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## ► To cite this version:

Adrien Hakimi, Cyrille Bergoin, Patrick Mucci. Immediate and 6-week after effects of a rehabilitation program for Ehlers–Danlos syndrome hypermobile type patients: A retrospective study. American Journal of Medical Genetics Part A, 2020, 10.1002/ajmg.a.61772 . hal-02922669

**HAL Id: hal-02922669**

**<https://hal.univ-lille.fr/hal-02922669>**

Submitted on 26 Aug 2020

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This is the peer reviewed version of the following article: “Hakimi A, Bergoin C, Mucci P. Immediate and 6-week after effects of a rehabilitation program for Ehlers–Danlos syndrome hypermobile type patients: A retrospective study. Am J Med Genet Part A. 2020; 1–9.”, which has been published in final form at <http://dx.doi.org/10.1002/ajmg.a.61772>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

**Title:**

Immediate and 6-week after effects of a rehabilitation program for Ehlers-Danlos syndrome hypermobile type patients: a retrospective study.

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**Abstract:**

Ehlers-Danlos syndromes are a group of inherited connective tissue disorders with an impaired quality of life in association with fatigue, pain and kinesiophobia. A retrospective evaluation of the effects of an outpatient rehabilitation program (RP) was performed in Ehlers-Danlos syndrome hypermobile type (hEDS) patients. The six-minute walk test (6MWT) was used to evaluate functional capacity. Kinesiophobia, fatigue, pain and quality of life were self-evaluated at the start, at the end and six weeks after the end of the RP. The retrospective analysis of patients’ records showed significant improvement for the walked distance during the 6MWT ( $491.8 \pm 72.5\text{m}$  vs  $439.4 \pm 100.9\text{m}$ ) maintained at 6-week follow-up ( $p = 0.001$ ), significant improvement for kinesiophobia ( $p = 0.033$ ) and the impact of fatigue on activity ( $p = 0.01$ ) and significant increase for quality of life with in particular improvements of vitality ( $p = 0.001$ ). This retrospective study showed encouraging results of a RP for hEDS patients on functional capacity and quality of life, and prospective studies with long-term follow-up are needed to confirm them.

**Keywords:**

Fatigue, functional capacity, kinesiophobia, quality of life, six-minute walk test.

**Main text:****Introduction:**

Ehlers-Danlos Syndromes (EDS) are a group of inherited connective tissue disorders mainly characterized by joint hypermobility, skin hyperextensibility, and tissue fragility (Malfait et al., 2017). These syndromes present a great clinical and genetic heterogeneity and, since 2017, are classified in 13 subtypes (Malfait et al., 2017). The most common is the Ehlers-Danlos syndrome hypermobile type (hEDS) whose diagnosis remains clinical (Sulli et al., 2018).

Fatigue and pain are widespread in hEDS and can impact daily activities and quality of life (Bénistan & Martinez, 2019; Chopra et al., 2017; Hakim et al., 2017). Kinesiophobia is also commonly associated with hEDS. A model was proposed to explain links between pain, fatigue and kinesiophobia (Celletti et al., 2013): repeated trauma would lead to pain reduction strategy with kinesiophobia and its consequent decrease in physical activity which would exacerbate fatigue (Celletti et al., 2013). Consequently, health related quality of life is also reduced in hEDS comparing it to a healthy population (Bovet et al., 2016). We can make a hypothesis that resumption of physical activity, for example with a RP, can break this insidious mechanism and contribute to improve the quality of life.

Nowadays, there are only a few recommendations on the non-medicated management of hEDS. Given the wide variability of symptoms associated with hEDS, a multidisciplinary approach in a health structure would allow a full and specific assessment and treatment for patients and would seem particularly appropriate. In a review of the literature (Corrado & Ciardi, 2018), the authors underlined that only one single pilot study (Bathen et al., 2013) on rehabilitation care has been published. However, this pilot study did not focus on fatigue and quality of life measurements which have an important role in hEDS (Bovet et al., 2016; Celletti et al., 2013; Hakim et al., 2017; Voermans et al., 2010). In addition, there are no data available on the potential benefits of a RP a few weeks after its end.

