Multiple sustainable benefits of a rehabilitation program in therapeutic management of hypermobile Ehlers-Danlos syndrome: A prospective and controlled study at short- and medium-term.

Adrien Hakimi, Cyrille Bergoin, Anna de Jesus, Anne Hoorelbeke, Philippe Ramon, Oana Florea, Claudine Fabre, Patrick Mucci

Running head:

Rehabilitation for hEDS patients

Title:

Multiple sustainable benefits of a rehabilitation program in therapeutic management of hypermobile Ehlers-Danlos syndrome: A prospective and controlled study at short- and medium-term

Authors:

Adrien Hakimi, PhD,[1,2] - https://orcid.org/0000-0003-2595-9819

Cyrille Bergoin, MD,[2,3] - https://orcid.org/0000-0001-6581-1056

Anna De Jesus, MD,[2,3]

Anne Hoorelbeke, MD,[2]

Philippe Ramon, MD,[2]

Oana Florea, MD,[2]

Claudine Fabre, PhD,[1] - https://orcid.org/0000-0002-0441-9090

Patrick Mucci, PhD,[1] - https://orcid.org/0000-0001-6703-1600

[1]Univ. Lille, Univ. Artois, Univ. Littoral Côte d'Opale, ULR 7369 - URePSSS - Unité de Recherche Pluridisciplinaire Sport Santé Société, F-59000 Lille, France.

[2]Clinique de la Mitterie, Lomme, France.

[3]Cabinet de pneumologie, Tourcoing, France.

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Corresponding Author: Adrien Hakimi - adrien.hakimi.etu@univ-lille.fr - URePSSS, Eurasport, 413, avenue Eugène Avinée, 59120 Loos, France

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Abstract:

Objective: To evaluate the effects of a 9 -week rehabilitation program (RP) for patients with hypermobile Ehlers-Danlos syndrome (hEDS) in the short- and medium-term.

Design: Nonrandomized controlled trial with 6 months follow-up

Setting: Outpatient rehabilitation program

Participants: A referred sample of 36 hEDS patients were assessed for eligibility, 25 were included, 22 completed the RP and 19 completed the follow-up.

Interventions: A 9 -week control period without intervention followed by a 9 week rehabilitation program (RP).

Main Outcome Measure: Functional exercise capacity was used as a primary outcome measure. Balance, kinesiophobia, fatigue, pain, quality of life, anxiety, depression, and hyperventilation were measured as secondary outcomes.

Results: No significant change was observed during the 9 -week control period before the RP. There was a significant improvement immediately after the RP for the functional exercise capacity, balance with eyes closed, fatigue and quality of life ($P<.05$). Even more improvements were found 6 weeks after the end of the RP, and there was still an improvement after 6 months in functional exercise capacity, kinesiophobia, depression, hyperventilation, and some components of the quality of life.

Conclusion: This study supports the effectiveness of an RP as a useful management tool for hEDS patients.

Keywords:

Exercise, Fatigue, Kinesiophobia, Physical activity, Quality of life

Abbreviations:

6M – 6 months after the end of the RP

6MWT – 6 -minute walking test

6W – 6 weeks after the end of the RP

BMI – body mass index

BPI – Brief Pain Inventory

CEA – 95% confidence ellipse area

CTRL – nine weeks before the beginning of the RP

EC – Eyes closed

EDS – Ehlers-Danlos syndromes

EO – Eyes open

HAD – Hospital Anxiety and Depression scale

hEDS – hypermobile Ehlers-Danlos syndrome

MFI – Multidimensional Fatigue Inventory

POST – end of the RP

PRE – beginning of the RP

RP – rehabilitation program

SP – sway path

TSK – Tampa scale for kinesiophobia

Ehlers-Danlos Syndromes (EDS) are a group of inherited connective tissue disorders mainly characterized by joint hypermobility, skin hyperextensibility, and tissue fragility.[1] These syndromes present a great clinical and genetic heterogeneity and, since 2017, are classified into 13 subtypes.[1] The most common subtype is the hypermobile Ehlers-Danlos syndrome (hEDS).[2] There is a high phenotypic variability in hEDS with both musculoskeletal and non-musculoskeletal symptoms,[2] and the most common and highly disabling symptoms are pain and fatigue.[3–5] Pain avoidance strategies can lead to kinesiophobia and reduced physical capacity.[6] Patients also experience a wide range of symptoms, like dysautonomia, gastrointestinal disorders, or breathing difficulties.[7–10] These symptoms are the cause of a diminished quality of life and have significant psychosocial impact that can lead to anxiety or depression.[11–13]

