Female fibromyalgia patients have the same ability to improve aerobic fitness as healthy sedentary controls

Abstract

Background: Several cross-sectional studies have reported lower aerobic fitness among fibromyalgia (FM) patients compared to healthy controls. At present it is unknown whether the inferior aerobic fitness is a cause or a consequence of the illness.

Objective: To examine if female FM patients have the same ability to enhance their aerobic fitness as healthy sedentary controls matched on age and BMI. A second objective was to investigate whether the FM patients experience an increase in pressure pain threshold (PPT) following an aerobic exercise program.

Methods: Fifty subjects (25 FM patients, 25 controls) were enrolled to a 12 week aerobic exercise program. The exercise program consisted of ergometer cycling two times a week (each session 45-55 min) at low to moderate intensity. An incremental ergometer test was performed to determine anaerobic threshold (AT), and exercise intensity was deduced from the AT data acquired. Main outcome was changes in spirometric values and watt production at AT. Second outcome was changes in PPTs measured by an algometer.

Results: FM patients were equally exercisable as healthy matched sedentary controls. No significant differences were found in average changes in VO_2 *(P*=0.53) and watt production (*P*=0.56) at AT following the exercise program. However, FM patients had lower VO_2 and watt production compared to controls at both the pre- and post test (*P*<0.03 for all comparisons). No significant increase in PPT was observed within the FM group following the exercise program (*P*>0.1 for all recorded PPT sits).

Discussion: Aerobic exercise with low to moderate intensity enhances aerobic fitness in FM patients to the same extent as in healthy sedentary controls. A substantial lower aerobic fitness was found in the FM patients at both pre- and post test. These findings indicate that the common observation of low aerobic fitness among FM patients is related to inactivity rather than the illness.

Introduction

Fibromyalgia syndrome (FM) is a musculoskeletal illness, with a prevalence of 2-5 % in the general population, afflicting about seven times more women than men (Wolfe et al., 1995; Kurtze & Svebak, 2001; Lawrence et al., 2008). FM is defined by the American College of Rheumatology (ACR) as an illness that includes a history of chronic widespread pain, and reduced pressure pain threshold (PPT) at 11 of 18 anatomically defined tender point sites (Wolfe et al., 1990). The definition of the illness emphasizes reduced PPT as the main contributing factor; however, FM patients often experience a wide range of other symptoms. Psychological symptoms like depression, anxiety, worries, sleep disturbances, and dissatisfactions with own health have all been reported among FM patients (Wolfe et al., 1997; Epstein et al., 1999). Fatigue, irritable bowel syndrome and migraines among others, are more somatic symptoms, that are often present in FM patients (Clauw, 1995). However, the comorbidity varies widely in the FM group, with some patients reporting a wide range of additional symptoms, and others reporting few additional symptoms (Wilson, 2009). The amount or combination of additional symptoms reflects the heterogeneity of the FM syndrome. In addition, the FM patients are often categorized by allodynia, which means that normally none-painful stimuli appear painful (Price & Staud, 2005).

The reason for developing FM is so far unknown. However, there has been some evidence connecting trauma and psychosocial work factors to the onset of FM. A review by White and co-workers (2000) investigated the relation between trauma and FM and found some evidence in support of a connection between the two. Harkness and co-workers (2004) found that psychosocial work factors were the strongest predictor for development of chronic musculoskeletal pain, which again is the first step against developing FM. Furthermore, Arnold and co-workers (2004) showed that first-degree relatives of FM patients had much higher tender point count compared to first-degree relatives of rheumatoid arthritis patients. This suggests that a genetic predisposition may be a contributing cause to developing FM.

