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Exercise as a multi-modal disease-modifying medicine in systemic sclerosis: *An introduction by The Global Fellowship on Rehabilitation and Exercise in Systemic Sclerosis (G-FoRSS)*☆

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☆Audience: Rheumatologists and pulmonologists to sensitize to these concepts; therapists to use as broad guidelines/roadmap; patients for inspiration, guidance, and self-management; researchers to sensitize to questions that need investigation; and global collaborators interested in joining forces.

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Abstract

Systemic sclerosis (SSc) is a heterogeneous multisystem autoimmune disease whereby its main pathological drivers of disability and damage are vascular injury, inflammatory cell infiltration, and fibrosis. These mechanisms result in diffuse and diverse impairments arising from ischemic circulatory dysfunction leading to painful skin ulceration and calcinosis, neurovascular aberrations hindering gastrointestinal (GI) motility, progressive painful, incapacitating or immobilizing effects of inflammatory and fibrotic effects on the lungs, skin, articular and periarticular structures, and muscle. SSc-related impairments impede routine activities of daily living (ADLs) and disrupt three critical life areas: work, family, social/leisure, and also impact on psychological well-being.

Physical activity and exercise are globally recommended; however, for connective tissue diseases, this guidance carries greater impact on inflammatory disease manifestations, recovery, and cardiovascular health. Exercise, through myogenic and vascular phenomena, naturally targets key pathogenic drivers by downregulating multiple inflammatory and fibrotic pathways in serum and tissue, while increasing circulation and vascular repair.

G-FoRSS, *The Global Fellowship on Rehabilitation and Exercise in Systemic Sclerosis* recognizes the scientific basis of and advocates for education and research of exercise as a systemic and targeted SSc disease-modifying treatment. An overview of biophysiological mechanisms of physical activity and exercise are herein imparted for patients, clinicians, and researchers, and applied to SSc disease mechanisms, manifestations, and impairment. A preliminary guidance on exercise in SSc, a research agenda, and the current state of research and outcome measures are set forth.

Keywords

Scleroderma; Disability; Exercise; Physical activity; Myokine; Muscle; Pulmonary rehabilitation; Interstitial lung disease; Pulmonary hypertension; Health-related quality of life; Breathlessness; Disease activity; Physical function; Symptom burden; Systemic sclerosis

Introduction

Systemic sclerosis (SSc) is a heterogeneous multisystem autoimmune disease with main pathological drivers of disability/damage being vascular injury, inflammatory cell infiltration, and fibrosis [1]. Skin thickening varies widely and its distribution creates a rudimentary subtyping: *sine scleroderma* (without skin thickening), *limited cutaneous (lcSSc)* (skin thickening of face and distal to elbows/knees), and *diffuse cutaneous (dcSSc)* (includes proximal skin thickening above elbows/knees) [2]. However, systemic manifestations are the true hallmark of SSc. *Sine* and *lcSSc* have more vasculopathic tendencies; but any SSc manifestation occurs in all subtypes, and all subtypes being potentially lethal and associated with severe and multiple disabilities [2–5].

In SSc, physical function, a predictor of health-related quality of life (HRQoL) and survival can be severely diminished by diffuse, diverse impairments arising from ischemic circulatory dysfunction (leading to painful skin ulceration and calcinosis, to neurovascular aberrations hindering gastrointestinal (GI) motility), to progressive painful, incapacitating or immobilizing effects of inflammatory and fibrotic effects on the lungs, skin, articular, and periarticular structures and muscle [4,5]. SSc-related impairments impede routine activities of daily living (ADLs), disrupt critical life areas: work, family, social/leisure, and also deteriorate psychological well-being [6,7].

Despite physical activity being vital to general health, muscle function, physical function, and aerobic capacity; attention to these cornerstone therapeutic concepts are often overshadowed by patients/clinicians feeling overwhelmed by other SSc medical management or fearful of overexertion [8,9]. Exercise, through myogenic and vascular phenomena, naturally targets key SSc pathogenic drivers by downregulating multiple inflammatory and fibrotic pathways [10,11] in serum and tissue [12,13] while increasing circulation and vascular repair. Based on evidence in SSc and other connective tissue diseases (CTDs), patients with SSc can benefit from exercise through reduced disease activity, systemic inflammation, pain and fatigue as well as improved muscle function, joint and bone strength, aerobic capacity/cardiopulmonary function, and HRQoL [14]. While SSc notoriously erodes body image, physical activity is elemental to embodiment practices, allays biochemical impact on depression/anxiety, stress, and physical pain burden, and improves self-esteem [15–18]. Myogenic and vascular mechanisms likely contribute to exercise's beneficial impact on sleep, pain, fatigue, and GI health and gut flora [19,20].

As a global collaborative, relying on scientific evidence and expert experience of developing exercise programs in SSc and other serious health conditions, we describe the current state of exercise as it relates to SSc disability and disease activity. We propose strategies targeting pathological SSc disease mechanisms and manifestations with the goal of reducing disease activity and optimizing physical function that include supervised-, home-, land-, water-based, pulmonary rehabilitative exercise, and newer evidence-based technologies [15–18,21–44]. Future research priorities in SSc rehabilitation medicine are highlighted.

Physical activity and exercise as medicine

Physical activity encompasses any bodily movement by skeletal muscle requiring energy expenditure above resting levels [45,46]. *Exercise,* a subset of physical activity, is planned, structured, repeated, and targets improvement or maintenance of physical fitness, performance, or health. “Physical activity/exercise,” herein refers to all the following: workouts, training, rehabilitation, physical therapy, including modalities such as martial arts, singing, yoga, and dance for which growing evidence supports improved articular and respiratory health [45].

A physically active lifestyle is essential for health, with higher aerobic fitness being strongly associated with the absence of disease [47]. Recommendations to improve muscle strength/endurance and aerobic capacity define exercise *type* and *dosing* (frequency, duration, and intensity) (Fig. 1 and Tables 1–4) [48–51], which correspond to health benefits, e.g., in obesity, type II diabetes, hypertension, cardiovascular disease (CVD), some forms of cancer [46,52], and in CTDs associated with increased risk of CVD, such as SSc. Exercise benefits extend to muscle, bone density, nerve and joint health, HRQoL, sleep quality, and mental health – areas that are more highly impacted in CTDs; while physical *in*activity rapidly erodes these benefits.

A phenomenal rate of emerging evidence points toward muscle and muscle contraction being pivotal and pervasive on vital pan-systemic function (Fig. 2). The muscle’s paracrine, endocrine, and cytokine regulation across multiple systems (brain, skin, cardiovascular, vascular, gastrointestinal, osseous, immunological, endocrine, and pulmonary), is increasingly prompting the consideration of muscle as an endocrine organ beyond and its roles of motility/mobility [12–14,19,33,45–47,50,53–60].

Longstanding inflammation in CTDs heightens CVD event risk, bone and muscle loss, pain, stiffness, poor sleep, and fatigue predisposing to further inactivity and muscle disuse. Aerobic and resistance training reduce ESR and CRP in several CTDs [61,62] with improvement in fatigue, pain, and stiffness. Muscle contraction activates multimodal cascades through mechanical and chemical mechanisms that systemically downregulates circulating and tissue inflammation while upregulating vascular support and repair that activate an anti-inflammatory cascade - thus interrupting this vicious inflammatory cycle [54]. Exercise mechanisms are numerous with instantaneous and lasting inflammatory transformations e.g., myriad myokine circuits through e.g., IL-6, IL-1, IL-10, IL-15, FSTL-1, etc., muscle-fat mass distribution impacting adipokine-inflammasome dynamics, mediate long-term reduced risk of cardiovascular disease [12,13,57], and endothelial function and repair [55–57] – a crucial dysfunctional pathway of SSc pathology.

A growing body of evidence supports the safety and efficacy of exercise in systemic inflammatory conditions such as myositis, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) with fatigue and depression reduction [61,62]. In myositis, exercise effects include: a) upregulation of anti-inflammatory genes and genes related to muscle growth and vascularization, with downregulation of proinflammatory genes and fibrosis; b) increased capillary density in the muscle tissue along with improved mitochondrial enzyme function [58,63–65]; and c) the prevention of mitochondrial damage and myofiber apoptosis through exercise-induced reduction of myositis-related Harakiri and TLR7 expression [58,66]. We submit that these clinical and preclinical exercise effects on inflammation and vascular repair and function also occur in SSc and could favorably impact disease manifestations related to these drivers.

Direct and indirect costs related to SSc and other CTDs are significant with reduced labor productivity that results in striking losses [67]. Physical *in*activity contributes significantly to overall SSc disease burden [67–71] with exercise being a potent antidote improving function and potentially diminishing disease-related economic burden. Exercise intervention has demonstrated a cost benefit in other conditions such as pulmonary hypertension (PH) and RA, when compared with medical treatment alone [72–74]. Evidence suggests analyses of exercise-related economic benefit in SSc and other CTDs are warranted [72–74].

Disease mechanisms in SSc treatment paradigms

Autoimmunity, inflammation, vasculopathy, and fibrosis in SSc

Inflammation is the hallmark of many autoimmune diseases which includes SSc. Unless halted, ongoing inflammation spurs further proinflammatory pathways and recruitment of immune cells that assault host tissue with histotoxic infiltrates, which result in tissue damage. Inflammation can be rapidly or slowly progressive or even punctuated by periods of inactivity. Quieting inflammation may decelerate disease progression and reduce symptoms. Ongoing inflammatory mechanisms trigger downstream pathways that lead to fibrosis, the final transition from reversible inflammation to permanent damage.

Diffuse vascular/endothelial injury, dysfunction, and disrepair occur in SSc. However, it is yet unclear if interruption of the inflammatory/autoimmune – fibrosis trajectory with pharmaceuticals also deters progressive vascular disease. If so, exercise hypothetically targets vascular SSc manifestations through both anti-inflammatory/anti-fibrosis and circulation mechanisms, including mitigating the endothelial shear stress of SSc vasculopathy [75,76] (Table 5).

Treatment in the context of the inflammation-fibrosis trajectory and circulation

SSc symptoms and impairments can result from *currently active drivers of disease,* which may recede with systemic treatment or from *tissue damage* that remains after the resolution of active disease. Ideally, SSc is pharmacologically treated in the inflammatory predominant, more reversible early stages to prevent permanent disability. Less ideal, but still important, is salvaging functional tissue by reversing resident inflammation in areas of coexistent fibrotic damage to prevent further fibrotic damage-related disability. SSc progression can span widely between *rapidly progressive* (robust inflammatory driver) or *indolently* *progressive* (subtle inflammatory driver) transformation to fibrosis. Newer antifibrotic medications decelerate fibrosis-transforming pathways, but are unable to reverse end fibrosis or significantly reduce inflammation.

Patient-reported experience and perceptions of exercise

Successful patient engagement requires respectful understanding of hopes, fears, needs, experiences, perceptions, priorities, and barriers of an intervention from the perspective of the targeted population. Limited yet substantive work investigate patients' perspective of exercise on SSc-related manifestations [77–80] with diverse impairments reported in physical capacity, which includes reduced muscle strength, impaired mobility, cardiopulmonary problems [78], substantial diseaserelated economic burden, and poor HRQoL [81,82].

