




REVIEW

Systematic literature review informing the EULAR recommendations for the non-pharmacological management of systemic lupus erythematosus and systemic sclerosis

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ABSTRACT

Through this systematic literature review, we assembled evidence to inform the EULAR recommendations for the non-pharmacological management of systemic lupus erythematosus (SLE) and systemic sclerosis (SSc). We screened articles published between January 2000 and June 2021. Studies selected for data extraction (118 for SLE and 92 for SSc) were thematically categorised by the character of their intervention. Of 208 articles included, 51 were classified as robust in critical appraisal. Physical activity was the most studied management strategy and was found to be efficacious in both diseases. Patient education and self-management also constituted widely studied topics. Many studies on SLE found psychological interventions to improve quality of life. Studies on SSc found phototherapy and laser treatment to improve cutaneous disease manifestations. In summary, non-pharmacological management of SLE and SSc encompasses a wide range of interventions, which can be combined and provided either with or without adjunct pharmacological treatment but should not aim to substitute the latter when this is deemed required. While some management strategies i.e., physical exercise and patient education, are already established in current clinical practice in several centres, others e.g., phototherapy and laser treatment, show both feasibility and efficacy, yet require testing in more rigorous trials than those hitherto conducted.

INTRODUCTION

Systemic lupus erythematosus (SLE)¹ and systemic sclerosis (SSc)² belong to the rheumatic connective tissue diseases (CTDs) and are characterised by multiorgan involvement and a considerable morbidity burden, with a large proportion of the latter comprising comorbidities. Although advances in pharmacotherapy and non-pharmacological management have contributed to substantially improved patient outcomes during the last

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Non-pharmacological management of systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) is a helpful tool for patients and healthcare providers alike.

WHAT THIS STUDY ADDS

- ⇒ Physical activity and patient education comprise the most evidence-based non-pharmacological management strategies for these diseases.
- ⇒ In SLE, research focus has been placed on exploring psychosocial interventions.
- ⇒ High-quality randomised controlled trials studying the long-term efficacy of non-pharmacological management of SLE and SSc are needed.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The insights from this review can serve as an evidence base for European Alliance of Associations for Rheumatology recommendations for the non-pharmacological management of SLE and SSc.

decades, sufferers from SLE and SSc still experience shorter life length compared with the general population and a severely impaired health-related quality of life (HRQoL).

Common organ systems that are afflicted in patients with SLE and SSc include the musculoskeletal, mucocutaneous, cardiopulmonary, vascular and nervous systems, resulting in activity limitations, pain, distress, skin eruptions and ulcers, shortness of breath, depressive symptoms and ultimately detrimental socioeconomic consequences.^{1,2}

Accumulating evidence suggests that non-pharmacological management should constitute an integral part of the management of patients with CTDs.³⁻⁶ In patients with



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SLE and SSc in particular, physical activity and exercise have been shown to reduce fatigue and improve HRQoL.^{4 5 7 8} The appropriateness and efficacy of different delivery methods for non-pharmacological management have also been addressed in the literature, including e-health settings,⁹ which recently were urgently necessitated due to the pandemic caused by SARS-CoV-2.

Although many studies have been conducted on non-pharmacological interventions, evidence-driven recommendations are sparse. The systematic literature review (SLR) presented herein was conducted to inform the European Alliance of Associations for Rheumatology (EULAR) recommendations for the non-pharmacological management of SLE and SSc.¹⁰

METHODS

Research questions

With the purpose of formulating recommendations for the non-pharmacological management of SLE and SSc, a task force was assembled in 2020 within EULAR, which comprised 25 experts across different healthcare professions and patient research partners. The literature search was steered by nine research questions (RQs) that were agreed on by the members of this EULAR task force. These RQs concerned the aims of non-pharmacological management (RQ1), types of interventions (RQ2), efficacy of interventions (RQ3), health-related domains or organ systems assessed (RQ4), outcome measures used (RQ5), time points of assessment (RQ6), patients' needs, expectations and preferences (RQ7), educational needs for patients as well as healthcare providers (RQ8), and facilitators and barriers to the non-pharmacological management of SLE and SSc (RQ9). The precise formulations of the research questions are detailed in [table 1](#).

Search strategy and article selection

The search strategy was designed in collaboration with expert librarians from Karolinska Institutet. On 22 June 2021, the MEDLINE (Ovid), EMBASE (embase.com), Web of Science Core Collection and CINAHL (EBSCO) databases were searched for content published from January 2000 to June 2021. We conducted a two-block search, including the diagnoses of interest and a list of non-pharmacological management strategies, presented in full in online supplemental file 1. We excluded case series of less than five individuals, and articles in languages other than English, Spanish and Swedish. Due to the diverse nature of the questions, we did not exclude articles based on study design. Two independent reviewers (AG and JWC) screened the identified titles and abstracts. Disagreements between reviewers were solved through a consensus, together with two more investigators (IP and CB).