The objective of this study is to analyze, immediately after and following six-weeks after the end of an outpatient RP, its effects on physical functional capacity, kinesiophobia, fatigue, pain and quality of life in order to determine the potential benefits of a multidisciplinary RP. The hypothesis is that a RP could improve the functional capacity of patients with hEDS as well as their quality of life by modifying the perception of various factors like pain, kinesiophobia or fatigue.

**Materials and method:****Patients:**

A retrospective analysis of patients' records which participated in a RP at the Clinique de la Mitterrie (Lomme, France) between September 2018 and June 2019 was conducted. Patients were diagnosed hEDS by physicians specialized in EDS before the RP and outside the clinic. As patients were diagnosed outside the clinic, the criteria used for these diagnoses were not available. Patients were excluded from analysis if they did not follow entirely the RP, if they missed the follow-up or if the diagnosis was different from the hEDS subtype (for example the vascular subtype of EDS). The total number of subjects was initially 29 and after exclusions was 21 (20 women and 1 man) with a mean age of  $45 \pm 13$  years old (21 to 69 years old) and a mean BMI of  $29 \pm 6 \text{ kg.m}^{-2}$ . All patients were French-speaking.

### **Study design:**

All patients participated to a RP for a total of 9 weeks. All assessments were conducted on the baseline (t0), at the end of the program (t9) and six weeks after the end (t15). These assessments have been already used in hEDS in the literature (e.g. Scheper et al. (2017); Celletti et al. (2013)) and all the questionnaires have been validated in French.

#### *1. Rehabilitation program*

The RP was performed for a total duration of 9 weeks (20 days): during 4 weeks two days a week, then, after a week of rest, during 4 weeks three days a week for a total of 81 hours of care. The distribution of activity time consists of approximately 2/3 of physical activities and 1/3 of educational or mental well-being activities. The program was multidisciplinary and included: balneotherapy, ergometer exercises, occupational therapy, physical activity, physiotherapy, walking, proprioception exercises, sophrology, yoga exercises as well as various therapeutic patient education workshops conducted by several professionals (dietitians, physiotherapists, doctors, psychologists). Details about the program are presented in Table 1. All patients were supposed to practice the whole program except in the event of a specific contraindication.

This RP is in accordance with recommendations for physical therapy treatment from the 2017 international consortium on the Ehlers-Danlos syndromes (Engelbert et al., 2017). These recommendations suggest 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. Only tape was not particularly used in the RP.

#### *2. Assessments*

##### *2.1. Functional exercise capacity*

Functional exercise capacity was assessed by the six-minute walk test (6MWT) (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002). It is validated and used in many pathologies (Singh et al., 2014). The minimal clinical important difference (MCID) varies between studies, but a review recommended the value of 30 meters (Singh et al., 2014). This test was performed

in a gymnasium on a 20-meter course with marks on the ground every 5 meters. The distance walked by the patient is the main measure. Its predictive value (PV) was calculated from the following formula: “ $PV (m) = 2.11 \times \text{height (cm)} - 2.29 \times \text{weight (kg)} - 5.78 \times \text{age (years)} + 667$ ” and the lower limit of the normal value (LLN) by subtracting 139 meters from PV (Enright & Sherrill, 1998). Only the women’s formula was used because 6MWT data for the only man who participated to this RP were not completed.

Arterialized hemoglobin oxygen saturation (SpO<sub>2</sub>) and heart rate (HR) were measured with a fingertip pulse oximeter (MD300C41, ChoiceMMED). These measures were recorded during the exercise: only maximal heart rate and SpO<sub>2</sub> nadir values were analyzed. No encouragement was given during the test to ensure reproducibility.

## *2.2. Kinesiophobia*

Kinesiophobia was evaluated with the Tampa Scale for Kinesiophobia (TSK) (French et al., 2002; Monticone et al., 2017). The TSK is a tool used in various painful conditions that measures the fear of movement. It is a self-administered questionnaire with 17 items including four with an inverted notation. Each item is evaluated on a 4-points Likert scale ranging from "strongly disagree" to "strongly agree". The total score ranged from 17 to 68. A high score indicates a greater fear of movement. The French version has been validated (French et al., 2002).

