A multicomponent physical activity home-based intervention for fibromyalgia patients: effects on clinical and skin biopsy features

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Abstract

Objective

Adapted physical activity (APA) has been recommended for fibromyalgia (FM) treatment as an essential component of a biopsychosocial therapeutic approach for patients. Previous studies report that aerobic and resistance training are the most effective programmes in improving the quality of life and psycho-physical well-being. Patients with FM are frequently affected by an impairment of small fibre innervation, which is evident in the proximal somatic districts. Therefore, this pilot randomised controlled not pharmacological trial aimed to investigate if a 12-week home-based multicomponent (aerobic and resistance training and mobility) physical activity (PA) intervention was effective in improving pain perception, FM-related disability, and IntraEpidermal Nerve Fibre Density (IENFD) in adult FM patients.

Methods

Thirty-four female subjects with a fibromyalgia diagnosis (51.5±11.88 years) were randomly assigned to an experimental group (n=17) that received a supervised home-based multicomponent PA intervention twice a week and a control group (n=17) that received a generic programme of aerobic exercise. Skin biopsy was performed before the physical programme and after 18 months with constant execution of the supervised PA intervention or generic aerobic exercise. Both groups assumed pharmacological treatment with duloxetine and/or pregabalin.

Results

We found that the group performing physical activity in a supervised and regular way showed a significant improvement in the Fibromyalgia-linked invalidity questionnaire (FIQ) as well as epidermal fibre density at proximal and distal sites.

Conclusions

Physical activity could improve FM outcomes, with a possible beneficial impact on peripheral factors contributing to pain-related disability.

Key words
adapted physical activity, fibromyalgia, skin biopsy

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Introduction

Fibromyalgia (FM) is a complex condition of chronic pain whose aetiopathogenetic mechanisms and causes are not yet clearly understood. The most typical symptoms of FM disease are diffuse skeletal muscle pain, fatigue (about 90% of the individuals), alteration of mood (about 75% of the individuals), sleep disturbance, cognitive dysfunction, physical deconditioning, and thus the poor quality of life (1, 2). In the last years' evidence emerged about a non-length dependent small fibre neuropathy, causes and treatment of which are currently not fully understood (3). Small fibre loss could in theory take advantage of physical activity, but evidence is still few in current literature (4).

In the management of FM, physical activity (PA) and physical exercise (PE) are well-recognised as important factors that contribute to an effective biopsychosocial approach (2).

Several reviews have highlighted the importance of PA in the last few years: Macfarlane *et al*. (2017) (5) proposed that exercise and, specifically, adapted physical activity (APA) is one of the bases for FM treatment. Specifically, the greatest evidence of several APA programmes has been observed on pain and quality of life (6) and the physical and psychological functioning of FM subjects (2). The same review reports that aerobic exercise and strength training are the most used training strategies in non-pharmacological FM management. However, a meta-analysis showed weak evidence of the efficacy of physical exercise (7). Anyway, recent studies suggested that aerobic exercise is associated with reductions in anxiety among adults with fibromyalgia (8) and that this type of training may be usefully applied in many different rehabilitation contexts for FM treatment (9).

Resistance training (RT), also associated with aerobic exercise, has been found useful in reducing several symptoms of FM (7, 10, 11).

The European Alliance of Associations for Rheumatology (EULAR) recommendations strongly suggest a combination of aerobic and strengthening exercises either on land or in water as a fundamental element among nonpharmacological treatment options for the management of FM (5).

In musculoskeletal conditions as well as in FM treatment online-distance-medical and non-intervention programmes including telerehabilitation have been carried out reporting improvement in pain intensity, mechanical pain sensitivity, and psychological distress (12, 13).

To our knowledge, there are no available studies that evaluated the effects of a multicomponent home-based exercise programme on clinical features and IntraEpidermal Nerve Fibre Density (IENFD) in FM patients. In a recent study, we evaluated the outcome of small fibre sufferance and clinical features in a cohort of FM patients. The observation of a programme of aerobic exercise seemed to condition a better outcome of fatigue in patients with less severe small fibre damage (14).