Data extraction

Using electronic forms customised for each RQ, two independent researchers per disease (AG and DP for SLE; AT and JWC for SSc) extracted information from

Table 1 Research questions formulated by the EULAR task force

#	Research questions
1	What should non-pharmacological management aim for?
2	Which non-pharmacological interventions have been used?
3	Which non-pharmacological interventions have been shown to be efficacious?
4	Which instruments have been used to assess the outcome of non-pharmacological management?
5	When should the outcome of non-pharmacological management be assessed?
6	Within which health-related domains or organ systems should non-pharmacological management be assessed?
7	What are the patients' needs, expectations and preferences with regard to non-pharmacological management of SLE and SSc?
8	What are the educational needs for healthcare professionals and patients regarding non-pharmacological management?
9	What are the facilitators and barriers to the use of non-pharmacological management?

For all research questions, the populations of interest were adult patients with SLE or SSc.
EULAR, European Alliance of Associations for Rheumatology; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

full texts, including author, year of publication, country, study design, number of participants, demographic and clinical characteristics, intervention, health-related domain, outcome measure, time point of assessments and reported results. Considering the diversity on study designs included herein, and that one of the RQs concerned outcome measures used (RQ5), outcomes were summarised as reported by the authors, and comprised dichotomous and continuous data, as well as effect measures for dichotomous outcomes (risk ratios and ORs) and continuous outcomes (mean and standardised mean differences).

Discrepancies were discussed among the four researchers until a consensus was reached; when needed, IP and CB were consulted to resolve disagreements.

Critical appraisal

Risk of bias (RoB) of all included articles was conducted by the same investigator (AT) under the supervision of IP, using the critical appraisal (CA) tools (online supplemental checklists) by the Joanna Briggs Institute.¹¹ Since study selection was not performed based on RoB, the overall appraisal terms “include”, “exclude” and “seek further info” were not applicable, and were thus replaced by “robust”, “weak” and “intermediate”, respectively. A

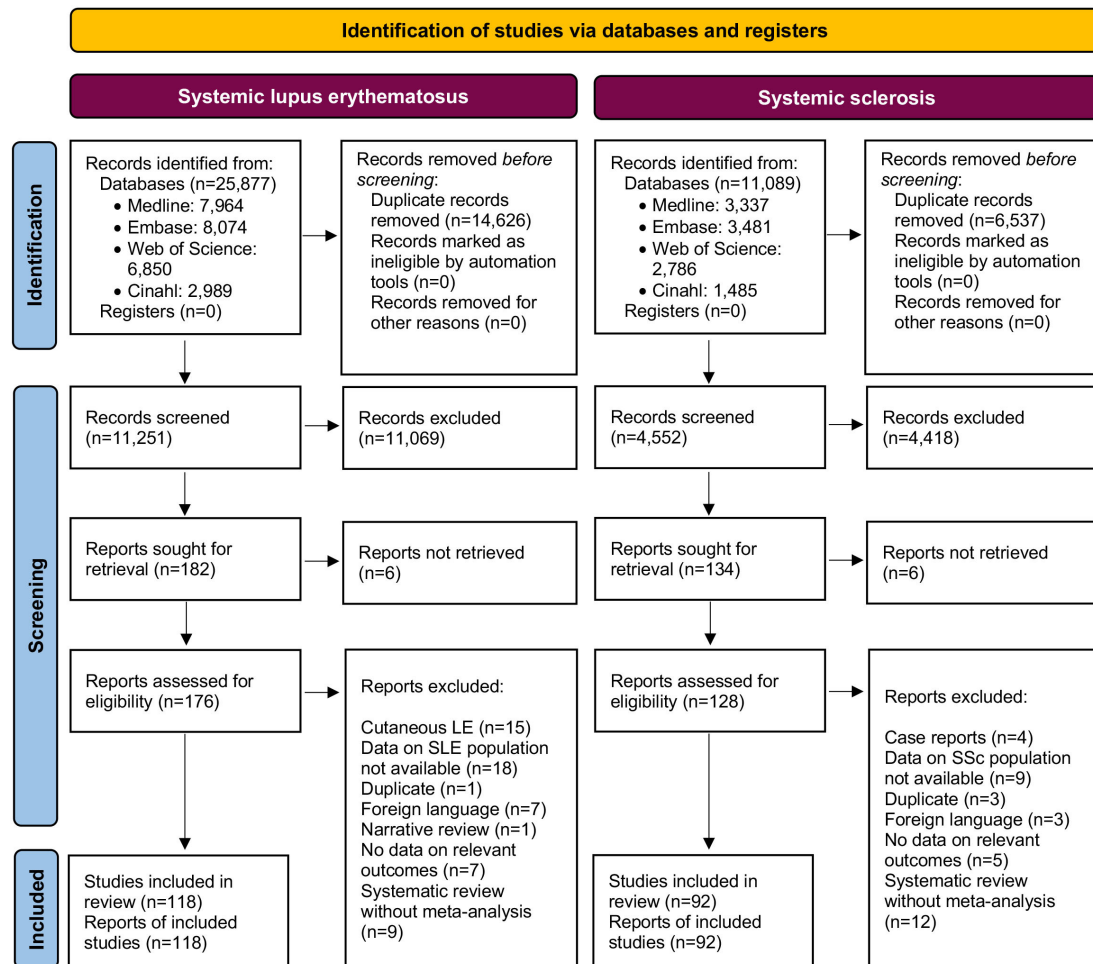


Figure 1 PRISMA flow diagram illustrating the steps followed for identification of studies. PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

