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ORIGINAL REPORT

EFFECTS OF A PROLONGED EXERCISE PROGRAMME ON KEY HEALTH OUTCOMES IN WOMEN WITH FIBROMYALGIA: A RANDOMIZED CONTROLLED TRIAL

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Objective: **To assess the impact of a long-term exercise programme vs usual care on perceived health status, functional capacity and depression in patients with fibromyalgia.**
Design: **Randomized controlled trial.**
Subjects: **Forty-two women with fibromyalgia were allocated randomly to 1 of 2 groups: an experimental group that carried out aerobic, strength and flexibility exercises for 24 weeks and a usual care control group.**
Methods: **Health status and functional capacity were evaluated using the Fibromyalgia Impact Questionnaire and the Short Form Health Survey 36. Depression was evaluated with the Beck Depression Inventory.**
Results: **Significant improvements were observed in health status and functional capacity for the exercise group over the control group. The magnitude of the effect size of these improvements, expressed as Cohen's *d*, was medium. The effect size (95% confidence interval) for the Fibromyalgia Impact Questionnaire was 0.58 (–14.12, –2.35), for the Short Form Health Survey 36. global score 0.54 (1.28, 14.52), and in the mental health domain of the Short Form Health Survey 36. 0.51 (1.20, 16.26). There was a large effect size in vitality. All the aforementioned improvements can be considered as clinically important changes.**
Conclusion: **Results confirm that a long-term combination of aerobic exercise, strengthening and flexibility improves psychological health status and health-related quality of life in patients with fibromyalgia.**

Key words: physical activity; fibromyalgia; exercise; health-related quality of life.

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INTRODUCTION

Fibromyalgia (FM) is a contentious clinical syndrome, characterized by diffuse musculoskeletal pain and reduced pain threshold, particularly at defined "tender points". The condition is often accompanied by generalized fatigue, sleep disturbance, and psychological distress (1). Patients with FM have decreased functional ability, poorer health status and decreased quality of life (QoL) compared with healthy subjects or those with other chronic diseases (2, 3). The pathogenesis of FM is not entirely understood, although the current theory is that FM is the result of central nervous system dysfunction, resulting in central sensitization and pain amplification (4). In addition, psychological factors may be implicated in the development and maintenance of FM (5).

Although there are several treatment options available, the optimal management for FM remains elusive. Clinical guidelines recommend a broad range of pharmacological and non-pharmacological therapies (6, 7), but the impact of such treatments on QoL and function is still debated (6). Nevertheless, there is evidence that physical exercise can have an impact on the clinical presentation of patients with FM. Exercise has been demonstrated to be effective in improving patients' health-related QoL, general function, psychological well-being, and other symptoms, such as anxiety and depression (8–13). Indeed, exercise is considered to be the main non-pharmacological strategy in the management of FM. However, many of the exercise programmes used in clinical trials in FM are limited due to the short duration of the interventions (13–15), with some interventions being as short as 3 weeks (16, 17).

There is clear evidence from the sports science literature that interventions aimed at improving aerobic capacity or muscle strength and endurance should be of at least 15–24 weeks' duration in order to attain most of the possible effects (18), although a duration of 6 months (at least 24 weeks) is recommended to obtain additional health benefits (19). Furthermore, many of the interventions used in clinical trials in FM use only single exercise interventions that do not reflect clinical practice (20) or clinical guidelines, which recommend a range of exercise interventions in FM, including aerobic and strengthening exercises (6, 21). There is broad agreement in the literature about the need for long-term studies assessing the benefit of exercise for FM (21), especially concurrent strength and endurance training (22).

The aim of the current study was therefore to assess the effectiveness of a prolonged exercise programme (24 weeks), based on a combination of aerobic exercise, muscle strengthen-

ing and flexibility exercises, on the psychological well-being and QoL of women with FM.

METHODS

Sample size calculation

Sample size was estimated following the recommendations of McCrum-Gardner (23) using PS software (available from: http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize). Using a mean difference between the two groups of 14, which is considered the minimally clinical important difference (MCID) for the primary outcome measure, the Fibromyalgia Impact Questionnaire (FIQ) (24) and a standard deviation (SD) of 14 (25), gives a sample size of 17 per group. Allowing for an attrition rate of approximately 20% gives a total sample 42, providing 80% power at the 95% significance level.

