

Effects of diaphragmatic breathing exercise on sleeping quality, cortisol, cardiovascular autonomic functions, depression, and fatigue: a randomized-controlled trial in women with systemic sclerosis

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Abstract

Introduction: The available pharmacotherapies (immunosuppressant therapies) for systemic sclerosis (SSc) are not curative, especially in cases with non-lethal but challenging manifestations or complications of the disease. Fatigue, anxiety, depression, an over-activated hypothalamic–pituitary–adrenal axis (stress axis), and low sleeping quality are the common SSc-induced non-lethal manifestations that need close management. Diaphragmatic breathing tele-exercise (DBTE), as a stand-alone deep breathing retraining and tele-interventional technique, has not been utilized in the rehabilitation context of non-lethal complications in women with SSc. This online interventional study aimed to explore the efficacy of DBTE in controlling depression, cardiovascular autonomic functions, stress, sleep, and anxiety in women with SSc.

Material and methods: This randomized controlled tele-interventional trial recruited 40 non-obese women with SSc (aged > 18 years old) from an Egyptian teaching hospital. Women were randomly assigned to the DBTE group ($n = 20$) or non-DBTE group ($n = 20$). The DBTE group underwent 12-week 20-minute morning and evening DBTE sessions (sessions were supervised daily through the Zoom video conference program). The non-DBTE group served as a waitlist control group. The outcomes of this study were diastolic blood pressure (BPD), serum cortisol, the total score of the Hamilton Anxiety Rating Scale (HARS-TS), systolic blood pressure (BPS), the general score of the Pittsburgh Sleep Quality Index (PSQI-GS), pulse rate (PR), the eight-item Patient Health Questionnaire (El-PHQ₈), respiratory rate (RR), and the Visual Analogue Scale of fatigue (VAS-F).

Results: In the DBTE group, there were significantly lowered values of PSQI-GS, HARS-TS, El-PHQ₈, serum cortisol, VAS-F, and cardiovascular/respiratory autonomic functions (BPS, BPD, RR, and PR). In the non-DBTE group, no significant changes were observed for any variables.

Conclusions: It can be concluded from this tele-interventional trial that the 12-week application of DBTE may reduce cortisol, El-PHQ₈, PSQI-GS, HARS-TS, BPS, BPD, RR, PR, and VAS-F in women with SSc.

Key words: diaphragmatic breathing exercise, anxiety, sleeping quality, systemic sclerosis.

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Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune connective tissue disorder that is overrepresented in women [1]. The complex interplay between genetic and environmental factors induces the pathogenesis of SSc. Three main pathogenic/pathological features characterize this disorder: 1) induction of SSc-related gene programs in different cell forms, 2) aberrant immune activation, 3) diffuse connective tissue vascular injury (small arteries and microvessels) followed by impaired or defective neovascularization and remodeling, and 4) massive tissue fibrosis of the skin and/or internal organs [2].

Clinical manifestations of SSc are variable. The symptoms vary from Raynaud's phenomenon to more serious or alarming complications such as pulmonary arterial hypertension or lung fibrosis [1].

The available pharmacotherapies (immunosuppressant therapies) of SSc are not curative, especially with the presence of non-lethal challenging manifestations/complications of the disease. Fatigue [3], anxiety, depression, an over-activated hypothalamic–pituitary–adrenal axis (stress axis) [4], and low sleeping quality are the common SSc-induced non-lethal manifestations that need close management [5].

Complementary or coping-strategy treatments (self-management, educational support/training, relaxation techniques, breathing exercise, cognitive/behavioral therapies, physical exercise, etc.) for the above-mentioned non-lethal manifestations are essential in chronic diseases [6]. Traditionally, the above-mentioned complementary or coping-strategy treatments are administered in a face-to-face environment. Competing demands, time, distance, occupational loads, and costs make face-to-face adherence to these treatments challenging. Telehealth delivery has been recently suggested as an alternative to providing necessary face-to-face care for patients with chronic diseases [7], including SSc.

