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Rehabilitation in Systemic Sclerosis

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Rehabilitation Interventions in Systemic Sclerosis: A Systematic Review and Future Directions

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ABSTRACT

Objective. To systematically review evidence of rehabilitation interventions for improving outcomes in systemic sclerosis (SSc) and to evaluate evidence quality.

Methods. Several electronic databases were searched to identify studies in which rehabilitation professionals delivered, supervised, or participated in interventions for individuals with SSc. Randomized (RCTs) or non-randomized trials, one-arm trials, and prospective quasi-experimental studies with interventions were included if they had ≥ 10 participants. Quality appraisal was done by two independent raters using the Physiotherapy Evidence Database (PEDro) Scale.

Results. Sixteen good or excellent quality studies (15 RCTs, 1 prospective quasi-experimental study) were included. Most rehabilitation interventions focused on hands/upper extremities, followed by multicomponent, orofacial, and directed self-management. Sample sizes varied between 20 – 267 participants (median = 38). In 50% of studies, participants in intervention groups significantly improved compared to controls. Most studies demonstrated within-group improvements in intervention groups. Interventions varied in content, delivery, length, and dose and outcome measures collected.

Conclusion. Existing evidence provides some support for rehabilitation in SSc, such as interventions that focus on hand and upper extremity outcomes or are multicomponent, although there is high study heterogeneity. The evidence base would benefit from interventions testing similar replicable components, use of common outcome measures, and incorporation of delivery modes that enable larger sample sizes. There are challenges in recruiting participants due to SSc's rarity and involving participants in rehabilitation studies that require active participation

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over time due to high disease burden. Intervention studies designed to reduce participation barriers may facilitate translation of effective interventions into practice.

SIGNIFICANCE AND INNOVATIONS

- This is the first systematic review of rehabilitation literature in SSc.
- Rehabilitation interventions demonstrate improvements in hand/upper extremity function, and health-related quality of life; however, the studies mainly involve small samples and vary in intervention content and dose.
- Multicomponent interventions and those that focus specifically on hands and upper extremities showed the most improvements in outcomes.
- Evidence-building in SSc will require attention to enhancing comparability across studies such as by testing similar interventions, using the same outcome measures, and reporting findings appropriately.

Rehabilitation in Systemic Sclerosis

Systemic sclerosis (SSc; also called scleroderma) is a rare, chronic, and progressive autoimmune disease characterized by skin fibrosis, vasculopathy, and visceral damage (1). SSc is often classified into two subtypes (2): limited and diffuse cutaneous SSc, which provides a clinically useful profile of people who have different progression of skin thickening and survival rates (2). People with both limited or diffuse subtypes commonly experience Raynaud's phenomenon, pain, fatigue, decreased flexibility, reduced strength, and visceral involvement. People with diffuse cutaneous SSc are more likely to have significant skin disease burden with large joint contractures and to have severe disease involvement in internal organs with lung fibrosis and renal crisis, whereas limited cutaneous SSc is likely to be associated with pulmonary arterial hypertension. Organ involvement, which can be life threatening, is a focus of clinical care in SSc, while less attention is spent on resultant disability and quality of life issues such as hand involvement, appearance changes, and fatigue (3-5). Yet, these symptoms are of significant concern to people with SSc (5). Regardless of subtype, there is a high symptom burden and disability that has significant effects on work and participation in life roles (6, 7). There have been treatment advances, but no approved disease-modifying drugs for SSc. Without a cure, strategies that help individuals with SSc with chronic disease management are needed.

Rehabilitation is an important tool to help individuals manage SSc and potentially slow its disabling effects; however, there are difficulties in translating evidence-based rehabilitation strategies into practice. Less than one in four people with SSc across several countries reported using rehabilitation services (physical or occupational therapy) (8) and there are low referral rates to rehabilitation (9). Additionally, most rehabilitation professionals do not have clinical experience with SSc due to its rarity, and there is little clinical guidance available for rehabilitation professionals when encountering these patients. There have been articles that have

discussed the effectiveness of rehabilitation treatments in SSc; however, the literature has not been systematically reviewed for interventions specifically performed or supervised by rehabilitation professionals. Since 2001, and the updated definition of diffuse and limited cutaneous subtypes (10), there have only been two narrative reviews that examined rehabilitation treatments either limited to musculoskeletal impairments (11) or to describing local and generalized rehabilitation treatments (12); and neither review examined evidence based on study quality. Systematic reviews done in SSc encompass some rehabilitation studies but also included other non-pharmacological treatments, such as nutrition and dental treatments (13), or examined effects of exercise but included studies that were not done within or as part of rehabilitation (14). A systematic review of rehabilitation treatments is still needed to provide a current understanding of the quality of this literature and provide the foundation to future directions to build evidence in this area. The objective of this systematic review was to examine the evidence for rehabilitation interventions in SSc. Therefore, our primary research question was: What is the effectiveness for rehabilitation interventions for individuals with SSc on clinical outcomes? Our secondary question was: What is the overall quality of the body of evidence in SSc rehabilitation?