Participants consistently expressed hopeful perceptions, "*The more I exercise, the more improved my health and the chance to survive longer* …. " Inactivity was consistently connected with further decline in health status: "… *because of my lung disease* … *I've been close to death a couple of times, so I notice a big difference between exercising and not exercising. It's as different as night and day.*" [77] However, despite perceiving exercise as essential for life and health [77], patients also report not engaging in exercise [77,78]. Multifactorial demotivators include: a) manifestation-related e.g., digital ulcers (DUs), joint pain, and restricted motion; b) constitutional effects of disease e.g., pain and fatigue; c) psychosocial struggles of living with SSc d) fear and lack of exercise safety knowledge, and e) logistical burden of preparation and participation [77].

Patient self-knowledge and experience provide a roadmap for researchers to understand both cohort and individually targeted interventions. In separate studies, patient report corroborated by physiotherapist assessment with markedly reduced muscle endurance in shoulder and hip flexion as well as reduced lower extremity strength [83]. Fatigue, Raynaud's phenomenon (RP), physical limitations, joint problems, and DUs persist as unmet needs in SSc care [77,80,84,85], though each is potentially modifiable by exercise [77]. SSc symptoms, such as pain, fatigue, breathlessness, and impaired hand function, influence self-rated work ability and employment status [86–89]. Raising awareness of SSc-related work impediments, such as these, may identify interventions for physical function that provide a path to diminish economic burden [77] and improve perceived well-being [89].

Patients report major exercise benefits being improved blood circulation particularly in hands, feet, and prolonged core-warming, breathing, fatigue, pain, sleep, vitality and musculoskeletal function [77]. Whether exercise exerts an effect on socially stigmatizing disease-related barriers, such as DUs [77,90] or body dissatisfaction, deserves investigative attention.

Patients conveyed that planning, adaptation, and post-exercise recovery time were important considerations particularly with severe lung disease or after vigorous exercise [77]. Patients report adapting intensity and activity type to facilitate exercise during inclement weather or increased symptoms. Furthermore, patients conveyed that healthcare professional counselling on exercise instruction, benefits, and cautions might be helpful, particularly early in the disease [77].

Though an SSc-specific patient-reported experience measure remains to be developed [91,92], a patient activation measure [93] assessing levels of disease knowledge, motivation, and support can be used to facilitate patient engagement in exercise protocols.

SSc manifestations and physical activity/exercise

The following section outlines the current state of exercise safety, efficacy, and assessment crossed with SSc symptoms and manifestations (Tables 6–10 and Fig. 3). It is not exhaustive nor comprehensive in potential benefits nor in the science that predicts the ability of exercise to prevent disease progression and disability in SSc.

Cardiopulmonary Involvement in SSc: is common with pulmonary parenchymal involvement/interstitial lung disease (ILD) being the leading cause of SSc death, followed by pulmonary vascular involvement/PH. Cylindrical bronchiectasis and severe esophageal reflux may also affect airways in SSc [94]. Cardiac decompensation may occur secondary to SSc pulmonary manifestations, pericardial disease, or malignant hypertension (renal crisis); however, primary SSc-cardiac manifestations can arise from muscle, microvascular, and neuronal dysfunction [95]. Resultant clinical correlates of cardiac involvement in SSc include diastolic dysfunction from either myofibrosis or microcirculatory insufficiency, dilated cardiomyopathy, or arrhythmias. Breathlessness is a common feature of cardiopulmonary manifestations of SSc, along with exercise intolerance, diminished HRQoL, and occasionally pleural or pericardial pain [96–98]. In ILD, a disabling inspiratory cough can exacerbate breathlessness [99]. In early stages, symptoms may be mild, and by unconsciously restricting or slowing activity levels many patients do not recognize early symptoms. Musculoskeletal impairments restricting activity also make the recognition of cardiopulmonary limitations less apparent.

Aerobic and muscle-strengthening exercises significantly improve [100] HRQoL as well as cardiovascular, endothelial, metabolic/glandular, muscle structure and function, lung mechanics, mobility, and systemic inflammation [95,100–103] with overall positive effect on the physiological and psychological components [101,104–106]. Exercise cultivates a fitness that can offset cardiopulmonary deficiency by facilitating greater ease, capacity, and reserve as patients interface with life activities [6]. For example, exercise promotes stronger, more supple, and neurologically responsive feet, important for efficient rising, balancing, propelling, and mobilizing the body. Diaphragmatic strengthening fortifies respiratory dynamics and improves attributes that support respiratory capacity, e.g., balance, core strength, and lower back health [107–109]. As intercostal and accessory muscles achieve improved postural strength and flexibility, increasingly easier bending, reaching, and twisting during activities is possible with less breathlessness. Furthermore, exercise practices movement coordinated with breath, thus increasing skilled capacity for complex, weighty, or increasingly intense activities. Strategies such as Singing for Lung Health [30,35,110–114], yogic breathing, Tai Ch'i [115,116] as well as some yoga and dance techniques, support healthier breath patterns and efficiency, e.g., abdominal relaxation increasing inspiratory capacity, stronger and efficient oral musculature, etc.

Pulmonary rehabilitation is supported as feasible, safe, and effective [117,118] regardless of underlying diagnosis (e.g., ILD and PH) and can improve breathing, exercise tolerance, fatigue, and cough [119]. Exercise safety in SSc-cardiopulmonary involvement [79,120–123] are outlined in Tables 7a and 7b, Tables 8–10 as are programmatic considerations and enhancements [105,106,121]. Cardiopulmonary-related breathlessness carries neurophysiological, cognitive, and emotional distress different from other exertional breathlessness [16,29,124]. Worries over breathlessness and what breathlessness might signify hinders exercise. Patient-clinician discussions are key to successful, confident engagement in exercise [16,99,124,125]. Patients require reassurance that *breathlessness* and *desaturation* are distinct attributes often independent of each other. Desaturation is a chemical phenomenon, while breathlessness is a complex multifactorial, multidimensional experience, and of itself is not physiologically harmful [124]. We explain the following to patients who feel frightened or frustrated: "*Being physically unfit causes breathlessness and fatigue*," "*Exercise treats unfitness, exercise also causes breathlessness*, but *can be done in non-distressing manners that will diminish breathlessness over time.*"

Along these lines, patients with underlying cardiopulmonary conditions, may be at a higher risk of dysfunctional breathing patterns such as hyperventilating or breath-holding, which contribute toward additional neurophysiological mechanisms related to breathlessness sensations [126]. Breathing pattern disorders can be rehabituated to healthier breathing patterns with practiced breath regulation that is strengthened by exercise.

Gastrointestinal Tract in SSc: is the most common internal organ involved in SSc, which affects >90% of patients with SSc. SSc can impair function from mouth to anus, hypothetically by the same vicious cycle of inflammation, vascular insufficiency and leak, immune dysfunction, and disrepair [127] as other organ systems. Myomucosal fibrotic infiltration and neuronal rarefaction results in damage, which include salivary glandular dysfunction, pan- or partial-GI dysmotility, and loss of GI sphincter muscle tone and dysmotility. Symptoms from these pathological processes include difficulty with ingesting food and mastication, acid reflux predisposing to esophagitis, dysphagia, esophageal stricture and malignancy, bloating, cramping, early satiety, nausea, emesis, regurgitation, constipation, bacterial overgrowth, diarrhea, fecal leakage or frank incontinence, and malnutrition. Symptoms should be managed early and aggressively [4,128,129]. GI symptoms severely diminish HRQoL greatly interfering with life participation [130] and potentially resulting in depression [131,132] and self-imposed isolation.

Though not expressly intuitive, exercise impacts GI function and symptoms via multimodal mechanisms [133–137]. Mouth exercise and physical activity correlate with improved salivation, oral health, and function [133,137]. Even minor physical activity such as walking stimulates digestion, reduces nausea, and promotes motility. Physical activity is linked to decreasing digestive system cancers, decreasing proinflammatory gut microbiota, and gut restoration of health-promoting microbiota resulting also in favorable effects on cognition and mental health [19,138–141]. Microbiome restoration could be a key influencer of lower GI health [20] as dysbiosis appears to be a feature of the SSc disease state [142–144].

In exercise, the large diaphragmatic muscle draws downward for chest expansion and lung aeration, exerting rhythmic mechanical massaging forces on the abdominal cavity contents; also creating pronounced intra-abdominal pressure differentials stimulating neuronal networks and parasympathetic action. These actions assist in GI motility and function and in reducing symptoms e.g., nausea, bloating, and constipation. Singing, chanting, martial arts, and yogic breathwork emphasize these actions; but all exercise potentially encourages synchronized breathwork that benefit GI health.

Online home-based exercise platforms are increasingly available, particularly for patients uncomfortable travelling due to diarrhea or fecal soilage.

Face Involvement in SSc: can change in appearance from the tightening and fibrous transformation of facial skin, mask-like (mauskopf) appearance, and perioral wrinkling with retracting lip-thinning and hollowed appearance of the cheeks. The changes can have devastating effects on body image, self-esteem, and well-being [145,146]. A mix of manual techniques and home exercise had a positive effect on mouth opening as compared to only home exercise [147]. Though the impact of facial exercises on self-esteem has not been directly examined, exercise leads to increased self-esteem and feelings of well-being [77,100,148]. Application of sauna techniques to optimize exercise is yet unstudied. In addition to optimizing breath, diaphragmatic strength, and GI dynamics, singing may have similar impact on oral/facial musculature, salivation, and circulation [133,137].

Mouth Involvement in SSc: can impair mouth opening, often noticed during dental examinations, oral care, eating and chewing [149]. The fibrous transformation of the facial skin, muscles, lips, and palatal structures with teeth shifting can lead to multiple oral problems such as reduced oral aperture, decreased salivary production, and increase in dental caries, pain with chewing, and tooth loss. Oral care requires heightened attention from diagnosis throughout the disease course. Oral stretching along with facial exercises [147] and massage have been shown to increase mouth opening with possible other structural, vascular, and glandular benefits and sometimes lead to better oral health [150,151].

Skin in SSc: portends diffuse functional impairment to the body beyond anatomical restriction. SSc disrupts the skin’s superficial and deep architecture of sweat and sebaceous glands, nerves, and blood vessels with biochemical, hormonal, glandular, neurological, immune, circulatory and thermoregulatory, and wound-healing dysfunction [152].

Exercise and manual manipulation increases blood flow to the skin, which provides nourishment, oxygenation, toxin removal, and warmth; muscle activity stimulates mitochondrial function in the skin essential for wound healing [8,153,154]. Exercise hastens lymphatic drainage of edema [147], important in early diffuse disease. Exercise increases circulation and sweating in those able to still sweat. Sweat facilitates toxin and inflammatory cytokine release through the skin.

Hands in SSc: are particularly subject to diffuse morphological changes, impairment, and pain due to inflammatory assault, vascular insufficiency and injury, and fibrous infiltration and damage. These pathological processes may result in infection, ulceration, calcinosis, acro-osteolysis, flexion contractures, carpal tunnel syndrome, cold sensitivity and RP, synovitis, tendinopathy, and amputation [155].

Hand and wrist impairment impacts remunerative and household work, self-care, nutrition, and the handling of exercise equipment. DUs and calcinosis are described as not only painful but also socially stigmatizing during exercise due to visible lesions or the need for bandages and/or gloves for hand protection [77]. Certified hand therapists/OTs can address hand strength, mobility, and contractures; and provide tools for improvement in self-care and work capacity.