Although the worldwide number of patients with hEDS was estimated at 255 million in 2017, with a female predominance and a prevalence considered to be about 1/5000,[2] there are only few evaluated therapeutic proposals, including for the one most cited, physical therapy, whose effects for hEDS patients are not validated to date.[14–17] The recommendations for physical therapy, mainly based on expert opinion, are the use of active physiotherapy with education, reassurance, manual therapy, tape, hydrotherapy, and relaxation training, as well as graded exercises applied carefully in order to avoid pain exacerbation.[18] Physical exercise aims to improve functional capacity, muscular endurance and strength, proprioception, and balance and is therefore recommended by experts.[18]

Given the wide variability of symptoms associated with hEDS, a multidisciplinary approach in a health structure allows full and specific assessment and treatment, and seems particularly appropriate. But, until nowadays, only one pilot study[19] and one retrospective study[20] investigated the effects of a multidisciplinary rehabilitation program (RP) for hEDS patients. These studies showed encouraging results, but the effects of an RP remain to be confirmed by a controlled prospective study. In addition, it is necessary to know whether such an intervention has benefits that are maintained over time.

The objective of this prospective study is to evaluate the effects of a RP for hEDS patients on functional exercise capacity, balance, kinesiophobia, pain, fatigue, quality of life, anxiety, depression and hyperventilation immediately after and in the short- and medium-term.

Methods

Participants

Patients were recruited at the Clinique de la Mitterie (Lomme, France) between September 2020 and May 2021. To be included, patients had to fulfill the 2017 diagnostic criteria for hEDS.[1] They were therefore assessed by physicians specialized in EDS. Exclusion criteria were cardiovascular contraindications to physical activity or severe depression (Beck questionnaire score ≥ 20).[21] All patients were volunteers and gave their informed consent. This clinical trial has been approved by a national ethics committee (CPP Ile de France IV, 2019/71) and registered on ClinicalTrials.gov (NCT04680793).

Study design

Inclusion and first assessment were conducted 9 weeks before the beginning of the RP (CTRL). No treatment changes were requested from patients during this 9 -week period (from CTRL to the beginning of the RP) used as a control period. Patients were again assessed at the beginning of the RP (PRE), at the end of the RP (POST), 6 weeks after the end of the RP (6W), and 6 months (6M) after the end of the RP (Figure 1). The assessments addressed the main symptoms of hEDS, namely functional exercise capacity, balance, kinesiophobia, fatigue, pain, quality of life, anxiety, depression, and hyperventilation.

Rehabilitation program

The RP was performed in an outpatient multidisciplinary service for a total duration of 9 weeks (20 days) with 2 days per week during 4 weeks, followed by 1 week of rest and 4 weeks including 3 days per week. Daily activities consisted of four one-hour workshops including: occupational therapy, physiotherapy, sophrology, various physical activities (ergometer, hydrotherapy, walking, yoga, etc.) focused on muscular endurance, coordination, balance, and proprioception, or various therapeutic patient education workshops.[20] This corresponds to around two-thirds physical activity and one-third educational or mental well-being activities.

Measurements

Demographical data and Beighton score

Sex, age, and body mass index (BMI) were recorded. The Beighton score for the articular hypermobility, and used for the New-York 2017 diagnostic criteria, was also recorded at inclusion.[22]

Functional exercise capacity

The functional exercise capacity was evaluated by the 6 -minute walking test (6MWT), which is a validated tool used in various pathologies.[23,24] This test was performed in a gymnasium on a 20 -meter course with marks on the ground every 5 meters. No encouragement was given during the test to ensure reproducibility.