MATERIALS AND METHODS

Search Strategy

The following databases were selected for the literature search: Medline through OVID, SCOPUS, Embase, CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL), OT Seeker, and PEDro. These databases were selected in conjunction with our university library informationist along with guidance from the rehabilitation literature (15). In addition to

searching these databases, we examined publication reference lists and other reviews for studies that would potentially meet study criteria. The informationist performed a literature search in these databases from year 2001 and later. Reviewing the literature starting at 2001 was done because the diagnostic classifications of SSc (diffuse and limited cutaneous) were updated that year (10) and we wanted to ensure we were including comparable patient samples. Searches involved subject headings unique to each database but similar to the Medline medical subject headings. The complete search strategy with terms used can be found in the Supplementary Material. The protocol for this systematic review is published in an online registry (16) and was conducted in accordance with PRISMA guidelines.

Inclusion and Exclusion Criteria

Because our intent was to select publications that examined rehabilitation practices, intervention studies were eligible for inclusion if the interventions included a rehabilitation professional (physical/physio therapist, occupational therapist, ergotherapist, rehabilitation specialist, or speech pathologist) for their delivery or supervision. Interventions that were multidisciplinary and included rehabilitation were also considered within scope. Interventions were excluded if they were conducted by related but different disciplines, like respiratory therapy, nursing, or dentistry, or if they were complementary and alternative treatments not conducted by rehabilitation, like acupuncture or spa treatments. Interventions performed for the primary purpose of examining effects on a biomarker or physiological outcome in a research environment and not a clinical treatment were also excluded. Publications needed to involve adult samples (≥ 18 years) who had a diagnosis of SSc (limited or diffuse according to 1988 classification and updated in 2001) (10). Studies also needed to include samples that had ≥ 10 participants, which excluded studies with a very low sample size given the heterogeneity of SSc, similar to another

review (13). Given the state of the evidence, we felt it was important to consider all intervention studies with designs in which participants were either randomized or not, including pre-post studies and prospective studies that involved interventions. We also included published abstracts for the purpose of identifying additional research studies based on that work. Because some team members were fluent in languages other than English, we also considered articles written in French or Chinese.

Article Selection

Citations generated from the search were imported into Covidence® systematic review software for title and abstract screening. A pair of reviewers independently screened all titles and abstracts to determine if the articles met inclusion criteria. Conflicts were resolved by a third reviewer. A full text review of each eligible article was then conducted by the same pair of reviewers. These reviewers independently coded each full-text for the inclusion criteria. Disagreements in the full-text evaluation were resolved through discussion, and misunderstandings were corrected to ensure consistency for the remainder of the article evaluation. After full-text evaluation, there were 33 articles to include in quality assessment and data extraction.

Assessment of Methodological Quality

Quality appraisal was used to answer the secondary research question. The PEDro scale was used to assess article quality (17). It was developed for rehabilitation literature quality appraisal and has been shown to be a more comprehensive measure for rehabilitation evidence than the commonly-used Jadad scale (18). The PEDro scale has a possible score of 10, in which one point is given for each quality metric that is met. Quality classification is: <4 = poor, 4-5 = fair, 6-8 = good, and 9-10 = excellent (19). Two independent raters trained in use of the PEDro scale independently rated each included article for quality. Any article for evaluation that was written

by members of the study team did not include that member as a rater. We calculated inter-rater agreement of methodological quality for 18% of the articles (i.e. 6 articles) using Cohen's Kappa. After all raters reached a high level of agreement of articles by quality category (.80 or above) (20), they completed evaluation of the remaining articles. Discrepancies on remaining articles were resolved through discussion.

Data extraction

We extracted data from articles that met a quality classification of ≥ 6 on the PEDro scale (good to excellent quality) (19). Data extraction was verified for 20% of articles. Data was independently extracted by a rater pair and then checked for consistency by a third rater. Only one discrepancy was found and resolved. One co-author then extracted data from the remaining articles with data verification by a different co-author.

Evidence Synthesis

Studies were summarized by aspects of the intervention, such as intervention content, setting in which it was delivered (clinic, home, telehealth, or some combination), length, and dose. After a review of intervention content of included studies, interventions were categorized as: hand/upper extremities (UE), orofacial, multicomponent, or directed self-management. Hand/UE included any treatments for hand or UE symptom reduction or increased mobility (like thermal treatments, manual therapy, or exercises). Orofacial included an exercise intervention addressing mouth opening. Multicomponent rehabilitation interventions involved more than one treatment for specific body part such as hand or face but also more generalized whole-body treatments, such as aerobic or water-based exercises. Directed self-management included a rehabilitation-involved self-paced symptom self-management program.

Sample characteristics were summarized by age, sex, ethnicity/race, subtype of SSc, and disease duration. Other elements of the synthesis included study design, timing of outcomes collection, assessment measures used, and whether study authors designated a primary outcome. Due to variability in outcome assessments, outcome domains were created to summarize findings.