study was rated as robust if it clearly fulfilled all, or all but no more than two checklist criteria, intermediate if it fulfilled all but three to five criteria, or weak if six or more checklist criteria were not clearly fulfilled.

RESULTS

Study selection

Stratified by diagnosis, the search resulted in 25 877 and 11 251 hits for SLE, and 11 089 and 4 552 hits for SSc before and after deduplication, respectively (figure 1 and online supplemental file 1). Of those 25 877 initial hits for articles on the non-pharmacological management of SLE, 118 articles were selected for full-text evaluation. Of the 11 089 initial hits for articles on the non-pharmacological management of SSc, 92 articles were selected for full-text evaluation (figure 1). Two studies, one cross-sectional study assessed as intermediate¹² and one qualitative study assessed as robust¹³ in CA, included both patients with SLE and patients with SSc, and were therefore included in the analysis for both diseases.

Study design and CA

For SLE, the largest study design categories were randomised controlled trials (RCTs; n=49), followed by

quasi-experimental studies (n=38) and cross-sectional studies (n=12). For SSc, the largest study design categories were quasi-experimental studies (n=37), followed by RCTs (n=33) and qualitative studies (n=8). For SLE, 28 articles were assessed as robust in CA, 52 articles were assessed as intermediate and 38 were assessed as weak. For SSc, 24 articles were assessed as robust, 52 articles were assessed as intermediate and 16 articles were assessed as weak. A summary of the CA of the studies, sorted by disease and study design, is presented in table 2.

Data extraction

Online supplemental tables 1–3 present the extracted data from all articles selected for data extraction, whereas online supplemental tables 4–11 detail the CA for each study, sorted by study design. Study design and overall appraisal for each study are also provided in online supplemental tables 1–3; in those tables, overall appraisal is colour coded to aid readability, with green denoting robust, yellow denoting intermediate and red denoting weak studies. The results (sorted by RQ) are summarised below.

Table 2 Critical appraisal of selected articles sorted by disease and study design

Study design, disease	Robust	Intermediate	Weak	Total
Randomised controlled trials				
SLE	0	16	33	49
SSc	2	18	13	33
Quasi-experimental studies				
SLE	8	29	1	38
SSc	13	23	1	37
Cross-sectional studies				
SLE	6	6	0	12
SSc	1	4	2	7
Qualitative studies				
SLE	6	0	2	8
SSc	7	1	0	8
Case series				
SLE	0	0	1	1
SSc	0	4	0	4
Cohort studies				
SLE	3	0	1	4
SSc	0	1	0	1
Meta-analyses				
SLE	5	0	0	5
SSc	0	0	0	0
Case-control studies				
SLE	0	1	0	1
SSc	1	1	0	2

SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

Aims of management (RQ1)

For SLE, effects on HRQoL and disease activity emerged as major aims of non-pharmacological management, being addressed in 47 and 44 studies, respectively. Other prominent aims included improvements in fatigue (n=28), depression (n=24) and pain (n=15), as well as prevention of organ damage (n=11), increased self-efficacy (n=9) and improvements in aerobic capacity (n=6).

For SSc, many studies investigated improvements of hand mobility (n=22), HRQoL (n=19) and microstomia (n=11). Other aims of the non-pharmacological management of SSc included improvements in skin sclerosis other than perioral (n=10), gastrointestinal symptoms (n=7), skin ulcers (n=7), Raynaud's phenomenon (n=5) and depression (n=4).

Categories of interventions (RQ2)

For SLE, the largest category of non-pharmacological management was physical exercise and physical activity (n=34),^{7 14-45} followed by patient education and

self-management (n=21),^{13 31 46-64} psychological interventions (n=21),^{37 65-84} dietary therapy and nutrition (n=14),^{19 85-97} complementary medicine (n=5),⁹⁸⁻¹⁰² photoprotection (n=5),¹⁰³⁻¹⁰⁷ healthcare models (n=4),¹⁰⁸⁻¹¹¹ laser treatment (n=2),^{112 113} social support (n=2)^{114 115} and others (n=6).¹¹⁶⁻¹²¹