Participants

Inclusion criteria for study participants were: women, aged 18 to 65 years, diagnosed with FM based on the America College of Rheumatology Criteria (1), and had to give written informed consent to participate in the study. Exclusion criteria were: any significant concomitant medical illness, such as inflammatory rheumatic diseases, respiratory or cardiovascular diseases that would prevent physical exercise, or severe psychiatric illness. Finally, those women with FM who had attended physical therapy or psychological therapy in the previous 3 months were excluded from the study to avoid possible carry-over to the present trial. Participants were asked not to start a new course of medication during the course of the trial; they were allowed to continue with their current medication and use "rescue analgesic" as normal.

Recruitment procedure

Participants were recruited from 3 local patient support groups in Seville, Spain, and screened for entry into the study from April 2007 to January 2008 by one investigator (DG) who was blind to the randomization sequence. Participants were interviewed by the examining physician using a standardized questionnaire to record sociodemographic characteristics and medication.

A total of 53 women were eligible for entry into the study, 11 participants were excluded due to co-morbidities, participation in another treatment, incompatible work, and 3 people declined to participate. The 42 patients who met the inclusion criteria were allocated randomly to an experimental group that would receive an exercise programme (EX, $n=21$) and a usual care control group (UC, $n=21$). Randomization was based on a computer-generated random number table, and group allocation was conducted by LC, who was unaware of the randomization sequence, and was not involved in the day-to-day running of the trial. The result of randomization was unknown until the participant accepted or declined to participate in the project. The randomization sequence was not disclosed to the researcher responsible for the day-to-day running of the trial (BS) until patients had completed their baseline assessments. Fig. 1 shows the flow of participants through the trial. The study was approved by the ethics committee of the University of Seville and conformed to the principles of the Declaration of Helsinki.

Outcome measures

Patients attended for initial assessment at the Physical Education and Sport Laboratory, University of Seville. At baseline (T1), demographic information, clinical details including medication and outcome questionnaire (perceived functional ability, QoL and psychological health status) were collected. Assessment of all outcomes was undertaken at baseline (before randomization) and after the 24-week intervention (T2). For both groups the outcome assessor was blind to group allocation throughout.

Primary outcome measure

The Fibromyalgia Impact Questionnaire (FIQ) was the primary outcome measure. The FIQ is a self-administered questionnaire validated in Spanish for its use in patients with FM (26). The FIQ measures physical functioning, work status, and overall well-being; it also contains 6 visual analogue scales for pain, sleep, fatigue, morning stiffness, anxiety, and depression. The range of the total score is 0–80, where a higher score indicates a more negative impact of FM. Bennett et al. (24) estimated the MCID for the FIQ based on the findings from 3 clinical trials and a total of 2228 patients. These authors reported that a 14% change represented a clinically important change in total FIQ score.

Secondary outcome measures

Short Form Health Survey 36 (SF-36). The Spanish version of the SF-36 is a self-administered questionnaire for measuring health-related QoL validated in Spanish populations (27). It contains 36 items grouped into 8 subscales: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional

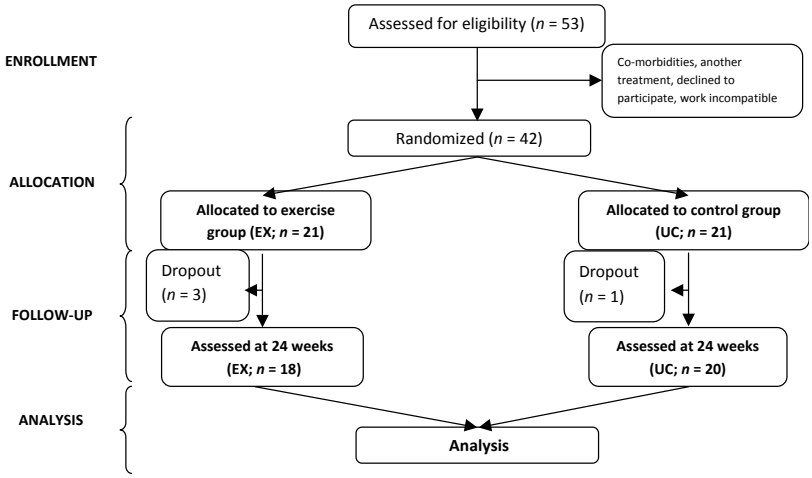

Fig. 1. Flow of participants through the trial. Enrolment, randomization and retention of study sample.