RESULTS

Search Results

The systematic literature search yielded 3478 publications in which titles and abstracts were screened by rater pairs. There was disagreement regarding eligibility among pairs in 2% of cases (79/3478), resolved by a third rater. The most common reason for exclusion was due to being an abstract with insufficient data on the involvement of a rehabilitation professional in the intervention (72% of those excluded). Ninety full texts were evaluated and 33 were selected for quality appraisal (Figure 1). There were 16 articles included in this review.

Characteristics of Studies

The characteristics and main findings of each study are shown in Table 1. Of the 16 articles, 15 were randomized controlled trials (RCTs) and one used a prospective quasi-experimental study design (49). The sample sizes ranged from 20 – 267 people (median sample size = 38). Thirty-eight percent of articles (6/16) came from Italy (three of which were by the same author), three were from the US, and remaining articles came from other countries. Most studies involved a high proportion of females to males (the lowest percentage of females was 47%, 15/16 studies ranged from 65 – 100% females). In the US, Yuen et al (21) had the highest proportion of minorities (52% of African Americans, followed by Murphy et al (22) with 22%). The average age of participants across studies ranged from 50 to 65 years. Only three studies involved

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patients early in their disease process [average of 1-3 years since diagnosis (22, 23), or median of 4 years since diagnosis (24)]. The average disease duration of participants in the remainder of articles was ≥ 6 years. With regard to disease subtype, 19% of articles did not specify. In terms of primary outcome, 6/16 articles (38%) did not specify a primary outcome.

Quality

Of potentially eligible articles reviewed, only 48% were considered of good quality or better on the PEDRO scale and were included. Of these 16 articles, the average PEDro score was 7.0 (SD = 0.97). Articles rated by each quality metric is located in the Supplemental Material. Only one article was rated as excellent (25). The number of included articles by quality criteria on the PEDro scale are shown in Figure 2. The aspect of quality that was met by the fewest studies was blinding. Over half of articles (56%) used blinded outcome assessors, only two had participants that were blinded, and no articles had therapists who were blinded.

Intervention Delivery and Content

Of the interventions which we classified by categories—hand/UE, orofacial, multicomponent, and directed self-management (Table 1)—hand/UE was the focus for over half of studies (9/16), followed by multicomponent interventions (5/16). All multicomponent interventions included treatments targeted to hands/UE, but also other aspects such as orofacial exercises, general aerobic or resistance exercise, or supervision or check-in calls from therapists. There was one intervention that focused only on orofacial exercises (21) and another that involved a rehabilitation-directed self-management program that had moderated online discussion boards with participants involving a rehabilitation professional (26). Intervention length ranged from 2 weeks to 12 months. Delivery mode was most often done in clinic either with a home

component, such as an exercise program (n=4), without a home component (n=4), or with a telehealth component, which was an app-delivered exercise program with education (n=1) (22). The remaining 7 studies were designed as home interventions with two having a telehealth component (26, 27).

Investigators in almost all studies regardless of intervention content, evaluated quality of life (Table 2). The most commonly used measures were the Health Assessment Questionnaire (HAQ and HAQ-Disability Index) (n= 9) and SF-36 (n=11), which are reliable and valid outcomes in persons with SSc. Furthermore, since the majority of the studies were categorized as hand/UE or multicomponent, the other most frequent outcome measure was the HAMIS (n = 9), also validated for people with SSc. Other outcomes, grouped in domains, such as skin, pulmonary, cardiac, were used less frequently and were specific to intervention content (Table 2).

Table 2 shows findings for articles based on between-group differences in outcomes measured; more details are contained in the Supplementary Material. Most effects from SSc interventions were in hand/UE function and health-related quality of life domains, followed by orofacial. Interventions with the most effects had a hand exercise component or were multicomponent. In the hand/UE intervention category, findings varied as did interventions. The two studies that examined the effect of heat (warm water, paraffin) reported no significant difference between intervention and control groups (28, 29) as did two studies that have focused on hand exercises or massage with or without glove wearing (23, 27). The exceptions were studies that incorporated manual lymph drainage (48) or negative pressure and stretching (22) reported significant between-group differences for some hand/UE outcomes. The only study that compared modality use (biofeedback, deep oscillation) to a control condition, did find a significant improvement in biofeedback compared to control, while the oscillation group

revealed a trend in improvement (24). Furthermore, within hand/UE interventions, in the intervention group, significant improvements were reported in 7/9 (78%) of studies for the hand/UE function outcomes and in 5/7 (71%) of studies that had quality of life outcomes.

More positive group differences were reported in the multicomponent studies especially ones in which the interventions took place over a longer time period (31-33). In these studies, significant differences were reported between intervention and control groups for hand/UE function, orofacial, and quality of life (31-33). Specifically, 4/5 (80%) of studies in the multicomponent category reported within-group improvements in the intervention group in hand/UE function outcomes and quality of life outcomes. In the one orofacial intervention, there were significant improvements in oral aperture (face/mouth function) in the intervention group which were significantly different than the control group (21). The one directed self-management study did not report significant group differences (26). In general, many studies did report significant improvements in outcome measures within the intervention groups but the improvements were not significantly different from changes observed in the control groups.

