

Effects of different types of exercises on pain, quality of life, depression, and body composition in women with fibromyalgia: A three-arm, parallel-group, randomized trial

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ABSTRACT

Objectives: This study aims to compare the efficacy of three different exercise types on pain, health-related quality of life (HRQoL), depression, and body composition in women with fibromyalgia (FM).

Patients and methods: Between June 2019 and December 2019, a total of 41 women with FM (mean age: 46.7±9.4 years; range, 24 to 62 years) were randomly allocated into Group 1 (n=13, supervised aerobic plus stretching), Group 2 (n=13, supervised resistance plus stretching), and Group 3 (n=15, home-based stretching). All exercises were performed three times per week for 12 weeks and were individualized by measuring the maximal oxygen consumption (VO_{2max}) for aerobic exercise and one-repetition maximum (1-RM) test for resistance exercise. The main measures were pain intensity assessed by the Visual Analog Scale (VAS), severity by the Fibromyalgia Impact Questionnaire (FIQ), symptoms of depression by the Beck Depression Inventory, HRQoL by the Short-Form Health Questionnaire (SF-36), and body composition by bioelectrical impedance analysis.

Results: The mean VAS difference (95% confidence interval): -2.61 (-1.94, -3.29); -2.61 (-1.82, -3.42); -1.07 (-0.49, -1.64) for Group 1, Group 2, and Group 3, respectively (p<0.05). The combined exercise groups showed a more significant reduction in pain compared to the only stretching group (p<0.001); however, there was no significant difference between the combined exercise groups. The FIQ scores decreased significantly in all exercise groups after training (p<0.05). At 12 weeks, 21 (80.8%) patients from combined groups and six (40%) patients from the stretching alone group achieved a minimal clinically significant difference defined as a 14% change in baseline FIQ scores (p=0.008). Other outcome parameters did not differ significantly among the groups.

Conclusion: Supervised aerobics/muscle strengthening combined with stretching exercises reduced pain, and FM severity more than a home stretching exercise alone.

Keywords: Aerobic exercise, fibromyalgia, resistance exercise, stretching exercise.

Although pain is the predominant symptom in fibromyalgia (FM), other symptoms affecting health-related quality of life (HRQoL) such as fatigue, unrefreshed sleep, mood disorders, and cognitive impairment are also common.¹ Since FM is a heterogeneous and complex condition, most patients require integrated and multidisciplinary approaches. In this context, exercise therapy appears to be an effective component of treatment, providing relief in pain and other symptoms, as well as improving the HRQoL in FM.²⁻⁴

Exercise training is commonly recommended for individuals with FM. The European League Against Rheumatism (EULAR) revised recommendations for the management of fibromyalgia declared based on meta-analyses, the only 'strong for' therapy-based recommendation was exercise.¹ The Cochrane reviews evaluated the effects of aerobic, resistance, flexibility, and mixed exercise training for adults with FM.⁵⁻⁸ It has been suggested that aerobic exercise improves HRQoL (moderate-quality evidence) and improves

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physical function and reduces pain (low-quality evidence).⁵ There was low-quality evidence that resistance exercise improves multidimensional function, pain, tenderness, and muscle strength in women with FM.⁶ It is unclear whether flexibility improves outcomes such as HRQoL, pain intensity, fatigue, and physical function.⁷ A recent systematic review and meta-analysis⁹ reported that combined exercise provided a large reduction in pain with moderate evidence, while a later Cochrane review.⁸ concluded that mixed exercise had uncertain effects.

Exercise training is an effective component in the management of FM. Nevertheless, it is still uncertain which option is better in FM treatment: the type of exercise (stretching/resistance/aerobic), combining or doing one type of exercise, supervised or home-based exercises. There is currently insufficient evidence to show which type of exercise is more beneficial.¹⁰ Furthermore, there is uncertainty regarding what the optimal intensity, duration, and frequency of the various types of exercise should be for people with FM.¹¹ Therefore, this is a clinically relevant research priority, and clinical trials comparing different exercises may be responsive.

As the optimal exercise intervention remains unclear, we aimed to compare the effectiveness of three different types of exercise (supervised aerobic/resistance plus stretching exercises or home-based stretching exercises alone) in FM women. To the best of our knowledge, this was the first, prospective, randomized trial evaluating the effects of these three different types of exercise programs on pain, symptoms, quality of life (QoL), depression, and body composition in women with FM and to determine which method is more effective.