The role of hand exercises in SSc cannot be overstated. The hands are often involved early and rapidly lose range of motion (ROM) and strength. Encouraging home-based "ritualised" practice has multiple benefits [156–158]. Exercise supports circulation [100], healthy vasculature, skin repair, and warmth - important factors in RP, DUs, and calcinosis. Exercise increases hand/wrist muscle strength and efficiency, adding to the already intrinsic benefits on local inflammation, stiffness, and joint lubrication [150,151]. Preventive strategies to maintain hand warmth and adjuvant, preparatory strategies described below, such as paraffin, sauna, and water-based exercise, optimize tolerability and outcomes [156,159]. Exercise gloves may improve handgrip when performing muscle strengthening exercises, particularly when handling/gripping cold metal. Grip and hand placement techniques can also be modified to enable the performance of particular exercises [77]. Assessment of hand/arm function at baseline and intervals (Table 9) can provide direction and encouragement [160–175].

Feet in SSc: often receive little attention although patients experience significant SSc-related challenges, including RP, ischemic injury, contractures, plantar rigidity, fat pad atrophy, and pain with impact on gait ability and pattern [77], comfort, balance, and other domains of mobility [176,177]. Furthermore, compromised strength of the lower extremity musculature and decreased ankle motion may create higher risk for falls [178]. Pedal soft tissue damage/loss renders standing and exercising painful for some patients, making good footwear or orthotic insoles an important consideration.

Developing strong supple, responsive feet and ankles through exercise and physical activity increases pedal circulation and improves performance efficiency of body mobility (rising, stairs, and walking) and balance. These are all important factors for people already limited by cardiopulmonary impairment, but also for anyone who negotiates rough or unexpected terrain [77].

Joint Involvement in SSc: is diverse both in *distribution* that involves large or small joints and in *mechanism* with intrinsic musculoskeletal pathology (inflammatory arthritis, tendonitis, etc) and overt changes (ulceration, calcinosis, inflammation, and fibrosis in overlying skin and fascial layers). Difficulty managing ADLs makes hand, finger, wrists, and elbow joints impairment more readily apparent, but the less overt lower extremity joint involvement of feet, hips, knees, and ankles interfere with mobility and balance [178–180]. Furthermore, downward cycle of *in*activity gradually compounds intra- and peri-articular adhesion of fibrous tissue that exacerbates joint stiffness and impairment.

Exercise can impede the impairment trajectory [181]. Joint activity instigates blood circulation that supports tissue health and repair. Myogenic activity decreases local and systemic inflammation. Motion mitigates tissue adhesion, relieves stiffness, and malalignment through lubricating and strengthening of periarticular, articular, and bony structures while promoting repair and regeneration of cartilage [181]. Repetitive exercise strengthens muscle, ligaments, tendons, and their insertion into the bone [182].

Counselling patients on ROM early in the disease course may preserve function, particularly in dcSSc [183–186]. Warm paraffin hand immersion prior to hand exercise sessions may significantly improve active ROM, reduce stiffness and hand dryness [187] as well as increase activity performance and participation [188–190] but these results are not reproduced consistently [189,190]. Sauna, often available at pool facilities and gyms, is reported to improve inner core temperature, decrease RP, and facilitate stretching before/during/after exercise, including aquatic exercise.

Bone Involvement in SSc: results from inflammation, vascular complications e.g., calcinosis/osteolysis as well as decreased physical activity, circulation, muscle mass, and nutrition leading to low bone density, fracture, and avascular necrosis [191–197]. Physical activity invokes muscle contraction and circulatory mechanisms setting off multiple pathways of benefits for strength and vascularization of the underlying bone as well as systemic skeletal structure [198–202].

Muscle Involvement in SSc: is under-recognized, but commonly found on physical exam and multifactorial with histological examination ranging from microangiopathy, inflammation, fibrosis, necrosis, or atrophy [203–205]. Muscle weakness and reduced muscle endurance are hallmark features of most myositis subsets [206] and reported in all serological subsets of SSc [207–210].

Proximal muscle weakness limits physical function in up to 20% of patients with SSc [78,205,211]. Muscle endurance is markedly reduced in both shoulder (53% expected) and hip flexion (40% expected) as measured by Functional Index-2 (FI-2) [212,213], proximating polymyositis and dermatomyositis impairment [214]. Regardless of subtype or degree of lung involvement, lower extremity functional muscle strength in SSc is significantly worse than standard values [212,215], while muscle endurance is lower in moderate to severe as compared to no or mild lung involvement [83,215]. Muscle involvement is associated with and possibly predicts cardiac abnormalities [216–224]. Upon exclusion of medication culprits, (e.g., statins, steroids, and hydroxychloroquine) appropriate, timely management of myopathy includes exercise and rehabilitation to improve long-term disability and function outcomes [225,226].

Health-related quality of life in SSc and the role of exercise

HRQoL is the interface of combined symptom distress and impairment with real-life. Numerous studies demonstrate, independent of traditional disease severity markers, the inverse correlation of HRQoL and survival and survival improvement with HRQoL-targeted interventions [4,52,128,227–235]. Whether SSc-specific manifestations or less well-defined symptoms such as fatigue, pain, psychic/cognitive discomfort, or sexual dysfunction [236], are the prominent aspects of symptom distress, targeted intervention may markedly improve HRQoL [103]. The information given below address less SSc-specific, but no less important, areas of symptom distress.

Pain in SSc: limits physical capacity in 39% of patients [78]. It is often multifactorial, diffuse, and unfortunately defaults to an inaccurate diagnosis of “fibromyalgia” [4,237]. RP, joint, and/or muscle pain, pruritus, skin tightening and subcutaneous pressure, calcinosis, and ulceration are common causes of SSc pain [4,238]. Though, empiric exercise impedes mechanisms driving these discomforting manifestations through multiple pathways [4,181], distinguishing causes of pain and tailoring interventions accordingly may hasten function [4,181]. Analgesia can improve engagement in those with disabling pre-/post-exercise pain [181].

Fatigue in SSc: may be multidimensional with mental/cognitive, motivational, physical, and muscular domains [239,240]. Although a nonspecific symptom often related to hypothalamic effects of systemic inflammation, fatigue in SSc often has other factors that include deconditioning, pain, and inflammation. Serious SSc complications associated with fatigue such as GI bleeding or undiagnosed PH or ILD or non-SSc comorbidities, such as clinically significant CVD, must be addressed medically prior to beginning an exercise program. Malnutrition and poor sleep quality cause fatigue warranting corrective intervention to optimize health and benefits of exercise [241].

Exercise can increase endurance improving fatigue associated with dyspnea and cough and ameliorate their psychological burdens of depression and anxiety [63]. Recalcitrant persistent fatigue, as well as sleep, physical function, and self-perceived general health, improves with exercise in other conditions [242].

Anxiety and Depression in SSc: have psychological and emotional consequences for individuals and their families. SSc requires continued adaptation to changing physiological burden and symptom severity, e.g., fatigue, pain, respiratory, as well as socioeconomic, self-image, and survival uncertainties resulting in elements of psychological distress. Adaptive psychological distress can give way to clinically significant anxiety and depression alongside impaired cognition and motivation.

“Watchful waiting” may be an acceptable strategy for mild depression [243] whereby symptoms are anticipated as transient. However, psychological symptoms can interfere with treatment adherence and key self-management strategies that optimize health and prevent complications. Non-pharmacological approaches, such as exercise, may require adjuvant anti-depressant medications even temporarily while patients adjust.

In SLE, inactivity is associated with tripled incidence of depression [70]. Exercise has been repeatedly demonstrated to improve cognition, depression, anxiety, self-image, work performance, and coping. Even a simple change in body positions and postures profoundly and swiftly shifts mood/affect [102,244–248]. Exercise significantly improves sleep quality that is foundational to cognitive and psychological health. Evidenced mechanisms through which exercise affects mental conditioning are numerous and continually growing including microbiome-gut-brain axis [19,139,249,250] enrichment, facilitating brain's discarding of depressive chemicals [251,252] and upregulating antidepressant chemicals [181]. The impact of yoga, singing [253], and gentle exercise positively impacts both physical and psychological outcomes [30,35,111–116,254].

Initiation, engagement, and exercise types

Documenting exercise/physical activity routinely along with medication history, during clinic visits provides opportunities for continued encouragement, education, and review of patient goals and priorities in relation to SSc care (Fig. 4).

Exercise interventions are most effective when guided by patient goals and their life priorities [90]. Tools such as the Patient-Specific Function Scale PSFS [165,166] support patients to monitor their own progress. Preventive exercise strategies initiated early in the disease course, ideally supported by Physical, Occupational, and Respiratory therapist education on the consistency of practice, stretching safety, and *incremental* progress, may preserve physical function and HRQoL [77] by offsetting progressive loss of flexibility and mobility. Screening for SSc-cardiopulmonary involvement is essential.

SSc presents additional physical and psychological taxes on motivation [16,255,256] for exercise. Early on this may include diagnosis-related trauma [15–18], which exercise may relieve. Both supervised and self-managed exercise initiation strategies require individualization and flexibility according to levels of fatigue, pain, muscle, skin, joint, and vital organ involvement. Anticipatory guidance helps patients manage fears, frustrations, and disappointments, particularly regarding fluctuating fatigue and pain, while sustaining commitment to exercise. Possible supports include apps/videos or exercise buddies [77]. RP may deter outdoor exercise in cold temperatures [77] and even indoor exercise that involves gripping equipment; but is potentially mitigated with exercise glove use.

Integrating mindfulness techniques and nurturing perceptions of exercise as a friendly, pleasurable experience, may lessen immobilizing tendencies such as perceived lack of control, self-consciousness, and defeatism [15–18]. Noticing pleasurable exercise sensations (e.g., air on skin, massage sensation, etc) may help cultivate parasympathetic (polyvagal) self-regulation, holistic "core" muscle recruitment, and integration resulting in improved musculoskeletal performance, balance, joint and postural alignment, and more rapid escalation of *exercise dose* (*frequency, intensity, time duration, and type* (*FITT*)) [30,257].

Exercise dose begins and escalates gently with a goal of 30 min [49,258] 3–5 days a week. Fluctuations in disease behavior may require dose adjustment under therapist supervision. Tables 6, 7a and 7b define exercise approaches, including ROM, muscle strength, muscle endurance, aerobic capacity, and functional capacity. Tables 8, 9 summarize, respectively, cumulative SSc exercise studies and preferential baseline and follow-up assessments [259].

Incremental increases in nonexercise physical activity, e.g., standing, walking, and as much body movement throughout the day enhances health benefits, physical function, and HRQoL [48,49]. But while patients with SSc may dedicate time to exercise for health improvement; nonexercise physical activity throughout the day may be impeded by fatigue, pain, GI symptoms, or disability prolonging time to complete a routine activity.