DISCUSSION

We systematically reviewed the literature in SSc to examine the effectiveness of rehabilitation interventions. From 33 studies identified, just under half (48%) met the quality standard for inclusion. Sixteen studies representing rehabilitation interventions focused on hand/UE or orofacial, were multicomponent, or involved rehabilitation-directed self-management were rated as good to excellent quality. Half of these studies showed between-group differences in which the intervention group had a statistically significant improvement compared to the control group on at least one outcome (21,22,24,25,31,32,33,48). Most studies in this review had relatively

small sample sizes which may have resulted in lack of power to detect between-group interventions in studies with active comparator groups. However, the heterogeneity in studies and interventions make it difficult to synthesize the literature. These findings can be framed around two main challenges which have implications for translation of research into practice: evidence-building of rehabilitation research and conducting rehabilitation studies in the SSc population.

The complexity and patient-centered nature of rehabilitation contribute to challenges of evidence-building and synthesizing results across rehabilitation trials. One problem is inconsistency in trial reporting, such as lack of pre-defined primary outcome measure, even among good quality studies. There is a lack of consensus in reporting in rehabilitation RCTs in many areas such as participant characteristics (34); randomization procedures, statistical analyses and power (35); and intervention description (36). Tools under development such as checklists to extend the CONSORT statement for rehabilitation trial reporting (37) should help increase study quality and ability to synthesize findings. Many studies in this review had variable reporting of patient characteristics, intervention description, comparator/control groups, and lacked power analyses. Blinding was not done frequently and is challenging in a real-world environment with therapists, outcome assessors and participants. Despite challenges, some recommendations have been discussed to help ensure study rigor without being impossible such as blinding assessors and using active comparator groups where participants can be blinded to which intervention is hypothesized to be better (38).

Interventions tested in this review were difficult to synthesize even within a specific category. Hands and UE were most commonly addressed in interventions, but intervention content and dose were highly variable. Description of treatment rationale, goals and expected benefits and

underlying theory of interventions are recommended for reporting (39) and consistent information across studies could help build evidence and reduce variability. In addition, thought about the mechanism of action is critical. While SSc rehabilitation treatments incorporate specific elements, such as thermal modalities, massage, and stretching, few studies discuss why these components are essential or investigate how they work. For example, to examine if negative pressure treatment affects skin thickness in SSc, Murphy and colleagues developed a protocol to use musculoskeletal ultrasound to examine changes in skin thickness after an occupational therapist-delivered treatment (40). Testing mechanism of action in rehabilitation treatments will help design and better target interventions in the future.

Most studies in this review required participants to come to clinics to receive all or some of the intervention. Even for interventions designed to be done at home, participants had to travel to receive a device (wax or exercise machine) and/or instruction. Only one intervention was done completely via telehealth (26). Participation in interventions requiring in-person attendance may be prohibitive for those who do not live in urban areas, near scleroderma centers, or have transportation. Telehealth is an emerging mode of intervention delivery within rehabilitation. The recent global pandemic has led to massive changes in how healthcare and interventions are delivered. People have been forced to be more “tech savvy” and virtual interventions are becoming more accessible. The increased opportunity for virtual interventions helps to respond to the unmet need identified by people with SSc who want information delivered via the internet (41). Yet, virtual telehealth intervention delivery presents challenges to those with limited internet access, no video capabilities on their phones, and/or in areas with unstable connections. Further, telehealth is limited in its ability to provide hands-on treatment like

massage or stretching by a rehabilitation professional which may reap greater benefits at least in the short-term or be preferred by patients.

A further complication is that the reviewed studies were conducted in many countries with different health care systems and reimbursement structures. These differences have implications for how interventions could be translated into clinical practice outside the study's country of origin. Becetti and colleagues (8) reported that use of rehabilitation was higher in Canada and France compared to the United States and speculated that referral could be related to access to rehabilitation and health care costs. Other studies that surveyed providers reported referrals driven by costs (42) and a lack of understanding of the role of rehabilitation in management of SSc (43, 44).

In the US, African Americans have a higher prevalence of diffuse cutaneous SSc and more severe disease (45). However, the number of African Americans in research studies on SSc remains low. Although the three US studies reported on race and/or ethnic characteristics of samples, inclusion of diverse samples will be needed to better understand differences by race and ethnicity in the future.

For many studies in this review, outcome measures used have psychometric support for SSc. Stronger support exists for HAQ-DI, CHFT, and SF-36 than for the other outcomes (46). While these outcomes are largely self-reported and considered patient-centered, they do not measure what is important to patients or patients' goals. Only the COPM or MACTAR used in two studies (25, 32) were truly patient-centered, and in one study, goals identified on the COPM guided the intervention (25). Engaging patient stakeholders as members of research teams may also help initiate use of goal identification as outcomes and to guide interventions thus improving adherence.