PATIENTS AND METHODS

This single-center, three-arm, parallel-group, prospective, randomized study was conducted at Pamukkale University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation (PMR) between June 2019 and December 2019. Female patients between the ages of 18 and 65 who were diagnosed with FM syndrome (FMS) according to the ACR 2016 FMS diagnostic criteria were identified.¹² Of the

120 eligible cases, 66 were excluded for refused to participate. Eighty-four eligible women who were able to communicate well, motivated and were willing to participate in the study were included in the study. Exclusion criteria were as follows: presence of uncontrolled systemic disorders (hypertension, diabetes), history of myocardial infarction or coronary artery disease, unstable angina pectoris, musculoskeletal or systemic diseases contradicting the exercise, a neurological or psychiatric disease affecting cooperation and cognitive function, presence of active inflammation and immunosuppression. Of 54 patients who started exercise training, data of 41 patients (mean age: 46.7±9.4 years; range, 24 to 62 years) were analyzed. Study flow chart is shown in Figure 1. The patients continued their current medical treatment; duloxetine monotherapy (n=12), pregabalin monotherapy (n=6), or a combination of duloxetine and pregabalin (n=4), but no new medical treatment for FM was initiated during the study period.

The participants were assigned into three groups by a random table number; supervised aerobic plus stretching exercises group (Group 1), supervised resistance plus stretching exercises group (Group 2), and only stretching home-based exercises group (Group 3).

Outcome measures

Demographic data were obtained at baseline assessment.

- Body weight, body height, and body composition measurements: In addition to bodyweight measurements, the components of body composition, total body fat percentage, and total body muscle percentage were assessed via bioelectrical impedance analysis (BIA) with a body composition analyzer (Tanita MC-580, Tanita Corp., Tokyo, Japan). The participants were asked to fast for 3h before, to void their bladder immediately before the assessment, and to wear only light sports clothing. Height was measured with a wall-mounted stadiometer and body mass index (BMI) was calculated by dividing the kg of body weight by the square of the height measurement (kg/m^2).

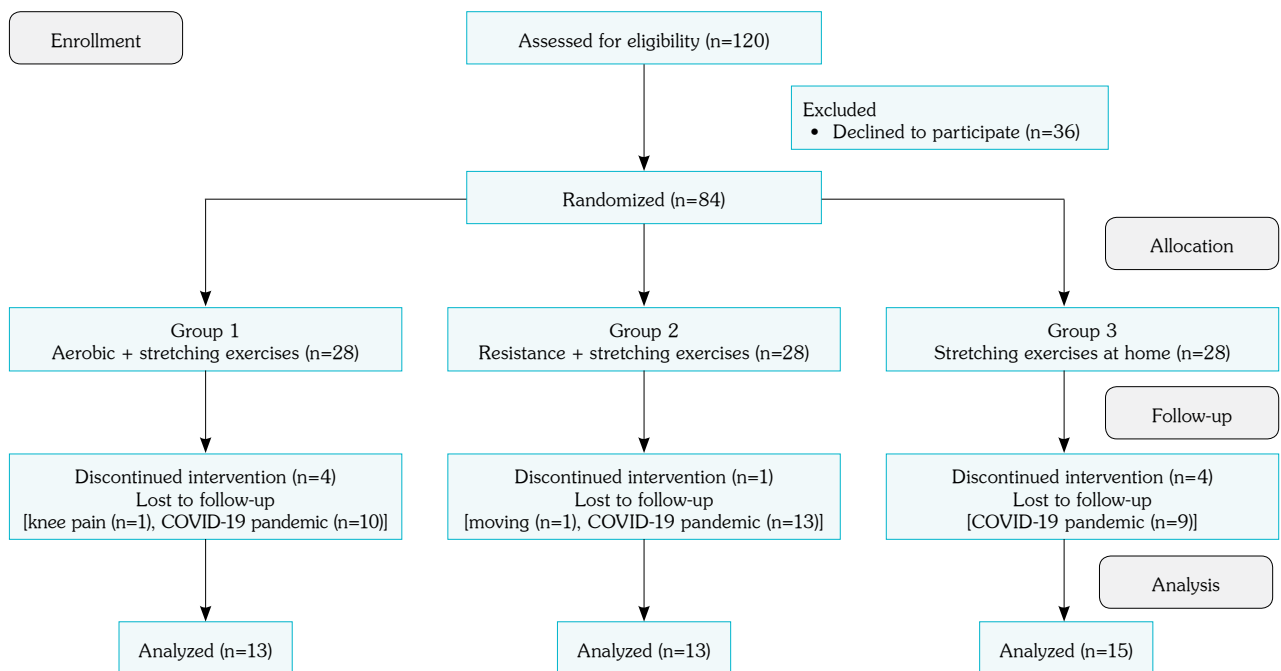


Figure 1. Study flow chart.