Therefore, we aimed to evaluate the clinical and IENFD outcome in a subgroup of FM patients treated with a supervised multicomponent home-based PA programme focused on aerobic and resistance training, compared with patients following a generic not supervised aerobic exercise.

Materials and methods

Subjects and study design

The present study was conducted in the Neurophysiopathology Unit of Bari Policlinico General Hospital. It was a randomised controlled interventional study, comparing the clinical and IENFD evolution in 2 groups of FM patients, one performing a multicomponent home-based PA programme focused on aerobic and resistance training, the other group receiving a prescription of not supervised aerobic exercise. A priori analysis with G*Power indicated that 34 subjects were sufficient to detect a medium effect size (f=0.25) with an 80% statistical power and α=0.05 using within-between subjects' design.

Forty-four consecutive FM patients were submitted to a basal clinical evaluation and skin biopsy (14). Inclusion criteria consisted in a diagnosis of FM, according to ACR Diagnostic Criteria

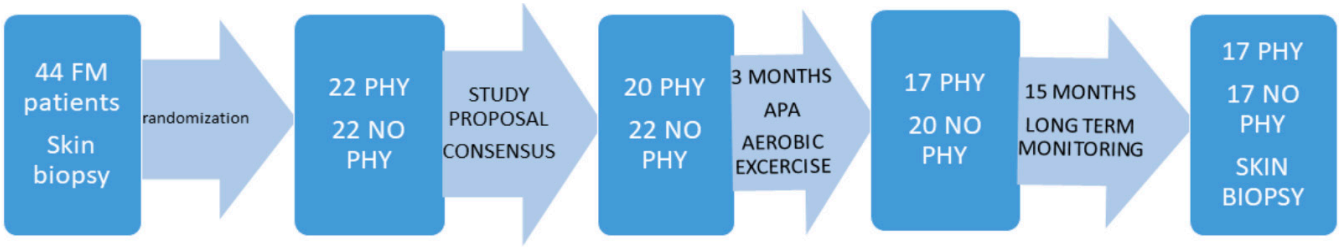

Fig. 1. Flow chart reporting the study design with 2 patients' groups, one following Assisted Physical Activity (APA) (PHY), the other performing a not supervised aerobic exercise (NO PHY).

for Fibromyalgia published in 2011 (15). Exclusion criteria were the following: low level of education (below 8 years), drugs acting on the central nervous system at baseline, a prior history of any other neurological conditions, active and inactive cancer, diabetes, renal impairment, active autoimmune/inflammatory/rheumatological disease, psychiatric disorders except for mild anxiety and depression, BMI >35. All of them agreed to repeat skin biopsy after 18 months of follow up. They were assigned with a 1:1 randomisation to a supervised multicomponent home-based programme (PHY) or a generic not supervised programme of aerobic exercise (NO PHY), consisting of 45' min brisk walking and/or cycling and/or swimming four times weekly. Twenty patients agreed to the assisted programme, but finally, 17 completed the 3 months and continued to follow it during the observation period. They received a supervised home-based PA intervention twice a week for a total of 3 months. In the following time, the same patients were suggested to continue the home programme, monitored with monthly telephonic interviews to assure the prosecution of physical activity. All patients underwent an in-person visit at 6 and 12 months and were also contacted by phone or e-mail at months 3 and 9, to re-evaluate the clinical conditions, compliance, and effects of treatment. The clinical and skin biopsy follow-up were performed after 18 months of clinical observation, between December 2018 and April 2021. Seventeen consecutive patients were assigned to a not supervised programme of aerobic exercise and completed the 18 months follow up (Fig. 1). Demographic data are reported in Table I. In accordance with the routine approach of our Centre, all patients were suggested to take pharmacological treatment with antiepileptics (pregabalin 150–300 mg) and antidepressants (duloxetine 60 mg) (14). All the enrolled subjects signed informed consent. The local Ethical Committee of Bari Policlinic General Hospital approved the execution of skin biopsy in FM patients at baseline and follow-up (Study number 254). The same Committee approved the study about the efficacy of physical activity in FM (Study number 5902). The study was conducted in accordance with the Helsinki Declaration of 1975/83.