Future Directions

The design of future SSc rehabilitation trials may benefit from lessons inherited from recent RCTs evaluating pharmacological treatments in SSc. Taking into account different subsets of the disease and impact of the natural history of SSc may help to include more homogeneous and comparable patient populations. Maddali Bongi and Del Rosso have recommended that rehabilitation treatments should be tailored to individuals based on phase of disease (47) because individuals with early disease tend to have a higher symptom burden. Another strategy is to focus on just one SSc cutaneous subtype, such as diffuse (22, 23). Specifying a clinically meaningful primary outcome measure that is tailored for a targeted disease subset [such as people in the edematous phase (48)], may help to improve statistical power of future RCTs. The coordination of centers of excellence with a multidisciplinary approach may also help expedite recruitment and ensure consistency of outcome measures. The use of web-based approaches for intervention delivery is a promising option to implement rehabilitation for daily SSc management as it may reduce some barriers to access, more readily allow for longer follow-up periods and facilitate treatment adherence. The long term impact of these techniques will also need to be demonstrated in RCTs as SSc remains a chronic disorder without available disease-modifying pharmacological agents and without demonstration of improved quality of life with current medications. Rehabilitation may thus play an important role to improve such patient reported outcomes with impact of more a holistic approach, including rehabilitation, on SSc patients' mental and social health as well as physical functioning.

Limitations

The conclusions drawn are limited by studies that are somewhat heterogeneous and consist of small sample sizes which may be underpowered to detect effects, even in this group of studies

considered to be of good to excellent quality. However, understanding weaknesses in study design and reporting can help to build the evidence by increasing potency of interventions and consideration of how to best tailor them. Importantly, interventions were of low risk to participants and had effects on both physical and quality of life outcomes, supporting the need for inclusion as part of clinical care.

Conclusion

Rehabilitation interventions have been recommended for people with SSc to address the musculoskeletal and systemic involvement leading to significant disability and reduction in meaningful activities (47). This comprehensive review of rehabilitation literature supports short-term efficacy of rehabilitation interventions and provides several future directions to further build the evidence and develop interventions that can reduce access barriers.

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Table 1. Characteristics of Rehabilitation Studies Included in Evidence Synthesis (N = 16)

Author, Year, Country	Sample Total N (IG/CG)	Participants	Intervention Length/ Dose*	Control/ Comparator Description	Delivery Mode	Intervention Content
Hand/UE						
Gregory 2019, UK(28)	36 (17/19)	Female = IG-76%, CG-63% % diffuse SSc = IG-41%, CG-42%	<i>9 weeks</i> Paraffin wax baths- no less than 4 times/ week; Hand stretch exercises- 3-10 times/day	Hand stretch exercise only	Home	Paraffin wax baths
Kristensen 2019, Denmark (29)	86 (43/43)	Female = IG-84%, CG-63% % diffuse SSc = IG-60%, CG-37%	<i>6 months</i> 30 minute sessions 2 times/day	Lukewarm water hand immersion prior to hand exercises	Home	Paraffin wax baths
Maddali-Bongi, 2009, Italy(30)	40 (20/20)	Female = IG-80%, CG-70% Subtype: N/S	<i>9 weeks</i> Massage and manipulation - 1 hour session 2 times/week; Home exercise- 20 minutes daily	Home hand exercise program	Clinic /home	Hand massage, joint manipulation

Maddali Bongi 2011, Italy(48)	35 (20/15)	Female = 100% Subtype: N/S	5 weeks 1 hour session/week	Waitlist	Clinic	Manual lymph drainage – UE focus
Murphy 2021, US(22)	32 (16/16)	Female = 72% % diffuse SSc = 100%	18 weeks OT sessions- 1hour session 1time/week for 8 weeks; App hand exercises- daily	App hand exercises only	Clinic/ telehealth	Thermal treatments to UE, negative pressure treatment, ROM, Home hand ROM exercises tailored by OT
Piga 2014, Italy(27)	20 (10/10)	Female = 100% % diffuse SSc = 40%	12 weeks maximum of 50 minutes 5 days/week	Home program of hand strength and mobility exercises using common objects	Telehealth	Hand exercises
Sporbeck 2012, Germany (24)	28† (10/8/ 10)	Female = Range/grp 80%-90% % diffuse SSc = range/grp 10-50%	4 weeks 3 times/week	Waitlist	Clinic	Biofeedback or deep oscillation to UE