For SSc, the largest category of non-pharmacological management was, as in SLE, physical exercise and physical activity (n=32),¹²²⁻¹⁵³ followed by patient education and self-management (n=12),^{13 144 148 154-162} bathing and thermal modalities (n=8),^{123 136 141-143 163-165} complementary medicine (n=8),^{146 163 166-171} manual therapy (n=8),^{126 127 129 136 139 172-174} dietary therapy and nutrition (n=6),¹⁷⁵⁻¹⁸⁰ phototherapy and laser treatment (n=6),¹⁸¹⁻¹⁸⁶ shockwave therapy (n=4),¹⁸⁷⁻¹⁹⁰ healthcare models (n=3),^{155 191 192} hyperbaric oxygen or ozone therapy (n=3),^{165 193 194} oral hygiene (n=3)^{131 191 195} and others (n=4).¹⁹⁶⁻¹⁹⁹

Efficacy of interventions (RQ3)

Systemic lupus erythematosus

Physical exercise and physical activity

Three meta-analyses, all assessed as robust in CA, evaluated the effect of physical exercise and physical activity. The first meta-analysis, performed in 2017 on six RCTs and five quasi-experimental studies, found that exercise improved aerobic capacity (mean difference: 1.85; 95% CI: 1.12, 2.58; p<0.001) and decreased fatigue (mean difference: -0.61; 95% CI: -1.19 to -0.02; p=0.04) and depressive symptoms (mean difference: -0.40; 95% CI: -0.71 to -0.09; p=0.01) in patients with SLE, yet did not affect disease activity (mean difference: 0.01; 95% CI: -0.54, 0.56; p=0.97). The second meta-analysis was conducted the same year on two RCTs and one quasi-experimental study, and found that exercise reduced fatigue in patients with SLE (mean difference: -0.52; 95% CI: -0.91 to -0.13; p=0.009).⁸ The third meta-analysis, conducted in 2019, included two RCTs and found that physical activity improved physical functioning as measured by the 36-Item Short Form Survey (SF-36; mean difference: -9.20; 95% CI: -18.16, -0.23; p=0.04), but not vitality.³⁷

Patient education and self-management

Ten RCTs, all assessed as weak in CA, examined patient education and self-management. Of these, five studies employed interventions aiming to improve medication adherence.^{50 51 53 57 60} The interventions that proved efficacious among those were patient information^{50 57} and targeted nursing (ie, tailored according to pathogenic condition and treatment period),⁵³ whereas text-message reminders⁵¹ and electronic pill boxes⁶⁰ did not show significant adherence improvement. Other RCTs (CA: weak) found web-based patient education to be efficacious in managing fatigue,⁶¹ self-efficacy,⁶¹ sleep disturbance⁶³ and anxiety.⁶³ Two non-RCTs in this category were assessed as robust in CA. These were both qualitative studies evaluating patient education programmes on

disease management, where patients expressed satisfaction with their respective programmes.^{13 48}

Psychological interventions

Three meta-analyses, all assessed as robust in CA, evaluated the effect of psychological interventions. The first meta-analysis, conducted in 2012 on six RCTs, found psychological interventions to be efficacious in managing anxiety (mean difference: -0.95; 95% CI: -1.57 to -0.34; $p < 0.001$), depression (mean difference: -1.14; 95% CI: -1.84 to -0.44; $p < 0.001$), disease activity (mean difference: -0.34; 95% CI: -0.57 to -0.11; $p < 0.001$) and stress (mean difference: -0.63; 95% CI: -1.02 to -0.23; $p < 0.001$).⁷⁵ The second meta-analysis, conducted in 2014 on six RCTs, found psychological interventions efficacious in managing depression (mean difference: -0.44; 95% CI: -0.78, 0.10; $p = 0.01$) and SF-36 physical component summary scores (mean difference: 8.85; 95% CI: 3.69, 14.0; $p < 0.001$).⁷⁷ The third meta-analysis, conducted in 2019 on two RCTs, found cognitive-behavioural therapy to improve HRQoL (mean difference: -17.7; 95% CI: -26.7, -8.63; $p < 0.001$).³⁷

Other categories

Studies on dietary therapy and nutrition that were assessed as robust in CA were all observational in nature^{86 90 97} and found that increased intake of vitamin B₆ and vitamin C was associated with lower SLE disease activity,^{86 90} and that adherence to a Mediterranean diet was associated with a lower cardiovascular risk.⁹⁷ One cross-sectional study on complementary medicine (CA: robust), defined as the use of any treatment not prescribed by an allopathic primary or specialist physician, was assessed as robust in CA and noted lower levels of organ damage and a better quality of life in patients who had used complementary therapies.¹⁰⁰ One quasi-experimental study (CA: robust) showed that sunscreen protected against upregulation of ICAM-1 mRNA.¹⁰³ Studies on healthcare models were few, non-robust in CA and diverse.^{108–111} Pulsed dye laser on discoid lesions was shown in one quasi-experimental study (CA: robust) to decrease mucocutaneous activity assessed using the Cutaneous Lupus Erythematosus Disease Area and Severity Index.¹¹² Two cross-sectional studies (CA: robust) found that social support associated with better HRQoL, illness uncertainty and coping skills.^{114 115} One cross-sectional study (CA: robust) found that smoking cessation was associated with lower SLE disease activity,¹¹⁸ and one quasi-experimental study (CA: robust) found warm showers efficacious in improving fatigue.¹¹⁹