- Cardiopulmonary exercise testing (CPET) was performed using a gas exchange analysis system ergospirometer (CareFusion Germany 234 GmbH, H \ddot{o} chberg, Germany) using the modified Bruce protocol with a treadmill (Technogym Excite Med, Cesena, Italy) available in the Sport Rehabilitation Unit of PMR Clinic. During testing, the patients were monitored with a 12-lead real-time electrocardiography and blood pressure. Heart rates (HRs) were recorded throughout the exercise testing period. The CPET was terminated, when 85% of maximal HR was reached and RER ≥ 1.10 . The maximal oxygen consumption (VO_{2max} , mL/kg/min) achieved during exercise was evaluated as aerobic capacity for the determination of training program only before initiation of 12-week exercise program.
- The pain intensity was measured using the Visual Analog Scale (VAS). Patients were asked to rate their pain on a 10-cm line anchored by two descriptors: 0: "no pain" and 10: unbearable pain.
- Multidimensional function, the health status, and effects of FM on daily life were assessed using the validated Turkish version of the Fibromyalgia Impact Questionnaire (FIQ).¹³ The FIQ was applied to assess the set of FM symptoms over the prior week. The FIQ is a FM-specific tool that captures the overall effect of FM symptomatology. The FIQ measures physical functioning, well-being, work status (missed days of work and job difficulty), pain, fatigue, morning tiredness, stiffness, anxiety, and depression. Total score ranges from 0 to 100, lower scores indicate greater health whereas higher scores indicate a greater impact of the syndrome on the individual.
- Depression status of the patients was evaluated with the Beck Depression Inventory (BDI). The reliability and validity of the Turkish version of BDI were also shown.¹⁴ The BDI is a 21-item questionnaire that investigates the symptoms of depression. Total scores range from 0 to 63, higher scores indicate higher levels of depression.

- The QoL was assessed using the validated Turkish version of the 36-item Short-Form Health Survey (SF-36).¹⁵ The SF-36 is a multidimensional tool measuring eight domains: physical functioning, physical role limitation, body pain, general health, vitality, social functioning, emotional role limitation and mental health. Domain scores range from 0 to 100, and higher scores indicate a better QoL.

The patients were evaluated at baseline and at the end of the study by a single examiner. All patients were called every two weeks and their compliance with the treatment was checked.

Interventions: Patients in all three groups exercised three times per week for 12 weeks. All groups did the same muscle stretching exercises detailed in Group 3.

Supervised Aerobic Plus Stretching Exercises Group (Group 1): The participants were instructed to do stretching exercises in addition to walking exercises on a treadmill at Pamukkale University Sports Rehabilitation Unit. An exercise prescription was developed for each woman based on the data acquired from the baseline submaximal treadmill exercise test. Target HR corresponding to values of 50-70% ergospirometric VO_{2max} (moderate intensity) was determined. The participants were instructed to perform their exercises at HR corresponding to 50% of VO_{2max} for six weeks. At the seventh week, their exercise intensity was increased to the target HR corresponding to 70% of baseline VO_{2max} . The HR was monitored by a Polar HR monitor (Polar Beat, Port Washington, NY, USA). The walking duration of the patients was 40 min. Stretching exercises were performed at the beginning and end of each exercise session.

Supervised Resistance Plus Stretching Exercises Group (Group 2): The participants were instructed to do stretching exercises and resistance exercises using weight machines at Sports Rehabilitation Unit of Pamukkale University. An exercise prescription was developed for each woman based on the data acquired from the one-repetition maximum (1-RM) test. The participants were instructed to perform their exercises with 50% of 1-RM for six weeks. In the seventh week, weights

were increased to 70 to 80% of 1-RM. The number of sets increased progressively (in the first two weeks, one set of 10 repetitions; at Weeks 3 and 4, two sets of 10 repetitions; at Weeks 5 and 6, three sets of 10 repetitions). The muscle groups which were involved in resistance exercises were bilateral biceps, deltoid, trapezius, pectoralis major and minor, serratus anterior, latissimus dorsi, levator scapulae, rhomboid, gluteal, quadriceps, hip adductor and abductor, hamstring, gastrocnemius, and abdominal muscles. Stretching exercises were performed at the beginning and end of each exercise session.