Pathophysiology behind FM still remains indistinct, and whether the disease has a central or peripheral origin has been debated the last decades. In recent years there have nonetheless been a tendency supporting a central mechanism as the main contributor to the persistent pain observed in FM patients (Abeles et al., 2007). One part of the evidence supporting a central mechanism is the biochemical abnormalities reported. Reduced concentration of dopaminergic neurotransmitters (Wood et al., 2007), reduced values of adrenalin during submaximal isometric exertion (Giske et al., 2008), and high concentrations

of substance P (Russell, 1995; Pillemer et al., 1997), have all been reported in patients with FM. This aberration in biochemical properties might cause reduced capacity for pain inhibitory signaling among FM patients (Edwards, 2005). Furthermore, a recent study by Goffaux and co-workers (2009) found evidence for permanent changes in excitability in the spinal neurons of FM patients. All these findings indicate that FM is an illness related to pain enhancement by central mechanisms. Nevertheless, there are some peripheral mechanisms associated with FM patients. Muscle abnormalities like ragged red muscle fibers, and the reduced amount of type 2 fibers, are both common in FM patients (Pongratz & Späth, 1998; Bengtsson, 2002). However, these latter findings may relate to inactivity rather than being a cause to the illness.

Another important aspect of patients with FM is their level of physical fitness. There are recent evidence suggesting that female FM patients have lower aerobic fitness than healthy controls (Valim et al., 2002; Valkeinen et al., 2008) and that female FM patients, and older healthy women may have similar lower-body strength (Panton et al., 2006). In addition to the decreased physical fitness, many FM patients have reduced ability to carry out high intensity exercise, and are frequently afflicted with post exercise pain and stiffness (Mengshoel et al., 1992; van Santen et al., 2002b). Post exercise pain might result in a more sedentary behavior among FM patients, which in turn reduces the physical fitness, and increases the likelihood of developing additional comorbiditis. However, it is currently unknown if low physical fitness is a contributing factor to the development of FM, e.g. due to a dysfunctional metabolic system in the muscles, or if it is a consequence of inactivity.

During recent years, a large number of studies have been conducted to investigate the effect of aerobic exercise on FM symptoms (Mengshoel et al., 1992; Meiworm et al., 2000; Meyer and Lemley, 2000; Sabbag et al., 2007). The main outcome from these studies seems to be that FM patients can safely participate in aerobic exercise with low to moderate intensity, as long as the intensity is individually tailored to best reduce pain and enhance physical function (Busch et al., 2008). Determination of intensity varies widely in the previous conducted exercise interventions among FM patients. Meyer and Lemley (2000) used a formula based on age predicted maximum heart rate. Mengshoel and co-workers (1992) used exercise intensity between 120-150 beats per minute, while Richards and Scott (2002) used self-chosen intensity. The heterogeneity of FM patients as a group makes it important to individualize exercise program to the fitness level of each patient (Mannerkorpi & Iversen, 2003). In addition, Valim and co-workers (2002) pointed out that the best way to

determine individual exercise intensity in FM patients prior to entering an exercise intervention was to use the AT as basis for the exercise intensity. AT was achievable for almost all FM patients on the contrary to VO_{2max}, which was proven difficult to attain for most of the FM patients.

Studies investigating the effect of aerobic exercise on PPT or number of tender points in FM patients have shown inconsistent results. Gowans and co-workers (2001) found no significant improvement in the number of tender points following a 23 week aerobic exercise program. Richards and Scott (2002) on the other hand, found significant improvements in number of tender points following a 12 week aerobic exercise program. The intensity in the Richards and Scott study were self-chosen, while Gowans and co-workers used an intensity of 60-75% of maximum heart rate retrieved from age predicted maximum heart rate (220-age) as their exercise intensity zone. A meta-analysis by Busch and co-workers (2008) confirm that changes in number of tender points following different types of aerobic exercise interventions among FM patients are highly inconsistent, and on an average not significant. However, due to the inconsistency among the results present, further research on PPT and aerobic exercise is needed. In the current study the exercise intensity was individually tailored for each subject on the basis of AT, which eliminates genetically predispositions as a source to wrong intensity assessment because the age predicted maximum heart rate does not apply equally to all subjects. Adaptation of individual tailored exercise intensity is often missing in the previous conducted studies. In addition, previous conducted studies have often (e.g., Gowans et al., 2001; Richards & Scott, 2002) treated the tender points as a dichotomous variable (present/not present), while an average change in PPT for each tender point site might be more sensitive in detecting changes in pain perception following an aerobic exercise program.