Systemic sclerosis

Physical exercise and physical activity

An RCT assessed as robust in CA evaluated the effect of a 4-week physical therapy programme followed by home exercise and found the intervention to be efficacious in managing microstomia, at a 12-month follow-up.¹³⁷ RCTs assessed as intermediate in CA found

physical exercise and physical activity to be efficacious in managing microstomia,^{132 149} aerobic capacity¹⁴⁷ and hand function.¹⁵¹ Quasi-experimental studies assessed as robust in CA found physical exercise and physical activity to be efficacious in managing microstomia,¹²² aerobic capacity,¹³⁰ pain¹⁴⁴ and hand function assessed with the Hand Mobility in Scleroderma Instrument (HAMIS), but not functional impairment assessed with the Health Assessment Questionnaire-Disability Index (HAQ-DI).¹²⁵

Patient education and self-management

The RCT rated highest in CA (CA: intermediate) evaluating patient education and self-management found face-to-face instruction combined with educational material more effective than educational material alone.¹⁶¹ Another RCT (CA: weak) found an internet-based self-management programme to improve quality of life.¹⁵⁹ In quasi-experimental studies assessed as robust in CA, educating patients on self-management was found to improve self-efficacy,¹⁵⁷ functional impairment¹⁵⁸ and pain.¹⁴⁴

Other categories

Two quasi-experimental studies (CA: robust) that investigated a combination of non-pharmacological interventions including bathing and thermal modalities found the interventions to be efficacious in improving hand function.^{136 141} A case-control study (CA: robust) found anorectal biofeedback therapy to ameliorate faecal incontinence.¹⁶⁹ An RCT (CA: robust) on manual lymph drainage was also found to improve hand function.¹⁷² One RCT (CA: intermediate) and one quasi-experimental study (CA: intermediate) found that probiotics improved gastrointestinal symptoms.^{175 178} Two pilot studies, both quasi-experimental in nature (CA: robust), found light therapy to improve telangiectases¹⁸² and pain in digital ulcers,¹⁸⁶ respectively. Four quasi-experimental studies on shockwave therapy (CA: intermediate) found the intervention to be efficacious in improving skin ulcers^{189 190} and skin sclerosis.^{187 188} A quasi-experimental study (CA: robust) on a multidisciplinary disease management programme found this to improve feelings of helplessness and acceptance of limitations.¹⁵⁵ One case series (CA: intermediate) and one quasi-experimental study (CA: intermediate) found hyperbaric oxygen¹⁹³ and ozone therapy¹⁶⁵ aiding resolution of skin ulcers. Studies on oral hygiene interventions were few, dissimilar in design and not robust in CA.^{131 191 195} Individual studies have shown efficacy of autologous fat transplantation in improving mouth opening,¹⁹⁶ of neuromuscular taping in improving hand mobility,¹⁹⁷ of animal-assisted intervention (pet therapy) in alleviating anxiety¹⁹⁸ and of application of amniotic membrane dressings in resolution of skin ulcers¹⁹⁹; these studies were assessed as intermediate in CA.

Outcome measures (RQ4)

Numerous outcome measures have been used to determine the efficacy of non-pharmacological interventions of SLE and SSc. For detailed listings of which outcome measures were used for each study, see online supplemental table 3.

For SLE, the physician-assessed Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)²⁰⁰ and Systemic Lupus Activity Measure (SLAM)²⁰¹ as well as the patient-reported Systemic Lupus Activity Questionnaire²⁰² were used to determine disease activity. Exercise capacity was often assessed with the maximal oxygen uptake (VO₂-max). Organ damage was mainly assessed through the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.²⁰³ Outcomes for the estimation of quality of life included the generic SF-36,²⁰⁴ EQ-5D²⁰⁵ and Patient-Reported Outcomes Measurement Information System (PROMIS),²⁰⁶ as well as the disease-specific Lupus Quality of Life questionnaire.²⁰⁷ Fatigue was mainly assessed with the Fatigue Severity Scale (FSS),²⁰⁸ Functional Assessment of Chronic Illness Therapy–Fatigue,²⁰⁹ Multidimensional Assessment of Fatigue²¹⁰ and Visual Analogue Scales. Depression was assessed with the Center for Epidemiological Studies–Depression Scale,²¹¹ Hospital Anxiety and Depression Scale (HADS)²¹² and Beck Depression Inventory (BDI).²¹³ Pain was mainly assessed through Visual Analogue Scales. Anxiety was mainly assessed with HADS and the State-Trait Anxiety Inventory (STAI).²¹⁴ Body composition was mainly assessed through the body mass index.²¹⁵ Self-efficacy was mainly assessed through self-efficacy scales.²¹⁶ For a detailed overview of all outcome measures used in the included studies, see online supplemental table 3. The main inflammatory markers assessed were tumour necrosis factor alpha, C reactive protein, C3 and C4, interleukin (IL)-6 and IL-10.