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Stephana ntoni 2016, Italy(25)	31 (15/16)	Female = IG-100%, CG-94% % diffuse SSc = IG-47%, CG-31%	<i>3 months</i> Home exercise- daily; Weekly check-in calls between first and second assessments	General hand exercise	Clinic/ home	Hand exercises tailored by OT
Vannajak 2014, Thailand (23)	28 (14/14)	Female = IG-64%, CG-25% % diffuse SSc = 100%	<i>2 weeks</i> Superficial heat-20 minutes daily; TTM-30 minutes daily; Hand stretches- 30 seconds each hand daily; Wearing gloves-6 hours daily	Same daily home program as IG without gloves	Home	Traditional Thai massage to UE, joint manipulation, home hand ROM exercises, insulation gloves
Orofacial						
Yuen 2012, US(21)	48 (26/22)	Female = IG-81%, CG-77% % diffuse SSc=44%	<i>6 months</i> 6 minute session 2x/day	Usual dental care	Home	Manual mouth-stretching and oral augmentation exercises with a wooden stick

Multicomponent

Filippetti 2020, Italy(31)	44 (22/22)	Female = IG-80%, CG-79% % diffuse SSc = IG-44%, CG-25%	<i>6 months</i> 3 times/week	Usual care with general recommendation to increase physical activity	Home	Aerobic exercise (bike), UE resistance exercise, hand stretching, PT calls
Horvath 2017, Hungary (49)	53 (31/22)	Female = IG-93%, CG-91% % diffuse SSc = IG-58%, CG-50%	<i>3 weeks</i> 5 days/week for all therapies except for UE mud baths every other day and thermal baths daily	Mud baths, thermal baths, exercise for large joints, without treating hands	Clinic	Thermal treatments to UE, Hand stretching, massage to trunk/UE, stretching and exercise to lower extremities
Maddali-Bongi 2009, Italy(50)	20 (10/10)	Female =65% Subtype: N/S	<i>9 weeks</i> Hands-1 hour session 2 times/week; Face-1 hour session 2 times/week; Global-1 hour session/week	Educational advice and medical information about SSc	Clinic	Connective tissue massage, Kabat's technique, kinesitherapy, and a home exercise program
Rannou 2017, France	220‡ (112/)	Female = IG-86%, CG-80%	<i>12 months</i> PT/OT-	Usual care by physician with no	Clinic/ home	Multidisciplinary intervention (PT/OT) aerobic and resistance

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(32)	108)	% diffuse SSc = IG-47%, CG-50%	3 weekly 3 hour sessions Splinting- 2 hours daily Resting splints- nightly home exercise-daily	restrictions on PT		exercise, ROM for mouth, face, UE/LE and splinting
Schouffer 2011, Netherlands(33)	53 (28/25)	Female = IG-68%, CG-84% % diffuse SSc = IG-54%, CG-60%	<i>12 weeks</i> Multi-disciplinary program-weekly; PT-weekly; Home exercise- 6 days/week	Usual care by physician with no restrictions on PT.	Clinic/home	General exercise, hand/mouth exercises, education, PT supervised home exercise
Directed self-management						
Khanna 2019, US(26)	267 (134/133)	Female = IG-92%, CG-90% % diffuse SSc = IG-43%, CG-44%	<i>16 weeks</i> Self-paced with weekly moderated discussion board	Received a copy of popular scleroderma resource	Telehealth	Self-paced web-based self-management program with rehab-directed discussion board

*Intervention length is italicized.

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†All study designs were randomized controlled trials except Horvath et al. (49) which used a prospective quasi-experimental design

‡Three groups are biofeedback, deep oscillation, or waitlist control respectively; ‡N = 218 analyzed in study; IG = intervention group; CG = control group; N/S = not specified; HAQ-DI= Health Assessment Questionnaire Disability Index; DASH = Disabilities of the Arm, Shoulder and Hand questionnaire; VAS = visual analog scale; HAMIS = Hand Mobility in Scleroderma test; TTM = traditional Thai massage; FIHOA = Functional Index for Hand Osteoarthritis; PROMIS = Patient-Reported Outcomes Measurement Information System.

Table 2. Between-Group Differences by Outcome in Rehabilitation Studies in Systemic Sclerosis (N = 16)

Outcome	Number of Studies Out of 16 Evaluating the Outcome (N)	Studies with a Significant Difference between Intervention and Control Groups (p<0.05)
Skin		
MRSS, hand MRSS	2	
Hand/UE function		
HAMIS	9	33,48
Durouze Hand Index/Cochin Hand Function Test	6	32
QuickDASH or DASH	2	
FIHOA	1	
Kapandji index	1	32
Mobility - Hand opening, hand abduction, fist closing, fingertips to palmer crease, Total Active Motion, HAI	5	
Hand volume	2	48
VAS hand pain, interference	2	48
VAS hand edema, VAS interference edema	1	48
Pinch strength	3	22
Grip strength	6	31, 33

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Biceps strength	1	31
Raynaud's Phenomenon		
Raynaud's symptoms VAS	2	24
Digital Ulcers		
VAS Digital Ulcers	1	
Orofacial		
Oral aperture or mouth opening, MMO, microstomia, face involvement	4	21,32,33
Cardiac		
6MW	2	31,33
Vo2 Peak/max, Aerobic capacity	3	
Pulmonary		
VAS shortness of breath	1	
Gastrointestinal		
VAS Gastrointestinal symptoms	1	
Musculoskeletal		
Quadriceps strength	1	31
Global Health		
Global health VAS or Questionnaire, General VAS	3	
VAS overall disease severity	1	