Table I. Demographic and clinic characteristics of fibromyalgia patients included (PHY) or not included (NO PHY) in a supervised physical exercise programme. No statistical differences were found by ANOVA and chi-square test for the main clinical variables and sex ($p<0.05$).

	GROUP	MEAN	SE	95% CI	
				lower	higher
Age (years)	NO PHY	53.37	2.13	49.07	57.67
	PHY	49.65	1.93	45.75	53.56
Duration (years of fibromyalgia)	NO PHY	6.89	1.52	3.81	9.98
	PHY	10.87	1.39	8.07	13.67
WPI (score)	NO PHY	13.11	1.01	11.07	15.14
	PHY	14.91	0.92	13.06	16.77
SS (score)	NO PHY	7.05	0.65	5.73	8.37
	PHY	7.30	0.59	6.11	8.50
IENFD Proximal (n. fibres)	NO PHY	9.98	0.56	8.19	11.57
	PHY	9.54	0.68	8.09	11.00
IENFD Distal (n. fibres)	NO PHY	8.28	0.72	6.74	9.80
	PHY	7.54	0.45	6.57	8.52
Sex (M/F)	NO PHY	20 F 2 M			
	PHY	23 F 3 M			

WPI: Whole Pain Index; SS: associate symptoms; IENFD: intraepidermal nerve fibre density; SE: standard error; CI: confidence interval.

Measures

Questionnaires. We tested patients with the following scales: Visual Analog Scale (VAS) (16), A self-rating depression scale (SDS) (17) and a self-rating anxiety scale (SAS) (18), Fibromyalgia-linked invalidity questionnaire (FIQ) (19), Neuropathic Pain Diagnostic Questionnaire (DN4) (20), Multidimensional Assessment of Fatigue (MAF) (21), and the Brief Pain Inventory (BPI) with pain severity and interference subscores (22). Diagnosis of FM was done in agreement with 2010 criteria, using the Wide Pain Index (WPI) and Symptoms Severity Scale (SS) (23).

Skin biopsy. As reported in previous studies (14, 24) patients underwent 3-mm punch biopsies from the thigh and distal leg following an intradermal injection of 1% xylocaine. Briefly, the specimens were fixed in 2% paraform-

Table II. Description of the 12-week multicomponent physical activity intervention programme (adapted physical activity for the fibromyalgia patient, 2 d·wk-1).

Phase	Exercise	Set	Reps	Guidelines
Warm-up	Head Rotation, flexion, extension and circles	1	20	Duration: 10 min
	Shoulders moving backward to forward	1	20	
	Shoulders circles	1	20	
	Leg extension	1	20	
	Ankle flexo-extension	1	20	
	Static marching	1	5’	
Core training	Thoracic breathing (seated)	1	2’	Duration: 40 min.
	Diaphragmatic breathing (seated)	1	2’	Training load: 1–2 sets of
	90° Arms Adduction (Standing cross)	2	10	8–15 repetitions with
	Alternating pushes	2	10	45 sec of slow walking
	French press	2	10	between each exercise.
	Half squat with chair	2	10	Progression: increase
	Leg extension from sitting	2	10 x leg	repetitions before sets.
Cool-down	Shoulders circles and move backward to forward	2	30’’	Total duration: 10 min.
	Triceps stretching	2	30’’	Overload: stretch beyond resting length but not
	Biceps stretching	2	30’’	beyond pain-free ROM.
	Trunk torsions with arm extension	2	30’’	Duration: 10–30 sec/stretch, repetitions: 2–4,
	Breathing with spine control (seated)	2	30’’	accumulate 60 sec per exercise.
				Progression:gradual increase in stretch
				duration or repetitions.

aldehyde-lysine-sodium periodate at 4°C overnight following which they were cryoprotected, serially cut with a cryostat, and immunostained using polyclonal anti-protein gene product 9.5 (Ultraclone Ltd). We calculated the intraepidermal nerve fibre density on three non-consecutive central sections by bright-field microscopy, using a stereology workstation (Olympus BX50. PlanApo oil-objective 40x/NA = 1.0) and compared them to sex-and age-adjusted normative values (25-27). Based on the cut-off values (25-27) patients were classified into those with proximal reduced IENFD (P) distal and proximal reduced IENFD (D) and normal IENFD (N). The same criteria were used at follow-up to define patients as stable, with persistence of normal IENFD, improved, with evolution from low to normal IENFD, or worsened, with evolution from normal to reduced IENFD, based on the above-reported classification and cut-off values (26, 27). In any case, the appearance of degenerative aspects determined a judgment of worsening.