For SSc, functional impairment was often measured with the HAQ-DI,²¹⁷ and hand-specific outcomes such as HAMIS²¹⁸ and Duruoz Hand Index.²¹⁹ Skin sclerosis was mainly assessed using the modified Rodnan Skin Score,²²⁰ but also with light microscopy, as well as with subjective assessments by both patients and clinicians. Microstomia was virtually always assessed using length measurements, such as maximal mouth opening and interincisal distance. Skin ulcers were mainly assessed with qualitative scoring, and quantitatively with, for example, number of ulcers and time to ulcer resolution. Digestion was mainly assessed with the University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument²²¹ among other questionnaires. Oral hygiene was mainly assessed through subjective patient reporting, or with scoring instruments such as the Löe-Silness Gingival Index.²²² Exercise capacity was often assessed with VO₂-max and the 6 min walk test.²²³ Quality of life was mainly assessed using the SF-36 and PROMIS. Pain was mainly assessed using Visual Analogue Scales. Circulation was mainly assessed using laser Doppler imaging. The main biomarkers assessed were von

Willebrand factor, vascular endothelial growth factor and IL-6.

Time points of assessment (RQ5)

Systemic lupus erythematosus

Studies on physical exercise and physical activity assessed outcomes at widely varying time points, from minutes after a single bout of exercise³² up to 36 months after baseline.⁴⁵ Interventions employing patient education and self-management were assessed between 1 week (at the earliest)⁵⁶ and 3 years (at the latest)⁵⁵ from baseline. Psychological interventions were assessed at the earliest after 1 week from intervention initiation⁸⁴ and at the latest after 15 months.⁷³ Studies dealing with dietary therapy and nutrition assessed outcomes between 4 weeks and 5 years from baseline. Assessment time points for complementary therapies varied largely, ranging from 12 weeks to 2 years from baseline. The effect of photoprotection was assessed after 24 hours at the earliest to 9 weeks at the latest. Healthcare models were assessed between 12 weeks and several years after initiation of the intervention. Laser treatment was assessed at 4, 8 and 12 weeks from baseline. Studies on social support were of cross-sectional design and did not evaluate social support after a defined time point (see online supplemental table 3).

Systemic sclerosis

Studies examining the impact of physical exercise and physical activity in SSc assessed outcomes of the intervention from immediately after the intervention,¹³⁶ with the study with the longest follow-up period in this category assessing participants yearly for 3 years.¹³⁹ Studies on patient education and self-management assessed outcome measures between 4 weeks¹⁴⁴ and 6 months¹⁵⁸ from baseline. Assessment time points regarding bathing and thermal modalities varied widely, ranging from a few minutes to a full year after baseline. Complementary therapies were assessed between hours and 6 months from initiation of the intervention. The effects of manual therapy were assessed between 2 weeks and 3 years after baseline. Effects of dietary therapy and nutrition were assessed between 1 and 18 months after baseline. Studies on phototherapy and laser treatment assessed effects after as little as one bout of treatment to a year post-baseline. Outcomes of shockwave therapy were assessed at time points between one round of therapy and 9 weeks after baseline. Studies on healthcare models assessed outcomes after 6 weeks–12 months. Studies on hyperbaric oxygen or ozone therapy had set assessment time points at 20 and 40 days. Outcomes of oral hygiene interventions were evaluated between 10 min and 1 year after baseline.

Health-related domains or organ systems assessed (RQ6)

Systemic lupus erythematosus

In patients with SLE, non-pharmacological management strategies that were found to be efficacious within the mucocutaneous domain included laser treatment¹¹³

and photoprotection.¹⁰⁵ Within the cardiopulmonary, vascular and musculoskeletal domains, exercise was found to improve aerobic capacity and neuromuscular responses, and lower the cardiovascular risk.^{16 42 86} Within the neuropsychiatric domain, anxiety and depression were efficaciously managed by cognitive-behavioural therapy.⁶⁹

Systemic sclerosis

In patients with SSc, challenges within the mucocutaneous domain mainly consisted of skin sclerosis, calcinosis, skin ulcers and microstomia; these were shown to be efficaciously managed with, for example, physiotherapy,¹²² multidisciplinary care models,¹⁵⁵ phototherapy¹⁸⁶ and shockwave therapy.¹⁸⁸ Within the cardiopulmonary and vascular domains, exercise improved VO₂-max and cutaneous vascular conductance, respectively.^{128 145} Within the musculoskeletal domain, high-intensity interval training was found efficacious for improving inspiratory muscle and grip strength.¹⁵⁰ Gastrointestinal manifestations, for example, bloating and distension, were efficaciously managed with probiotics.¹⁷⁵ Within the neuropsychiatric domain, anxiety was efficaciously managed with, for example, animal-assisted interventions.¹⁹⁸

Patients' needs, expectations and preferences (RQ7)