Health-Related Quality of life

PROMIS physical function	1	
PROMIS-29	1	
Patient Activation Measure	1	
Pain VAS	2	32
PROMIS Self-Efficacy for Managing Symptoms	1	
Checklist Individual Strength	1	
HAQ-DI or HAQ, SHAQ	9	31,32,33,48
MACTAR	1	32
SF-36	11	31,48
VAS satisfaction with health	1	
COPM	1	25
EQ-5D, QALYs, SWAP	1	

† UE = upper extremity; HAMIS = Hand Mobility in Scleroderma; CHFT = Cochin Hand

Function Test; MRSS = Modified Rodnan Skin Score; VAS = Visual analog scale; PROMIS =

Patient Reported Outcome Measure Information System; SHAQ = Scleroderma Health

Assessment Questionnaire; DASH = Disabilities of the Arm, Shoulder and Hand questionnaire;

RP = Raynaud’s phenomenon; HAQ-DI = Health Assessment Questionnaire Disability Index;

SF-36 = Short Form 36 health survey; FIHOA = Functional Index for Hand OsteoArthritis; HAI

= Hand Anatomical Index; COPM = Canadian Occupational Performance Measure; HAQ =

Health Assessment Questionnaire; MMO = maximum mouth opening; 6MW = six-minute walk;

MACTAR = McMaster Toronto Arthritis Patient Preference Disability Questionnaire; EQ-5D

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=EuroQol-5 Dimension; QALYs=Quality Adjusted Life Years; SWAP=Brief Satisfaction with Appearance Scale