Deep breathing exercise is a recommended relaxation maneuver used to improve psychological health (stress, anxiety, and depression) [8], regulate cardiovascular autonomic functions [9], and decrease insomnia and fatigue [10] in chronically diseased adults [8].

Despite the above-mentioned importance of deep breathing exercise, diaphragmatic breathing tele-exercise (DBTE), as a standalone deep breathing retraining and tele-interventional technique, has not been utilized in the rehabilitation context of SSc-induced non-lethal complications. Exploring the effect of DBTE on sleeping quality, cortisol, cardiovascular autonomic functions, depression, and fatigue was the aim of this innovative tele-interventional trial in women with SSc.

Material and methods

Design and settings

This study was a randomized controlled tele-interventional trial.

The period of October (15, 2022) to March (15, 2023) was the designated duration of SSc participants' recruitment. Via wall posters, participants were recruited from El-Sahel Teaching Hospital in Cairo, Egypt.

Inclusion and exclusion criteria

Participants' inclusive criteria: Forty women with SSc aged > 18 years old were included in this tele-interventional trial. A physician diagnosed women's disease according to the American College of Rheumatology criteria [11].

Participants' exclusive criteria: Before the application of this tele-intervention, besides pregnancy and lactation, women with neoplasia, concurrent rheumatic/ autoimmune diseases, myopathies, systemic/renal diseases, neurogenic disorders, inflammatory arthropathies, abnormalities of pulmonary artery blood pressure (such as pulmonary hypertension), interstitial lung diseases, obstructive/restrictive lung disorders, heart diseases, and mental/psychogenic disorders were excluded by a physician.

Randomization

Using closed enveloped randomization, a person (a physical therapist who had recently obtained a master's degree in physical therapy) who did not take part in this SSc trial randomly divided the women into a 12-week DBTE group (20 women with SSc) or a waitlist group (20 women with SSc who did not receive DBTE; Fig. 1).

Intervention (diaphragmatic breathing tele-exercise)

Firstly, the day before conducting the first DBTE session, a face-to-face interview was conducted with women to introduce a presentation session on the importance and steps of DBTE.

At the pre-determined morning and evening times for all participants, 8:00 a.m. and 8:00 p.m. respectively, the therapist and women were online daily for 12 weeks. In the beginning, using the Zoom videoconference program (Zoom Communications, Inc, version 6.3.1, USA) which was previously installed on participants' Android cell phones, the therapist asked the women to rest in a supine position for 5 minutes. Next, the women were asked to put their cell phones aside from their bodies while remaining online (Zoom's sound level was kept at its maximum loudness). Next, the patients were asked

