included in this systematic literature review. Applying the PICOS framework, we sought to evaluate publications that fulfilled the following study characteristics:

Participants: Adults (18 years or older) with a diagnosis of SSc

Intervention: Studies reporting the outcome of dietary intervention for GI symptoms of SSc. All dietary and lifestyle interventions for managing GI symptoms (e.g. advice on size, timing and frequency of meals, vitamin supplementation, exclusionary diets, probiotic use, antioxidants, etc.) were included. We didn't include assessment of non-dietary parenteral interventions.

Comparison: Where applicable, comparison shall be made with outcomes in active treatment arms versus control groups. Uncontrolled open-label interventions were also eligible providing they reported GI symptoms/physiological studies at baseline and following dietary modification.

Outcomes: The primary objective is to evaluate the clinical value of dietary interventions in managing GI *symptoms* of SSc. All methods for reporting change in GI disease including symptoms (from mouth to anus) and surrogates of GI dysfunction (such as GI physiology and/or imaging) before and after dietary modification were eligible for inclusion. Studies examining nutritional status (e.g. BMI, nutrition scores) as a solitary endpoint were not included.

Study design: Longitudinal studies reporting an assessment of the efficacy/impact of dietary modification (of any description) on GI manifestations of SSc were eligible for inclusion. All applicable study methodology (open-label, controlled, randomised, prospective, retrospective etc.) were eligible for inclusion. The following studies were excluded from the analysis; pre-clinical/animal studies, studies of childhood/juvenile SSc, studies of mixed patient populations (e.g. primary Raynaud's phenomenon, undifferentiated connective tissue diseases or overlap syndromes) in which a SSc cohort was not adequately reported, studies designed to develop/validate measurement scales, case reports, qualitative research, non-original research publications (i.e., editorials, reviews), abbreviated reports (e.g. letters to

editors), conference proceedings and non-English language publications. Details of the grounds for article exclusion were captured during study selection.

Information sources and search criteria

Electronic searches were undertaken in Medline and EMBASE databases using search criteria piloted during the planning phase. No publication date or language restrictions were applied to the searches. The following search criteria were developed and applied in both databases to capture articles relevant to the scope of this review:

((systemic sclerosis) OR (CREST) OR (scleroderma)) AND (diet* OR fibre OR fiber OR supplements OR probiotics OR anti-oxidants OR vitamins OR meal OR nutrition OR eating OR food) AND (gastrointestinal OR intest* OR GI OR abdominal OR bloating OR nausea OR reflux OR diarrhoea OR constipation OR faec*)

Study selection

All titles and abstracts generated by the search were screened independently by two review authors (JP and LS) for relevance and eligibility of studies for full text review (See appendix 1). Cohen's Kappa statistics were used to assess agreement between reviewers for articles considered relevant for full text review during the study selection process. Any divergence in agreement was resolved through discussion at each step of the study selection process. A "grey search" of potentially relevant articles cited on review of full text manuscripts was undertaken.

Data extraction from selected studies

Data was independently extracted by both reviewers (JDP and LS) using a standardized form piloted during protocol development (Appendix 2). The data extraction form collated relevant study details including date of publication, country of origin, intervention, study design, initial population of the study, study attrition, eligibility criteria, endpoints, adverse events, study attrition and a summary of key findings. Plans were in place to contact study authors should additional clarification be required.

Risk of Bias Assessment

Risk of bias within randomised and non-randomised controlled trials was assessed by both reviewers (LS and JP together) using the Cochrane Risk of Bias Assessment Tool for Randomised Trials or the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS), as appropriate. Each tool assesses bias across the domains relating to patient selection, performance, detection, attrition and reporting [10, 11] (see Appendix 3). Eligible studies were rated as high, low, or unclear (risk of bias), on each of these dimensions, culminating in an overall risk of bias (high/moderate/low).

Strategy for data synthesis

A qualitative data synthesis of the study findings was anticipated due to an expected high degree of study heterogeneity in terms of study design, intervention and outcome reporting; rendering any meaningful attempt at meta-analysis impossible.