Intervention

A home-based multicomponent exercise programme was administered for 12 weeks, twice a week through the Zoom online platform. To guarantee a 1:4 educator/subject ratio, the EG was divided into 6 subgroups each one followed and instructed by a Physical Education graduate teacher. The same educator followed the same subgroup throughout all the experimental interventions. As to the content of the intervention, the adapted physical activity programme is shown in Table II Each lesson was divided into three phases: a warm-up lasting 10 minutes characterised by mobility, dynamic stretching exercises and aerobic exercise; a central phase lasting 40 minutes focused on the combination of muscular strength exercises for upper and lower limbs with active rest; finally, a cooldown phase of 10 minutes with an emphasis on static stretching, mobility and breathing technique. At the end of the intervention, the educator instructed patients for the prosecution of the programme in the following months (Table II).

Statistical analysis

We tested the parametric distribution of data with Kolmogorov-Smirnov test. Demographic and clinical data were compared with one-way ANOVA test. We employed two levels repeated measures ANOVA with the condition before and after the intervention as within cases factor, group as between cases factor and IENFD and clinical features as variables. We applied the linear regression analysis between the rate of change of clinical variables and IENFD, to establish the correlation of clinical and skin biopsy outcomes after 18 months of follow-up. We used the SPSS (v. 21) statistical package for all analyses. Statistical significance was set at $p<0.05$.

Results

The groups following or not supervised physical activity programmes were homogeneous for demographic, clinical and IENFD characteristics (Table I).

All the patients included in the control group confirmed to follow the not supervised programme of aerobic exercise, but most of them self-proclaimed not being regular for the number and duration of weekly activities.

Eleven patients included in the supervised physical programme activity, and 14 not following the supervised programme presented with proximal small fibre denervation in basal condition, while only 1 patient for group had also denervation at the distal site. In the PHY group, the IENFD remained stable in 13 cases, 3 patients showed normal values and 1 patient worsened, in the NO PHY group, 12 patients remained stable, 2 improved and 3 patients worsened at follow-up (chi-square 1.24, $p=0.48$).