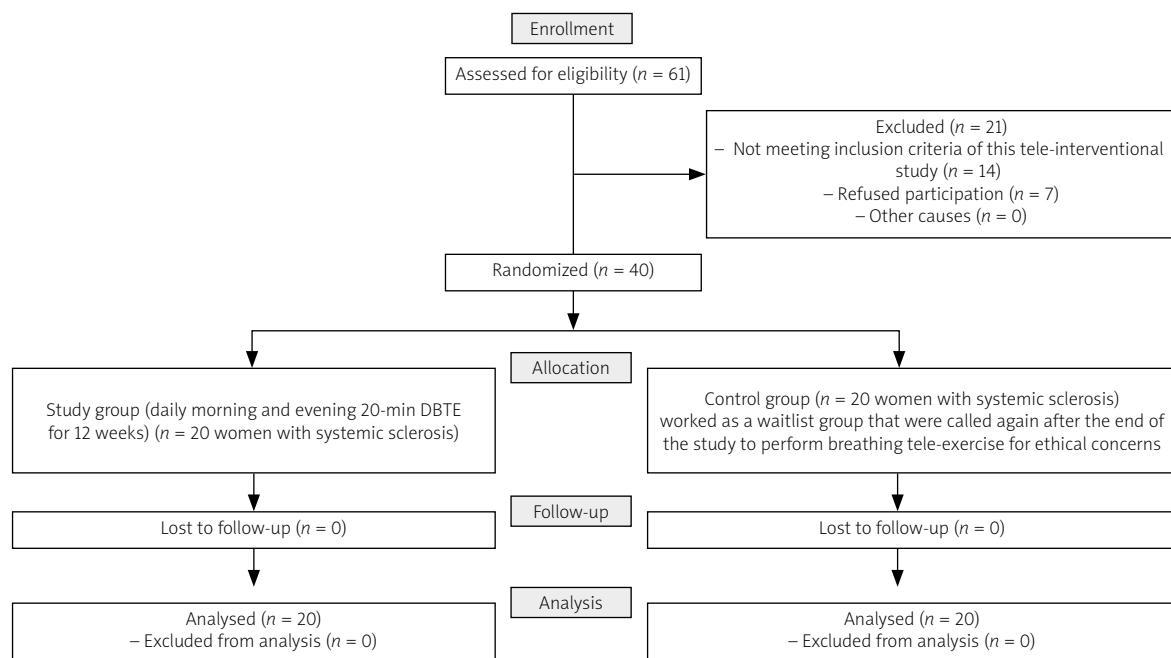


Fig. 1. PRISMA flow chart of women with systemic sclerosis.

to listen to the therapist's instructions emitted from the women's phones. The women were asked to put their right palm on the anterior chest wall while their left palm was kept below their anterior costal margin. Women were asked to take deep, slow breaths through their nose, with their shoulders relaxed. During inspiration, the upper chest remained still to allow the abdomen to rise (women were instructed to inflate their abdomen like a balloon). Using controlled expiration, the women were asked to slowly let all the air out from their mouths with a sigh. Continuous guidance was given to the patients, stating that their left hand should rise while breathing in and fall while breathing out, whereas their right hand should remain still. During the DBTE sessions, the therapist constantly instructed the women to relax and concentrate on their breathing patterns. To avoid hyperventilation, some precautions were taken: no prolonged inspiration, no forceful expiration, and every 5 repetitions of diaphragmatic breathing exercises were followed by a 3-minute rest. During this rest period, the women were instructed to place their hands down in a resting position. Every morning or evening, DBTE sessions were applied daily for 20 minutes [12].

Outcomes

Respiratory and cardiovascular autonomic functions:

A manual assessment of respiratory rate (RR), pulse rate (PR), systolic blood pressure (BPS), and diastolic blood pressure (BPD) was performed.

Pittsburgh Sleep Quality Index (PSQI): To assess subjective sleep quality, the general score of PSQI (PSQI-GS) was utilized in this tele-interventional trial. With a PSQI-GS ranging from 0 to 21, this PSQI questionnaire rated the responses from 19 questions [13].

Hamilton Anxiety Rating Scale: The intensity of mental and physical anxiety was assessed via the 14-item Hamilton Anxiety Rating Scale (HARS). With a pre-determined score ranging from 0 to 4 for every item, the total score of HARS (HARS-TS) ranged from 0 to 56 [14].

Serum cortisol: In-serum cortisol was measured by radioimmunoassay at 8:00 a.m. (RIA measurement, Byk-Sangtec-Diagnostica, Germany) for all women with SSc. Serum cortisol was the primary outcome of this tele-interventional trial.

Eight-item Patient Health Questionnaire (EI-PHQ₈): To assess the frequency of depressive symptoms, the EI-PHQ₈ was used. With a pre-determined score ranging from 0 to 4 for every item, EI-PHQ₈ ranged from 0 to 24 [15].

Visual Analogue Scale of fatigue (VAS-F): The perception of fatigue was tested on a 10-cm VAS.

Blinding

A physical therapist who had recently obtained a doctoral degree in physical therapy assessed our study's outcomes (except serum cortisol, which was assessed by a specialist of medical laboratory tests). The assessors of our study's tele-interventional outcomes

Table I. Data of systemic sclerosis groups

Data	DBTE group, mean \pm SD	Waitlist group, mean \pm SD	p
Age [years]	37 \pm 9.83	38.55 \pm 9.58	0.616
Systemic sclerosis duration [years]	12.90 \pm 2.61	13.30 \pm 3.15	0.664
Body mass index [kg/m ²]	25.40 \pm 3.35	24.95 \pm 2.79	0.647

*p-value is non-significant ($p > 0.05$).