Home-Based Stretching Exercises Group (Group 3): The group performing stretching exercises at home was determined as an active control group. Each exercise was described to the patient. For each muscle group exercise was performed for three to four times and each repeat was 30 sec long. The muscle groups which were involved in stretching exercises were upper trapezius, rhomboid, hip flexor, hamstring, pectoral, piriformis, quadriceps, gastrocnemius, soleus, levator scapulae, hip adductor, and tensor fasciae late muscles. Exercise program was applied three days in a week for 12 weeks. Each participant was called every two weeks to maintain compliance.

Statistical analysis

The sample size was calculated using the changes in VAS score and FIQ score before and after training (Wilcoxon test) with a power of 98% and an alpha level of 0.05 and beta value of 0.01 using G*Power version 3.1.9.4 software (Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany). A minimum of 13 subjects were required for each group. Effect sizes for VAS scores were 2.329, 1.965, 1.140 and effect sizes for FIQ scores were 1.140, 1.820, 0.976 for Groups 1, 2, and 3, respectively.

Statistical analysis was performed using the IBM SPSS for Windows version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean \pm standard deviation (SD), median (min-max) or number and frequency, where applicable. When parametric test assumptions were provided, one-way analysis of variance was used for independent group comparisons; otherwise, the Kruskal-Wallis test was used.

The post-hoc Tukey test or Mann-Whitney U test was used, where appropriate. Dependent group comparisons were made using the paired t-test for parametric tests and Wilcoxon test for non-parametric tests. The chi-square test or Fisher exact test was used for the comparison of number of patients achieving the minimum clinically important difference (MCID) score in FIQ or VAS. A *p* value of <0.05 was considered statistically significant. When the Bonferroni correction was applied, a *p* value of <0.017 was considered statistically significant.

RESULTS

Groups 1, 2, and 3 included 13, 13, and 15 women with FM whose mean age were

48.3±10.0, 46.0±11.2, 45.9±7.6 years, respectively. The mean height, BMI, VO_{2max}, fat and muscle rate, VAS score, FIQ score, BDI score, and SF-36 subscores were not significantly different among the groups in the pre-training period. The number of patients with medication and without medication did not show any significant difference among groups (Table 1) (*p*>0.05). The number of the patients taking each type of medication did not significantly differ with respect to groups (*p*>0.05).

The effect of training with respect to inter-group and intra-group comparisons is presented in Tables 2 and 3, respectively. There was a statistically significant difference among the groups only in the VAS scores. Other parameters

Table 1. Demographic and outcome measures at baseline

	Group 1 (n=13)			Group 2 (n=13)			Group 3 (n=15)			<i>p</i>
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Age (year)			48.3±10.0			46.0±11.2			45.9±7.6	0.730
Sex										0.999
Male	0			0			0			
Female	13			13			15			
Height (cm)			161.4±6.8			161.5±4.8			159.2±6.1	0.521
Weight (kg)			73.2±10.6			72.2±14.3			70.9±12.6	0.886
BMI (kg/m ²)			28.3±5.0			27.8±5.8			28.0±5.0	0.968
VO _{2max} (mL/kg/min)			23.5±4.8			25.5±4.4			25.6±3.3	0.355
Fat rate (%)			32.5±6.4			32.4±6.6			32.4±6.6	0.998
Muscle rate (%)			63.8±6.0			64.2±6.2			64.2±6.3	0.986
VAS score			6.9±1.6			6.5±1.9			7.0±1.4	0.842
FIQ score			61.0±22.3			55.9±19.4			55.5±15.5	0.710
BDI score			20.9±9.7			16.2±6.0			14.6±8.5	0.134
Administration of medical treatment										
Medical treatment	6	46.2		7	53.8		9	60		0.764
No medical treatment	7	53.8		7	53.8		6	40		
SF-36 components										
General health			34.0±22.7			41.5±18.0			39.7±25.5	0.672
Physical functioning			52.7±20.9			52.3±28.0			61.3±19.4	0.498
Social functioning			43.3±26.3			55.8±26.3			58.8±24.5	0.260
Role-physical			19.2±34.1			23.1±36.0			41.7±41.9	0.232
Role-emotional			18.0±32.3			28.2±35.6			33.4±41.9	0.515
Mental health			47.1±22.6			55.4±19.2			58.0±22.3	0.391
Bodily pain			32.5±23.8			42.1±18.3			38.0±15.7	0.454
Vitality			35.4±20.4			39.6±14.8			44.0±22.2	0.513

SD: Standard deviation; BMI: Body mass index; VAS: Visual Analog Scale; FIQ: Fibromyalgia impact questionnaire; BDI: Beck depression inventory; SF-36: Short-Form Health Survey; Group 1: Aerobic + Stretching exercises; Group 2: Resistance + Stretching exercises; Group 3: Only stretching exercises at home.