Results

Study selection

Searches of EMBASE (708 articles) and Medline (324 articles) were undertaken on 13th July 2018 identifying a total of 1032 articles. After removal of duplications (n=141), the remaining 891 articles were screened for eligibility during a title and abstract review undertaken by both reviewers. A total of 8 studies fulfilled inclusion criteria but excluded on other grounds (5 conference abstracts and 3 case reports/series, Figure 1). There was good agreement between the reviewers (Kappa 0.726) for studies eligibility for full text review. Four studies were identified by both reviewers for full text analysis after title and abstract review. There was discordance as to whether 3 studies should proceed to full text review that was resolved through discussion, without the need for independent arbitration. One was excluded as it was agreed "bowel rest" (with nasogastric decompression) was *not* a dietary modification [12], whilst another was excluded as the principle endpoint was nutritional status (rather than GI symptoms/signs) [13]. It was agreed a 3rd study should proceed to full text review despite doubts regarding whether it would fulfil eligibility criteria (inclusion and exclusion) [14]. Of the 5 studies taken forward to full text review, 2 were

excluded; the first for being a short case series (4 patients) presented in an abbreviated non-original research publication [15] and the second for not fulfilling the inclusion criteria (in addition to grounds for exclusion based on insufficient reporting of the SSc population) [14]. No studies were excluded due to language. An overview of the study selection process is summarised in Figure 1. A summary of the key study characteristics and major findings of the 3 remaining studies are presented in Table 1. There was full agreement with the risk of bias assessment across all domains for the 3 studies.

Study characteristics

Each of the 3 selected studies were published within the last 7 years from centres in the USA (2 studies [16, 17]) and France (1 study [18]) respectively. All 3 studies were single centre, small (total of 56 subjects with mean 19 per study completing trial), short-term (with an average of 6 weeks) open-label non-randomised studies (Table 1). The studies applied different inclusion criteria and interventions, precluding any formal meta-analysis, as anticipated. Highly selective study eligibility limits the generalizability of each of the study findings. Study attrition was reported to be generally low, indicating dietary modifications are generally well tolerated in an interventional study setting.

Interventions

The three selected studies examined the use of probiotics [16], a low-fermentable oligo-saccharides, disaccharides, monosaccharides, and polyol (low FODMAP) diet [18] and a highly individualised medical nutrition therapy (MNT) counselling (emphasizing need for increased calorie and protein intake, modified textures, and lifestyle modifications) [17].

Reported outcomes

Each study utilised validated patient-reported outcome instruments as the primary endpoint for analysis. The University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 questionnaire (UCLA GIT 2.0) was used in 2 studies [16, 17] and the Global Symptomatic Score (GSS) in the 3rd [18] (Table 1). There were reported improvements in patient-reported GI symptoms following probiotic therapy [16] and adherence to the low-FODMAP diet [18]. MNT counselling improved self-

reported nutritional status but did not improve GI symptoms (or health-related quality of life) [17]. Despite the open-label study design, none of the reported studies incorporated objective endpoints (e.g. GI physiological studies or imaging) as surrogate markers of GI disease severity.

Study quality and risk of bias

A summary of the risk-of-bias assessment of each study is presented in Table 2. Each of the 3 studies were felt to have a moderate overall risk of bias. All three studies were considered at high risk of bias for the potential impact of confounding variables and blinding; primarily relating to the open-label study design and reliance upon PRO instruments as the primary endpoint (Table 2). The eligibility criteria for each study may have limited the generalizability of the study findings. For example, the study by Frech et al. required moderate-severe distension/bloating scores on baseline SCTC GIT 2.0 questionnaire, as opposed to more objective assessment of small intestinal bacterial overgrowth/pseudo-obstruction [16]. Improvements in subjective PRO instruments such as the UCLA GIT 2.0 and GSS may have also been influenced by issues such as regression to the mean or placebo response. Each of the studies were comparatively small and possibly under-powered risking type II error (i.e. missing a clinically meaningful improvement to intervention when present).