DBTE – diaphragmatic breathing tele-exercise, SD – standard deviation.

were not informed about the treatment introduced to the women with SSc.

Sample size calculation

Acting as a pilot test, 16 women with SSc provided the minimum number to conduct this tele-interventional trial. The assumed number of 36 women was the net result. The settings of the G*Power program (Franz Faul, Uni Kiel, Germany) were the power of 80% and 5% type-1 error. The net result of cortisol's effect size was 0.96. Cortisol was used in this calculation as the primary outcome for this tele-interventional trial. The authors added 4 women with SSc in every group to avoid women's dropouts (10%).

Statistical analysis

The collected basic data (age, duration of disease, and body mass index [BMI]) and outcome (HARS-TS, BPS, serum cortisol, BPD, PSQI-GS, RR, VAS-F, PR, and EI-PHQ₈) data were processed using the program SPSS version 18 at a significance level of $p < 0.05$. All data of this tele-interventional trial, which were subjected to the normality test and Kolmogorov-Smirnov test, confirmed a normal pattern of distribution. Consequently, the within-group analysis of women's outcomes (HARS-TS, BPS, serum cortisol, BPD, PSQI-GS, RR, VAS-F, PR, and EI-PHQ₈) was performed using a paired test. Also, the among-group analysis of women's pre-treatment basic variables or outcomes was performed using unpaired tests.

Bioethical standards

NCT05623917 was the number of this tele-interventional trial. The trial was registered at www.clinicaltrials.gov. P.T.REC/012/004115 was the institutional (Cairo University) approval number for this SSc study and its consent form. The 5 authors asked women with SSc to sign the consent form. The Declaration of Helsinki recommendations for clinical trials were respected and applied.

Results

At the baseline of this tele-intervention, regarding the pretreatment comparison of basic data (age, BMI, and duration of SSc disease, as shown in Table I) or out-

come data (HARS-TS, BPS, serum cortisol, BPD, PSQI-GS, RR, VAS-F, PR, and EI-PHQ₈, as shown in Table II), there was no significant difference between SSc groups.

Pre-to-post comparison of PSQI-GS, HARS-TS, EI-PHQ₈, serum cortisol, VAS-F, and cardiovascular/respiratory autonomic functions (BPS, BPD, RR, and PR) in women with SSc showed significant improvements in the DBTE group. Outcomes of the waitlist SSc group did not show any significant changes (Table II).

Post-comparison of PSQI-GS, HARS-TS, EI-PHQ₈, serum cortisol, VAS-F, and cardiovascular/respiratory autonomic functions (BPS, BPD, RR, and PR) between waitlist and DBTE groups showed significant improvements in favor of the DBTE group (Table II).

Discussion

This is the first DBTE trial reporting significantly lowered values of PSQI-GS, HARS-TS, EI-PHQ₈, serum cortisol, VAS-F, and cardiovascular/respiratory autonomic functions (BPS, BPD, RR, and PR) in women with SSc.

Elevated baroreflex sensitivity, increased parasympathetic activity, activated pulmonary and cardiac mechanoreceptors, inhibited activities of sympathetic nerves, and lowered chemoreflex activation may be the causes of arteriolar dilatation after any type of relaxation techniques. DBTE-induced arteriolar dilatation explains the gained reduction of BPS and BPD [16] in our study.

The DBTE-induced reduction of BPS and BPD increases the time between two consecutive heartbeats. This time is known as the heart-rate-variability time (HRVT). The DBTE-increased HRVT is the cause of the reported PR reduction in this tele-interventional trial [17, 18]. Also, DBTE-induced lung-motion regulation is the cause of the reported RR reduction in this tele-interventional trial [19].