Balance

Balance was assessed by stabilometry on a multi-axis motorized platform equipped with force sensors (Huber 360® Evolution, LPG systems, France). The assessments integrated into the device were used, namely the recording of the excursions of the center of pressure (CoP) in a standardized position without shoes for 50 seconds with eyes open (EO) and 50 seconds with eyes closed (EC); always in this order. The data were acquired with a frequency of 40 Hz. Feet position was standardized with a foot wedge (feet forming an angle of 30° degrees and heels slightly apart). The measurements were the 95% confidence

ellipse area (CEA, area of the ellipse encompassing 95% of CoP samples in mm²) and the sway path (SP, total length of CoP in mm).

Kinesiophobia

Kinesiophobia was evaluated with the Tampa Scale for Kinesiophobia (TSK), a self-administered questionnaire validated in French.[25,26] The TSK measures the fear of movement and is used in various painful conditions. It includes 17 items evaluated on a 4-point Likert scale. The total score range is 17 to 68 and a high score indicates a greater fear of movement.

Fatigue

Fatigue was assessed by the Multidimensional Fatigue Inventory (MFI), which is a self-administered questionnaire with 20 items validated in French.[27] Each item is transcribed on a scale of 1 to 5 points. Five dimensions are explored: general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation.[28] A high score indicates significant fatigue (or impact of fatigue).

Pain

Pain was assessed with the Brief Pain Inventory (BPI), a reliable self-administered questionnaire about pain severity (four items) and interference with daily living (seven items) validated in French.[29] Each item is evaluated on a numerical scale from 0 to 10. A high score indicates significant pain or significant interference in daily living. The pain interference score is the mean of the seven items' score on the interference.

Quality of life

Quality of life was assessed by the Medical Outcome Study Short Form (SF-36).[30] This self-administered questionnaire includes 36 items divided into nine dimensions and validated in French.[31] Each item is assessed on a Likert scale. The scores for each dimension range from 0 to 100. Mental Composite Score (MCS) and Physical Composite Score (PCS) have been calculated using the French recommendations for standardization.[32]

Anxiety and depression

The Hospital Anxiety and Depression scale (HAD) includes 14 items, seven for anxiety and seven for depression validated in French.[33–35] Each item is rated from 0 to 3 and the scores for each dimension range from 0 to 21. Cut-off scores were established with 8 to 10 being uncertain symptomatology and above 10 being definite symptomatology.[33]

Hyperventilation

In clinical practice, a tendency to hyperventilation has been observed in hEDS patients. The Nijmegen Questionnaire was therefore introduced in order to identify symptoms suggestive of hyperventilation.[36] It is a self-administered questionnaire with 16 items on the frequency of symptom occurrence. Responses are given on a 5-point ordinal scale ranging from "never" to "very frequent". Scores range from 0 to 64 points. A high score indicates severe hyperventilation. A cut-off score of > 23 points was determined to identify hyperventilation. The results are divided into four components: dyspnea, central tetany, peripheral tetany, and tension.

Statistical analysis

Statistical analysis was performed on SigmaStat Version 3.5 (Systat Software Inc). The calculated sample size was 24 subjects to detect a minimal change of 54 meters[37] on the 6MWT distance with $\alpha = 0.05$ and $1-\beta = 0.8$ and an estimated standard deviation of 90 meters.

Before each statistical test, normality of the data distribution and equality of variances were tested. If they failed, the non-parametric equivalents of these tests were performed. The effects of the control period were analyzed with a paired t-test between CTRL and PRE. The effects of the RP were analyzed with a one-way repeated measure analysis of variance (ANOVA) on PRE, POST, 6W, and 6M. If a significant difference was observed with ANOVA, post-hoc tests were performed (Bonferroni t-test for parametric tests or Tukey test for non-parametric tests). Results were considered as significant for $P<.05$. Data are expressed as mean ± standard deviation.