The main purposes of this study was to investigate whether FM patients can attain the same amount of progress in aerobic fitness as healthy matched sedentary controls, following a 12 week aerobic exercise program with low to moderate intensity. A second objective was to investigate whether the exercise program enhanced PPT among FM patients.

Method and materials

Subjects and study design

Fifty female subjects (25 patients and 25 controls), age ranging from 40 to 65 years, were recruited to participate in the study. The FM patients were recruited mainly through the local FM association, but some were also recruited through an advertisement in the local newspaper. All the FM patients had their FM diagnosis, on the basis of the criterions set by the ACR (Wolfe et al., 1990), confirmed by a general practitioner at St. Olavs hospital prior to entering the exercise intervention. The controls were also recruited through newspaper advertisement, but also through administrative employees at the local university; Norwegian University of Science and Technology (NTNU). Subjects who were pregnant, or had other illnesses or diseases (high blood pressure, endocrine or metabolic diseases, circulatory diseases, stroke, and cardiovascular diseases) apart from FM were excluded from the study. Only subjects with none- or low leisure time activity levels were included in the study. The study was approved by the local ethical committee, and all subjects gave their written consent prior to entering the study. The study was carried out with a case-control design. Patients and controls were matched on age (±2 years). In addition, an attempt was also made to match BMI between cases and controls.

Pain measurements

Measurements of PPTs were conducted at 5 different anatomical landmarks using an algometer (Somedic algometer type 2, Sweden). These landmarks included; occiput near the base of the skull at suboccipital muscle insertions, supraspinatus origin at the superior medial scapula corner, trapezius at the middle of its muscle belly, quadriceps femoris tendon just proximal to the patella, and rectus femoris approximately 7-8 cm proximal to the quadriceps femoris tendon measure site. The probe of the algometer had an area of 1 cm^2, and the applied pressure slope was 40 kPa/s. Measurements were conducted on each side of the body (right and left), making a total of 10 PPT measurements (Fig 1).

All the measurements of PPT were done perpendicular to the PPT sites, while the patient was seated on a chair. Subjects were instructed to push the button when the pressure from the algometer was perceived as painful. If the subject did not push the button before reaching 900 kPa, the measurement of the PPT site was automatically ended.

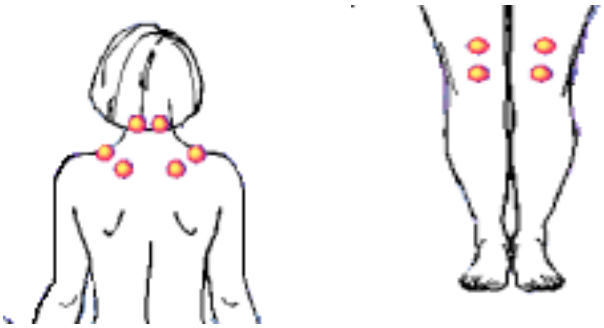

Figure 1. Pressure pain measuring sites. The dots indicate where the PPT measurements were conducted (Occiput, supraspinatus origin, trapezius, quadriceps femoris tendon and rectus femoris).