## *2.3. Self-perceived fatigue*

The Multidimensional Fatigue Inventory (MFI-20) is a self-administered questionnaire validated in French (Gentile et al., 2003) with 20 items to assess fatigue in five dimensions: general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation (Smets et al., 1995). Reduced activity and reduced motivation reflect a reduction due to fatigue. The answers are transcribed on a scale of 1 to 5 points. A high score indicates significant fatigue. An equal number of items are turned in a positive direction and in a negative direction.

## *2.4. Pain*

The Brief Pain Inventory (BPI) is a reliable self-administered questionnaire about pain severity (four items) and interference with daily living (7 items) validated in French (Poundja et al., 2007). 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 of pain on daily life.

## *2.5. Quality of life*

Quality of life was assessed with the self-administered questionnaire: Medical Outcome Study Short Form 36 (SF-36) (Ware & Sherbourne, 1992). Briefly, it includes 36 items in 8 dimensions: physical functioning, role limitation due to physical health (RLPH), role limitation due to emotional problems

(RLEP), vitality, emotional well-being, social functioning, pain and general health. One item does not belong to any dimension but evaluates the perception of change in health. Scores for each item range from 0 to 100. A low score indicates an impaired quality of life. Physical and Mental component scores (PCS and MCS) have been calculated. This questionnaire has been validated in French (Perneger et al., 1995).

### 3. *Statistical analysis*

For each assessment, only complete data were analyzed statistically. Data are described in Tables 2-7 with mean and standard deviation. Statistical analysis was performed on SigmaStat Version 3.5 (Systat Software Inc). Before each test, normality of the data distribution and equality of variances were tested. The changes across t0, t9 and t15 were analyzed with a one way repeated measure analysis of variance (ANOVA). If normality distribution failed, a Friedman test a.k.a. one way repeated measures ANOVA on ranks was launched. If a significant difference was observed with ANOVAs, post-hoc tests were performed (Bonferroni t-test for parametric tests or Tukey test for non-parametric tests). Results were considered as significant for a p-value < 0.05.

## **Results:**

### 1. *Patients*

Twenty-nine patients were included for the multidisciplinary RP between September 2018 and June 2019. Three had not completed the course, and four did not come to the follow-up. One patient was excluded from the analysis because he had a vascular form of EDS. Demographical data of the 21 remaining patients (twenty women and one man) are presented in Table 2. Data on ethnicity have not been collected, but the patient population was overwhelmingly Caucasian. For these patients, five records of the 6MWT test were incomplete (patients n°5, 16, 17, 20 and 21), three of the MFI-20/TSK questionnaires (patients n°4, 14, 16) and three of the SF-36 questionnaire (patients n°3, 10, 14). A flowchart of inclusion and completed data is presented in Figure 1.

### 2. *Functional capacity*

There is a significant improvement ( $p=0.001$ ) in the walked distance during the 6MWT between t0 and t9 and between t0 and t15 (see Table 3). There is no significant difference for the SpO<sub>2</sub> or HR at exercise. Comparison with predicted values and MCID are described in Table 4. Four patients improved their walking distance up to the LLN at t9 while they were under the LLN at t0, and one patient improved up to the PV at t9 while she was between the PV and the LLN at t0. These improvements were maintained at t15. Seven patients (43.75%) improved more than MCID (30 meters) between t0 and t9, and 11 patients (68.75%) between t0 and t15. No patient decreased more than MCID, one patient decreased at t9 and 3 at t15 in comparison with t0.

### 3. *Kinesiophobia*

There is a significant improvement for kinesiophobia on the TSK score ( $p=0.033$ ) specifically between t0 and t9, however not maintained at t15 (see Table 5). Fourteen patients (77.78%) improved at t9 and 10 patients (55.56%) at t15 in comparison with t0. Three patients (16.67%) decreased at t9 and 5 patients (27.78%) at t15 in comparison with t0.

### 4. *Fatigue*

There is a significant improvement in the MFI-20 reduced activity subscale ( $p=0.01$ ) between t0 and t9 which is not maintained at t15 (see Table 5). There is no significant change for other MFI-20 subscales.

### 5. *Pain*

There is a significant increase for pain at its worst in the BPI ( $p=0.023$ ) between t9 and t15 (see Table 6). There is no other significant difference for the BPI.