Results

Patients

A flowchart of inclusions and exclusions is presented in Figure 2. Thirty-six patients were initially assessed for eligibility, seven of whom did not meet the diagnostic criteria for hEDS, and four of whom cancelled their RP before the beginning. Thus, 25 patients were included at CTRL. Among these, three patients interrupted their RP (between PRE and POST) for health problems independent of the RP (cancer diagnosis and vascular disorders), twenty-two patients completed the RP (POST) and 19 completed the follow-up (6M). The data analyzed are those of patients who completed the follow-up (n = 19).

Of the 19 patients, there were 18 women and one man. The mean age at inclusion was 45 ± 12 years, the mean BMI was 28 ± 7 $kg.m^{-2}$, and the mean Beighton score was 4.6 ± 1.4.

Control period

Regarding the control period, which corresponds to an absence of treatment change during the 9 weeks before the RP, there was no significant difference between CTRL and PRE for all the data collected.

Rehabilitation program

Regarding the effects of the RP, significant changes were found using analysis of variance for 20 of the 35 variables measured. The data are presented in Table 1. The significant results of the post-hoc tests are described below.

Immediate changes after RP

There was a significant improvement between PRE and POST for functional exercise capacity with the distance walked during the 6MWT (*P*=.002); balance with EC-CEA (*P*=.023); fatigue with MFI total score (*P*=.033); and, quality of life with the following SF36 subscales: physical functioning (*P*=.023), role limitation due to emotional problems (RLEP; *P*=.038), health change (*P*=.001), and MCS (*P*=.017).

Six-week changes after RP (short-term effects)

There was a significant improvement between PRE and 6W for balance with EC-CEA (*P*=.001) and EC-SP (*P*=.003); fatigue with the following MFI subscales: physical fatigue (*P*=.007), mental fatigue (*P*=.034), and total score (*P*=.003); pain with BPI average pain (*P*<.001); quality of life with the following SF36 subscales: physical functioning (*P*=.023), RLEP (*P*=.004), vitality (*P*=.028), emotional well-being (*P*=.041), social functioning (*P*=.011), general health (*P*=.034), health change (*P*=.005), and MCS (*P*=.003); depression with HAD depression (*P*=.034); and, hyperventilation with the following Nijmegen Questionnaire subscales: dyspnea (*P*=.012) and total score (*P*=.004).

There is a significant improvement between POST and 6W for balance with EO-SP (*P*=.023).

Six-month changes after RP (medium-term effects)

There was a significant improvement between PRE and 6M for functional exercise capacity with the distance walked during the 6MWT (*P*=.008); kinesiophobia with TSK score (*P*=.012); quality of life with SF36 physical functioning (*P*=.014); depression with HAD depression (*P*=.028); and, hyperventilation with the Nijmegen Questionnaire subscales dyspnea (*P*=.023) and total score (*P*=.04).

Discussion

The objective of this study was to evaluate the effects of an RP for hEDS patients on physical and mental health immediately after and in the short- and medium-term.

The main results showed significant improvements immediately after the RP in functional exercise capacity, balance with eyes closed, fatigue, and quality of life. Oppositely, no measured variable changed during the 9 -week control period. At 6W, numerous physical and mental parameters were maintained, and even more improvements were found with 17/35 of the measured variables improved. More interesting, after 6 months, there was still an improvement in functional exercise capacity, kinesiophobia, depression, hyperventilation, and some components of the quality of life.

A RP for hEDS patients: Why and how does it work?

Rehabilitation is widely used and has been shown to be effective in many other chronic diseases [38,39] but it has never been prospectively investigated in hEDS. One aim of the RP for hEDS patients is the return to a higher level of functional capacity in patients who are often deconditioned due to kinesiophobia for fear of injury.[6,14]

In a disease with several manifestations, with one-third of patients experiencing 15 to 25 symptoms,[40] and with recommendations for global management,[2] an RP (supposed to be global) therefore seems particularly appropriate for the management of these patients.

The immediate improvements after the RP, both physical and mental, affect many areas of health considered important by the patients themselves.[10] It also results in an improvement in quality of life immediately after the end of the RP.