***Stretching*:** is a naturally occurring phenomenon that regulates muscle fiber length and excess force for optimal muscle tone and protection of periarticular structures (e.g., tendon, muscle, and ligaments). Stretching is a pivotal conditioning mechanism for ROM, balance, global and limb proprioception, and movement efficiency [260,261]. Stretching elicits vasodilatation intensifying blood flow to muscle, increasing oxygenation, warmth and tissue waste removal, and relieving stiffness. Habitual stretching induces proangiogenic factors increasing neo-angiogenesis and capillary density [262], potentially impacting multiple SSc therapeutic avenues. Effective stretching occurs when muscle fiber exceeds its optimal length and/or the magnitude of stretch is guided by ROM and pain limitations Implementation is gentle, and held for 30–60 seconds synchronized with breath cycles for sufficient relaxation [50]. Long-term benefits of therapeutic hand stretching with marked improvement in hand, arm, and overall function in SSc [156] warrant further investigation in diverse SSc manifestations.

***Water-based*:** Water's properties of buoyancy, depth-graded hydrostatic pressure, viscosity, surface tension, hydromechanics, thermodynamics, and density [263–270] allow for uniquely efficient rehabilitation strategies (Table 11). Growing high-level evidence of aquatic exercise in autoimmune and other conditions demonstrates *safety* without neuromusculoskeletal exacerbations or other adverse effects. Additionally, demonstrated are *efficacy* in diminishing stiffness, pain, muscle spasm, fatigue, and improving cardiovascular endurance as well as physical function, including ROM, balance, and walking [183,263,264,266–269,271–278]. Despite strong rationale only one study [183] as yetinvestigated aquatic exercise in SSc, which demonstrated significantly improved HRQoL, physical function, and activity [183].

Though a more easy exercise medium [266], water deceptively requires greater muscle activity and provides an optimal environment for wide-ranging therapeutic interventions, including strength-training, cardiopulmonary rehabilitation, and for circulatory disorders [272,279]. Joint mobilization and stretching, balance, gait, resistance, strength [269] and endurance training, and weight-bearing activities are more easily modified in water to accommodate a spectrum of abilities. Patients explore movement strategies and patterns against gravity without anxiety or fear of falling.

Water temperatures between 30 °C and 34 °C/86 °F –93 °F preserves optimal body heat, exercise tolerability, and HRQoL effects [273–277]; cooler/cold water can induce RP and increase joint and muscle stiffness. Water *bidirectionally* conducts heat 25 times faster than air facilitating deeper, more rapid tissue penetration [263,264], but also more rapid body heat dissipation, thus enabling increased exercise duration and intensity with less fatigue [267,270]. These sublime factors can unwittingly lead to overexertion. Patient logistical concerns regarding oxygenation, fatigue, and mobility challenges with dressing, drying, and skincare are important considerations [280].

G-FoRSS preliminary research agenda

Despite significant evidence of exercise effects on inflammation and circulatory flow and repair, further work is needed to define exercise as a medicinal disease-modifying intervention with patient-centered strategies that support sustained patient engagement. We provide a roadmap to examining exercise in SSc (Table 11) with the hopes of building collaboration and to stimulate interest in the wider research community in the disease-modifying and HRQoL-preserving effects of exercise in SSc. These include examining, and ultimately, prescribing FITT in terms of quantifying exercise intensity, duration, and type to target circulatory, anti-inflammatory, and respiratory effects; along with how these effects translate to meaningful changes for patients in terms of physical and psychological function and HRQoL. The potential impact of both general and targeted exercise on skin tightening, RP, wound healing, and mobility is compelling for both the prevention and treatment of SSc complications.

With few therapeutics demonstrating improvement of SSc manifestations, exercise and physical activity demonstrate convincing mechanisms of action, with virtually no downside. Instead exercise consistently promises major and diverse benefits, and deserves robust research attention. Furthermore, engaging in exercise allows patients to foster some control and self-efficacy in managing a frightening disease.

G-FoRSS is committed to supporting research efforts in addition to the following:

- Patient experiences of exercises prior to and concurrent with SSc diagnosis:
- Patient perceived and quantitative impact of exercise on SSc manifestation, symptom, and HRQoL domains
- Patient perceptions, fears, hopes, and worries related to engaging in exercise
- Patient perceived barriers/hindrances to initiating and to sustaining exercise practice
- Patient perception and quantified impact of early ROM intervention on face, mouth, hands, shoulders, and feet
- Characterizing optimal FITT in both aerobic and resistance exercise on land and in water, in patients without/with cardiopulmonary involvement
- The use of minimally invasive / sutureless muscle biopsies to evaluate response to exercise
- A focus on optimal hand exercise regimens and implementations

- A focus on the impact of facial exercises on oral health, salivation, and nutrition
- A focus on the impact of exercise, including singing and diaphragmatic strength on GI symptoms and GI-related quality of life
- Examining the impact of exercise interventions from a health economics perspective
- Establishing clear safety parameters for exercise in relation to the presence and extent of cardiopulmonary involvement
- Examining treatment effects of exercise on SSc-myopathy
- Assessing patient-preferred education and engagement modes for initiation and sustained exercise

Summary

Exercise possesses essential health benefits for everyone and perfectly addresses the World Health Organization's preamble to their constitution to '*address health as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*' [281]. The therapeutic underpinnings of exercise target the specific mechanisms behind the pervasive SSc-disease biophysical and psychosocial manifestations. Exercise engagement should be a routine treatment-based discussion with respect to patients' goals and clinical assessment.

The expanse of exercise as a treatment intervention in SSc warrants dedicated investigation with standardized approaches. This group has convened to prioritize a research agenda for exercise in SSc and accelerate selected research through the development of a global network of interdisciplinary SSc specialists and patient research partners.

Acknowledgments

G-FoRSS is an open interdisciplinary network of SSc experts including rehabilitation, physical, occupational, speech and respiratory therapists, basic scientists, patients, physicians and SSc organizations convened to accelerate the research and practice of exercise as a disease-modifying treatment in SSc. For more information please contact: lsaketk@tulane.edu.

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APPENDIX

SUPPLEMENTAL FILES and RESOURCES:

Patient and Physician Education and Advocacy Organizations:

Scleroderma Foundation: www.scleroderma.org.

Federation of European Scleroderma Associations (FESCA): www.fesca-scleroderma.eu/wordpress/

Scleroderma Australia: https://www.sclerodermaaustralia.com.au/

Scleroderma & Raynaud’s UK (SRUK): https://www.sruk.co.uk/scleroderma/

Swedish National Association of Systemic sclerosis: https://rss.reumatiker.se/

Instructional Resources:

Janet Poole Hands/Face Instructional Links: https://www.youtube.com/watch?v=1F02FxdOgwI

https://www.youtube.com/watch?v=8MztM3zItik

https://www.youtube.com/watch?v=YwWP7mgcYhU.

Stretching exercises for the hand and face.
The Scleroderma Foundation, http://www.scleroderma.org/site/DocServer/Form_16c_low_res.pdf?docID=19809&AddInterest=1281.

Taking Charge of Systemic Sclerosis (TOSS): an internet program for systemic sclerosis. https://www.selfmanagescleroderma.com/

Living Well: Heart, Lung, Muscle & Mind: A collection of videos dedicated to yoga rehab and dance rehab for heart, lung, muscle, and autoimmune conditions

https://www.youtube.com/channel/UCRgvkbyzep-Q3LGBiAksQZw/videos.

3–3-1 Exercise Tutorial https://www.youtube.com/watch?v=zsBRxmkzAnM&t=2s.

Move Towards Health: UMC CPHC Instructional Booklet on Safe Home-based Dance Practice https://doi.org/10.13140/RG.2.2.25576.49927.

Sleep Booklet: https://www.dropbox.com/s/0axd782mi818smc/SF%20Arizona%20Conference%20-%20SLEEP%20-%20DOUBLE%20Booklet.docx?dl=0.

Mindfulness
Booklet: https://www.dropbox.com/s/mrpl33zxjsk20br/SF%20Arizona%20Conference%20-%20RESTORE%20YOURSELF-%20DOUBLE%20Booklet.docx?dl=0.

Mindfulness in Scleroderma Videos: https://www.youtube.com/watch?v=pNK9RP4Abyw.

https://www.youtube.com/watch?v=lmQKOCDJ19Y

Clinical Resources:

Patient Specific Functional Scale (PSFS) User Manual: https://www.physio-pedia.com/Patient_Specific_Functional_Scale.

Functional Index-2: https://www.youtube.com/watch?v=qw4XvWKQErU.

Manual Muscle Test 8 (MMT8): https://www.niehs.nih.gov/research/resources/assets/docs/mmt8_grading_and_testing_procedures_for_the_abbreviated_8_muscle_groups_508.pdf.

Timed Up and Go Test: https://youtu.be/auqAb_AWM1U.

TImed sit to stand test: https://www.youtube.com/watch?v=puJhQXUlbdA.

30-s Sit to Stand Test: https://www.youtube.com/watch?v=PzCTwkJVhWg.

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Practice points

- Progress in exercise and physical activity should be documented on the history of present illness, with physical activity goals clearly stated
- Discussions and counselling on physical activity and exercise are an essential component of SSc care and overall health
- Highlighting the impact of exercise on improved circulation and decreased inflammation may support patient engagement in exercise
- Explaining the benefits of exercise according to patients' individual SSc symptoms may support patient engagement
- Initiating face, mouth, hand, and possibly shoulder ROM exercises early may prevent disability and impact skin tightness as well as local circulation and inflammation
- The need for referral to OT/PT/RT should be considered at each patient visit
- Reminding patients at each visit of available online Scleroderma instructional resources e.g., The Scleroderma Foundation

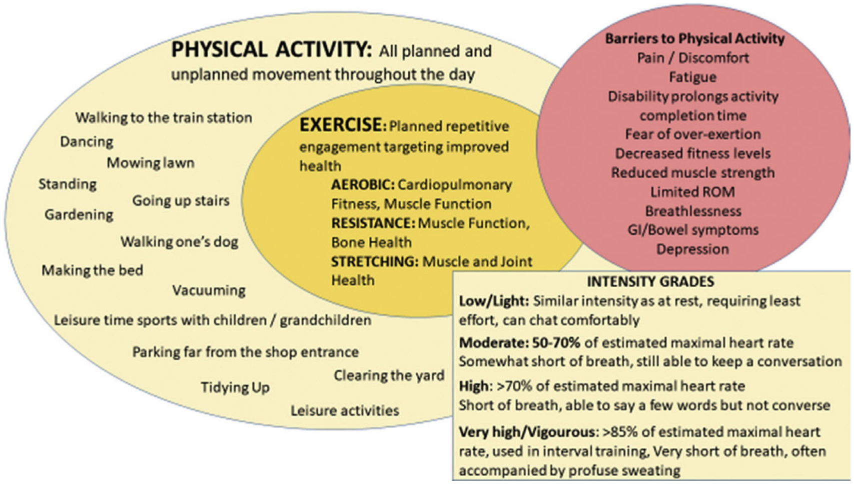

Fig. 1.