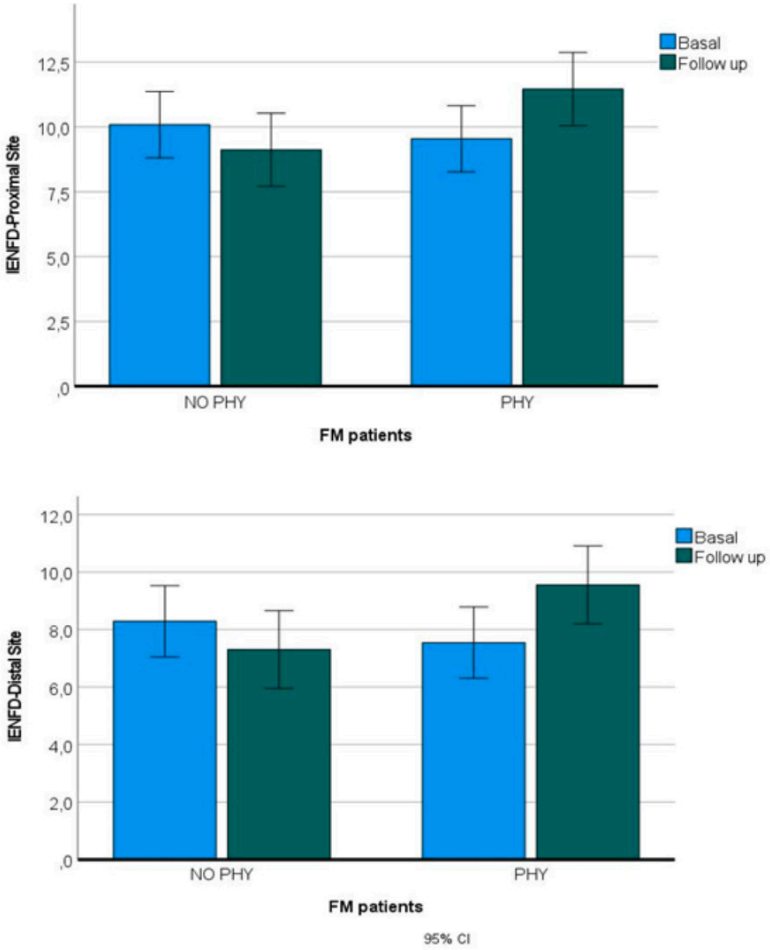

Fig. 2. A: IENFD (intraepidermal nerve fibre density at proximal site in fibromyalgia (FM) patients performing (PHY) or not performing (NO PHY) supervised APA. Repeated measures ANOVA with follow up as factor F= 2.26, p= 0.13; interaction follow up and physical activity: F= 21.59, p <0.001. **B**: IENFD (intraepidermal nerve fibre density) at distal site in Fibromyalgia (FM) patients performing (PHY) or not performing (NO PHY) supervised APA. Repeated measures ANOVA with follow up as factor F=1.01, p= 0.32; interaction follow up and physical activity: F=8.60, p<0.006.

Table III. Means, Standard errors (SE) and 95% confidence intervals of intraepidermal nerve fibre density (IENFD) in fibromyalgia patients following (PHY) or not following (NO PHY) the adapted physical activity programme.

			mean	SE	95% lower	higher
IENFD proximal site	basal	NO PHY	10.05	0.66	8.71	11.39
		PHY	9.78	0.62	8.53	11.03
	follow up	NO PHY	9.87	0.61	8.64	11.10
		PHY	11.00	0.57	9.85	12.15
IENFD distal site	basal	NO PHY	8.25	0.53	7.16	9.33
		PHY	7.19	0.59	5.99	8.39
	follow up	NO PHY	8.00	0.49	7.00	8.99
		PHY	9.13	0.54	8.02	10.23

However, the IENFD density improved on average in patients following a supervised programme of physical exercise, as compared to the other group, at both proximal and distal sites (Fig. 2 and Table III).

Disability linked to Fibromyalgia (FIQ) improved at follow-up, more in patients performing the APA programme (Fig. 3a). Fatigue improvement in patients observing supervised programme of physical exercise approached the statistical significance (Fig. 3b). The disability linked to pain improved in both groups at follow-up, without a relevant effect of group (Brief Pain Inventory Pain subscore: ANOVA with follow up as factor F=11.76, p=0.002; interaction follow up and physical activity: F=0.002, p=0.96). The DN4 and subjective pain intensity measured with a 0-10 numerical scale were similar at follow-up between the 2 groups, as well as anxiety and depression.

We found a correlation between the rate of change of FIQ score and IENFD density at the proximal site in the whole of FM patients (Fig. 4).

Discussion

To the best of our knowledge, this is the first study evaluating the effect of a supervised long-term programme of physical activity in FM patients, taking into consideration both clinical symptoms and skin biopsy data.

We observed that in the small group regularly following the physical programme for 18 months, there was a general improvement in disability and IENFD, in comparison to patients following a generic programme of physical inactivity.

We cannot establish if it was the specific modality of APA, consisting of aerobic and resistance training, or if it was the generic physical exercise, in comparison with a not supervised and quite irregular activity, to favour the reduction of FM disability and small fibre reinnervation. In general, physical activity is recommended in FM, with aerobic exercise and strength training suggested for pain and fatigue (28). Our cohort followed a supervised training in a remote mode, and they were further suggested to continue with the same home-based programme in the following months. They were compliant with the programme, and they adhered to it with continuity, as we assessed during phone contacts and in-person visits. This modality of remote programme, based on the telemedicine approach, deserves further controlled studies based on the comparison with other methods of supervised motor training. The present study is a primary confirmation of its potential interest for FM, also giving

the high compliance patients demonstrated (13, 29, 30).