Besides the improvement of cardiovascular/respiratory autonomic functions (BPS, BPD, RR, and PR), regular application of relaxation techniques including DBTE reduces the production of stress hormones (including cortisol) and increases the release of relaxing substances such as endorphins and opioids. These substances improve a patient's psychological health via the induction

Table II. Outcomes of DBTE vs. waitlist groups

Parameters	DBTE group, mean \pm SD	Waitlist group, mean \pm SD	<i>p</i> (between DBTE and waitlist SSc groups)
BPS [mmHg]			
Pre-value	126.75 \pm 9.62	127.65 \pm 9.47	0.767
Post-value	121.95 \pm 7.01	127.95 \pm 9.68	0.030*
<i>p</i> (within group)	< 0.001*	0.330	
BPD [mmHg]			
Pre-value	79.00 \pm 8.09	79.40 \pm 6.15	0.861
Post-value	74.90 \pm 6.46	79.50 \pm 6.28	0.028*
<i>p</i> (within group)	< 0.001*	0.428	
PR [beating/min]			
Pre-value	82.30 \pm 8.38	85.00 \pm 7.45	0.288
Post-value	79.65 \pm 6.15	85.15 \pm 7.49	0.015*
<i>p</i> (within group)	0.003*	0.625	
RR [respiration/minute]			
Pre-value	17.85 \pm 2.56	18.15 \pm 2.77	0.724
Post-value	15.70 \pm 1.75	18.20 \pm 2.72	0.001*
<i>p</i> (within group)	< 0.001*	0.959	
El-PHQ ₈			
Pre-value	7.60 \pm 1.50	8.40 \pm 1.46	0.095
Post-value	5.50 \pm 1.39	8.95 \pm 1.43	0.0001*
<i>p</i> (within group)	< 0.001*	0.270	
PSQI-GS			
Pre-value	6.40 \pm 1.56	6.55 \pm 1.63	0.767
Post-value	5.05 \pm 1.23	6.95 \pm 1.46	0.0001*
<i>p</i> (within group)	< 0.001*	0.379	
HARS-TS			
Pre-value	7.10 \pm 1.55	8.00 \pm 1.93	0.101
Post-value	5.20 \pm 1.28	8.70 \pm 1.41	0.0001*
<i>p</i> (within group)	< 0.001*	0.115	
Cortisol [μ g/dl]			
Pre-value	7.37 \pm 1.76	7.79 \pm 1.83	0.464
Post-value	5.45 \pm 1.36	8.08 \pm 1.67	0.0001*
<i>p</i> (within group)	< 0.001*	0.599	
VAS-F [cm]			
Pre-value	6.59 \pm 1.52	7.05 \pm 1.42	0.328
Post-value	5.12 \pm 1.29	7.52 \pm 1.56	0.0001*
<i>p</i> (within group)	< 0.001*	0.223	

**p*-value is significant (*p* < 0.05).

BPD – diastolic blood pressure, BPS – systolic blood pressure, DBTE – diaphragmatic breathing tele-exercise, HARS-TS – Hamilton Anxiety Rating Scale (total score), El-PHQ₈ – eight-item Patient Health Questionnaire, PR – pulse rate, PSQI-GS – Pittsburgh Sleep Quality Index (general score), RR – respiratory rate, SD – standard deviation, SSc – systemic sclerosis, VAS-F – Visual Analogue Scale of fatigue.

of positive feelings such as calmness, relaxation, happiness [16], vitality, and good mood/sleeping quality [19].

The results of this DBTE trial were concordant with other studies that reported that regular paced (slow) breathing training (combined with biofeedback training) significantly improved BPD [18, 20], BPS [17, 18, 20], PR, and HARS-TS [20] in pre-hypertensive [18] or hypertensive patients [17, 20]. The daily application of 30-minute slow inhalation and exhalation exercises showed significantly lowered variables of cardiovascular/respiratory autonomic functions (PR, RR, BPS, and BPD) in older adults [9].

In the domain of selecting diaphragmatic breathing exercises as a relaxation intervention, regular use of this intervention significantly improved HARS-TS [21, 22], depression, PR, and RR [21]. Besides the lowered perception of symptomatic anxiety, a Taiwanese study reported that prescribing a program of diaphragmatic breathing retraining reduced adults' PR and RR [23].