Table 2. Comparison of FMS groups with respect to anthropometry, body composition, lactate, VAS, FIQ, BDI in the pre-training and post-training period

	Group 1 (n=13)			Group 2 (n=13)			Group 3 (n=15)			p	Bonferroni correction		
	%	Mean±SD	MD	95% CI	%	Mean±SD	MD	95% CI	%			Mean±SD	MD
Weight (kg)													
Pre-training		73.2±10.6	0.13	-0.86, 1.12		72.2±14.3	0.82	-0.01, 1.64		70.9±12.6	-1.26	-2.12, -0.40	0.886
Post-training		73.1±10.5				71.3±13.9*				72.2±12.8*			0.938
BMI (kg/m ²)													
Pre-training		28.3±5.0	0.05	-0.35, 0.45		27.8±5.8	0.32	0.0, 0.63		28.0±5.0	-0.51	-0.87, -0.15	0.968
Post-training		28.2±4.8				27.4±5.7*				28.5±5.1*			0.86
Fat rate (%)													
Pre-training		32.5±6.4	-0.01	-1.12, 1.09		32.4±6.6	-0.89	-0.99, 0.82		32.4±6.6	-0.93	-1.7, -0.16	0.998
Post-training		32.5±6.5				32.5±6.4				33.4±6.7*			0.923
Muscle rate (%)													
Pre-training		63.8±6.0	-0.25	-1.21, 0.71		63.8±6.0	0.14	-0.72, 1.0		64.2±6.3	0.91	0.18, 1.65	0.986
Post-training		64.1±6.3				64.1±6.3				63.3±6.4*			0.928
VAS													
Pre-training		6.9±1.6	2.61	1.94, 3.29		6.5±1.9	2.61	1.82, 3.42		7.0±1.4	1.07	0.49, 1.64	0.842
Post-training		4.3±1.7*				3.9±1.2*				5.9±1.0*			0.001
Change		-37.92				-39.26				-13.48			Group 3 < Group 1# Group 3 < Group 2# Group 1 = Group 2
FIQ score													
Pre-training		61.0±22.3	17.23	8.09, 26.36		55.9±19.4	18.48	12.35, 24.62		55.5±15.5	6.04	2.62, 9.45	0.71
Post-training		43.8±19.2*				37.5±15.5*				49.5±15.4*			0.178
Change		-27.27				-32.91				-10.87			
BDI score													
Pre-training		20.9±10.0	5.69	3.02, 8.37		16.2±6.0	4.62	1.07, 8.16		14.6±8.5	1.8	-0.11, 3.71	0.134
Post-training		15.2±6.2*				11.6±3.9*				12.8±6.8			0.302

FMS: Fibromyalgia syndrome; VAS: Visual Analog Scale; FIQ: Fibromyalgia impact questionnaire; BDI: Beck depression inventory; SD: Standard deviation; MD: Mean difference; CI: Confidence interval; BMI: Body mass index; Group 1: Aerobic + Stretching exercises; Group 2: Resistance + Stretching exercises; Group 3: Only stretching exercises at home; * p<0.05 comparison with respect to baseline within same group; # p<0.017 comparison among groups.

Table 3. Comparison of FMS groups with respect to SF-36 subscores in the pre-training and post-training period