We did not observe a substantial improvement in anxiety and depression in the group following the supervised programme, so a direct effect of the physical activity programme on physical performances could have improved disability and, in a weaker way, fatigue, more than its psychological impact. This mild effect of physical aerobic exercise on depression was also confirmed by FM specialists (28).

While the subjective perception of maximal pain did not change considerably at follow-up, the disability linked to pain improved in both groups, suggesting a pharmacological effect, a benefit from a general improvement of physical activity and lifestyle and resilient behaviour. Long-term studies showed substantial stability of FM symptoms, with a general improvement in patients observing regular physical training (31). All patients were also treated with duloxetine and/or pregabalin (14), which could have reduced the impact of pain on daily life activities.

FM patients showed reduced motor skills, together with reduced metabolism of motor cortical networks (32). Physical exercise could improve motor behaviour, with a role in FM severity. In a recent study (32), we also observed that the motor cortex metabolism improved with other's movement observation, which was realised during the remote training in the home-based programme. While the effect of APA on fatigue approached the statistical significance, its mild reduction, due to constant physical exercise, might improve the general impact of the disease.

The new finding, in the present study, is the improvement of peripheral small fibre density and its correlation with the reduction of disability in patients observing the APA motor programme. The role of small fibre neuropathy in FM is a matter of debate (3). It was associated with severe phenotype (33), but it seemed not to influence somatosensory system function (34).

In our recent follow-up study, conducted on a total of 62 patients, we observed that patients with reduced IENFD and motor skills had more severe disability outcomes (14). The present analysis, taking into consideration the direct effect of motor exercise, confirms that the enrichment of small fibre innervation in patients observing regular motor programmes is associated with a better