All movement is healthful. This diagram perspects the relation of exercise in the larger arena of physical activity with the description of activity intensity by estimated heart rate and lay description *(Courtesy of LA Saketkoo on behalf of G-FoRSS, rights reserved).*

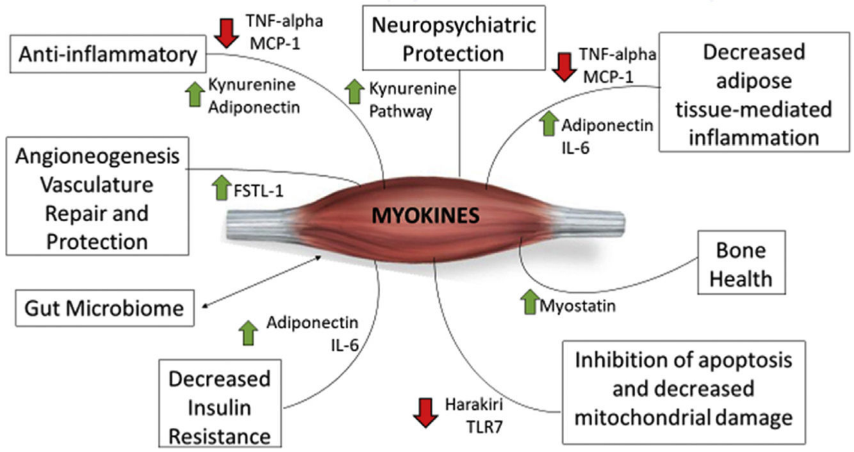

Fig. 2.

Muscle Contraction-Induced Myogenic Mechanisms Facilitating Health. FSTL-1: Follistatin-like 1 IL: interleukin, MCP: monocyte chemoattractant protein-1, TLR-7: Toll-Like Receptor-7, and TNF: Tumour Necrosis Factor *(Courtesy of LA Saketkoo on behalf of G-FoRSS, rights reserved).*

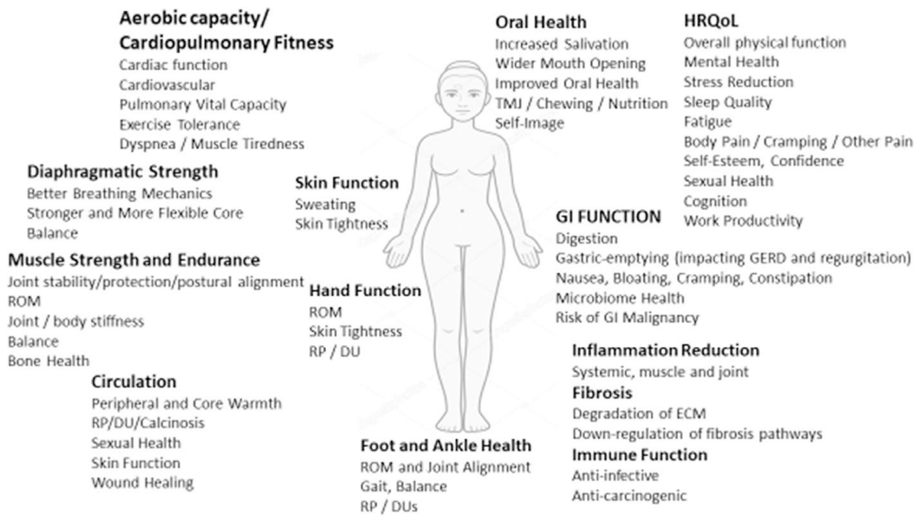

Fig. 3.

Overview of Potential Exercise Benefit relational to anatomical manifestations of SSc in Male and Female subjects. Abbreviations: DU: Digital Ulcer, ECM: Extracellular Matrix, GERD: gastroesophageal reflux; GI: Gastrointestinal, HRQoL: Health-Related Quality of Life, ROM: Range of Motion, RP: Raynaud Phenomenon, and TMJ: Temporal-Mandibular Joint *(Courtesy of LA Saketkoo on behalf of G-FoRSS, rights reserved)*.

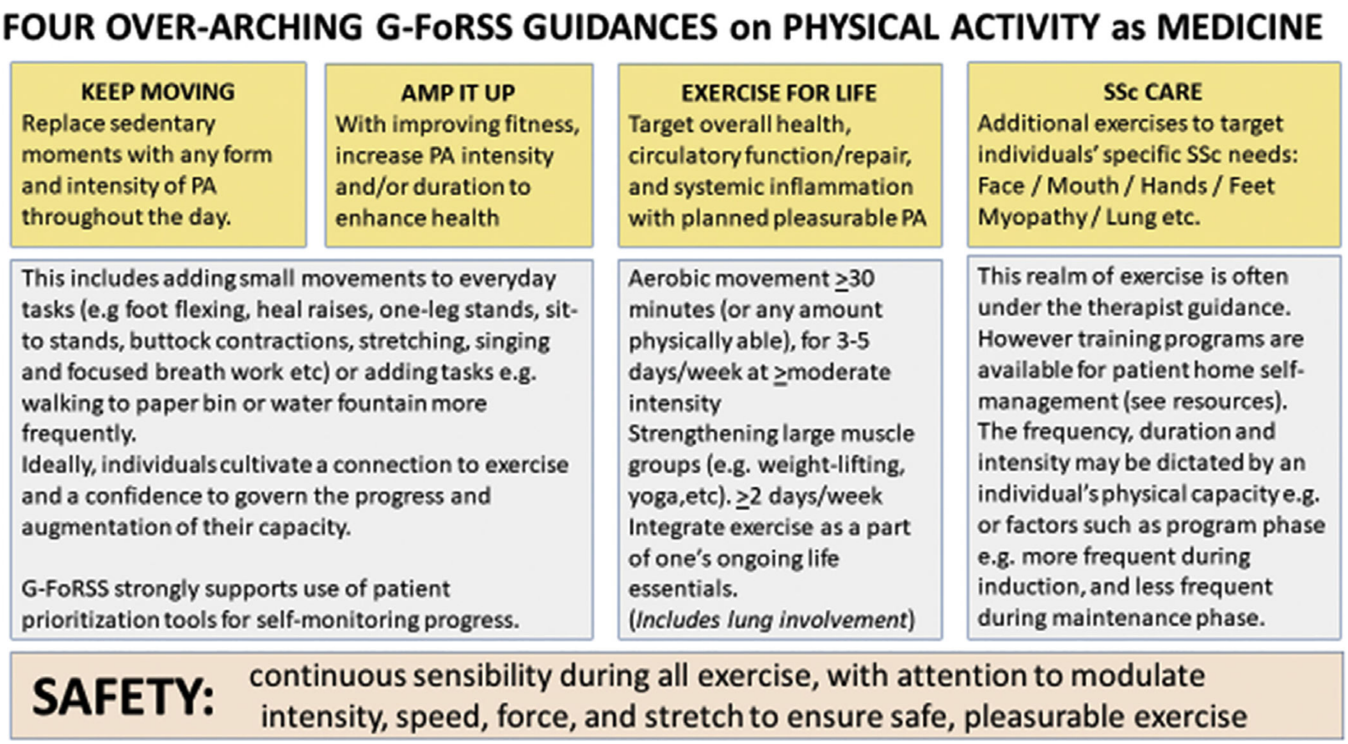

Fig. 4.

G-FoRSS preliminary recommendations for physical activity and exercise in SSc. Based on evidence collated from the WHO, SSc disease mechanisms and health promoting mechanisms of exercise *(Courtesy of LA Saketkoo on behalf of G-FoRSS, rights reserved)*.

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Table 1

Summary of definitions and recommendations for physical activity, related to health benefits and exercise [45,48–50,282] *(Courtesy of LA Saketkoo on behalf of G-FoRSS, rights reserved).*

Physical Activity (PA)				
Definition of Physical Activity	*Any* everyday activity producing increased energy expenditure above resting (sitting) levels. The antithesis of sedentary/ nonmotion moments			
	An unrestricted spectrum of activity, including *exercise*, household and employment tasks, mobility, leisure activity such as sports, hobbies, and singing			
	Occurs in varying intensities: *light/low, moderate, high, and vigorous*			
	Any PA is healthy and contributes to fitness; general health is more favorably impacted with increasing time and intensity of relevant PA			
Recommended Weekly Dosage of Physical Activity	150 min of moderate-intensity PA weekly for ≥10 min at a time			
	OR			
	75 min of vigorous-intensity PA weekly for ≥10 min at a time			
	OR			
	an equivalent combination of moderate- and vigorous-intensity PA for ≥10 min at a time			
	PLUS			
	-Strengthening exercise involving major muscle groups (*legs, back, chest, abdomen, shoulders, and arms*) ≥2 days weekly			
	* Additional health benefits can be attained by doubling the minutes per week above			
Physical Activity for Special Populations	**For Adults ≥ 65 Years Old**		**People with Chronic Illness**	
	Same recommendations as above.			
	OR			
	If limited by health condition, engagement in PA as abilities and conditions allow			
	PLUS			
	Limit amount of sedentary time, replacing it with PA of any intensity (including light intensity)			
	PLUS			
	If mobility is impaired, PA to enhance balance and prevent falls for ≥3 days weekly			
Intensity of Physical Activity	**Light/Low**	**Moderate**	**High**	**Vigorous**
	Similar intensity as rest Minimal effort Able to chat easily	50%–70% of max HR 3–6x effort as rest A bit difficult to converse	>70% of max HR 6–10x effort as rest Difficult to converse	>85% max HR >10x effort as rest Unable to converse
	Even light intensity PA can support cardiovascular health and can help with weight loss			
	An activity's intensity is dependent on an individual's baseline fitness level			
	An activity's intensity decreases with an individual's increasing fitness			
Definition of Exercise (*a subset of PA*)	A *subset* of PA that is repeated over time with specified *intensity, duration, and frequency*			
	Directed targets improvement of any aspect of physical fitness: cardiorespiratory, mobility, muscle strength, general health, wound healing, psychological, cognitive, etc.			
	Recommendations for exercise to improve aerobic fitness is 30 min/day for ≥3–5 days weekly at ≥ moderate intensity, at least a bit difficult to converse			
	Recommendations for exercise to improve muscle strength *(weights allowing a maximum of 8–12 repetitions)* or muscle endurance (*weights allowing a maximum of 15–25 repetitions*) is 2–3 days weekly with a rest period of 48–72 h			

Table 2

Summary of the American College of Sports Medicine exercise recommendations for general population and in rheumatic and musculoskeletal diseases [50,282] *(Courtesy of LA Saketkoo on behalf of G-FoRSS, rights reserved).*

Exercise type	Exercise Goal	Intensity	Duration	Frequency
Aerobic exercises	Improve aerobic capacity, i.e., cardiopulmonary fitness	55%–90% of HRmax	20–90 min	3–5 days/week
Resistance exercises	Improve muscle strength	60%–85% of 1 RM	8–12 repetitions, 2–4 sets. Exercises should induce fatigue but not exhaustion	2–3 days/week
	Improve muscle endurance	30%–50% of 1RM	15–25 repetitions with variable number of sets	2–3 days/week
Stretching	Improve range of motion and flexibility	Most effective when muscles/ tissue is warm, e.g., after exercise and/or external heating (sauna, heat packs, or paraffin bath)	Approximately 10 min	≥2–3 days/week

Abbreviations: HRmax: maximum heart rate and RM: repetition maximum.