SF-36	Group 1 (n=13)			Group 2 (n=13)			Group 3 (n=15)			p
	Mean±SD	MD	95% CI	Mean±SD	MD	95% CI	Mean±SD	MD	95% CI	
General Health										
Pre-training	34.0±22.7			41.5±18.0			39.7±25.5			0.672
Post-training	52.7±19.8*	-18.69	-29.76, -7.62	61.9±19.5*	-20.39	-31.09, -9.67	49.7±21.9*	-10.0	-16.37, -3.63	0.279
Physical functioning										
Pre-training	52.7±20.9			52.3±28.0			61.3±19.4			0.498
Post-training	67.7±17.4*	-15.0	-23.36, -6.63	69.2±17.7*	-16.93	-27.64, -6.20	64.0±18.4	-2.67	-9.59, 4.27	0.728
Social functioning										
Pre-training	43.3±26.3			55.8±26.3			58.8±24.5			0.26
Post-training	53.7±23.6*	-10.39	-18.84, -1.93	76.0±13.9*	-20.19	-32.73, -7.65	68.3±22.1*	-9.5	-16.25, -2.75	0.05
Role-physical										
Pre-training	19.2±34.1			23.1±36.0			41.7±41.9			0.232
Post-training	34.6±29.8	-15.38	-31.16, 0.39	48.1±25.9*	-25	-41.32, -8.68	53.3±38.8	-11.67	-32.51, 9.18	0.308
Role-emotional										
Pre-training	18.0±32.3			28.2±35.6			33.4±41.9			0.515
Post-training	35.9±31.8*	-17.91	-28.34, -7.48	48.9±26.0	-20.72	-41.77, 0.32	42.3±34.5	-8.93	-29.31, 11.46	0.571
Mental health										
Pre-training	47.1±22.6			55.4±19.2			58.0±22.3			0.391
Post-training	55.1±24.3	-8.0	-23.78, 7.78	63.7±18.3	-8.31	-18.82, 2.21	59.5±20.4	-1.43	-10.92, 8.06	0.586
Bodily pain										
Pre-training	32.5±23.8			42.1±18.3			38.0±15.7			0.454
Post-training	50.8±25.9*	-18.27	-28.63, -7.91	62.7±20.1*	-20.58	-26.84, -14.31	48.3±12.9*	-10.33	-15.87, -4.80	0.151
Vitality										
Pre-training	35.4±20.4			39.6±14.8			44.0±22.2			0.513
Post-training	52.7±19.0*	-17.31	-27.96, -6.65	59.6±12.3*	-20.0	-27.29, -12.70	52.7±22.0	-8.67	-17.33, -0.01	0.54

FMS: Fibromyalgia syndrome; SF-36: Short-Form Health Survey; SD: Standard deviation; MD: Mean difference; CI: Confidence interval; Group 1: Aerobic + Stretching exercises; Group 2: Resistance + Stretching exercises; Group 3: Only stretching exercises at home; * p<0.05 comparison with respect to baseline.

of interest did not show any significant difference for the comparison among the groups.

The VAS and FIQ scores were significantly reduced within all the groups after training compared to the baseline ($p<0.05$). The VAS was found to be significantly lower in combined exercise groups compared to Group 3 at the post-training period ($p<0.001$); however, Groups 1 and 2 were not significantly different from each other.

Percent change in their VAS score was -37.92%, -39.26%, and -13.48% in Groups 1, 2, and 3, respectively. The effect size for the change in VAS among the groups was 0.439. Percent change in their baseline FIQ score was -27.27%, -32.91%, and -10.87% in Groups 1, 2, and 3, respectively. At 12 weeks, 21 (80.8%)

patients from combined groups and six (40%) patients from Group 3 achieved a minimal clinically significant difference defined as a 14% change in baseline FIQ scores ($p=0.008$).

Weight and BMI decreased in Group 2 and increased in Group 3 ($p<0.05$); on the other hand, it did not change in Group 1 in the post-training period compared to the pre-training. The fat rate increased, and muscle rate decreased significantly in Group 3 ($p<0.05$). The BDI scores were significantly reduced in Groups 1 and 2 ($p<0.05$), while no significant differences were found in Group 3 (Table 2).

General health, social functioning, and bodily pain subscores of SF-36 were significantly increased after training for each of all groups compared to baseline

($p < 0.05$). Physical functioning, and vitality components were significantly increased in Groups 1 and 2 after training ($p < 0.05$). Physical role scores significantly improved only in Group 2 and emotional role scores increased only in Group 1 ($p < 0.05$) after training (Table 3).

DISCUSSION

In the present study, both the supervised aerobic and resistance exercise groups combined with stretching had higher reductions in pain and the severity of FM, compared to the home-based stretching group alone. The strength of our study is that we prepared detailed and precise exercise prescriptions by taking measurements of each individual according to the American College of Sports Medicine (ACSM) recommendations.^{16,17}

A recent meta-analysis noted poor adherence to ACSM exercise recommendations in FM treatment and suggested improved standardized reporting to determine the optimal exercise prescription for FM.¹⁸ In one study, the authors preferred using the self-perception of effort for modulation of exercise intensity; therefore, they were concerned that 1-RM test could cause physical overload and trigger a flare-up of FM symptoms.¹⁹ However, we chose to calculate resistance training intensity based on the 1-RM percentage, as recommended by the ACSM,²⁰ and there was no increase in pain or symptoms in our patients.