Synopsis of excluded studies

The identification of 5 conference abstracts raises the possibility of publication bias and as the number exceeded the number proceeding to full data extraction, we felt it appropriate to offer the findings some consideration. Accepting the limitations of conference proceedings, a summary of the interventions and reported findings of the 5 potentially eligible studies reported as conference proceedings that were identified at study selection is presented in Table 3. None of the abstracts identified have been published subsequently or are related to the published studies that comprise this review. A recent conference proceeding is noteworthy as it reports the findings of a comparatively large (n=73) randomised, double blind, placebo-controlled trial of probiotic therapy [19]. The study identified significant improvements in GI symptoms in both the active treatment arm (as was found in the aforementioned open label study)

and placebo arm, but changes did not differ between the 2 groups suggesting probiotic therapy may not have a role in managing GI symptoms in SSc [16, 19]. The remaining abstracts were smaller, un-blinded or open label studies (Table 3). A number of case reports/small case series were excluded from the formal data synthesis; some of which may allude to dietary modifications that could be of value in SSc e.g. a case series of 4 SSc patients highlighting the potential deleterious effects of a high-fibre diet [15]. A number of other ineligible studies raised points of interest, such as the timing of proton pump inhibitor administration on gastro-oesophageal reflux symptoms in scleroderma-spectrum disorders [20].

Discussion

To our knowledge, this is the first systematic literature review to address the impact of dietary modification on GI symptoms of SSc. At present, we are unable to draw conclusions regarding the efficacy of dietary modification in SSc as the evidence-base is limited to a low number of small non-randomised uncontrolled open-label trials. Nonetheless, it has become routine for clinical practice guidelines to make recommendations on this subject. This guidance ranges from judicious advice to promote "a mixed balanced diet that meets their requirements for both macro and micro nutrients (assuming there are no other medical contraindications)" [21] to more specific non evidence-based recommendations advocating dietary supplementation with medium-chain triglycerides, the avoidance of lactose or fructose-containing foods and encouraging intake of "stool bulking agents (bran and fibres)" [22]. The evidence base for such guidance is weak, at time contradictory and could result in an imbalanced diet, nutritional deficiency and, possibly, worsened symptoms. For example, the use of high-fibre diets has never been formally studied in SSc and the aforementioned small case series suggests it may actually aggravate GI symptoms in SSc [15]. Indeed, previous observations indicate dietary intake of food rich in fibre is generally lower in people with SSc, which invites speculation as to whether patients encounter aggravation of GI symptoms with high-fibre foods [23, 24]. Some clinical practice reviews, meanwhile, specifically advocate the avoidance of high fibre foods in SSc patients with GI involvement [7]. Recent work has focussed on the potential contribution of the GI microbiota in the pathogenesis of SSc [8]. Whether distinct microbiome signatures are the cause or consequence of the disease has yet to be elucidated but this work has resulted in renewed

interest in dietary modification (including low-FODMAP) and probiotic therapy; both of which could be used to modify the GI tract microbiota. The contrasting findings of recent open-label versus randomised double-blinded placebo-controlled trials of probiotic therapy highlights the importance of robust trial design to provide the evidence-base for future recommendations in this area [16, 19, 25].

Pragmatic general approaches for the alleviation of symptoms such as elevation of the head of the bed, multiple small meals, small bites, cut/chew food well, avoidance of dry food, avoidance of recumbency within 3 hours of eating and advice to take plenty of water with solid foods [7, 26] appear to be, on face value, sensible and unlikely to cause physical harm, but could impact on quality of life and social participation in other ways. Generic advice of this nature could be amenable to formal testing and the use of registries capturing patient-reported outcomes following recommendations to adopt such measures could provide much-needed "practice-based evidence" to inform future clinical practice guidelines.

Conclusions

At present, the evidence-base around dietary intervention for GI involvement in SSc is very limited and future clinical practice guidelines should take a measured approach to such recommendations. Recent interest around the potential pathogenic role of the GI microbiome in SSc and the emergence of large registries capable of capturing vital practice-based evidence could greatly enhance our understanding of both the pathogenesis and specific role of dietary modification in the management of GI involvement in SSc.