Test Protocol

An incremental load test was used to assess the AT of each subject (Fig 2). The test was performed on a Monarch (939E) ergometer bicycle. Individual seat adjustments were made prior to the test. Furthermore, subjects were instructed to cycle in an upright position (e.g., not lean their elbows on the handlebars) with a cadence of 60-90 rounds per min. This was done to achieve the most similar cycling condition for all the subjects. The first 6 min of the test was a warm-up period with a fixed watt load. Starting watt was determined through a qualitative assessment of each subject; on the basis of if they, and if so, how much they used a bicycle during a regular week. After the warm up period the load was increased with 10W every minute until the criterion of a blood lactate more than 4.0 mmol/l, and therefore also AT (Sjödin & Jacobs, 1981), was achieved. The blood for the lactate measurements was gathered from the fingers. For each lactate measurement the finger was wiped thoroughly to avoid perspiration in the lactate sample. The lactate measuring unit was placed perpendicular to the blood drop, and was only touching the blood drop, not the skin, during the collection of the blood sample. Blood was gathered only 3 times from each finger to avoid problems with coagulation. Rating of perceived exertion (RPE) was measured by the Borg scale (6-20), and the lactate measurements were performed using a Lactate Pro analyzer. The Lactate Pro has proven to be an accurate tool for measuring blood lactate concentrations (Medbøe et al., 2000; Saunders et al., 2005), and the Borg Scale have been found to be an appropriate tool to assess sub maximal exertion (Grant et al., 1999). Both the Borg Scale assessment and the lactate measurements were performed every minute following the warm-up period.

After the desired blood lactate concentration was achieved (i.e. >4.0 mmol/l), the subject was instructed to sit still on the ergometer for 3 min, so that the decrease in heart rate following the test could be monitored. Heart rate data was collected throughout the whole test

using a heart rate monitor (Polar rs800x). Ventilation and oxygen consumption values during the test were measured using a spirometer unit (MetaMax II). Prior to each testing period a gas calibration was performed using a reference gas with known oxygen- and carbon dioxide concentrations. In addition, volume calibration of the turbines used for measuring the spirometric activity was carried out every morning prior to testing, using a 3 liter calibrated air syringe. Before each individual test an ambient air calibration was performed to check that the spirometric unit was measuring the correct air concentrations in the laboratory (20.93 oxygen, and 0.03 carbon dioxide). During the test one person was closely monitoring the spirometric values to prevent or control for any abnormalities in the data collected, and to ensure that spirometric data was collected as correctly as possible from each subject.