However, the question of how this overall improvement works may arise. The reintroduction of physical activity in a controlled environment with professionals familiar with the disease shows hEDS patients that it is possible to practice physical activity. This could break the vicious circle of kinesiophobia, deconditioning, and injury.[6] An increase in fatigue could have been expected at the end of the RP related to the increase in physical activity during the 9 weeks of the RP. On the contrary, there was a significant improvement in fatigue as represented by the total MFI score. Physical deconditioning was suggested as a cause for fatigue in hEDS,[5] it is therefore possible that the beneficial effect of reconditioning was superior than the fatigue induced by physical activity. The spreading of the program over 9 weeks with a 1 -week break in the middle, the gradual increase from 2 to 3 days of rehabilitation per week, and the rest days between the rehabilitation days, probably also allowed good management of fatigue during the program.

Improvements and maintenance at 6 weeks and 6 months of physical and mental health

After the RP, most of the immediate effects of the RP are maintained at 6W and, just as important, even more improvements were found at 6W. This can be considered as a post-RP improvement. It is possible that the positive effects of the RP are only fully perceived (for subjective measurements) after a recovery period and with a return to daily life. Another hypothesis is that the RP led to behavioral changes in the patients' daily lives that were implemented after the RP and are responsible for the improvements observed at 6

weeks. Behavioral changes are one of the corner-stones of rehabilitation in other diseases like COPD,[41] and physical activity counseling and rehabilitation can increase physical activity level.[42] Unfortunately, level of daily physical activity was not measured in this study and further investigations are needed to respond to these hypotheses.

Maintenance of some physical benefits of the RP at 6M is indicated by the significant differences (with PRE) for functional exercise capacity, kinesiophobia, some components of the quality of life, depression symptoms and, hyperventilation symptoms. Although these improvements at 6M are positive and, to our knowledge, among the only ones objectified to date for these patients, the maintenance of a greater number of improvements would be desirable and raises the question of the patient follow-up after the RP. Although several strategies for maintaining benefits were developed during the RP (including some recommended for self-management intervention),[43] they could have been reinforced, for example, with implementation of a post-RP with weekly interventions. Post-RP have been evaluated in pulmonary rehabilitation and seem to be effective if the patient is adherent.[44,45] Different forms of post-rehabilitation programs are possible, such as monthly follow-up and advice, or more regular physical activity sessions. The best form has not yet been established for COPD rehabilitation,[44] which is the subject of extensive clinical research. Rehabilitation for hEDS will need to be informed by the results of future studies on the subject.

Hyperventilation: A disabling symptom

Respiratory symptoms in hEDS, and in particular dyspnea, have been described by various authors.[7,8,46,47] However, hyperventilation is absent from the commonly described respiratory manifestations.[7,47] The Nijmegen Questionnaire was introduced in this study because a tendency to hyperventilation was clinically observed in several hEDS patients. The hypothesis of symptoms suggestive of hyperventilation in hEDS patients is reinforced by the high rate of arguments for hyperventilation (Nijmegen Questionnaire scores > 23) that were found in 17 patients (89%) in this study. Hyperventilation in hEDS needs to be further investigated, especially with clinical tests, as it may contribute to the dyspnea frequently encountered in

hEDS. The respiratory techniques learned during the RP, with specific sessions focused on ventilation control and early identification of abnormalities such as hyperventilation, may explain, in part, the improvement in Nijmegen Questionnaire scores.

Study limitations

One limitation of this study may be the number of patients that is below the sample size calculated (n = 19 vs. 24). This study was delayed due to the COVID-19 pandemic, and it was not possible to further extend the recruitment. Despite this, significant differences were found for the main outcome (6MWT distance) used for sample size calculation, suggesting that the number of patients included can be sufficient. The control period design, used in this study, has the advantage of offering the same treatment to each subject. As the number of treatment options for these patients is very small, this was, in our opinion, the most ethical solution. In addition, each subject is his or her own control, which limits inter-group variability, especially in a population with very high phenotypic variability.