role, and mental health. The range of scores is between 0 and 100 in every subscale, where a higher score indicates better health-related QoL. Angst et al. (28) reported that, in rehabilitation interventions, effects larger than 12% of baseline score can be interpreted as the MCID for the SF-36.

Beck Depression Inventory

The Beck Depression Inventory (BDI) contains 21 items that assess the cognitive, affective, and neurovegetative factors associated with depression. The score ranges from 0 to 63, where values greater than 13 indicate presence of depression, and values greater than 21 indicate major depression (29). This instrument was also recommended for assessment of change in depression after exercise interventions in patients with a diagnosis of FM (21). Dworkin et al. (30) reported that a change of 5 points on the BDI could be considered a reasonable estimate of a clinically important change for patients with chronic pain.

Interventions

The EX group performed twice-weekly sessions of combined aerobic and muscle strength training exercises for 24 weeks. The exercise intervention was based on a 3-arm randomized controlled trial in which we investigated the feasibility of implementing our intervention combining different types of exercise in women with FM (31), but also on a recent study conducted by Valkeinen et al. (22) using concurrent strength and endurance training in low to moderate volume. The intervention was further refined after discussions among the research group. The exercise intervention consisted of a 10-min warm-up including multi-joint movements, followed by 10–15 min of aerobic exercise at 65–70% maximum heart rate (HRmax: estimated as 220 – age of the participant), which was recommended for estimating HRmax and for exercise prescriptions in women with FM (32). This intervention is in accordance with the American Pain Society's guidelines on FM, where it is recommended that patients perform moderately intense aerobic exercise at an intensity of 60–70% age-adjusted predicted HRmax 2 or 3 times per week (33). Steady-state aerobic exercise was conducted in small groups in which patients performed continuous walking with arm movements and jogging. They were taught how to monitor their heart rate and adjust their activity to maintain the correct exercise intensity. Following aerobic exercise participants completed 15–20 min of muscle strengthening exercises, which consisted of a circuit of 8 exercise stations. The 8 muscle groups targeted were: shoulders (deltoids and biceps), neck (trapezius), hip (gluteus and quadriceps) and back-chest-torso (latissimus dorsi, pectoralis major, abdominals). Examples of exercises were: shoulder press, dumbbell press, shoulder elevation with resistance, biceps curl, dumbbell bent over row, squats, hip flexion and extension and standing hip abductor. At each station participants carried out 1 set of 8–10 repetitions (reps) with 1–3 kg weight. At the outset of the study resistance was deliberately set at a level that the patients could easily manage. Across the course of the study, however, resistance was increased gradually according to patient's tolerance, as recommended by Bircan et al. (13). Finally, participants performed a "cool-down" of 10 min, which consisted of flexibility exercises (8 or 9 exercise stations, each station 1 set of 3 reps, holding the stretched position for 30 s). HR was used to measure the intensity of exercise and was determined by using a HOSAND® TM200 telemetric system (Hosand Technologies Srl, Italy). This enabled participants to exercise within their established exercise intensity thresholds (i.e. 60–75% HRmax). Participants were instructed not to exert themselves and to perform exercises at a comfortable level for the first 5–6 weeks. After this, participants could increase exercise intensity within their own capacity using a heart rate monitor and individual knowledge of symptoms and level of overall fatigue as a guide. Classes were progressed to ensure that target heart rates were attained as subjects' conditioning improved. For example, subjects were progressed from gentle arm and leg movements (week 1) to intermittent jogging in the gymnasium (week 24). The UC group continued with their normal medical treatment for FM and continued their normal daily activities during the period of the intervention, which did not include any structured exercise.