References

1.   Denton, C.P. and D. Khanna, *Systemic sclerosis.* Lancet, 2017.

2.   McMahan, Z.H., et al., *Determining the risk factors and clinical features associated with severe gastrointestinal dysmotility in systemic sclerosis.* Arthritis Care Res (Hoboken), 2017.

3.   Frech, T.M. and D. Mar, *Gastrointestinal and Hepatic Disease in Systemic Sclerosis.* Rheum Dis Clin North Am, 2018. **44**(1): p. 15-28.

4.   Murtaugh, M.A. and T.M. Frech, *Nutritional status and gastrointestinal symptoms in systemic sclerosis patients.* Clin Nutr, 2013. **32**(1): p. 130-5.

5.   Hansi, N., et al., *Consensus best practice pathway of the UK scleroderma study group: gastrointestinal manifestations of systemic sclerosis.* Clin Exp Rheumatol, 2014. **32**(6 Suppl 86): p. S-214-21.

6.   Shah, A.A. and F.M. Wigley, *My approach to the treatment of scleroderma.* Mayo Clin Proc, 2013. **88**(4): p. 377-93.

7.   Shreiner, A.B., et al., *Gastrointestinal Manifestations of Systemic Sclerosis.* J Scleroderma Relat Disord, 2016. **1**(3): p. 247-256.

8.   Volkmann, E.R., *Intestinal microbiome in scleroderma: recent progress.* Curr Opin Rheumatol, 2017. **29**(6): p. 553-560.

9.   Shamseer, L., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation.* Bmj, 2015. **349**: p. g7647.

10.   Higgins, J.P., et al., *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.* BMJ, 2011. **343**: p. d5928.

11.   Kim, S.Y., et al., *Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity.* Journal of Clinical Epidemiology, 2013. **66**(4): p. 408-414.

12.   Mecoli, C., et al., *Mortality, recurrence, and hospital course of patients with systemic sclerosis-related acute intestinal pseudo-obstruction.* J Rheumatol, 2014. **41**(10): p. 2049-54.

13.   Ortiz-Santamaria, V., et al., *Nutritional support in patients with systemic sclerosis.* Reumatol Clin, 2014. **10**(5): p. 283-7.

14.   Conti, V., et al., *High prevalence of gluten sensitivity in a cohort of patients with undifferentiated connective tissue disease.* Eur Ann Allergy Clin Immunol, 2015. **47**(2): p. 54-7.

15.   Gough, A., et al., *Dietary advice in systemic sclerosis: the dangers of a high fibre diet.* Ann Rheum Dis, 1998. **57**(11): p. 641-2.

16. Frech, T.M., et al., *Probiotics for the treatment of systemic sclerosis-associated gastrointestinal bloating/ distention.* Clin Exp Rheumatol, 2011. **29**(2 Suppl 65): p. S22-5.

17. Doerfler, B., et al., *Medical Nutrition Therapy for Patients With Advanced Systemic Sclerosis (MNT PASS): A Pilot Intervention Study.* JPEN J Parenter Enteral Nutr, 2017. **41**(4): p. 678-684.

18. Marie, I., et al., *Fructose Malabsorption in Systemic Sclerosis.* Medicine (Baltimore), 2015. **94**(39): p. e1601.

19. Marighela, T., et al., *Effect of Probiotics on the Gastrointestinal Symptoms and Immune Parameters in Patients with Systemic Sclerosis: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial.* Arthritis & Rheumatology, 2017. **69**.

20. Iwata, A., et al., *Pre-dinner administration increases the efficacy of proton pump inhibitors on refractory GERD symptoms in connective tissue disease patients.* Mod Rheumatol, 2013. **23**(2): p. 357-64.

21. Baron, M., et al., *Screening and management for malnutrition and related gastro-intestinal disorders in systemic sclerosis: recommendations of a North American expert panel.* Clinical and Experimental Rheumatology, 2010. **28**(2): p. S42-S46.

22. Sakkas, L.I., et al., *Intestinal Involvement in Systemic Sclerosis: A Clinical Review.* Dig Dis Sci, 2018. **63**(4): p. 834-844.