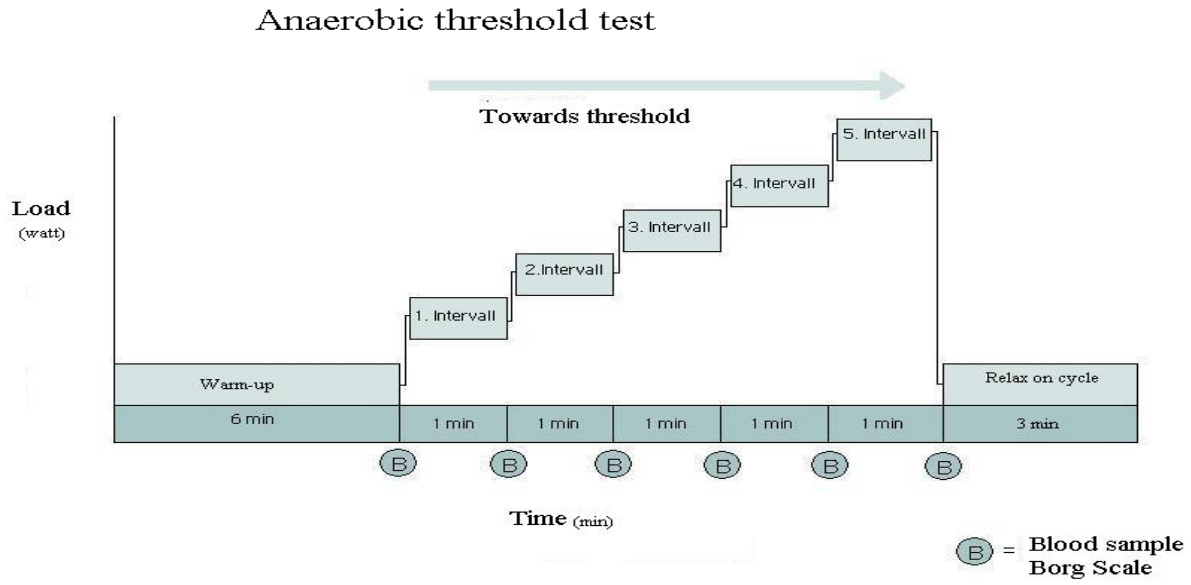

Figure 2 - Illustration of the AT test. An initial 6 min warm-up period was followed by an increase in work load (10W) every minute until reaching a lactate concentration above 4.0 mmol/l. The number of intervals is just for illustrational purposes, since every subject cycled until they reached their AT (i.e >4.0 mmol/l). The B indicates when Borg scale and lactate measurements were performed. The test ended with a 3 min relaxation period on the ergometer.

Exercise period

The exercise period was carried out for 12 weeks, with an intention of two sessions for each subject every week. Sessions consisted of spinning sessions performed in groups with an instructor. Exercise sessions lasted approximately 45-55 min, and were in principle interval based, with some differences in build up due to the use of several instructors. A mix of patients and controls attended each session. Intensity of the work-out should be below AT, and was individually tailored through the AT data for each subject acquired from the test prior to the exercise period. Each subject was given a heart rate monitor (Polar FS2C) to wear

during the exercise sessions, so that the they could monitor their own heart rate to make sure that they did not exceed their heart rate value corresponding to their AT. Random lactate tests were performed among the subjects during some of the exercise sessions, to control or confirm that the subjects were exercising below their AT.

Statistics

The distribution of the data was tested by a Shapiro-Wilk normality test. All over, both the spirometric and algometric data material was normally distributed, and was therefore analyzed with parametric statistical tests. To compare changes from pre- to post-test within groups a two-tailed paired-sampled t-test was used, while a two-tailed independent sample t-test was used to compare groups, as well as changes between the groups. The RPE sub-group data showed a non-parametric distribution, and within group changes were therefore analyzed by a Wilcoxon-test. A statistical significance level of $P \leq 0.05$ was used for all analysis. The statistical analysis was performed using SPSS 17.0 (2009) and Microsoft Excel (2007) for Windows.

Results

Attrition rates and baseline characteristics

Of the 50 subjects enrolled to the intervention, 37 (17 patients, 20 controls) participated at both pre- and post-testing. Hence, 13 subjects (8 patients, 5 controls) dropped out of the exercise program. The reasons for dropout among the 8 patients whom did not complete the exercise program were; 5 patients got other diseases which forced them to quit the exercise program, one patient listed personal reason, and two of the patient felt that the exercise program was too strenuous, and that it made their symptoms worse. For the 5 controls that dropped out following reasons were given; one got a disease, and 4 controls listed personal reasons as of why they chose to drop out of the exercise program. One patient did not conclude the spirometric measurements at post-test, and are therefore only included in the PPT analysis. Anthropometric data of the subjects who completed the spirometric pre- and post-test measurements are shown in Table 1. BMI score at pre-test were the only variable that differed significantly between the control and patient group. Due to technical problems with the spirometric equipment, and lactate concentration above 4 mmol/l on the first measurement, only 32 subjects (14 patients, 18 controls) will be included in the spirometric analyses. The exercise attendance rates varied widely between subjects. Average attendance rate was 72 % (range 20-100) for the patient group and 81 % (range 16-100) for the control group, respectively. Due to the variation in average attendance rate, subgroup analysis was performed on the subjects who attend 60% (60 minutes on average each week) or more of the scheduled exercise sessions (14 controls, 9 patients).

Table 1. Anthropometric data of the pre- and post-test participants.