### 6. *Quality of life*

There is a significant improvement for the SF-36 subscales, regarding the vitality score ( $p=0.001$ ) between t0 and t9 which is not maintained at t15 (see Table 7). The emotional well-being score ( $p=0.006$ ) and the mental component score ( $p=0.022$ ) decreased between t9 and t15 without significant difference between t0 and t15. There is no other significant difference for the SF-36.

## **Discussion**

The objective of this study was to analyze, immediately after and six weeks after the end of the program, the effects of an outpatient RP on physical functional capacity and perceived benefits, like: kinesiophobia, fatigue, pain and quality of life in order to determine the potential benefits of a multidisciplinary RP. To our knowledge this is the first study which explores a multidisciplinary outpatient RP with a follow-up for patients with hEDS. This is also the first study which includes quality of life and fatigue measurements for the evaluation of the RP outcomes. The main results showed significant improvement of the physical functional capacity with an increase in the 6MWT walked distance which was maintained six weeks after the end of the RP. Kinesiophobia was also significantly reduced at the end of the program as the impact of fatigue on activities. Quality of life was also partly improved immediately after the RP but it returned to its initial values six weeks after the end.

The only pilot study which evaluated a rehabilitation program for hEDS patients showed also encouraging results with improvement in perception of daily activities, muscle strength, muscle endurance and kinesiophobia (Bathen et al., 2013). Similarly to our study there was no improvement for pain.

We can see that 43.75% of our patients were under the LLN and 87.5% under the PV at t0. This underlines that our patients had an impaired physical functional capacity at the baseline. There is no change for the HR or the SpO2 although there is a greater walking distance. All these results demonstrate a significant benefit in muscle exercise tolerance which is maintained even six weeks after the end of the RP. Long-term follow-ups are needed to confirm benefits over a longer period. The 6MWT distance was likely enhanced by an improvement of the aerobic pathway. This improvement of physical functional capacity can also be explained by the content of the program in which muscle strengthening and proprioception are important elements and have been suggested to be related to activity limitations (Scheper et al., 2017). We found a significant mean improvement for the 6MWT distance higher than the minimal clinical important difference (MCID). Besides, when we look at the individuals' results, seven patients improved the walking distance up to the 30 meters from the MCID between t0 and t9 and 11 patients between t0 and t15. This further improvement could be linked to a maintained higher level of activity after the program.

At the same time there was a significant reduction of kinesiophobia and the impact of fatigue on activity. We can make a hypothesis, that making physical activity during the RP reveals to patients what they are able to do and encourage them to continue after the program. If we take into account the model proposed by Celletti et al. (2013), we can suppose that a RP with physical activity by decreasing kinesiophobia and the impact of fatigue on activity leads to change pain reduction strategies. Obviously, this hypothesis needs further investigations. At the same time, we didn't show any change for pain between t0 and t9, whereas the physical activity level and the exercise capacity during the RP increased. This could be partly explained by the background mentality that we used for the program that is "to cope with". We assumed that the pain remained present for the patients, but that they had to learn to do more things in the same painful condition. In this way patients only had a few pain treatment sessions during the RP (which consist mainly of massage and mobilization) but more exercise sessions. It is, therefore, not surprising that we have no change in pain, but the objective was achieved since the patients practiced more activity with a similar level of pain.

Our study shows similar baseline values as the one of Celletti et al. (2013) for the MFI-20 with a total score of 73.9 out of 100. These results are similar to other studies that have shown that fatigue has an important role in hEDS (Celletti et al., 2013; Hakim et al., 2017; Voermans et al., 2010). We showed moreover, that rehabilitation allowed to improve the impact of fatigue on activities. This means that patients are more likely to consider or carry out activities and are less limited because of their fatigue. The increase in physical activity during the program could have increased fatigue level. But none of the MFI-20 subscale showed an increase, and moreover patients are less impacted by their fatigue on their activities. It's interesting to note that there is no significant improvement on the total score of MFI-20 nor on the general or the physical component. Patients seem to be as tired as before but their perception of fatigue and, besides, its influence seem to have changed.



We also saw improvement in quality of life with a significant increase in the vitality subscale of the SF-36 but a return to baseline values 6 weeks-after. In addition, there were reductions of emotional well-being sub-scale and mental composite score between t9 and t15 with a similar level than t0 values. This suggests a potential improvement of these components of quality of life between t0 and t9 which is not significant in this study and which is not maintained at t15. To our knowledge, this is the first study to assess the effects of a multidisciplinary RP on quality of life. Rehabilitation seems to be a good therapeutic solution for hEDS for which there is no validated treatment to date. The implementation of prospective studies on this subject should allow its development in the years to come.