23. Lundberg, A.C., A. Akesson, and B. Akesson, *Dietary-Intake and Nutritional-Status in Patients with Systemic-Sclerosis.* Annals of the Rheumatic Diseases, 1992. **51**(10): p. 1143-1148.

24. Kayser, C., et al., *EVALUATION OF NUTRITIONAL STATUS AND DIETARY INTAKE IN WOMEN WITH SSc.* Rheumatology, 2012. **51**: p. 85-86.

25. Garcia-Collinot, G., Cruz-Dominguez MP, Madrigal-Santillán EO, Vera-Lastra OL, Jara LJ, Martínez-Bencomo MA, Carranza-Muleiro RA, Montes-Cortes D, Medina G, *Effectiveness of probiotic fungus plus antibiotic in bacterial overgrowth associated with systemic sclerosis.* Journal of Clinical Rheumatology, 2018. **24**(S3): p. S172.

26.   Sjogren, R.W., *Gastrointestinal motility disorders in scleroderma.* Arthritis Rheum, 1994. **37**(9): p. 1265-82.

27.   Luchetti, M.M., et al., *Gastrointestinal Disease and Microbial Translocation in Patients with Systemic Sclerosis: An Observational Study on the Effect of Nutritional Intervention and Implications for the Role of the Microbioma in the Pathogenesis of the Disease.* Annals of the Rheumatic Diseases, 2016. **75**: p. 65-65.

28.   Malgorzewicz, S., Kolak P, Wojteczek A, Zietkiewicz M, Zdrojewski Z. , *Oral supplementation in malnourished patients with scleroderma.* 37th European Society for Clinical Nutrition and Metabolism, Lisbon, Portugal, 2015.

29.   Guillen-Del Castillo, A., et al., *Coeliac Disease In Scleroderma - Clinical Features, Frequency and Impact Of Screening In Scleroderma.* Arthritis and Rheumatism, 2013. **65**: p. S1112-S1112.

Figure 1. Flow chart summarising study selection process
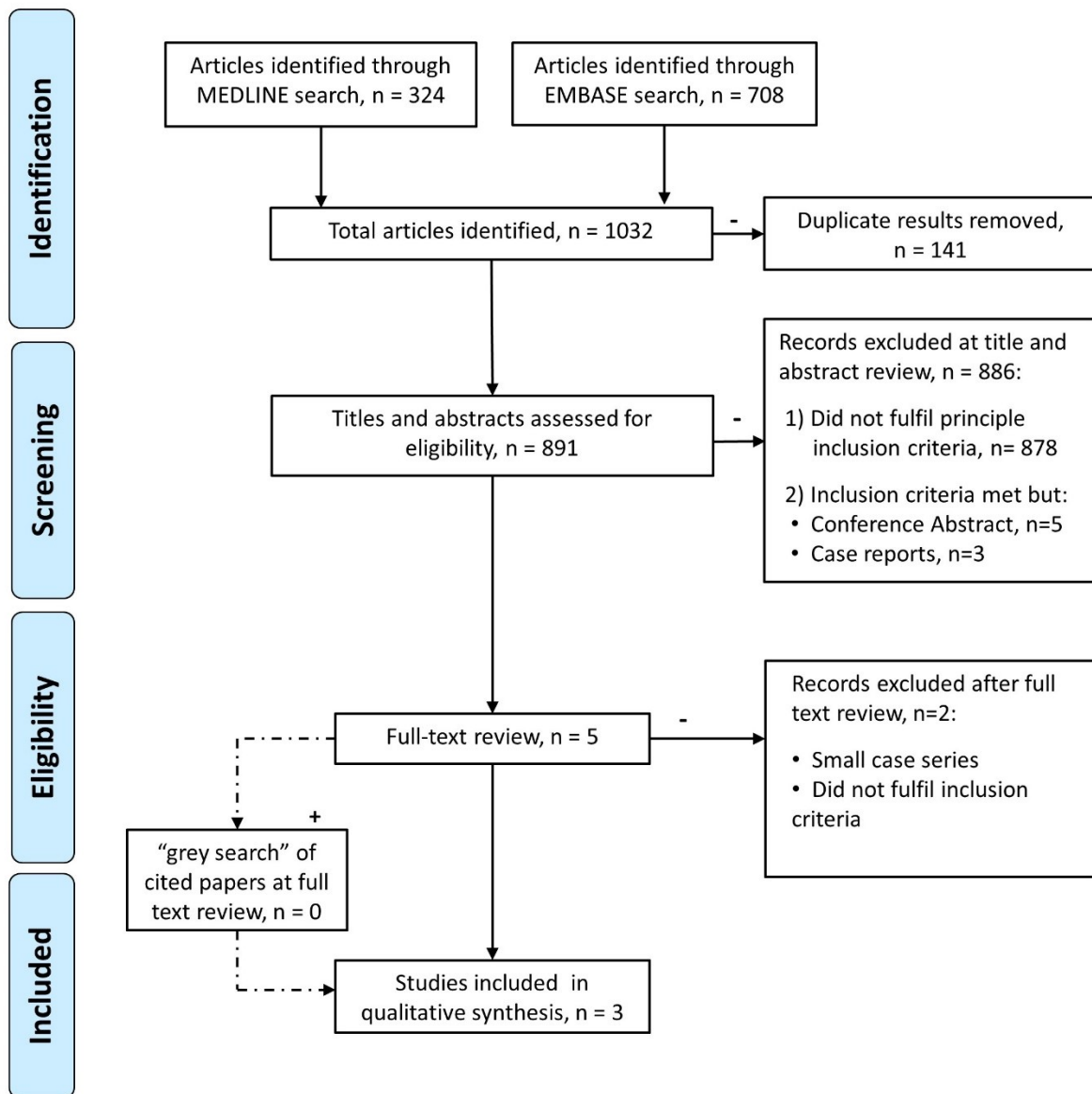
Table 1. Summary table of study characteristics and major findings of studies examining the prognostic value of nailfold capillaroscopy in systemic sclerosis