Table 3

Overall benefits of exercise in general populations *(Courtesy ofLA Saketkoo on behalfofG-FoRSS, rights reserved).*

SYSTEMIC	Brain Health
	Cardiovascular health
	Cardiopulmonary health
	Circulatory function and repair
	Immune Function
	Decreased inflammation
	Malignancy prevention
	Bone density
	Bone circulation
	Increased muscle mass
	Skin health
	Gastrointestinal health
	Endocrine health
	Exocrine health including sweat and salivation
	Malignancy prevention
GLOBAL FUNCTION	Activity capacity
	Physical conditioning and strength
	Health-related Quality of Life
	Alertness
	Cognition/Reduced Risk of Cognitive Decline
	Mobility (walking, climbing, running, and cycling)
	Balance
	Improved self-care
	Workability
	Social Function
	Sexual health
CONSTITUTIONAL	Decreased anxiety
	Decreased depression
	Decreased pain
	Decreased fatigue
	Improved sleep
LOCAL	Lung mechanics
	Chest kinematics
	Muscle pathology
	Range of motion
	Articular strength
	Articular and Periarticular Lubrication
	Muscle strength
	Muscle mass

	Decreased inflammation
	Decreased stiffness

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Table 4

SSc disease mechanisms and drivers targeted by exercise.

Circulation
Heat generation
Nutrient delivery
Aerobic exchange
Toxin clearance
Vascular repair
Vascular responsiveness
Systemic Inflammation
Downregulation of inflammatory cytokines
Downregulation of inflammatory cell recruitment
Resultant decreased triggering of fibrotic pathways
Fibrosis
Degradation of fibrosis
Possible halting or reversing of fibrosis in evolution

Table 5

Potential impact of exercise on SSc disease manifestations *(Courtesy of LA Saketkoo on behalf of G-FoRSS, rights reserved).*

SSc Manifestation	Potential Impact of Exercise
Inflammation	Downregulated with exercise
Immunosuppression/Immune dysfunction	Probable improved immune function
Fatigue	Reduction of multidimensional fatigue
Sleep	Improved sleep after exercise Sleep quality correlates to inflammation fatigue and HRQoL
Psychological Impact	Improved confidence
	Increased self-esteem Improved mood
	Self-perceptions of healthy/“not sick”
	Reduced stress, anxiety, and worries
	Reduced depression
	Improved HRQoL
Cold sensation/cold injury	Increased heat to core body
	Increased distal extremities
Ischemia/RP	Increased oxygenation/gas exchange to extremities
	Improved wound healing
	Possibly reduced DUs, calcinosis, and osteolysis
	Possibly improved sexual function
Gastrointestinal Dysmotility	Reduced nausea
	Reduced bloating
	Enhanced peristalsis/digestion and reduced constipation
Diarrhea	Improved microbiome profile
Arthropathy	Joint lubrication
	Decreased stiffness
	Decreased inflammation
	Increased mobility, flexibility, and dexterity
	Strengthening of periarticular muscle support
Skin tightness	Possible reduced skin tightening
	Possible degree of preservation of skin function e.g., sweating
	Possible reduction of subcutaneous edema
Myopathy	Improved muscle strength
Myositis	Improved muscle endurance
Atrophic myopathy	Improved aerobic capacity and vascularization of muscle
	Reduced muscle inflammation
	Enhanced muscle recovery
	Increased muscle mass, with correlates to decreased inflammation
Oral aperture	Improved mouth opening
	Oral health improvement
Facial changes	Improve mouth function
	Possibly improved facial expression and verbal communication

SSc Manifestation	Potential Impact of Exercise
Pain	Pain reduction
	Decreased stiffness
Respiratory capacity and breath phrasing	Improved tolerance to dyspnea
	Improved exercise tolerance
Need for pharmaceutical treatment	Less need of pharmaceuticals to improve blood circulation

Table 6

Eligibility and safety of exercise in SSc *(Courtesy of LA Saketkoo on behalf of G-FoRSS, rights reserved).*

Who can Exercise:	
SSc patients without pulmonary involvement	*Concluded to partake without restriction* [120]
SSc patient with cardiopulmonary involvement	*Considered feasible, safe, and effective* [118,283] *regardless of underlying diagnosis (*e.g.*, ILD and PH)* [120]
SSc patients with mild pulmonary involvement	*Safely able to engage in moderate aerobic intensity with moderate-load resistance exercises* [120]
SSc patients with myopathy and cardiopulmonary involvement	May warrant special attention focusing on strengthening
Pre-Exercise Screening for:	
ILD	- Symptomatology
	- Serial FVC
	- Serial DLCO
	- 6MWT for desaturation
	+/− HRCT of Chest
PH	- Symptomatology
	- Annual echocardiogram at rest and with exercise
	- Serial DLCO
	- 6MWT for desaturation
	- Right heart catheterization (gold standard) if symptomatology or testing is concerning
Further screening	Cardiac magnetic resonance imaging (CMR) is the gold standard to assess:
	- right and left ventricular systolic function (LVSF)
	- myocardial fibrosis
	- pericardial disease [284]
Safety Parameters	- Regular monitoring of blood pressure, heart rate and preferably, forehead oximetry [123] with formal exercise programs.
	- Severe symptoms and exercise-induced desaturation require individualized modification of intensity and duration [285]
	- Supplemental oxygen [118,285] is required for abnormal desaturation Forehead oximetry [123] over digital oximetry SpO2 may reduce Raynaud-related falsely low readings
	- Borg CR-10-scale to assess dyspnea and leg tiredness [286] as well as the Borg RPE-scale, Rating of Perceived Exertion can inform baseline and follow-up assessments [287]
	- The treating physician should always be notified of any unexpected abnormal assessments, e.g., heart rate, oxygen saturation, etc. or large drops in saturation
Programmatic Considerations	Regardless of SSc manifestations, load intensity, and repetitions are adjusted according to symptoms and tolerance (ref 7).
	Diverse effective modalities such as continuous versus interval aerobic training can be intensified up to 75%–80% of the patient's projected maximal load based on their physical condition and comorbidities while monitoring intensity parameters e.g., breathlessness severity, leg fatigue, and heart rate.
	Combined aerobic, resistance, and respiratory muscle training induces the strongest improvement in functional capacity reflected by 6MWD and VO2 peak [104]
	In severe cardiopulmonary disease, unilateral resistance training may be more accessible over dynamic resistance training.
	In exercise-related induced sPAP elevation, interval training is the preferred safer approach due to load reduction on the vessels of the systemic and pulmonary circulation.

Who can Exercise:	
	In ILD, initiating endurance training between 70% and 80% of max exercise capacity.
	Interval training may be an alternative in ILD with periods of relative high-intensity training interspersed with periods of rest/low-intensity training allowing for time to recuperate and lessen breathlessness and fatigue [285]
	In PH, it is advisable to avoid interval training due to the associated risk ofrapid changes in pulmonary hemodynamics and risk of syncope [288–290] However, new research and guidelines may bring clarity to optimal exercise strategies in both ILD, PH and the combination of ILD and PH.

Table 7a

Stratifies patients with SSc for engagement in exercise *(Courtesy of LA Saketkoo on behalf of G-FoRSS, rights reserved).*

Strata of Engagement	Advisement	Comments
No pulmonary involvement	Unrestricted but targeted to patient needs and tolerance	Gradual increment of intensity, repetitions, and duration
Mild cardiopulmonary symptoms	Moderate aerobic intensity with moderate-load resistance exercises	Gradual increment of intensity, repetitions, and duration
Severe cardiopulmonary symptoms	Individualized modification of intensity and duration, with supplemental oxygen as needed [118,290]	Can be intensified up to 75%–80% of patient's projected maximal load
Desaturation with exercise	As above for severe cardiopulmonary symptoms	
Increase of systolic pulmonary artery pressure with exercise	Load reduction on systemic and pulmonary circulation is an important consideration	Rapid changes in pulmonary hemodynamics Interval training may increase the risk of syncope [290]

Table 7b

General considerations for exercise in SSc* *(Courtesy of LA Saketkoo on behalf of G-FoRSS, rights reserved).*

Concept	Advisement	Comments
Exercise Initiation	All patients screened for clinically significant ILD and PH Assess current activity levels with FITT Consider assessing patient goals with PSFS	
	Aerobic and muscle testing prior to start of exercise	Submaximal ergometer cycle test or treadmill test and muscle tests like TST, 30-sec CST, and FI-2
Sustaining exercise	Anticipatory guidance of fluctuating fatigue/pain challenging exercise.	Encourage mindfulness practice and pleasure principals during exercise to redirect frustration and disappointments.
	Education on stretching safety	Emphasis on consistency of practice and expectations of incremental improvement.
	Developing alternate options for inclement weather or GI exacerbations	Adaptations Indoor options Online class options
	Consider monitoring achievement with PSFS	
	Start gently and escalate with improvement	
	Recommendation for home general physical activity (e.g., walks) 30 min/5 days weekly	
	Aerobic and muscle testing after exercise period to evaluate intervention	Submaximal ergometer cycle test or treadmill test and muscle tests like TST, 30-sec CST, and FI-2
Myopathy	Screen for myopathy	In tandem with rheumatologistyet, determine if targeted strengthening required
	Assess degree of myopathy preferably using FI-2 or FI-3	
Nutritional status	Assess for low nutritional status	Consider adjustment of calorie intake to exercise-related consumption
Face, Mouth, Hand, Wrist, and Shoulder ROM exercises	Ideally encouraged to be daily or twice daily “ritual”	Frequency may be increased at induction and decreased for maintenance.
		Patients can also implement throughout the day as needed for relief.
Raynaud	Indoor temperature Outdoor temperature Gripping equipment Erroneous oximetry results	Alternate plans for inclement weather Use of exercise gloves Forehead oximetry to avoid falsely low readings
Digital ulcers	Require bandaging and protective gloves prior to handling equipment Require bandaging and gloving with paraffin wax emersion	
Warming	Hands for improved exercise performance	Consider paraffin bath immersion
	Sauna	To improve core warmth prior exercise, both in water and on land
Feet	Screen for foot pain	
	Assess degree and cause of foot pain	Advise on proper footwear with insoles or referral to podiatry where necessary
Cardiopulmonary	Screen for extent and severity Interval monitoring pulse, blood pressure and forehead oximetry Adjust exercise for symptom severity Use supplemental oxygen to keep levels appropriate for exercise [285,291] in ILD [290] and PH [285,290] Combined aerobic, resistance, and respiratory muscle training induces the strongest improvement in functional capacity	
	Dynamic resistance training in severe cardiopulmonary disease may require a switch to isolated, unilateral resistance training	
Stretching	Stretching ideally is done regularly to condition anatomic proprioception, balance, and muscular responsiveness.	Stretching is also performed *before* and *after* other forms of exercise to increase circulation into the

Concept	Advisement	Comments
	Stretching is essential to maintain ROM and protect the muscle from excessive force	muscle, warm muscle, and prepare the muscle to be responsive enough to protect itself and articular structures by the regulation of force and stretch
	Each flexibility exercise is held for a total of 30–60 s (e.g., 45 s once or 15 s thrice), preferably synchronized with breath cycles, to allow for muscle fibers to relax into its optimal length	Bouncing or pulsing a stretch is considered unsafe. Stretching the point of a *"resistance sensation"* or "pleasurable pain" but not a *"bad pain"* to avoid damage ≥30 s may be more beneficial
	Warming the area of the body prior to stretching with loose fluid movements, sauna, or warm wax	Moving the general body area for about a minute with arm circles shaking, marching, etc., warms and relaxes muscle before stretching.
Aquatic exercise	Rinse off chlorinated or salted water Moisturize skin post-exercise	
	Exhaustion may occur with changing of clothes and being wet at room air for extended length of time	Provide attendant support
	Water temperature between 30 °C −34 °C and 86 °F −93 °F	Water is a rapid conductor of heat. Lower temperature water draws heat from the body
	Advisement on pacing with gradual increase of duration and intensity	To protect against unintended overexertion

Abbreviations: FITT: frequency, intensity, time duration and type; FI-2: functional index 2; FI-3: functional index 3; ILD: interstitial lung disease; PH: pulmonary hypertension; PSFS: Patient-Specific Function Scale; TST: Timed-stands test; and 30-s CST: 30-s chair stands test.