Apart from the functional exercise capacity, many improvements seem to disappear at the follow-up. This raises the question of management of the patients after the program. Although they have benefited from a lot of advices both for their lifestyle and their physical activity; this seems not enough to maintain results in all areas (fatigue, pain or quality of life). Perhaps the implementation of interviews following the program could improve the maintenance of benefits.

Our study is retrospective with the limitations of this type of study as the lack of control group. Given the limited literature on guidelines for management or rehabilitation studies for hEDS patients, this study is encouraging and may allow the development of other similar rehabilitation programs that may be the subjects of prospective studies to offer a therapeutic solution for hEDS patients. Prospective studies are however necessary to confirm these results. Diagnostic criteria were not available as patients were diagnosed outside the clinic. For this reason, it is not possible to know if all patients meet the latest diagnostic criteria. But as they were mostly diagnosed by EDS specialists, we can reasonably suppose that they all meet the recommended criteria on the date of their diagnosis. For the same reason, the Beighton Score was not reported as usual in other studies on EDS because this information was therefore not available in patients' records. This lack of information may constitute a potential selection bias. There is also a small number of subjects in this study which can be explained by the restrained number of places in the RP and the difficulty of keeping all participants during the whole training period and during the follow-up. Some of our patients were still working and had difficulties participating in follow-up assessments. This is also why four patients were excluded from this study because of missing the six-week assessment. Only a single appointment was given for each assessment due to the institution functioning. This small number of participants could probably partially explain the lack of some significant results. A larger number of patients and the development of other similar rehabilitation programs would improve quality of studies. Nine patients presented missing data for at least one outcome and two of the nine patients for two outcomes. The missing data for the questionnaires are mostly due to the lack of response for all or part of these questionnaires. This can be explained by the large number of questionnaires given to them and is often due to an oversight. Because the study is retrospective there was no particular attention at the time of assessments about completion of questionnaires. The missing data for the 6MWT could be related to a temporary inability to perform the

test at the time of assessment. The physical capacity of patients is fluctuating, and the test was not performed if it was not possible for the patient at the day of assessment. The exclusion of these patients from the analysis can lead to being cautious about the generalization of the results to all of the patients included in this study. Another limitation in this study is the lack of information about comorbidities and it cannot rule out a potential influence of these confounding variables.

In conclusion, this retrospective study showed encouraging results with a significant improvement for functional capacity, kinesiophobia, the impact of fatigue on activity and quality of life, particularly on vitality. We can hope that all these improvements may impact the daily life of hEDS patients who conventionally show a reduced functional physical capacity, as well as kinesiophobia and a reduced quality of life. Prospective studies are needed to confirm them. Since only the functional exercise capacity is maintained at follow-up, a solution is needed in order to maintain other benefits after the program.

### **Acknowledgement**

The authors would like to thank the patients who have agreed to participate in this study as well as the entire staff of the Clinique de la Mitterie who took part in the good progress of the RP.

### **Conflict of interest**

The authors declare that they have no conflict of interest.

### **Data availability statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table 1: Description of the rehabilitation program content.