	Controls (n = 20)	FM patients (n = 16)	*P**
Age (yrs)	52.1± 8.8	54.8± 7.3	0.33
Height (cm)	167± 5.6	164± 6.6	0.14
Weight pre (kg)	71.2± 10.3	75.2± 8.9	0.23
Weight post (kg)	71.3± 10.9	74.8± 9.1	0.32
BMI pre (kg/m2)	25.5± 3.4	28.1± 3.2	0.03
BMI post (kg/m2)	25.6± 3.6	27.9± 3.4	0.06

Values are mean±SD
*Independent samples t-test

Pre- and post-test measurements

Table 2 present pre- and post exercise values for oxygen uptake, work rate, HR, respiratory exchange ratio (RER), and RPE at AT (i.e. blood lactate = 4 mmol/l) for all the subjects who had sufficient spirometric and lactate data on pre- and post-test (14 patients, 18 controls). Oxygen uptake (l/min and ml/min/kg) as well as work rate at threshold differed

significantly between groups at both pre- and post-test (P<0.04 for all comparisons). In contrast, there was no difference in HR (P>0.020 for both comparisons), RER at threshold (P>0.15 for both comparisons) or RPE (P>0.40 for both comparisons) between the groups in pre- or post-test. There was no significant difference between pre- and post-test within the FM group, when all subjects were included (P>0.06 for all comparisons). Within the control group on the other hand, a significant increase in oxygen uptake (l/min and ml/min/kg), work rate, and RER was found (P<0.04 for all comparisons), while the HR and RPE remained more or less unchanged (P>0.42 for both comparisons).

Table 2. Oxygen uptake, work rate, HR, RER and RPE at AT for controls and patients who had sufficient spirometric and lactate data on pre- and post-test

			FM patients (n=14)	Controls (n=18)	*P**
O_2 (l/min)	Pre		1.5±0.3	1.7±0.3	0.03
	Post		1.5±0.3	1.8±0.3	0.02
		*P***	0.13	0.02	
VO_2 (ml/min/kg)	Pre		19.3±3.7	23.7±4.7	0.005
	Post		20.7±3.8	25.5±5.7	0.01
		*P***	0.08	0.01	
Watt (W)	Pre		69±22	88±21	0.01
	Post		79±24	98±23	0.03
		*P***	0.06	0.001	
HR (bpm)	Pre		134±14	137±18	0.50
	Post		134±13	141±16	0.20
		*P***	0.98	0.42	
RER	Pre		1.00±0.03	1.01±0.02	0.55
	Post		1.01±0.04	1.03±0.04	0.15
		*P***	0.64	0.04	
RPE	Pre		14.7±2.5	14.3±1.5	0.53
	Post		15.0±2.1	14.5±1.3	0.40
		*P***	0.78	0.79	

Values are mean±SD
*Independent samples t-test
** Paired samples t-test
Abbreviations: O_2 = oxygen consumption, VO_2 = oxygen rate, HR = heart rate, RER = respiratory exchange ratio, RPE = rating of perceived exertion.

Sub group analysis – patients versus controls

Table 3 presents change (post values – pre values) in oxygen uptake, work rate, HR, RER and RPE at AT in patients versus controls with exercise rate ≥60 % (9 patients, 14 controls). There was no difference in change between groups indicating that controls and patients had similar gain in aerobic fitness in terms of oxygen uptake (l/min and ml/min/kg) and work rate. HR at threshold increased slightly in both groups, while the RER and RPE remained more or less the same

Table 3. Changes (post-values – pre-values) in oxygen uptake, work rate, HR, RER , and RPE at anaerobic threshold for controls and patients. Only subjects with an attendance rate equal to 60% or above were included in the analysis.