Conclusions

To our knowledge, this is the first study evaluating the effects of an outpatient RP for hEDS patients with a control period and a follow-up. Given the few therapeutic proposals, it was important to demonstrate that rehabilitation could be effective for these patients, and this was demonstrated by the results of this study. Moreover, the results obtained show a multidimensional improvement on both mental and physical health. Many of these effects are maintained or improved further at 6W follow-up and some of them are maintained at 6M follow-up. These results show the value of multidisciplinary management, based on physical activity, and associated with educational or mental well-being activities for patients with hEDS.

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Figure captions

Fig. 1 Graphical representation of the study design.

Abbreviations: 6W, assessment at 6 weeks after the end of the rehabilitation program; 6M, assessment at 6 months after the end of the rehabilitation program; CTRL, assessment 9 weeks before the rehabilitation program; POST, assessment at the end of the rehabilitation program; PRE, assessment at the beginning of the rehabilitation program; RP, rehabilitation program.

Fig. 2 Inclusion flow diagram.

Abbreviations: 6W, assessment at 6 weeks after the end of the rehabilitation program; 6M, assessment at 6 months after the end of the rehabilitation program; CTRL, assessment 9 weeks before the rehabilitation program; POST, assessment at the end of the rehabilitation program; PRE, assessment at the beginning of the rehabilitation program; RP, rehabilitation program.

Fig. 1

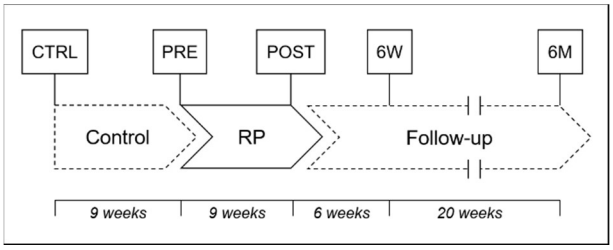
CTRL
PRE
POST
6W
6M
Control
RP
Follow-up
9 weeks
9 weeks
6 weeks
20 weeks

Fig. 2

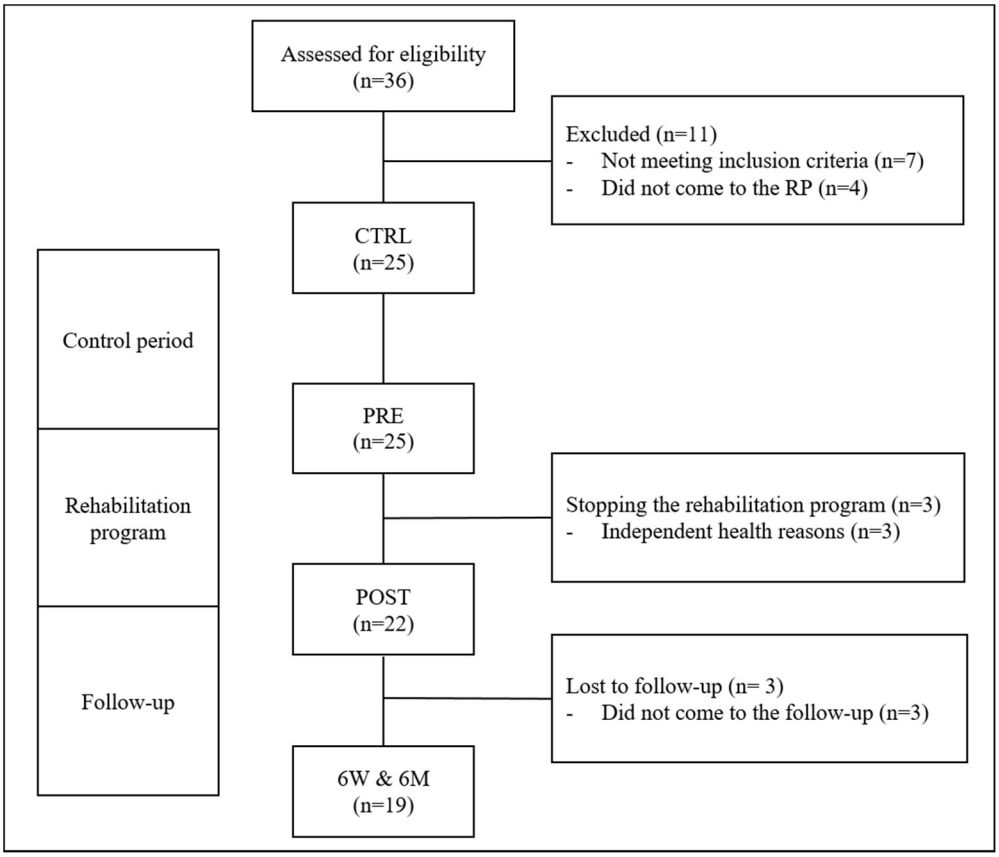
Assessed for eligibility
(n=36)
Excluded (n=11)
- Not meeting inclusion criteria (n=7)
- Did not come to the RP (n=4)
CTRL
(n=25)
Control period
PRE
(n=25)
Rehabilitation program
Stopping the rehabilitation program (n=3)
- Independent health reasons (n=3)
POST
(n=22)
Follow-up
Lost to follow-up (n= 3)
- Did not come to the follow-up (n=3)
6W & 6M
(n=19)