Author & Date	Origin	Design	Description	Study Population	Intervention	Attrition	Eligibility criteria	Primary outcome	Adverse events	Reported outcomes
Frech et al. 2011 [16]	USA	Open-label study	2-month prospective study of probiotic therapy for GI symptoms of SSc	N =10 (8 lcSSc, 9 female). Mean age 51.7 years	Align (bifidobacterium infantis) or Culturelle (lactobacillus) taken once a day.	Nil reported	1980 Preliminary ARA criteria with moderate to severe distension/bloating scores on SCTC GIT 2.0 questionnaire	UCLA GIT 2.0 questionnaire (total and sub-scales)	Diarrhoea reported 1 patient (?disease or related to intervention)	Significant improvement in total UCLA GIT 2.0 score (mean 0.73 to o.43, P<0.01), reflux scale (mean 0.74 to 0.64, p<0.05), bloating/distention scale (mean 2.15 to 0.97, P<0.01) and emotional scales (0.59 to 0.3, P<0.05) were identified at two months. Largest improvement reported for bloating/distention (ES=1.76).
Marie et al. 2015 [18]	France	Open-label study	1-month prospective study of low-FODMAP diet	Initial cohort of 80 patients (14 men, median age 52.5 years). 32 SSc patients with positive fructose breath test (40% of initial cohort) entered study.	The low-FODMAP diet	91% of subjects were compliant (55% of meals adherent with low-FODMAP guideline)	"based on" 2013 ACR/EULAR classification criteria*	The 11-item GSS (GI symptoms)	Nil reported	Despite high rates of severe oesophageal dysmotility (60%) and delayed gastric emptying (40%) within the study population the median GSS at baseline was only 2 (range 0-21).The fructose breath test cause GI symptoms in 25/32 patients with positive test. Participants with fructose malabsorption had higher GSS score at baseline than those without (despite lower rates of delayed gastric emptying). There was Significant improvement in GSS and individual domains including nausea, vomiting, abdominal pain, bloating, diarrhoea and abdominal tenderness. No change in constipation.
Doerfler et al. 2017 [17]	USA	Open-label study	6-week tailored nutrition counselling	18 (16 female, mean age 51 years)	Individualised medical nutrition and lifestyle counselling. Weekly phone/email contact to enhance intervention adherence.	4 lost to follow up: 2 required PN and/or hospitalisation and 2 lost interest in study	Clinician diagnosis of SSc referred to gastroenterology for both GI symptoms and unintentional weight loss	Primary outcome was nutritional status. UCLA GIT 2.0 used as secondary outcome	2 subjects required parenteral nutrition and/or hospitalisation [likely disease-related events]	Significant improvement in abridged patient generated subjective global assessment (abPGSGA) (13.1 to 7.6, p<0.05) and proportion classified as sarcopenic. GI symptoms did not decrease significantly (either total GIT 2.0 score or individual subscales). There was a statistically insignificant rise in calorie intake, BMI, total fat mass, percent adiposity, appendicular lean height and total lean body mass.