	FM patients (n=9)	95% CI	Controls (n=14)	95% CI	*P**
ΔO_2 (l/min)	0.11±0.12	(0.03-0.19)	0.15±0.16	(0.06-0.23)	0.56
ΔVO_2 (ml/min/kg)	1.8±1.7	(0.73-2.94)	2.4±2.5	(1.1-3.8)	0.53
ΔWatt (W)	16±12	(8.4-24.2)	13±11	(7.4-19.3)	0.56
ΔHR (bpm)	2.3±10.6	(-4.6-9.3)	3.0±11.3	(-1.9-8.0)	0.87
ΔRER	0.01±0.05	(-0.01-0.04)	0.02±0.03	(-0.01-0.03)	0.43
ΔRPE	0.4±1.8	(-0.7-1.6)	-0.2±1.8	(-1.1-0.8)	0.46
ΔVO_2 (%)	9.7±9	(3.6-15.8)	10.6±11	(4.9-15.7)	0.84
ΔWatt (%)	26±21	(12.4-39.8)	17±21	(6.4-27.1)	0.33

Values are mean±SD

*Independent samples t-test

Abbreviations: Δ= change in, O_2 =oxygen consumption, VO_2 = oxygen rate, HR = heart rate, bpm = beats per minute, RER = respiratory exchange ratio, RPE = rating of perceived exertion, % = percentage.

Figure 3 shows the average watt production at AT (A), and the average VO_2 (ml/kg/min) rate at AT (B) at both pre- and post-test for patients and control who attended ≥60% of the exercise sessions. There was a significant difference between patients and controls in watt production at pre-test (*P*=0.02). This difference was no longer significant (*P*=0.06) at the post-test. For the VO_2 rate there was also a significant differences at pre-test (*P*=0.01), but this was also attenuated to non-significant at post-test (*P*=0.08).

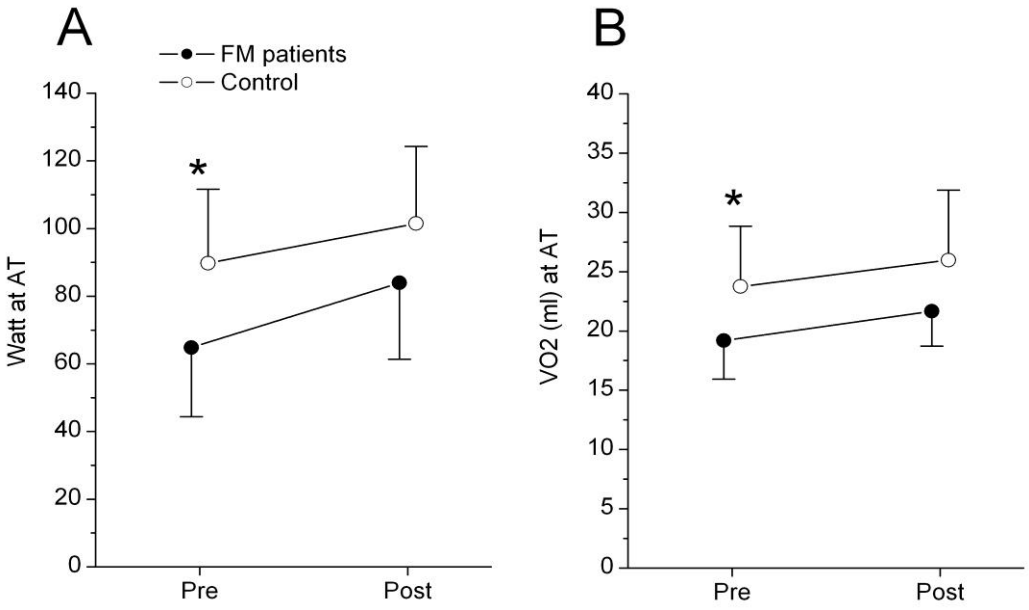

Figure 3 - **A**: Average watt production at anaerobic threshold at pre- and post test among both FM patients and controls. **B**: Average VO_2 (ml/kg/min) at anaerobic threshold at pre- and post test among both FM patients and controls. Only subjects with attendance rates above 60% (patients n=9, controls n=14) are included.
* indicates significant difference between the groups (*P*<0.05).