Table 1

Measurements at nine weeks before the beginning of the RP (CTRL), at the beginning (PRE), at the end (POST), and six weeks (6W) and six months (6M) after the rehabilitation program (n = 19).

Domain	Variable	CTRL	PRE	POST	6W	6M
Functional exercise capacity (6MWT)	**Distance (m)**	437 ± 140	450 ± 110	**507 ± 120****	493 ± 128	**501 ± 117****
Balance (Huber 360)	EO-CEA (mm²)	596 ± 568	563 ± 488	385 ± 259	427 ± 419	489 ± 558
	EO-SP (mm)	775 ± 284	763 ± 246	733 ± 212	**630 ± 173†**	691 ± 222
	EC-CEA (mm²)	2210 ± 1805	2224 ± 1966	**1458 ± 1420***	**1058 ± 1015****	1693 ± 1626
	EC-SP (mm)	1478 ± 548	1603 ± 581	1449 ± 599	**1174 ± 487****	1406 ± 558
Kinesiophobia (TSK)	**Total score**	38.4 ± 7.4	38.6 ± 6.2	36.2 ± 5.5	36.7 ± 6.2	**34.3 ± 7.1***
Fatigue (MFI)	General fatigue	17.4 ± 2.5	16.5 ± 2.5	15.1 ± 3.2	14.6 ± 3.1	15.4 ± 3.5
	Physical fatigue	14.9 ± 3.1	14.8 ± 2.8	12.8 ± 3.8	**11.9 ± 2.7****	13.0 ± 2.5
	Mental Fatigue	14.4 ± 3.6	14.7 ± 3.5	13.8 ± 4.2	**13.1 ± 3.9***	13.9 ± 4.5
	Reduced activity	13.6 ± 3.7	13.1 ± 3.4	11.1 ± 3.8	11.0 ± 3.2	11.0 ± 3.4
	Reduced Motivation	9.6 ± 3.4	9.4 ± 2.5	8.0 ± 2.9	7.9 ± 2.7	8.7 ± 3.5
	Total score	69.9 ± 9.8	68.5 ± 8.0	**60.8 ± 12.3***	**58.6 ± 11.4****	62.1 ± 13.6
Pain (BPI)	Worse pain	7.6 ± 1.6	7.5 ± 1.6	7.3 ± 2.1	6.8 ± 2.0	7.3 ± 2.1
	Least pain	3.2 ± 2.1	2.8 ± 1.8	2.3 ± 1.8	2.1 ± 1.6	2.1 ± 1.6
	Average pain	5.5 ± 1.8	5.1 ± 1.7	4.4 ± 2.0	**3.8 ± 1.7*****	4.5 ± 1.9
	Immediate pain	5.2 ± 2.5	4.8 ± 1.9	4.6 ± 2.1	4.7 ± 2.2	4.2 ± 1.9
	Interference	5.0 ± 2.1	5.2 ± 2.3	4.4 ± 2.5	3.8 ± 2.3	4.2 ± 2.3
Quality of life (SF36)	**Physical functioning**	37.1 ± 23.2	38.9 ± 23.5	**51.8 ± 21.8***	**51.8 ± 23.5***	**52.6 ± 22.7***
	RLPH	10.5 ± 20.9	19.7 ± 27.1	21.1 ± 30.3	46.1 ± 44.3	27.6 ± 31.1
	RLEP	54.4 ± 43.3	45.6 ± 43.3	**70.2 ± 45.7***	**77.2 ± 38.6****	63.1 ± 39.9
	Vitality	20.5 ± 13.5	24.7 ± 15.6	36.3 ± 17.0	**38.9 ± 18.1***	35.3 ± 18.2
	Emotional well-being	55.2 ± 20.9	56.6 ± 23.9	65.1 ± 21.2	**66.1 ± 19.3***	62.9 ± 21.9