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; low-FODMAP, low-fermentable oligo-saccharides, disaccharides, monosaccharides, and polyol; GSS, Global Symptomatic Score; ARA, American Rheumatology Association; GI, gastrointestinal; ES, effect size; UCLA GIT 2.0 questionnaire, The University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 questionnaire, lcSSc, limited cutaneous systemic sclerosis; USA, United States of America; * recruitment commenced before the publication of these classification criteria

Table 2. Risk of bias assessment of studies using the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) tool

Author & Year of Publication	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Overall risk of bias	Comments
Frech et al. 2011 [16]	LOW	HIGH	UNCERTAIN	HIGH	LOW	LOW	MODERATE	Open label study. The inclusion criteria requiring threshold patient-reported outcomes limits generalizability. The improvement may be related to regression to mean (as a confounding effect).
Marie et al. 2015 [18]	LOW	HIGH	LOW	HIGH	LOW	UNCERTAIN	MODERATE	Open-label study. Selection bias with results only applicable to SSc patients with objective evidence of fructose intolerance. The improvement may be related to regression to mean (as a confounding effect).
Doerfler et al. 2017 [17]	LOW	HIGH	HIGH	HIGH	HIGH	LOW	MODERATE	Open-label study. Small study with high drop out. Highly selective inclusion criteria. The improvement may be related to regression to mean (as a confounding effect).

Table 3. Summary of the interventions and reported findings of conference abstracts reporting effects of dietary modification in systemic sclerosis[25]

Authors	Conference	Intervention	Study design	Reported outcome
Garcia-Collinot et al. 2018 [25]	PANLAR Congress 2018	Probiotic fungus and antibiotic therapy for bacterial overgrowth in SSc	40 SSc patients assigned to 3 groups: probiotic, antibiotic or both	All 3 interventions helped with symptoms of bacterial overgrowth but combination of probiotic and antibiotic appeared most effective with fewer adverse events
Marighela et al. 2017[19]	ACR Annual Meeting 2017	Probiotic therapy	8-week double-blind, placebo-controlled RCT (n=73)	No difference in GI symptoms between groups at 8 weeks but alteration in circulating T-cell populations.
Luchetti et al. 2016 [27]	EULAR Congress 2016	Mediterranean diet with low introduction of meat and dairy products	6-month open label study in 38 patients with SSc and GI involvement	"Patients reported a consistent improvement in GI symptoms and quality of life"
Malgorzewicz et al. 2015 [28]	ESPEN Congress 2015	Supplementary Resource Protein	3 month open label study of supplementary protein in malnourished patients with SSc (n=10)	Improvement in appetite (and nutritional status) observed at 3 months
Gullen-del Castillo et al. 2013 [29]	ACR Annual Meeting 2013	Adherence to gluten-free diet in patients with SSc and coeliac disease	Identified 4 patients with SSc and GI symptoms who had concomitant coeliac disease	Improvement in small bowel symptoms (diarrhoea, abdominal distension/bloating and weight loss) in all patients following institution of gluten-free diet (sustained remission in 50% of patients)

PANLAR, Pan-American League of Rheumatology Associations; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; ESPEN, European Society for Clinical Nutrition and Metabolism; SSc, systemic sclerosis; RCT, randomised controlled trial; GI, gastrointestinal