[*] Treating physician must be apprised of any new oxygen requirement or new cardiopulmonary symptomatology e.g., arrhythmia, syncope/pre-syncope, etc.

Table 8

Comprehensive profile of published exercise studies in SSc to date.

Publication	Population/Dropouts	Interventions and Exercise Type	Primary outcomes	Secondary outcomes	Adverse events
Aerobic and Muscle Performance					
Oliveira et al. (2009) [292]	7 SSc(2 dcSSc and 5 lcSS) and 7 healthy controls. No pulmonary involvement on CT or PASP ≤40 mmHG or FVC and DLCO <75% of predicted. 2 dropouts in SSc.	**Aerobic exercise** 2x/wk for 8 wks of 40 min on treadmill.	VO_{2peak} improved significantly in both groups.	Improved peak exercise oxygen saturation in SSc after it was compared to baseline.	No adverse effects reported.
Pinto et al. (2011) [121]	11 SSc (8 dcSSc and 3 lcSSc). No evidence of moderate or severe pulmonary involvement or PASP ≤40 mmHG or FVC and DLCO <75% of predicted.	**Aerobic exercise** 2x/wk for 12 wks of 20 min on treadmill. **Resistance** training for 30 min for 5 main muscle groups in 8–12 reps x 4 sets.	VO_{2peak} Improved.	Significant improvements in muscle strength.	No adverse effects reported.
Alexanderson et al. (2014) [293]	SSc, n = 4. 2 with lung fibrosis with FVC 50% resp 80% while the other 2 had FVC 100%.	**Aerobic exercise** on ergometer cycling of 30 min. **Muscular endurance exercise** of shoulder and hip flexors for 30–50 min 3x/wk for 8 wks.	6MWT, no significant change.	Muscle function: (Functional Index 2, shoulder flexion and hip flexion) improved significantly in 3 patients. No significant changes, but trend of reduced fatigue in 3 patients.	No exercise-related adverse events.
Mitropoulos et al. (2018) [100]	LcSSc, n=34. No lung involvement nor myositis or NYHA class 3–4. Dropouts: 1 patient in each group.	**Aerobic exercise** with ACE, n = 10 or CE n = 10. ACE = 2 days/wk for 12 wks of 30 min sessions of30 s HIIT followed with 30 s passive recovery. CE = 2 days/wk for 12 w of 30 min with bouts of 30 s HIIT followed with 30 s passive recovery. CG, n = 11, and no exercise.	VO_{2peak} improved significantly in ACE and CE after intervention.	Life-satisfaction improved in both ACE and CE. Discomfort and Raynaud's pain decreased in both ACE and CE as well as improved life satisfaction.	No exercise-related adverse events.
Mitropoulos et al. (2019) [294]	LcSSc, n = 32. No PAH or ILD or myositis or NYHA class 3 or 4.	**Aerobic Exercise** (n = 16), ACE = 2 days/w for 12 wks of 30 min sessions of 30 sec HIIT followed with 30 sec passive recovery. **Resistance training**, 5 upper body exercises in 10 reps x 3 sets. CG, n = 16, and no exercise.	VO_{2peak} improved statistically in ACE compared with CG.	Improved endothelia-dependent reactivity in ACE as well as improved transcutaneous oxygen pressure in finger.	No adverse events reported.
Filippetti et al. (2019) [103]	SSc, n = 44, and 22 each in both IG and CG No PH, VC ≤50%, and DLCO ≤30% or NYHA class 3 or 4. Dropouts in IG n = 6 and CG n = 5.	A 6 months, 3 days/wk, minimally supervised home rehabilitation program in IG, no exercise in CG. **Aerobic Exercise**, CG, stationary bike at 60% intensity for 15 min, 3 min rest, and 15 min bike. **Muscular endurance exercise** for upper limbs with load of 60% of 1RM. **Stretching** for hands.	6 MWD improved statistically in IG compared with CG.	Improved q-ceps, biceps, and grip strength as well as improved physical score in SF-36 in IG when compared with CG.	3 patients in IG dropped-out due to pain in joints and other parts.

Publication	Population/Dropouts	Interventions and Exercise Type	Primary outcomes	Secondary outcomes	Adverse events
Oro-Facial Exercises					
Pizzo et al. (2003) [295]	10 SSc with oral aperture <30 mm.	Mouth stretching and oral augmentation exercises for 15 min twice a day for 18 wks.	Mouth opening significantly increased; subjective improvements in eating, speaking, and ability to perform oral hygiene.	N/A.	Mild muscle fatigue in cheeks.
Poole et al. (2010) [296]	17/21 SSc (9 dcSSc and 8 lcSSc) completed all visits.	Mouth exercises and oral augmentation exercises in combination with education on brushing and flossing teeth and adapted dental appliances.	Dental hygiene improved significantly for decreased bleeding, supragingival calculus, and increases in caries. No significant improvement in mouth opening.	N/A.	None reported.
Yuen et al. (2011, 2012) [297,298]	IG: 26(13 dcSSc and 13 lcSSc). CG: 22 (8 dcSSc and 14 lcSSc).	IG: powered toothbrush and flosser plus mouth stretching and oral augmentation exercises held for 15–20 s, 3 times each, 2 times/day for 6 months if oral aperture <40 mm CG: manual toothbrush and dental floss 2 times/ day for 6 months.	Oral aperture significantly increased as compared to controls at 3 mo but not at 6 mo. Gingival inflammation was significantly reduced in both groups. IG showed a significantly larger reduction in inflammation than CG.	N/A.	None reported.
Hand Exercises					
Mugii et al. (2006; 2019) [299,300]	45 SSc (32 dcSSc and 13 lcSSc). 2 dropouts from yr 1 to yr 9.	Stretching exercises for joints of the hand. Position held 10 s with 3–10 repetitions.	TPM improved at 1 month postintervention, which improved or was maintained at 1 yr. No change in HAQ but individual item score improved.	N/A.	None reported.
			At 3-yr follow-up, TPM improved and was maintained or improved at 9 yrs after the first visit. No change in HAQ at 9 yrs except in patients who also had decreased TPM related to worse skin scores.		
Piga et al. (2014) [301]	IG: 10 SSc (2 dcSSc and 8 lcSSc). CG: 10 SSc (2 dcSSc and 8 lcSSc). No irreversible anatomical damage, active arthritis, or digital ulcers. 2 dropouts in CG.	IG: 5 mobility and 3 strengthening exercises for the hand to be done at home 5 d/wk for 12 wks monitored remotely for number of repetitions, force, speed, and correctness.	No group differences. Both groups showed improvements in hand function; HAQ and HAMIS for the R hand improved significantly only in IG.	No group differences. Pinch strength and MCP ROM for R hand increased significantly in both groups; no increases in pain, global health, or SF-36.	None reported.
		CG: Home program of 3 mobility and 3 strengthening hand exercises to be done 5 d/wk for 12 wks.			
Stefanantoni et al. (2016) [158]	15 IG (7 dcSSc and 8 lcSSc). 16 CG (5 dcSSc and 10 lcSSc). No active synovitis, DU.	Hand exercises tailored to participants' goals; met at 1 mo and 3 mo with weekly phone calls between sessions. CG: general instruction to do exercises 1x/day.	IG had significant improvements with perceived satisfaction and performance of daily tasks (COPM), HAQ and SF-36 mental health at 3 months. Significant differences between IG and CG at 3 months was	N/A.	None reported.

Publication	Population/Dropouts	Interventions and Exercise Type	Primary outcomes	Secondary outcomes	Adverse events
			perceived performance on daily tasks.		
Landim et al. (2017; 2020) [184,186]	IG: 40 (22 lcSSc and 18 dcSSc). CG: 17 (11 lcSSc and 6 dcSSc). No previous hand rehab, hand disease not due to SSc, or unable to perform exercises.	IG: Home hand exercise program consisting of booklet and video disc; revaluated at 4,8, and 24 wks. CG: usual care; revaluated at 24 wks.	VAS-pain, CHFS, ΔFTP, grip, and tip and pinch strength increased significantly in IG but not in the CG.	SHAQ and SF-36 improved in IG but not in CG.	None.

ACE, arm crank ergometer; CE, cycle ergometer; CG, control group; CHFT, Cochin Hand Function Test; COPM, Canadian Occupational Performance Measure; CT, computerized tomography; dcSSc, diffuse cutaneous SSc; DLCO, diffusing capacity for carbon monoxide; DU, digital ulcers; ΔFTP change finger to palm; FVC: forced vital capacity; HAMIS, hand mobility in scleroderma; HAQ, health assessment questionnaire; HIIT; high-intensity interval training; IG, intervention group; ILD: interstitial lung disease; lcSSc, limited cutaneous SSc; MCP ROM: metacarpophalangeal range of motion; N/A, not applicable; NYHA: New York heart association (class 1e4); 1RM, one repetition maximum; PAH: pulmonary arterial hypertension; PASP: pulmonary artery systolic pressure; PH: pulmonary hypertension; R hand, right hand; SF-36: Medical Outcomes Survey Short Form; SHAQ, Scleroderma HAQ; 6MWT: Six-minute walk test; TPM, total passive range of motion; VAS: visual analogue scale; VC: vital capacity; q-ceps: quadriceps muscle; and VO_2peak: peak oxygen uptake.

Table 9

Clinically feasible assessments in patients with SSc.

Quality to Assess	Test	Description	Comments
Range of motion	Functional Shoulder Assessment (FSA) [302]	Assessment of 6 functional movements of the upper extremity.	
Muscle endurance	Functional Index 2 (FI-2) [213]	Dynamic assessment of quantity of repetitions before exertion in 7 muscle groups.	2FI-2 is feasible, good to excellent inter- and intrarater reliability in SSc (unpublished data, Pettersson).
	FI-3 [303] revised shorter version of FI-2, feasible for clinic visit physical exam	As above, examining 1 to 3 muscle groups.	Especially hip, shoulder, or neck flexion.
Muscle strength	Timed-Stands Test TST [78,215],	Time required to rise from chair 10 times.	Only valid if patient can do all 10 reps.
	30-s Chair-Stands Test CST [304],	Number of full rises from chair during 30 s.	Particularly for patients unable to complete TST.
Aerobic capacity	Treadmill, Ebbelings test [51]	Submaximal aerobic test, walks for 4 min at a selfselected pace followed by 4 min, at the same pace, but with a 5% elevation.	More suitable for older/ more lung-impaired patients.
	Cycle ergometer test, Astrand test [305]	Submaximal aerobic test, 6 min ergometer biking.	
Functional capacity	6MWT, 6-min walk test [306]	Walking distance on flat ground for 6 min.	Functional capacity test for patients with cardiopulmonary problems.
Hand grip force	Grippit [173]	An electronic handheld dynamometer to measure grip strength (finger flexion force).	
	Jamar Dynamometer [168]	An hydraulic handheld dynamometer to measure grip strength (finger flexion force).	
Upper Extremity Activity limitation	Disabilities of the Arm, Shoulder, and Hand (DASH) [169]	Assesses the disability of the upper extremity and can monitor change in symptoms and upper limb function over time.	
	Patient Specific Functional Scale (PSFS) [166]	Patients identify up to five important activities they are having difficulty with as a result of their disease.	
	Scleroderma Health Assessment Questionnaire SHAQ [160,164,171]	Self-reported questionnaire assessing disability and function, adopted for SSc with VASs for pain, DU, RP, breathing, and GI problems	
	Cochin Hand Function Test (CHFT) [161,171,172] (aka Duruoz Hand Index) Abilhand [171,172,174]	18-item questionnaire measuring manual ability of daily activities. 26-item questionnaire assessing level of difficulty of upper extremity tasks.	
Hand function and motion	Hand Mobility in Scleroderma (HAMIS) [170]	9 items designed to measure all movements assessed in an ordinary ROM-measured hand test.	
	Hand Anatomic Index (HAI) [162,163]	Measurement of open hand span minus closed hand span/lateral height of hand.	
	Hand Function Index (HFI) [175]	9 items of the Keital Functional Test that assess global hand and wrist mobility.	Requires less than 1 min.
Mouth Function	Mouth Handicap in Systemic Sclerosis Scale (MHISS) [149]	12-item scale representing impairment related to mouth opening, sicca, and esthetic concerns.	