Activities	Description	Number of sessions	Duration by session (minutes)
<b>Balneotherapy</b>	Balneotherapy is conducted in a swimming pool. It consists of performing exercises in water in order to work with alleviate body weight or to use the progressive resistance offered by water. The hot water allows analgesia and muscle relaxation. The alleviation in body weight and the immersion produce a global sensory and proprioceptive work and allows to work safely.	13	60
<b>Ergometer exercises</b>	Ergometer exercises are performed on 30 minutes sessions included warm-up and recovery. Additional time is required for patient installation and cleaning at the end of the session. The working heart rate and initial workload were calculated with an exercise stress testing prior to the RP in order to define an aerobic work. These training sessions are relatively light in order to avoid exacerbation of the pain after the sessions. The workload is increased only in the absence of pain. If conventional ergometer is not possible for any reason, patients can use an arm ergometer. The objective is to improve endurance capacity.	4	60
<b>Occupational therapy</b>	Occupational therapists aim to work on positioning and energy conservation techniques. Various life situations and advice are used to improve these skills.	4	60
<b>Physical activity</b>	Physical activity sessions aim to increase muscular endurance capacity and patient coordination. The activities are varied including, badminton, muscular strengthening, table tennis or use of gymnastic balls. Muscular strengthening is performed mainly without load (body weight) or with low loads. Warm-up and recovery are systematic. Sufficient time is left between the different exercises.	4	60
<b>Art Therapy</b>	Use of art and creative media as therapeutic support. These tools were used to have a better understanding of how the patient represents himself the disease.	3	120
<b>Physiotherapy</b>	Physiotherapy include respiratory control and management of musculoskeletal troubles. Exercises are given to work on volumes and respiratory flow. For the management of musculoskeletal troubles, individual sessions with a physiotherapist have been set up.	9	60
<b>Walking</b>	Walking is mostly done outside (as often as possible) and aims to improve endurance. This is a well-tolerated, daily life activity with moderate intensity. The aim is to walk the longest distance possible without increasing pain.	4	60
<b>Proprioception exercises</b>	Proprioception exercises are performed in the gymnasium and include thematic obstacle course. The objective is to improve proprioception in order to limit the risks of dislocation and improve their balance. These exercises also allow a dexterity and coordination work.	4	60
<b>Sophrology</b>	Sophrology is a relaxation technique and aims to work on emotional well-being with the use of breathing, stretching, muscle relaxation and visualization. These sessions aim to improve body perception and pain management.	5	60
<b>Yoga exercises</b>	Yoga exercises are used to work on respiratory control, body perception, balance and proprioception by the use of soft muscle stretching and postures.	4	60
<b>Assessments</b>	Patients were evaluated at the beginning and at the end of the RP. Beyond the data presented in this article, patients are seen by different professionals for clinical investigation (a physician, a dietician, a physiotherapist, a nurse, a caregiver and an adapted physical education teacher).	7	60
<b>Workshops</b>	Workshops were talking about advices for hEDS self-management or about knowledge of the disease: - presentation of the disease, the last recommendations and potentials therapeutics options by physicians - presentation of TENS for pain management and knowledge about breathing physiology by physiotherapists - focus groups on the problems caused by the disease and patients limitations by psychologists - presentation and discussion on advice for nutrition by dieticians, - presentation at the beginning of the RP of the various hygiene proceedings to be observed during the program by nurses and caregivers	14	60-90

Table 2: Demographical data.

<b>Data (n=21)</b>	<b>Mean <math>\pm</math> SD</b>
Age (years)	45 $\pm$ 13
Height (cm)	164 $\pm$ 9
Body mass (kg)	78 $\pm$ 18
BMI (kg.m <sup>-2</sup> )	29 $\pm$ 6

*Data are expressed as mean  $\pm$  standard deviation for age, height, body mass and BMI.*

Table 3: Results of the six-minute walk test (6MWT).

		<b>t0</b>	<b>t9</b>	<b>t15</b>	<b>p</b>
<b>6MWT</b> (n=16)	Walking distance (m)	439.4 ± 100.9	491.8 ± 72.5 <sup>a</sup>	491.3 ± 69.3 <sup>a</sup>	p=0.001
	Nadir exercise SpO <sub>2</sub> (%)	95.3 ± 1.8	95.6 ± 1.7	94.6 ± 2.7	NS
	Exercise HR (bpm)	110.4 ± 18.3	115.3 ± 11.3	110.2 ± 17.6	NS

*Outcomes at the baseline (t0), at the end (t9) and six weeks after the end of the program (t15).*

*HR, heart rate; NS, statistically not significant.*

<sup>a</sup> *Significant difference with t0*



Table 4: Comparison of the walking distance with predicted values and minimal clinical important difference (MCID) for the six-minute walk test (n=16).