Statistical analysis

The normality of the data was evaluated by the Kolmogorov-Smirnov test. Chi squared tests were used to compare clinical categorical variables between both groups. To compare means, analysis of variance (ANOVA) 2×2 (group×evaluation) was used for each outcome measure (FIQ, SF-36, BDI, physical function, physical role, bodily pain, general health, vitality, social functioning, role emotional and mental health). Data were analysed from an intention-to-treat (ITT) perspective. For the purposes of analysis, participants remained in the groups to which they were randomly assigned. Those with missing data had the last recorded observation carried forward. This method for imputing missing values is conservative (i.e. it assumes no change), and therefore it is unlikely that differences will result purely on the basis of the method of imputation.

In addition, effect sizes (ES) for each outcome measure were calculated. Rosnow & Rosenthal's modified version of the Cohen's *d* method for ES calculation was used, as recommended by Carville & Choy (34):

$$d = M1 - M2/SD \text{ (pooled)}$$
$$SD \text{ (pooled)} = \sqrt{[(SD1^2 + SD2^2)/2]}$$

where d = ES, M1 = mean of the intervention group and M2 = mean of the control group, SD = standard deviation. The thresholds used for interpretation were as follows: values > 0.2 – 0.5 = small ES > 0.5 – 0.8 = medium ES, and > 0.8 = large ES.

The results are expressed as the mean (SD) or 95% confidence interval and the significance level was determined at $p < 0.05$. Statistical analysis was carried out using SPSS for Windows 15.0 (SPSS, Chicago, IL, USA).

RESULTS

The total number of patients who completed the trial was 38 (EX group $n = 18$ and UC group $n = 20$) (Fig. 1). Three patients in the EX did not complete the trial. One patient dropped out because of concomitant illnesses (pneumonia), another two could not participate due to personal reasons. In the UC group, one patient was lost to follow-up and did not complete the trial. Despite the relatively low attrition rate, the results are presented from an intention-to-treat perspective ($n = 42$).

The rate of compliance with exercise sessions was high, with patients attending mean of 85% of the sessions. At baseline there were no significant between-group differences in any demographic variables (all p-values > 0.05; Table I). Participants were similar to other study populations (22), in that they were in their mid-50s, they were overweight, bordering on obese (BMI < 30 kg/m^2 obese) and the vast majority were on medication for FM.

Table I. *Participants demographic details and medication use at baseline*

Outcomes	Exercise group ($n = 18$)	Controls ($n = 20$)
Age, years, mean (SD)	55.48 (7.14)	56.15 (8.48)
Weight, kg, mean (SD)	69.49 (11.32)	72.48 (11.97)
Height, m, mean (SD)	1.57 (0.08)	1.58 (0.07)
Body mass index, kg/m^2, mean, SD	28.19 (5.1)	29.03 (5.4)
Medication, %		
None	18.75	15.79
Analgesic or NSAID	43.75	36.84
Antidepressant or SSRI	6.25	10.53
Combination analgesic + other	31.25	36.84

NSAID: non-steroidal anti-inflammatory drugs; SSRI: selective serotonin reuptake inhibitor; SD: standard deviation.

The mean (SD) outcome scores at baseline and after the 24-week intervention period are shown in Table II. The exercise intervention resulted in significant improvements in the total FIQ score, total SF-36 score, and in some domains of the SF-36 (physical function, general health, vitality and mental health). The ES (*d*) of these changes are noted to be medium for the total FIQ and total SF-36. The change in the vitality subscale of the SF-36 demonstrated a large ES, but only small effects are noted for the other variables. In considering the improvements demonstrated in the intervention group, it is also worth stating that the magnitude of these changes demonstrate an important clinical impact on those with FM. The magnitude of the change in SF-36 total score was 20% (MICD 12%), and although the change in the FIQ was slightly less than the MCID, an improvement of 13% was noted. In addition, with regard to depression, there was no significant decrease in BDI scores; however, those in the intervention group reported an 18% improvement. In contrast, patients in the UC group did not show an improvement in depression scores.

DISCUSSION

The aim of this study was to evaluate the effectiveness of a combined programme of aerobic, strengthening and flexibility exercises, compared with usual care, in women with FM. The results show that a 24-week moderate-intensity combined exercise programme delivered twice a week, improved health-related QoL and function, although ES were modest the findings reinforce the importance of active exercise in FM. In contrast, patients receiving usual care did not show an improvement in any domain, indeed they experienced deterioration in some of the outcomes measured.