Supplementary Online Appendix 1: Study Selection criteria for Dietary Modification in SSc SLR

Inclusion Criteria	Assessment
Studies must satisfy the following criteria: • Studies reporting an assessment of the efficacy/impact of dietary modification of any description on GI manifestations in patients with SSc • Longitudinal study reporting with at least 2 assessments (baseline and following intervention)	✓ If fulfils both inclusion criteria X if does not fulfil both inclusion criteria

Exclusion Criteria	Corresponding Letter
Pre-Clinical/Animal studies	A
Studies of childhood or juvenile SSc	B
Studies including patients with mixed connective tissue disease, undifferentiated connective tissue disease or overlap syndromes, where an SSc cohort is not described and reported separately	C
Studies designed to develop or validate measurement scales	D
Case reports	E
Qualitative research	F
Non-original research publications (i.e. editorials or reviews)	G
Abbreviated reports (i.e. letters to editors)	H
Conference abstracts	I
Non-English language	J

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Supplementary Online Appendix 2: data extraction form

Systematic review of dietary modification in SSc: Data Extraction Form

Data extraction form

Citation		**JP**
Retrieval information (date/location)		**LS**

Eligibility criteria

Studies reporting an assessment of the efficacy/impact of dietary modification of any description in patients with SSc Longitudinal study reporting with at least 2 assessments (baseline and following intervention) Doesn't fulfil exclusion criteria	Tick if correct and proceed:

Study Details

Year of publication	
Diagnostic criteria used	
Study design	
Format of Intervention	
Study setting / country	
Sample characteristics (incl. size & subgroup)	
Gender	
Age	
Active treatment Interventions	
Control intervention	
Duration of study	
Primary end-points	
Secondary end-points	
Primary Outcomes:	
Adverse events	
Withdrawal	
Secondary Outcomes:	

Comments

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Supplementary Online Appendix 3: Risk of bias tools used

1. **Cochrane Risk of Bias Assessment Tool for Randomised Trials**

Study Validity Domains	Assessment	Comments
1. Sequence Generation: Was the allocation sequence adequately controlled?	Yes ☐ No ☐ Unclear ☐	
2. Allocation concealment: Was the sequence generation adequately concealed before group assignments?	Yes ☐ No ☐ Unclear ☐	
3. Blinding of participants and personnel: Was knowledge of the allocated interventions adequately hidden from the participants and personnel after the participants were assigned to respective groups?	Yes ☐ No ☐ Unclear ☐	
4. Blinding of outcome assessors: Was knowledge of the allocated interventions adequately hidden from the outcome assessors after participants were assigned to respective groups	Yes ☐ No ☐ Unclear ☐	
5. Incomplete outcome data: Were incomplete outcome data adequately addressed?	Yes ☐ No ☐ Unclear ☐	
6. Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting?	Yes ☐ No ☐ Unclear ☐	
7. Other sources of bias: Was the study apparently free of other problems that could put it at a risk of bias?	Yes ☐ No ☐ Unclear ☐	

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2. The risk-of-bias assessment tool for nonrandomized studies (RoBANS)

Domain	Details	Risk of bias	Comments
Selection of participants	Selection bias caused by the inadequate selection of participants	Low ☐ High ☐ Unclear ☐	
Confounding variables	Selection bias caused by the inadequate confirmation and consideration of confounding variable	Low ☐ High ☐ Unclear ☐	
Measurement of exposure	Performance bias caused by the inadequate measurement of exposure	Low ☐ High ☐ Unclear ☐	
Blinding of outcome assessments	Detection bias caused by the inadequate blinding of outcome assessments	Low ☐ High ☐ Unclear ☐	
Incomplete outcome data	Attrition bias caused by the inadequate handling of incomplete outcome data	Low ☐ High ☐ Unclear ☐	
Selective outcome reporting	Reporting bias caused by the selective reporting of outcomes	Low ☐ High ☐ Unclear ☐	
Overall risk of bias		Low ☐ Mod ☐ High ☐	