Figure 1. Flow Diagram Studies of Rehabilitation in Systemic Sclerosis

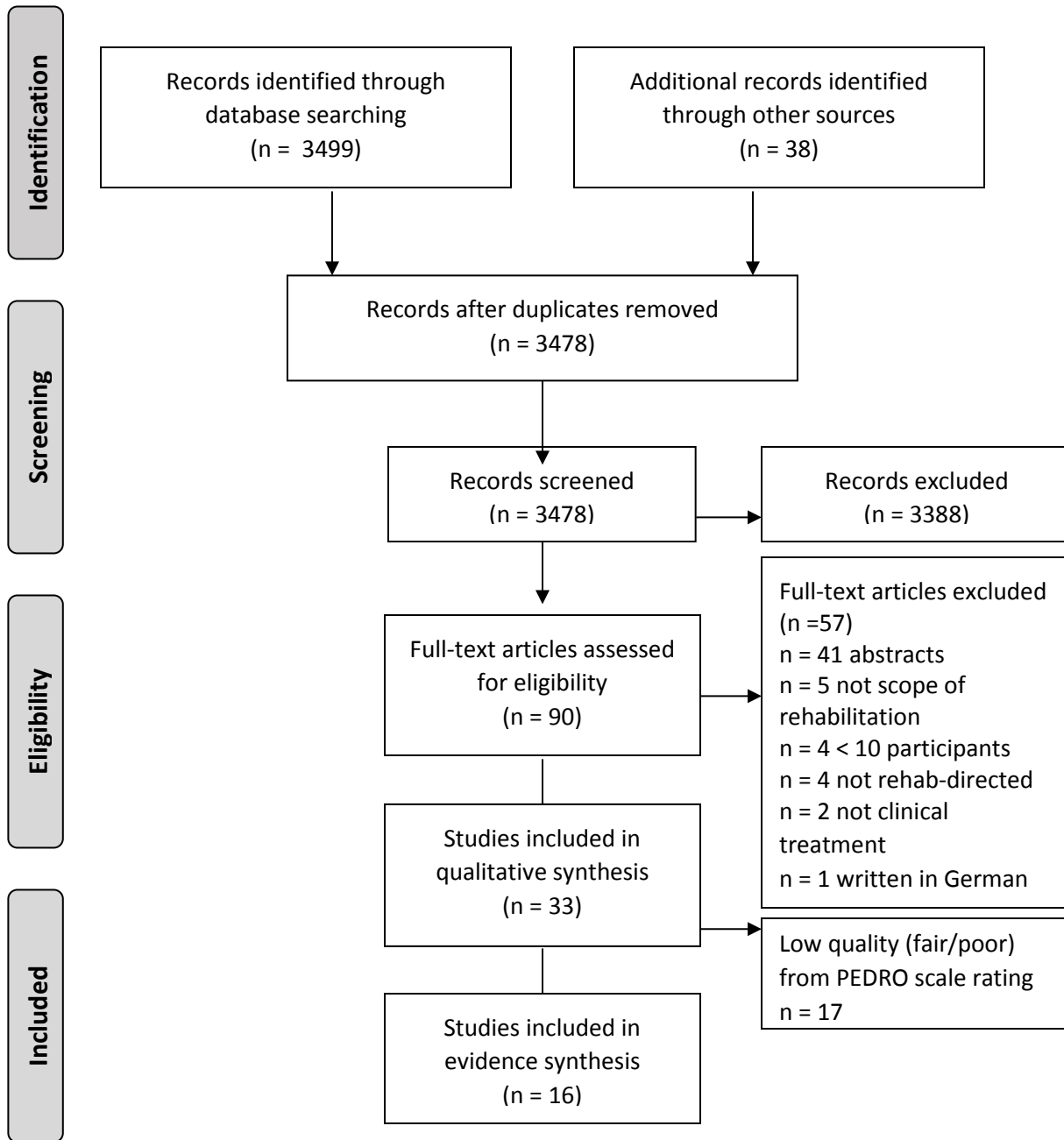
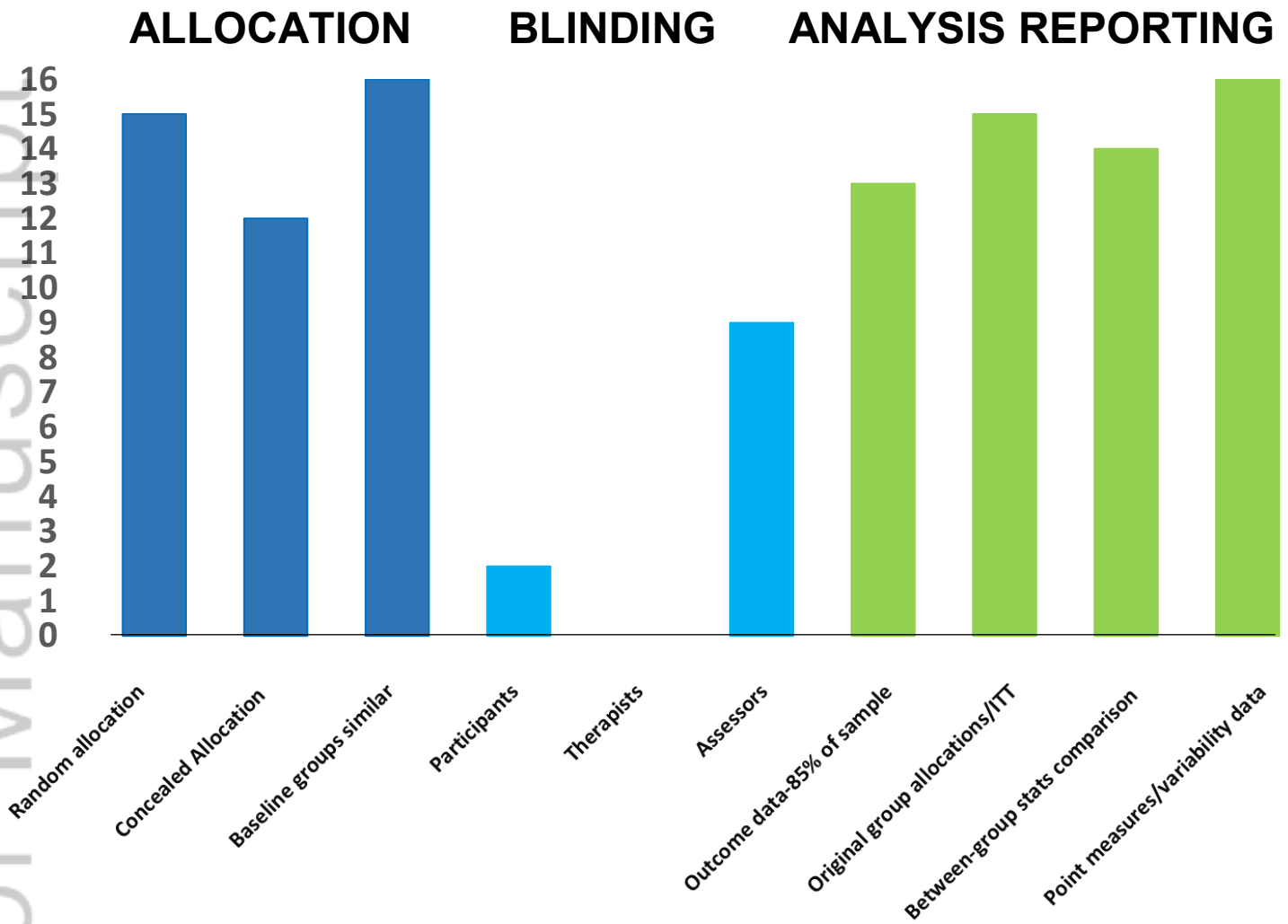


Figure 2. Articles rated by Quality Criteria on the PEDro Scale



Note. ITT = Intent to Treat

FIGURE LEGEND

Figure 1. Flow Diagram Studies of Rehabilitation in Systemic Sclerosis

Figure 2. Articles Rated by Quality Criteria on the PEDro Scale