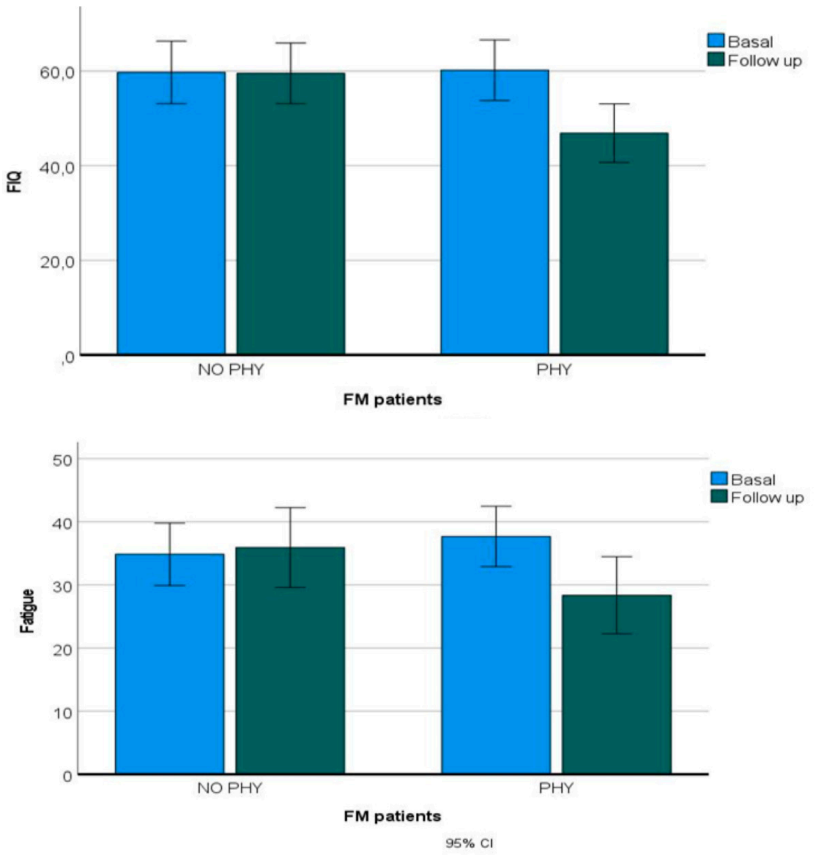

Fig. 3. A: Fibromyalgia impact questionnaire in fibromyalgia (FM) patients performing (PHY) or not performing (NO PHY) supervised APA. Repeated measures ANOVA with follow up as factor F=5.90, p=0.022; interaction follow up and physical activity: F=5.55, p=0.025.
B: Multidimensional assessment of fatigue in fibromyalgia (FM) patients performing (PHY) or not performing (NO PHY) supervised APA. Repeated measures ANOVA with follow up as factor F=2.62, p=0.11; interaction follow up and physical activity: F=4.16, p<0.05.

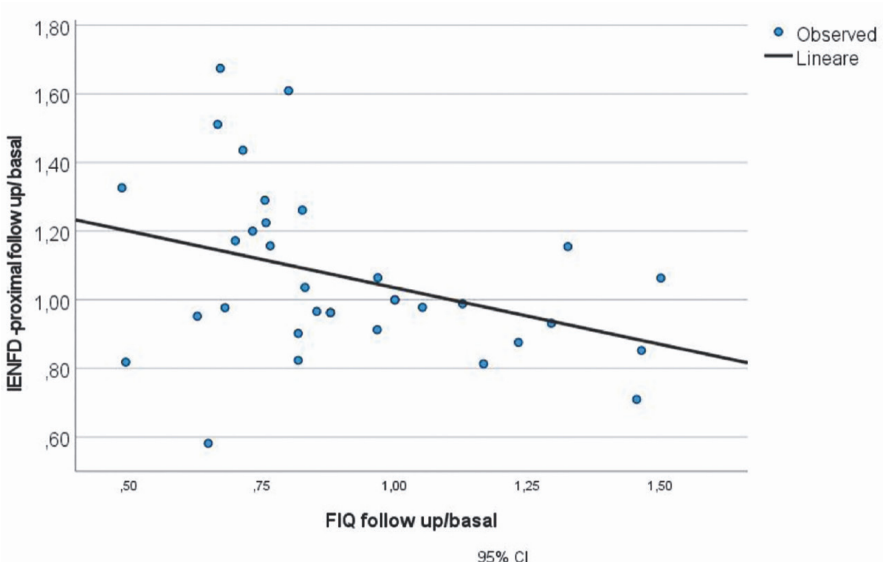

Fig. 4. Linear regression curve between the rate of change of fibromyalgia impact questionnaire (FIQ) and intraepidermal nerve fibre density (IENFD). ANOVA F=4.88, beta = -0.36, t= -2.29, p=0.034.

evolution of the disease. Presently we do not have an explanation for the phenomenon of small fibre reinnervation in movement-active patients. Animal and human studies (35, 36) found that motor exercise selectively improved sensory nerve fibre function in diabetic neuropathy. Evidence supports the beneficial effect of motor exercise on large myelinated sensory nerve function in polyneuropathies (36), so an effect on unmyelinated and small myelinated fibres is also conceivable. Nolano *et al*. (37) evaluated the outcome of skin biopsy in Parkinson's disease patients displaying small fibre denervation and subjected to a rehabilitative programme. They found an improvement of IENFD in a subgroup of early Parkinson's disease patients and supposed that regenerative/restorative phenomena may counteract nerve degeneration/dysfunction in patients submitted to motor rehabilitative treatment.

Study limitations

This was a study conducted in a small sub-cohort of FM patients followed for 18 months. The reliability of physical activity and adherence to the supervised programme or the generic programme of aerobic exercise was assessed with in-person visits and phone contacts, but we have no objective tests to prove the patient's adherence.

Conclusions

This study provides the first evidence that a multicomponent physical activity home-based intervention could improve small fibre pathology and disease severity in a small group of FM patients. We think that these results could be worthy of confirmation in larger groups, pending a comparison among different supervised motor programmes by randomised controlled multicentre trials.

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