The majority of the randomized-controlled trials in the meta-analysis reported incomplete information regarding the characteristics of exercise interventions in the management of FM.¹⁸ Exercise intensity was the parameter with the most missing data. Due to inconsistent and/or insufficient information about exercise parameters, no clear conclusion could be drawn about the effect of exercise in adults with FM.^{18,21,22} Our study provides detailed exercise variables such as exercise intensity, frequency, duration, sets, repetitions, and progression. The lack of a personalized approach to the exercise training program at most randomized-controlled trials is another crucial weakness. The superiority of our study is that we create an individual

exercise program for each patient after personal measurements.

In the literature, both aerobic and resistance exercise were found to be effective in reducing pain, but they were not superior to each other, consistent with our study.²³⁻²⁵ While in some studies,^{24,25} only aerobic and resistance exercise groups were compared with each other, Kayo et al.'s²³ study also compared them with the control group. It is noteworthy that the exercise frequencies are also different from each other in the studies. The exercises were done three times a week for 12 weeks in one study,²³ three days a week for eight weeks in one,^{24,25} and five days a week for three weeks in the other.^{24,25}

In the study of Genç et al.,²⁶ in patients with FM, aerobic plus stretching for six weeks was more effective in reducing pain than the group who only performed stretching at home. Hernandez et al.¹⁰ showed that stretching exercises added to aerobic exercises were more effective on VAS scores than aerobic exercises alone in women with FM, similar to our study. However, unlike ours, no group did resistance exercise alone in these studies.

Jones et al.²⁷ compared the effectiveness of stretching exercises and a personalized muscle strengthening program for a total of 12 weeks, twice a week, in women with FM. While significant improvements were observed in the VAS scores in both groups, there was no statistically significant difference between them, but the magnitude of the change was greater in the strengthening group. Assumpção et al.¹⁹ divided 44 women with FM into three groups as stretching exercises, resistance exercises, and control. They exercised twice a week for 12 weeks. While there was a significant pain reduction in the stretching and resistance exercise groups, there was no significant difference with the control group. In our study, unlike the other two studies, the effect of resistance plus stretching exercises on VAS scores was found to be more effective than stretching exercises alone.

Gavi et al.²⁸ compared the effectiveness of resistance exercises and stretching exercises in 80 FM women. The exercises were done two days a week for 16 weeks. Resistive exercises were given to eight main muscle groups at 45% of 1 RM and performed as three sets

of 12 repetitions. Significant improvements in VAS were observed in both groups, and resistance exercises were found to be more effective than stretching exercises. The results of our study suggest that performing stretching exercises together with resistance/aerobic exercises prepared according to the patient's condition are more effective in reducing pain in women with FM.

The FIQ and SF-36 are outcome measures in FM trials of the United States Food and Drug Administration (FDA)-approved medications.²⁹ The FIQ is an extensively validated FM-specific tool that captures the overall effect of FM symptomatology. The average FM patient scores about 50; severely afflicted patients usually score 70 plus.³⁰ The FIQ has been mostly used as an outcome measure in treatment trials and, in general, has demonstrated an ability to detect clinical change.³¹ In our study, FIQ scores were significantly reduced within all the groups after exercise training.

A recent study suggested that a 14% change or an absolute change of 8.1 (95% confidence interval [CI]: 7.6-8.5) in the FIQ total score represented a MCID in FM status.^{29,31} At 12 weeks, 80.8% of patients in the combined groups and 40% patients in the stretching group alone achieved an MCID defined as a 14% change in baseline FIQ scores, which was statistically significant. Only the FIQ score has a defined MCID; therefore, we used statistically significant difference for the outcome measurements other than the FIQ score.

Rooks et al.³² compared the effectiveness of aerobic + stretching exercises, aerobic+stretching+ resistance exercises, and patient education. While significant improvements were observed at depression scores evaluated with BDI in the combined exercise program, no significant change was observed between the groups. Similarly, in our study, while there were significant improvements in the BDI scores of the combined exercise groups, there was no improvement in the stretching alone exercise group. However, there was no statistically significant difference among the groups.