The findings from the current study are similar to those reported by Häuser et al. (7). In a comprehensive systematic review and meta-analysis of randomized controlled trials evaluating exercise in FM ($n=28$), these authors reported that aerobic and mixed exercise interventions improved (effect size; 95% confidence interval (CI)) QoL (–0.44; –0.60, –0.20), physical function (0.65; 0.38, 0.93) and depression (–0.44; –0.88, 0.01) in those with FM.

There is little consensus in the literature over the most effective exercise protocol in FM; however, there is some evidence that exercise interventions of longer duration are most effective. Valim et al. (35), for example, compared aerobic fitness training and stretching exercises in patients with FM in relation to QoL. After 20 weeks' intervention, aerobic exercise was superior to stretching in relation to the emotional aspects and mental health domains of SF-36, with ES even greater than those reported in this study ($d=0.61$ and 0.90, respectively). In another study in which patients performed either deep-water running or land-based exercises for 15 weeks, again both the physical and psychological aspects of FM improved (10).

When the duration of the exercise programme used in FM is reduced, the results are less clear. Cedraschi et al. (14) evaluated the efficacy of a mixed programme for patients with FM for 6 weeks, although the treatment group showed improvement in all of the SF-36 scores, results were not statistically significant. The ES reported were all lower than those reported in the current study, although Cedraschi et al. (14) reported significant improvements for role physical ($d=0.24$) and social functioning ($d=0.27$). This can also be seen in the study conducted by Redondo et al. (15), in which only the bodily pain domain showed a significant improvement after 8 weeks of exercise treatment. This indicates that a short-term exercise programme may not be sufficient to induce significant improvements in health-related QoL in FM. Redondo et al. (15) reported modest changes in ES for the SF-36; the ES changes for emotional aspects and vitality were $d=0.02$ and $d=0.28$, respectively, which may suggest that these domains are more influenced by the duration of the programme.

Strengthening exercise seems to have positive effects in those with FM; however, there are few previous studies that have used a similar strength-training programme as that used in the current study and have also used the FIQ as their primary outcome (36). Kingsley et al. (36), after 12 weeks' intervention, showed a slight improvement in FIQ scores, but this did not

Table II. Effects of a 24-week combined exercise programme on functional capacity, perceived health status and depression in women with fibromyalgia syndrome compared with usual care ($n=42$)

	Baseline			24 weeks			
	Exercise	Control	*p*-value between group	Exercise	Control	*p*-value between group	*d* (95% CI)
FIQ (0–80)	63.1 (17.4)	61.6 (17.1)	0.761	54.9 (12.5)	64.5 (11.4)	0.027*	0.58 (–14.12, –2.35)
SF-36 (0–100)	38.9 (15.9)	37.3 (14.9)	0.758	46.8 (13.0)	35.9 (16.2)	0.043*	0.54 (1.28, 14.52)
Physical Function	50.0 (22.7)	44.6 (15.9)	0.422	56.8 (17.4)	45.2 (14.1)	0.043*	0.34 (.38, 13.56)
Physical Role	13.5 (17.4)	19.8 (27.6)	0.451	21.3 (26.5)	19.4 (29.1)	0.848	0.35 (–8.49, 24.09)
Bodily Pain	23.2 (17.4)	23.6 (17.7)	0.942	29.9 (16.8)	19.5 (18.1)	0.100	0.39 (–0.54, 13.81)
General Health	39.8 (16.1)	33.4 (12.1)	0.205	43.1 (11.0)	33.5 (11.4)	0.021*	0.24 (–5.28, 11.88)
Vitality	29.4 (15.3)	27.7 (17.5)	0.762	41.3 (13.8)	28.6 (18.8)	0.031*	0.82 (2.65, 21.22)
Social Function	55.2 (22.9)	48.6 (16.5)	0.313	63.9 (23.8)	52.2 (21.1)	0.142	0.37 (–5.47, 22.93)
Role Emotional	53.3 (45.3)	45.6 (40.4)	0.608	71.1 (41.5)	52.1 (44.3)	0.216	0.41 (–16.62, 52.22)
Mental Health	51.3 (18.9)	44.0 (20.7)	0.304	60.0 (14.9)	44.2 (23.9)	0.034*	0.51 (1.20, 16.26)
BDI (0–63)	35.1 (14.1)	31.4 (12.8)	0.437	28.9 (13.6)	31.5 (11.2)	0.556	0.45 (–8.76, –3.64)