	<b>t0</b>	<b>t9</b>	<b>t15</b>
<b>Walking distance <math>\geq</math> PV</b> number of patients (% patients)	2 (12.5%)	3 (18.75%)	3 (18.75%)
<b>PV <math>&gt;</math> Walking distance <math>\geq</math> LLN</b> number of patients (% patients)	7 (43.75%)	10 (62.5%)	10 (62.5%)
<b>LLN <math>&gt;</math> Walking distance</b> number of patients (% patients)	7 (43.75%)	3 (18.75%)	3 (18.75%)
<b>Walking distance increase <math>&gt;</math> MCID vs t0</b> number of patients (% patients)		7 (43.75%)	11 (68.75%)
<b>Walking distance decrease <math>&gt;</math> MCID vs t0</b> number of patients (% patients)		0 (0%)	0 (0%)

*Lower limit of normal (LLN) and predicted value (PV) at the baseline (t0), at the end (t9) and six weeks after the end of the program (t15).*

Table 5: Results of the Tampa Scale for Kinesiophobia and the Multidimensional Fatigue Inventory.

		<b>t0</b>	<b>t9</b>	<b>t15</b>	<b>p</b>
<b>TSK</b> (n=18)	Score	44.3 ± 5.7	41.2 ± 4.6 <sup>a</sup>	41.7 ± 4.1	p=0.033
<b>MFI-20</b> (n=18)	General fatigue	17.4 ± 2.2	16.4 ± 2.5	16.9 ± 2.4	NS
	Physical fatigue	15.0 ± 2.5	13.6 ± 2.7	14.6 ± 2.3	NS
	Mental fatigue	15.3 ± 4.1	14.9 ± 3.6	14.5 ± 3.1	NS
	Reduced activity	13.7 ± 3.3	10.9 ± 3.9 <sup>a</sup>	12.6 ± 1.9	p=0.01
	Reduced motivation	12.5 ± 3.2	11.6 ± 3.6	12.8 ± 3.4	NS
	Total	73.9 ± 9.1	67.4 ± 11.5	71.4 ± 9.3	NS

*Outcomes at the baseline (t0), at the end (t9) and six weeks after the end of the program (t15).*

*TSK, Tampa Scale for Kinesiophobia; MFI, Multidimensional Fatigue Inventory.*

<sup>a</sup> *Significant difference with t0*

Table 6: Results of the Brief Pain Inventory.

		<b>t0</b>	<b>t9</b>	<b>t15</b>	<b>p</b>
<b>BPI</b> (n=17)	Pain at its least	3.1 ± 1.7	3.3 ± 1.9	3.5 ± 2.1	NS
	Pain at its worst	7.3 ± 1.2	7.0 ± 1.3	7.9 ± 1.1 <sup>b</sup>	p=0.023
	Pain on the average	5.9 ± 1.2	6.1 ± 1.6	5.9 ± 1.5	NS
	Pain right now	5.4 ± 1.7	5.6 ± 1.8	5.7 ± 2.0	NS
	Pain interference	6.1 ± 1.9	5.8 ± 1.8	5.7 ± 2.1	NS

*Outcomes at the baseline (t0), at the end (t9) and six weeks after the end of the program (t15).*

*BPI, Brief Pain Inventory. Pain at its least, at its worst and on the average is asked about the last week.*

*<sup>b</sup> Significant difference with t9*

Table 7: Results of the The Medical Outcome Study Short Form 36 (SF-36) questionnaire.