Systemic lupus erythematosus

A qualitative study (CA: robust) assessing patients with SLE from medically underserved communities found that patients desired more education about their disease, as well as assistance in navigating the healthcare system.²²⁴ Patients also favoured peer support and the idea of a lupus health passport, that is, a notebook containing a personalised treatment plan, preventive health tips and health information.²²⁴ A thematic analysis of patient responses to open-ended questions posed online (CA: robust) identified increased visibility as a need of patients with SLE, both in social and healthcare settings.²²⁵

Systemic sclerosis

A qualitative study (CA: robust) aiming to characterise illness perception of patients with early SSc identified low personal control and concerns about the future as needs to be addressed.²²⁶ Another qualitative study (CA: robust) noted strong expectations from patients with SSc on the patient-physician relationship, including involvement in research and individualised treatment decisions.²²⁷

Educational needs (RQ8)

Systemic lupus erythematosus

An interview study including six participants (CA: robust) found poor communication and lack of validation to be shortcomings experienced by patients with SLE in interaction with their healthcare providers.²²⁸ This study concluded that there was a necessity to integrate physicians into social support interventions. To increase visibility and improve the care provided to patients with SLE, a study advocated that medical professionals might

benefit from training of their skills in managing the psychosocial consequences of the disease.²²⁵

Systemic sclerosis

An observational study (CA: intermediate) employing open-ended questioning specifically addressing educational needs for healthcare professionals in the non-pharmacological management of SSc found that the educational needs were mainly oriented around the management of stiffness, pain and impaired hand function.²²⁹ A series of focus group interviews (CA: intermediate) found physical manifestations and disclosure of one's disease to be central themes defining the experience of living with SSc, and concluded that healthcare professionals may stigmatise individuals due to ignorance of rare conditions.²³⁰

Facilitators and barriers (RQ9)

Systemic lupus erythematosus

Difficulty in navigating healthcare systems emerged as a barrier to disease management in patients with SLE.^{224 225} A qualitative analysis of the LUPUS UK online forum (CA: robust) found that diagnostic delays due to disbelief or dismissal of symptoms, along with medical miscommunications and misunderstandings, were perceived as barriers by patients.²³¹ An interview study on smoking cessation (CA: weak) identified concerns for one's health and concerns for others as facilitators, whereas enjoyment and using smoking as a coping mechanism emerged as barriers to quitting smoking.²³²

Systemic sclerosis

Two qualitative studies (CA: robust) found barriers of physical exercise in patients with SSc related to disease, such as shortness of breath and pain.^{233 234} Adjustments of duration, intensity and choice of physical activity were identified as facilitators for exercise.²³³ A study employing focus group discussions (CA: robust) found that for social support, careful choice of support source and honest communication could constitute facilitators, while aversion to speaking about one's disease emerged as a barrier.²³⁵ This study also highlighted the importance of close relationships for enhanced social support.²³⁵

DISCUSSION

In summary, this review examined current evidence on the non-pharmacological management of SLE and SSc. Physical exercise was the most studied management strategy in both diseases, and was found to be efficacious with regard to several outcomes, such as fatigue (in SLE) and hand function (in SSc) in studies assessed as robust in CA. Studies on patient education and self-management found improvements regarding self-efficacy, although these studies were of varying robustness in overall CA. Psychological interventions represented a prominent management strategy for depressive symptoms in SLE, while many studies on SSc pertained to phototherapy

and laser treatment and found these interventions to be efficacious in improving cutaneous manifestations.

In several studies, interventions aimed to improve quality of life. In SSc, particular focus was also placed in functional impairment. Interventions identified during a systematic literature search were categorised thematically; key intervention categories included physical exercise, patient education and self-management. Non-pharmacological management of both SLE and SSc was mostly assessed for its effects within the mucocutaneous, cardiopulmonary, vascular, musculoskeletal and neuropsychiatric domains, whereas gastrointestinal manifestations were mainly assessed in SSc only.

The instruments for assessing outcomes of management were largely similar for both diseases in domains such as quality of life (SF-36), depression (HADS, BDI), anxiety (STAT-I) and fatigue (FSS). SLE disease activity was often assessed using SLAM or SLEDAI. In SSc, assessment of functional impairment using HAQ, the Mouth Handicap in Systemic Sclerosis scale (MHSS) or HAMIS appeared central. Within many intervention categories, outcomes were assessed at or around 12 weeks after baseline.

Patients' needs, expectations and preferences involved the difficulty of navigating healthcare systems. This was in line with educational needs for healthcare professionals, which included an increased understanding of patients' experience of their disease. Intervention-specific facilitators and barriers to non-pharmacological management related to social relationships of the patients, among other facets.