Saudo et al.³³ investigated the effectiveness of aerobic and aerobic + resistive and stretching exercises in women with FM. Both aerobic and combined exercise programs had positive effects

on depression assessed with the BDI, compared to controls. In our study, all groups performed stretching exercises. Significant improvements were observed in BDI scores in combined exercise groups. Jones et al.²⁷ compared the efficacy of 12-week strengthening and stretching exercises in female patients with FM. While there were significant improvements in BDI scores in the performing resistance exercises, stretching exercises were not found to be effective. As in both studies, no significant change was observed in stretching exercise group in our study. This result suggests that combined exercise programs are more effective on depression scores.

Valim et al.³⁴ found that the effects of aerobic exercises on mental health and emotional role limitation of SF-36 subscores were superior to stretching exercises in females with FM. Aerobic exercise was superior to stretching in depression, emotional and mental health domains of SF-36. The patients in the stretching group showed no improvement in depression, role emotional, and mental health. In our study, physical function, vitality, and emotional role limitation SF-36 subscores were improved in the group performing aerobic + stretching, but there was no significant change in the group performing only stretching. All the groups increased significantly general health, social functioning, and bodily pain subscores of SF-36 after training. Physical functionality and vitality components increased significantly in the combined groups after exercise. When the groups were compared, the superiority of exercises groups to each other was not shown in accordance with the study of Kayo et al.²³

Recently, it has been shown that higher BMI values are associated with poorer FIQ scores, and symptom severity is higher in overweight and obese women with FM. It has been suggested that an optimal BMI may contribute to the improvement of some FM symptoms.³⁵ Low physical fitness has been considered as one of the potential contributors to pain sensitivity in FM.³⁶ The cross-sectional design of these studies does not allow for causal relationships. Due to the prospective design in our study, it was possible to investigate the effects of different types of exercise on fitness and body fat levels in women with FM. Compared to pre-training, weight and BMI did not change in the aerobic plus stretching group, but decreased in the

resistance plus stretching group and increased in those who only did stretching exercises. An undesirable increase in fat ratio and a decrease in muscle ratio were detected in the group that only performed stretching exercises. The lack of difference between the groups may be related to the small number of patients, and the effectiveness of the exercises can be shown more clearly in future studies with more participants.

Andrade et al.³⁷ investigated the effects of water-based bicycle ergometer exercises plus stretching exercises on body composition in women with FM. They reported no significant changes in weight, BMI, body fat percentage, and lean body weight in the exercise group with control group. Unlike this study, the aerobic exercise was applied using a land-based treadmill in our study. Significant improvements in body composition were observed in the resistance plus stretching exercise group, worsening in the stretching alone group, and no change in the aerobic plus stretching exercise group.

The 12-week resistance exercises were compared with stretching exercises in the study of Jones et al.²⁷ and with the control group in the study of Kingsley et al.³⁸ Both studies found no significant changes in weight and body fat percentage in women with FM. In our study, unlike both studies, stretching exercises were also performed in addition to resistance exercises. While a significant decrease was seen in weight and BMI only in resistance plus stretching exercise, no significant differences were observed in weight and body composition in all three groups.

The limitations of this study are as follows: lack of a non-exercise control group, and lack of follow-up after the intervention. Additionally, only women were included in the study, as FM predominantly affects women. The CPET after a 12-week exercise could not be performed due to unpreventable restrictions caused by the novel coronavirus disease 2019 (COVID-19) pandemic. Since VO_{2max} measurement values were not an outcome measure, we only used them as an evaluation parameter in prescribing aerobic exercise. The pre-training values of VO_{2max} helped us to demonstrate statistical indifference among groups; however, the

post-exercise change can also be evaluated by further studies.

In conclusion, our study results indicate that 12 weeks of exercise training in women FM reduce pain and improves FIQ. In addition, supervised aerobic/muscle strengthening, combined with stretching exercises, reduces pain and FM severity more than a home-based stretching exercise alone.

Ethics Committee Approval: The study protocol was approved by the Pamukkale University Faculty of Medicine Ethics Committee (No. 2018/19). The study was conducted in accordance with the principles of the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (NCT04426864).

Patient Consent for Publication: A written informed consent was obtained from each patient.

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

Author Contributions: Contributed to the conception, and design of data, draft an article and gave approval to the final version to be published: E.K.; Contributed to the conception, design, analysis, and interpretation of data, revised it critically for important intellectual content, and gave approval to the final version to be published: F.A.; Contributed to the conception, design, and analysis of data, draft an article and gave approval to the final version to be published: G.F.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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