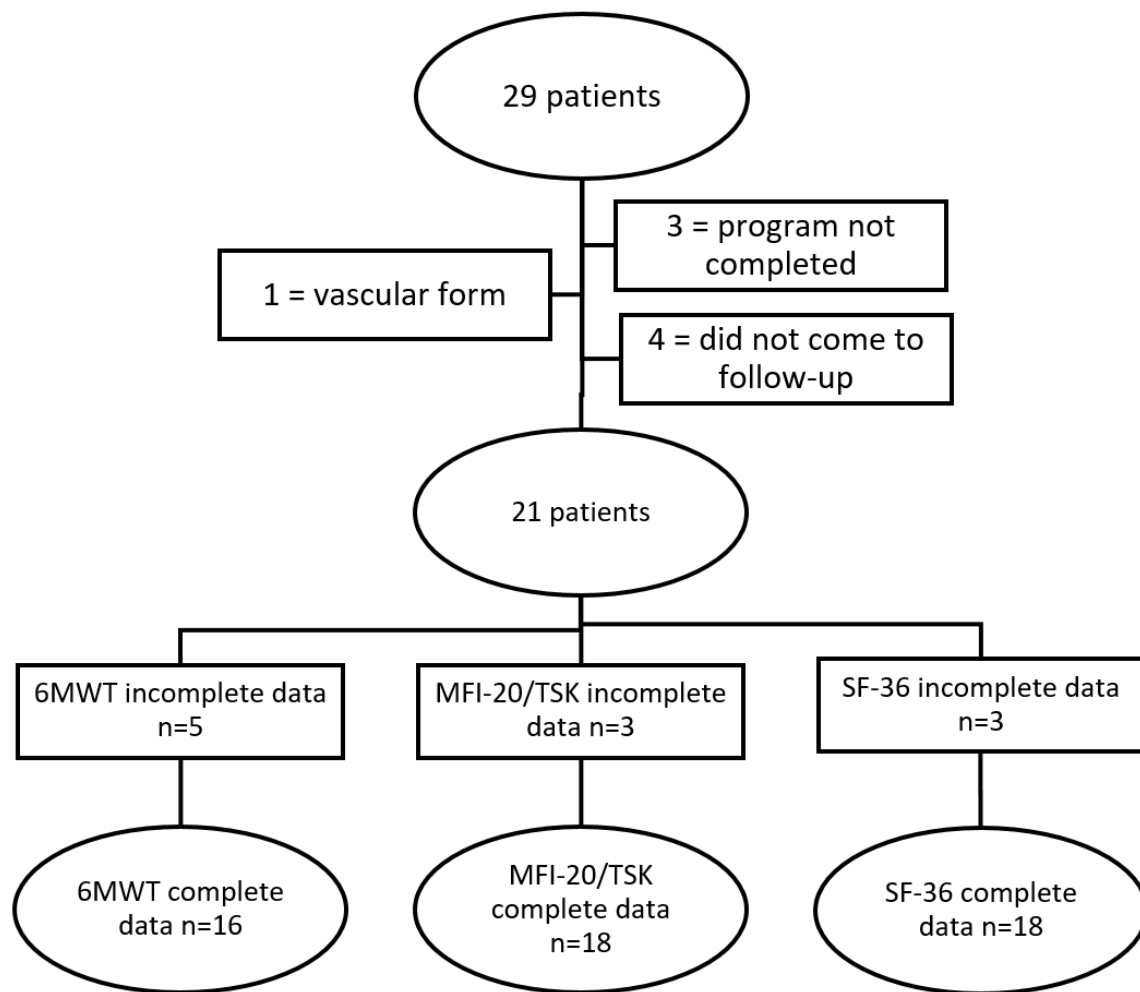
		<b>t0</b>	<b>t9</b>	<b>t15</b>	<b>p</b>
<b>SF-36</b> (n=18)	Physical functioning	42.8 ± 18.7	47.8 ± 21.6	40.7 ± 23.9	NS
	RLPH	18.1 ± 31.8	24.5 ± 26.3	19.9 ± 23.8	NS
	RLEP	33.3 ± 41.2	48.1 ± 41.6	33.3 ± 44.3	NS
	Vitality	21.6 ± 13.8	35.8 ± 12.7 <sup>a</sup>	29.4 ± 14.1	p=0.001
	Emotional well-being	47.1 ± 21.7	58.9 ± 20.9	43.1 ± 23.4 <sup>b</sup>	p=0.006
	Social functioning	45.1 ± 29.7	45.8 ± 14.8	37.5 ± 22.7	NS
	Pain	31.0 ± 24.3	34.4 ± 17.1	33.5 ± 15.5	NS
	General health	29.4 ± 16.6	30.0 ± 20.1	31.1 ± 14.2	NS
	Health change	45.8 ± 35.6	54.2 ± 32.4	49.7 ± 28.5	NS
	PCS	30.5 ± 7.0	32.1 ± 6.8	31.1 ± 6.4	NS
	MCS	35.7 ± 10.9	41.2 ± 9.6	34.7 ± 11.9 <sup>b</sup>	p=0.022

*Outcomes at the baseline (t0), at the end (t9) and six weeks after the end of the program (t15).*

*RLPH, role limitations due to physical health; RLEP, role limitation due to emotional problems; PCS, physical composite score; MCS, mental composite score.*

<sup>a</sup> *Significant difference with t0*

<sup>b</sup> *Significant difference with t9*



*Figure 1: Inclusion and completed data flowchart*