Within the SLE literature selected for analysis, studies on healthcare models were few, non-robust in CA and diverse; thus, no firm conclusions could be drawn regarding the efficacy of healthcare models.^{108–111} Likewise, studies on oral hygiene interventions within the selected SSc literature were few, dissimilar in design and non-robust in CA; thus, no firm conclusions could be drawn regarding their efficacy.^{131 191 195} Regarding organ systems for which interventions were evaluated, the gastrointestinal tract emerged as an important health-related domain that was often subject to investigation in SSc, but not in SLE. While gastrointestinal symptoms also constitute SLE manifestations, the higher number of studies addressing gastrointestinal symptoms in SSc may reflect that these symptoms comprise a larger area of concern in patients with SSc, or that efficacy of non-pharmacological management of the gastrointestinal domain within SLE has yet to be thoroughly explored.

Qualitative studies explicitly evaluating patients' needs, expectations and preferences were not as intervention specific as the studies investigating facilitators and barriers to non-pharmacological management.^{232–234} Several studies that were selected for systematic data extraction were aimed at investigating tolerability and feasibility of different interventions.^{19 58 60 99 160 186}

A subgroup of studies on patient education and self-management in SLE evaluated medication

adherence,^{50 51 53 57 60} whereas a subgroup of studies within the same category in SSc evaluated self-administered rehabilitation programmes.^{144 148 161} These subcategories within educational interventions were unique for SLE or SSc, suggesting that certain issues addressed in studies are specific to each disease, presumably reflecting disease-specific patient needs. Furthermore, educational interventions were oftentimes managed and assessed by nurses, physiotherapists or occupational therapists.^{53 57 154 158 161} Since physicians have an overarching responsibility for the patients' well-being, this poses to physicians the requirement of, at minimum, an understanding of the patient needs and patient education strategies.

Physical exercise was the most studied non-pharmacological management strategy in both SLE and SSc. Although many studies, especially on the management of SSc, examined combinations of different therapeutic modalities rather than only one intervention,^{126 129 131 135 136 143} none of the selected studies aimed at replacing pharmaceutical treatment with non-pharmacological alternatives.

The high degree of heterogeneity of the management strategies explored in literature limited us from performing in-depth analysis of individual strategies. Another shortcoming of the present SLR was that systematic cut-offs for overall appraisal with the CA tools from the Joanna Briggs Institute,¹¹ conducted as described in the Methods section, have not been validated, and different ways to interpret the checklists could impact what studies were deemed as robust. A measure taken to assure quality in highly appraised studies was treating unclearly fulfilled criteria as unfulfilled, which may have led to a somewhat conservative selection of studies assessed as robust.

This review mapped a wide range of non-pharmacological interventions, as well as gaps in the current knowledge in the field of non-pharmacological management of SLE and SSc; most RCTs conducted on this subject lacked assessment time points after 1 year from baseline, and RCTs included in the review were often unclear about the blinding strategies followed for study participants, treatment providers and outcome assessors.

Apart from physical exercise, patient education and self-management, other large categories of interventions were distinct between SLE and SSc, that is, psychological interventions in SLE and phototherapy and laser treatment in SSc; laser treatment also emerged as an intervention category in SLE, although with fewer studies evaluating its efficacy.

All RCTs evaluating psychological interventions for the management of SLE were assessed as weak in CA.^{66 68 72–74 78 84} This may be due to the method followed for systematically evaluating overall appraisal, since RCTs are assessed by a higher amount of criteria compared with other study designs.¹¹ Phototherapy and laser treatment,^{181–186} as well as shockwave therapy,^{187–190} were found to be efficacious for the management of SSc, and studies of these were all assessed as intermediate or robust in CA. However, none of these studies had an RCT design.

These findings underpin an encouragement for future studies of RCT design to clarify blinding strategies, and to assess outcomes in the long term, that is, a year or beyond. Also, while several quasi-experimental studies suggest that phototherapy and laser treatment strategies have favourable effects on skin sclerosis and wound healing in patients with SSc, future RCTs evaluating their efficacy are desirable.

The literature search was restricted to articles published between January 2000 and June 2021, which may be considered a limitation. This decision was made due to several reasons. First, since the SLR was conducted to inform the EULAR recommendations for the non-pharmacological management of SLE and SSc, it was important to ensure that the recommendation statements were not based on dated evidence. Second, major changes in the pharmacological management of rheumatic diseases were introduced in the beginning of the current century, for example, the introduction of biological agents. This had implications in the overall management of patients with rheumatic diseases; even though the first biological therapy for SLE was approved in 2011, off-label use of, for example, rituximab can be traced in literature back to the early 2000s. Lastly, important papers published earlier than January 2000 were captured through citations in more recent papers, including comprehensive reviews used for the background and discussion of the present SLR, as well as through experts' awareness.

In conclusion, non-pharmacological management of SLE and SSc encompasses a wide range of interventions, which can be combined and provided either with or without adjunct pharmacological treatment, but should not aim to substitute the latter when this is deemed required. While some of the management strategies supported in this review, that is, physical exercise and patient education, are already established in current clinical practice in several centres, others, for example, phototherapy and laser treatment, show both feasibility and efficacy, yet require testing in more rigorous trials than those hitherto conducted.

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