	Social functioning	38.2 ± 18.9	42.8 ± 22.2	52.1 ± 22.0	**59.2 ± 22.8***	54.6 ± 24.0
	Pain	35.5 ± 18.6	34.6 ± 20.3	38.2 ± 21.9	44.2 ± 19.8	45.0 ± 19.3
	General health	37.6 ± 10.7	38.9 ± 12.9	46.1 ± 13.9	**48.4 ± 14.0***	45.8 ± 16.2
	Health change	36.8 ± 19.3	38.2 ± 24.1	**63.2 ± 25.5****	**60.5 ± 28.0****	52.6 ± 23.4
	PCS	27.8 ± 8.3	29.5 ± 8.3	31.0 ± 9.8	34.2 ± 10.7	33.4 ± 8.7
	MCS	40.4 ± 10.3	40.2 ± 12.3	**46.5 ± 13.4***	**47.7 ± 11.6****	44.9 ± 11.1
Anxiety and depression (HAD)	Anxiety	9.8 ± 4.0	9.7 ± 3.9	9.0 ± 3.2	8.8 ± 3.9	9.1 ± 4.0
	Depression	7.6 ± 4.8	7.6 ± 4.2	6.4 ± 3.6	**5.8 ± 3.9***	**5.9 ± 4.8***
Hyperventilation (Nijmegen)	**Dyspnea**	9.2 ± 3.5	8.9 ± 2.8	8.2 ± 3.0	**6.5 ± 2.4***	**6.7 ± 2.4***
	Central tetany	9.6 ± 3.2	9.3 ± 3.4	9.3 ± 4.0	8.5 ± 3.9	9.2 ± 4.3
	Peripheral tetany	8.8 ± 3.4	8.7 ± 3.5	7.5 ± 4.0	7.1 ± 4.3	7.3 ± 4.8
	Tension	7.9 ± 2.6	8.1 ± 2.6	7.4 ± 2.5	7.1 ± 3.1	7.2 ± 3.2
	Total score	35.5 ± 7.9	35.1 ± 8.0	32.4 ± 10.1	**29.2 ± 10.6****	**30.4 ± 10.2***

Values are Mean ± SD. Abbreviations: 6MWT, six-minute walking test; 6W, assessment at 6 weeks after the end of the rehabilitation program; 6M, assessment at 6 months after the end of the rehabilitation program; BPI, brief pain inventory; CEA, 95% confidence ellipse area; CTRL, assessment 9 weeks before the rehabilitation program ; EO, eyes open; EC, eyes closed; HAD, hospital anxiety and depression scale; MCS, mental composite score; MFI, multidimensional fatigue inventory; PCS, physical composite score; POST, assessment at the end of the rehabilitation program; PRE, assessment at the beginning of the rehabilitation program; RLEP, role limitation due to emotional problems; RLPH, role limitation due to physical health; SF36, medical outcome study short form; SP, sway path; TSK, Tampa scale for kinesiophobia.
*Significant difference with PRE (post-hoc test): * P<.05, ** P<.01, *** P<.001.*
Significant difference with POST (post-hoc test): † P<.05.