Abbreviations: DUs, digital ulcers; GI, gastrointestinal; ROM, range of motion; RP, Raynaud's phenomenon; Sicca, oral dryness; and VAS: visual analog scale.

Table 10

Potential exercise enhancing qualities of water-based exercise and therapies.

Possible effects of aquatic exercise in general populations [271–273]	
Improved domains	HRQoL
	Pain
	Fatigue
	Muscle function, strength, and endurance
	Aerobic capacity
	Physical function
	Range of motion
	Stiffness
	Muscle spasm
	Circulation
	Reduced disease activity in some Inflammatory diseases
Safety	Water properties minimize the risk of injury/re-injury
	Buoyancy and immersion anti-gravity offloading effects provide protective measure
	Advisement on pacing to protect against unintended overexertion
Tolerability	Increase ability to focus body movement
	Stretching more tolerable
	Increased exercise duration
	Increased exercise intensity
Patient-centered considerations	
Skin	Rinsing after chlorinated and salted water
	Moisturizing skin post-exercise to minimize skin dryness/irritation
Temperature	Aqueous and ambient temperatures facility and changing room require assurance of warmth
Logistical feasibility and patient effort	Planning time, energy, and assistance for pre/post preparations. Patients report feeling more exhausted by logistics of clothes change than the exercise, and state exercise benefit is worth it but needs to be addressed.
	Consider attendants to assist
Mobility	Support for descending/ascending into pool

Abbreviations: AROM, active range of motion and HRQoL, health-related quality of life.

Table 11

Preliminary research agenda for the investigation of exercise inSSc as advocated by *The Global Fellowship on Rehabilitation and Exercise in Systemic Sclerosis (G-FoRSS)*

QUALITATIVE INVESTIGATIONS	**Patient experiences of exercises prior to and concurrent with SSc diagnosis:** Personal feelings before SSc diagnosis
	Activity profile
	Observation of sweating in SSc
	Type of exercises
	Pleasure
	Preferential time of day and frequency
	Exercise adherence to sustain benefit over time
	Home-based versus hospital-based settings for exercise
	Patient perceived impact of exercise on:
	SSc Manifestation Domains:
	Raynaud, circulation, and sustaining core warmth
	Wound healing
	Calcinosis
	Lung symptoms
	Gastrointestinal: SICCA, bloating, and constipation
	Muscle function
	Articular function
	Sexual function, e.g., erectile dysfunction improvement after aerobic exercise
	Symptom Domains:
	Dyspnea
	Cough
	Pain
	Fatigue
	Sleep
	HRQoL Domains:
	Body Image and Self-esteem
	Well-being and vitality
	Depression/Anxiety
	Meaningful activities
	Worker productivity/performance
	Body perception
	Patient perceptions of engaging in exercise:
	Fears and worries
	Hopes, goals, and benefits
	Benefits of individual or group PT led “SSc School on Exercise"
	Home-based versus hospital-based settings for exercise
	Goals are to fulfil anticipated benefits and provide knowledge to address concerns
	Patient-perceived barriers/hindrances to initiating and to sustaining exercise practice:
	Logistical management (oxygen, changing clothes/shoes, physical, and work)

	Time restraints (work and family)
	Time management/prioritizations
	Climate
	Access to pleasurable self-directed exercise
	Access to home or hospital-based exercise
	Modality of delivery:
	Digital/Print
	Audio/Visual Recording
	Community/collective learning
	Community/collective exercise
	Combined approaches
	Medication side effects
	Presence of pain
QUANTITATIVE INVESTIGATIONS	Characterizing FITT in both aerobic and resistance exercise to target circulatory, antiinflammatory, and respiratory effects.
	Best submaximal exercise testing method in SSc – with special focus on different degrees of lung involvement
	Priority systemic exercise types (e.g., resistance, aerobic, etc.) in SSc
	As a general approach to SSc
	With and without lung/heart involvement:
	- In severe pulmonary disease
	- Across varying degrees of lung involvement?
	- In combined PH and ILD
	- Respiratory training – inspiratory muscle training and/or positive expiratory pressure
	With further definition in land- and water-based applications
	The use of minimally invasive muscle biopsies to evaluate response to exercise
	Home-based versus hospital-based settings for exercise
	Effects of exercise on:
	Raynaud phenomenon
	Sexual function
	Circulatory and hemodynamic effects
	Worker productivity/performance
	Serum and histological biomarkers:
	Muscle tissue mRNA expression of inflammatory and fibrotic pathways
	Inflammatory serum biomarkers
	Angiogenesis
	NT-Pro-BNP and Uric acid
	SSc Manifestation Domains:
	Raynaud, circulation, and sustaining core warmth
	Wound-healing
	Calcinosis
	Skin tightening
	Gastrointestinal: sicca (oral dryness), bloating, and constipation
	Muscle function
	Articular function: strength and AROM/PROM

	Symptom Domains:
	Dyspnea
	Cough
	Pain
	Fatigue
	Sleep
	HRQoL Domains:
	Body Image and Self-esteem
	Well-being and vitality
	Depression/Anxiety
	Meaningful activities and participation
	Self-perception of general health
	Effects of stretching/AROM/PROM (as above)
HANDS:	Optimal treatment protocols
	Comparative efficacy of different delivery methods
	Hand function and joint motion
	Optimal time in disease progression to emphasize hand exercises
	Impact of hand exercise on:
	Raynaud
	Digital ulcers/Wound healing/Calcinosis/Infection rate
	Contracture development/improvement
	Skin tightening
	Manual dexterity
	Worker productivity/performance
	Self-esteem
OROFACIAL:	Impact of orofacial exercises on:
	Prevention or delay of facial changes in people with SSc
	Dental/oral hygiene
	Dental/palatal structure changes
	Oral aperture: diameter and mobility
	Changes in lip thickness
	Nutritional intake/status
	Salivary production
	Well-being/self-esteem
	Progression of telangiectases
	Sauna as adjuvant to exercise
HEALTH ECONOMIC PERSPECTIVE	Cost-efficiency of supervised or educational interventions for patients Cost return on PT/OT/RT supervised structured exercise retreats in warmer climates to develop exercise safety and efficacy knowledge, intensify patient interest, and empowerment, and explore variance of self-directed exercise Patient costs related to supervised or patient-directed exercise interventions Hospital visits and need of medical treatment
SUSTAINABILITY	Patient general knowledge regarding exercise programs and continuance
	Patient-reported experiences of successful maintenance prior to and concurrent with SSc diagnosis
	Patient perceptions of potential external strategies to sustain exercise
	Patient perceptions of self-regulating strategies to sustain exercise

SAFETY	Screening for safety
	Screening for individually tailored safety modifications – baseline assessment – to tailor exercise and safety measures to the individual
	Range of safe parameters in:
	- non-cardiopulmonary involvement
	- ILD, PH or combined ILD/PH or heart failure
	- patients with other vital organ involvement
	Self-monitoring devices e.g., oximetry
	- Guidance on efficient use
	- Distress related to use
PROGRAMMATIC EXERCISE DESIGN	Intensity
	Session duration
	Frequency
	Escalation protocols
	Safety assessments
	Equipment
	General vs. SSc Manifestation Targeted
	Transition to Patient-managed continuance
INVESTIGATION OF EXERCISE TYPES and QUALITIES	Patient Preference/Aspirations
	Patient Experience
	Types Deconstructed by Programmatic Components
	Resistance
	Aerobic
	Singing
	Water-based
	Yoga
	Balance
	Combined approaches with borrowed elements to maximize benefit
PATIENT SELF-ASSESSMENT	Patient perceptions and patient experience of utility
	Patient experience of self-governance
	Track own metrics – authentic supported self-management
	Patient as their own control
	Metrics that are personalized to patient context
	- Patient-specific activity profile
	- Mouth diameter card
	- Hand tracings for extension
	- Duration, Intensity, and Load of selected exercise
	- VAS for fatigue, pain, RP, and muscle tiredness and dyspnea
	- Patient-Specific Functional Scale (PSFS)
	- VAS for patient-selected goal activities
TRIAL DESIGN	Relative importance of cohort assembly
	SSc criteria confirmation
	Targeted manifestation (ILD, PH, DU, etc)

	Phenotype (e.g., sine, dcSSc, and lcSSc)
	Degree of lung involvement (e.g., No – Mild vs Moderate – End-stage)
	Acceptable blinding and randomization procedures Optimal study duration for efficacy
	Harmonized patient support/check-ins across trials
	Standardized adherence monitoring
	Safety assessment
	Procedures for selecting primary, co-primary, secondary, and exploratory endpoints
	Standardized components of warm-up, cool-down, and stretching of muscles/skin
	Qualitative collection of patient experience data related to intervention and trial
	Global consensus on harmonization of outcome measures
	Promote interstudy comparative potential
	Ensure COSMIN thresholds of reliable performance and patient-reported outcome measures
	- Identification of optimal existing outcome measures
	- New instrument development or modification where needed e.g., Activity Profile
	- Acceptability to patients
	- Defining interval outcome measure assessment
	- Define best practice of pulse oximetry during exercise
MODALITY	How people learn
	Hard copy of learning resources versus web-based resources
	What impacts preferred modalities of learning and participation – age, gender, etc.
	Inherent challenges in home-based / telehealth /virtual sessions:
	- measuring range of motion e.g. joints of hands
	- predicting in home safety e.g. tripping hazards
	Use of apps, pictures, and videos to collect outcome data.

Abbreviations: AROM, active range of motion; dcSSc, diffuse cutaneous SSc; COSMIN, Consensus-based Standards for the selection of health Measurement Instruments; DU, digital ulcers; HRQoL, health-related quality of life; ILD, interstitial lung disease; lcSSc, limited cutaneous SSc; mRNA, messenger ribonucleic acid; NT-pro-BNP, N-terminal prohormone ofbrain natriuretic peptide; OT, occupational therapist; PH, pulmonary hypertension; PROM, passive range of motion; PT, physiotherapist; RT, respiratory therapist; and VAS, visual analog scale.