*$p<0.05$.
Results reported as mean effect sizes (Cohen's *d*) (95% confidence interval (95%)).
CI: confidence interval.

reach statistical significance. It is argued that a more prolonged strength training programme, such as that used in the current study, is necessary to achieve meaningful improvements in patients with FM. Some weight is given to this argument by the findings of Panton et al. (37), who utilized a comparable strength training regime as Kingsley et al. (35) (1 set of 8–12 repetitions, starting at 60% of the one repetition maximum), over a period of 16 weeks, and reported a reduction in the FIQ in women with FM (ES between $d = 0.98$ and 1.24 using resistance training with or without chiropractic treatment). It is suggested that the findings from the current study lend further weight to the argument that exercise interventions (particularly strength training) should be more prolonged than that currently used in the clinical setting.

Several studies have used a combination of different exercise therapies in FM and demonstrated improvements in the FIQ (9, 13, 14, 38). Even some short-term interventions have been demonstrated to be beneficial for this population (13, 14, 38). However, the improvements reported tend to be smaller ($d < 0.44$) than those reflected in the present study and of limited duration. It is also worth noting that the overall health status of patients in the present study at baseline was worse in all dimensions than those reported by other authors (8).

The current study investigated whether a combined exercise programme was as effective as usual care in the management of FM. The results suggest that there may be a synergistic benefit of conducting aerobic, strengthening and flexibility exercises together, and that a combined intervention is greater than the sum of its parts. There is some evidence to support this hypothesis from the exercise and cardiovascular health literature, where a number of authors have reported that the combination of resistance training and aerobic exercise yields greater improvements in the cardiovascular end-points of exercise performance, skeletal muscle function, and body composition, compared with aerobic training alone (39); this may also be the case in FM.

People with FM have higher levels of depression than the general population and those with other chronic diseases, such as rheumatoid arthritis (40). Some studies have suggested that combining different types of exercise programmes results in significant improvements in depression for patients with FM (10–12, 14, 15). It appears that long-term interventions resulted in improvements of 10–20% in depression (10, 25, 36); in the current study an improvement in depression scores of 18% was achieved; however, this did not reach statistical significance. Conversely, a significant medium effect improvement was noted in the mental health domain of the SF-36.

The improvement in psychological status in those with FM may be related to the duration and intensity of the treatment programme; the longer the treatment, the better the results. In fact, correlations have been established between the amount of physical activity and BDI scores after a 12-month exercise programme (25). In this study, the exercise programme was conducted in groups; it may be that improvements in mental health resulted in part from the interaction between participants. However, even combined exercises performed at home involved significant benefit in terms of psychological well-being, mood disturbance and somatic symptoms 12 month after completing a 12-week intervention based on aerobic home-exercises (9).

The current study has two main limitations. First, the sample size may have resulted in a type II error, and may not have been sufficiently powered to detect between-group differences where they exist, while the study was powered to detect changes in the primary outcome measure this may not be the case for the other outcomes (such as the BDI). However, the findings also suggest that this novel treatment intervention is acceptable to patients and may have some beneficial effects. Nevertheless, further studies examining the effectiveness of combined exercise programmes should ensure they are appropriately powered to reduce the possibility of type II error. Secondly, participants were assessed at the end of treatment only and no long-term follow-up was conducted, the long-term effects of the intervention are therefore unknown. Notwithstanding these limitations, it appears that patients with FM can tolerate an extended exercise intervention with no deterioration in the clinical presentation of the syndrome. From these results it may be concluded that a 24-week moderate intensity programme of aerobic exercise, muscle strengthening and flexibility exercises, twice a week, is effective for improving functional capacity and QoL in patients with FM, and that positive effects on psychological well-being can be expected.

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