During forced social distancing during pandemic times, a telerehabilitation trial that utilized breathing (relaxation) retraining for 1 week significantly improved fear, HARS-TS, and PSQI-GS in adults who had not contracted COVID-19 [19]. A study conducted on nurses who were on the first lines of defense in hospitals during the coronavirus crisis reported that regular diaphragmatic breathing exercises significantly lowered their anxiety levels and the majority of PSQI sub-items [24]. In agreement with the present results for PSQI, in patients with heart failure, regular practice of deep breathing training significantly lowered the values of PSQI [25]. Corroborating our results, in older adults, the daily practice of deep breathing training, as part of a body-scan-meditation program supported with music listening, significantly improved the majority of their PSQI sub-items [26].

In healthy adults [27] or patients with low back pain [28], abdominal breathing and progressive muscle relaxation as the main components of behavioral/cognitive therapeutic programs significantly improved EI-PHQ_g. Parallel to our results, in adults with coronary artery disease, regular home-based performance of deep breathing training significantly improved their depression levels (assessed by EI-PHQ_g) [29].

Breathing exercises – as part of an 8-week yoga course – improved depression, anxiety, and fatigue perceptions in women with breast cancer [30]. Consistent with the analyzed results of our study, in patients with allogeneic hematopoietic stem cell transplantation, the daily application of a 30-minute session of supervised deep relaxation connected with breathing exercise for 6 weeks improved patients' perception of fatigue [31]. In agreement with our results, in children and adolescents with slowly recovering concussion, a 5-minute

session of virtual-reality-paced deep breathing retraining produced significant decreases in stress and fatigue [8].

In line with our study results, an 8-week diaphragmatic breathing retraining trial conducted in China reported that practicing this form of relaxation technique could regulate emotions and lower salivary cortisol in healthy adults (via stimulation of the vagal nerve) [32]. Another study reported that practicing a 60-minute session of diaphragmatic breathing retraining significantly lowered the cortisol of athletes due to the enhanced activity of antioxidant enzymes [33]. Also, a 1-month web-based breathing exercise program significantly lowered stress perception in healthcare providers serving people with intellectual/developmental disabilities [34].

Opposite to the results of this DBTE intervention, despite the reduction of BPD, cortisol did not improve after 8 weeks of relaxation therapy (deep breathing combined with progressive muscle relaxation) in parents of children and adolescents with type-1 diabetes. This may be due to the salivary estimation of cortisol, unlike our study [35]. Blood pressure (BPS and BPD) showed a non-significant difference between the intervention group that underwent 3-month diaphragmatic breathing exercises and the control non-trained group. It may be due to the absence of assertive criteria utilized in randomizing the patients to studied groups [12].

In the context of recommending patients with rheumatologic diseases to adhere to regular tolerated performance of exercise, it is believed that exercise improves vascular functions, decreases over-dominance of sympathetic activity, decreases systemic inflammation, and increases the production of the muscular force – and hence, overall fatigue, stress, anxiety, and depression improve [36]. This was supported by a recent study that reported a significant improvement in PR, fatigue, RR, sleep quality stress, BPD, anxiety, BPS, cortisol, and depression after the daily application of 6-week breathing retraining in women with systemic lupus [37].

Study limitations

The follow-up to the results of this tele-interventional trial in women with SSc after the 12-week application of DBTE is the main limitation of this tele-interventional trial, which must be explored in future interventions of SSc.

Conclusions

It can be concluded from this tele-interventional trial that the 12-week application of DBTE may reduce cortisol, EI-PHQ_g, PSQI-GS, HARS-TS, BPS, BPD, RR, PR, and VAS-F in women with SSc.

Disclosures

Conflict of interest: The authors declare no conflict of interest.

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Ethics approval: This study was approved by the Ethics Committee of the Cairo University (approval number: P.TREC/012/004115).

Data availability: The data that support the findings of this study are available on request from the corresponding author (A.M.A.I.).

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