Sub-group analysis - changes within the patient group

Table 4 present change (post values – pre values) in oxygen uptake, work rate, HR, and RER at AT in patients with an exercise rate ≥60 % (9 patients) compared to the patients with <60% exercise rate (5 patients). A significant difference in change in oxygen rate (ml/min/kg) and work rate was found between the groups (P<0.03 for both comparisons). Oxygen consumption (l/min) increased in the ≥60 % group and decreased in the <60 % group but failed to generate any significant difference in change between the groups (P=0.08). Furthermore, HR and RER did not change significantly between the groups (P>0.23 for both comparisons).

Table 4. Changes (post-values – pre-values) in oxygen uptake, work rate, HR, and RER at AT for patients with more than- and less than 60% attendance rate.

	FM >60% (n=9)	FM <60% (n=5)	*P**
ΔO_2 (l/min)	0.11±0.12	-0.03±0.13	0.08
ΔVO_2 (ml/min/kg)	1.8±1.7	-0.4±1.7	0.03
ΔWatt (W)	16±12	-6±9	0.005
ΔHR (bpm)	2.3±11	-4.4±6.5	0.23
ΔRER	0.01±0.04	-0.01±0.06	0.42
ΔVO_2 (%)	9.7±9.0	-2.0±8.8	0.05
ΔWatt (%)	26±20	-8±9	0.005

Values are mean±SD

*Independent samples t-test

Abbreviations: Δ= change in, O_2 =oxygen consumption, VO_2 = oxygen rate, HR = heart rate, bpm = beats per minute, RER = respiratory exchange ratio, % = percentage.

Rating of perceived exertion (RPE)

Figure 4 shows the RPE (measured with the Borg scale) at AT at pre-test, against the same fixed watt load at post-test. There is a tendency that both controls and patients are located below the line of identity, suggesting a lower RPE at post-test compared to pre-test at a fixed watt load. However, the change in RPE did not reach significance (P=0.13 for patients, P=0.06 for controls).

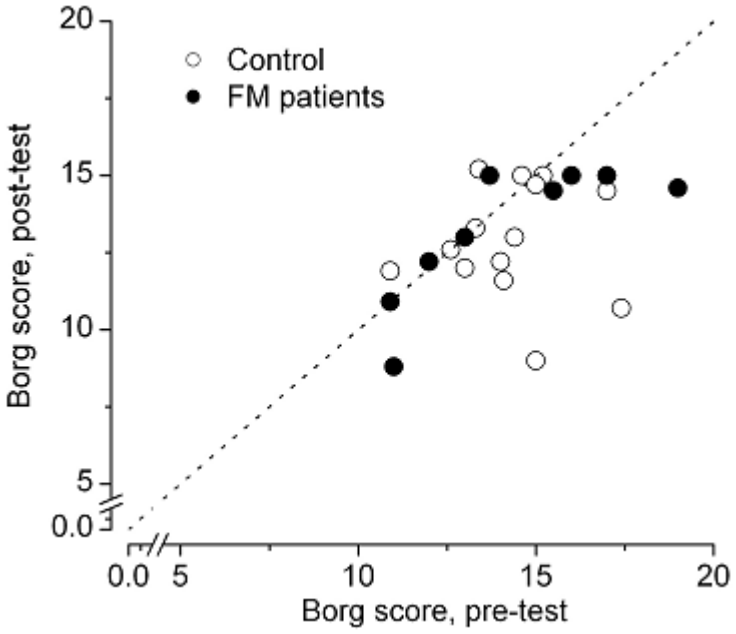

Figure 4 - Perceived exertion measured by the Borg scale at anaerobic threshold at pre-test, with the same fixed watt load at post-test. Only the subjects with attendance rates ≥60% (patients n=9, controls n=14) are included. Line of identity is indicated by the dotted line.

Pressure pain threshold within the patient group

Table 5 present PPT values at pre- and post exercise testing among patient with attendance rate ≥60%. Overall changes were small and did not reach significance for any of the recorded tender point sites (P>0.11 for all comparisons). Similar results were also obtained when including all patients (n=17) that performed both the pre- and post PPT testing in the analysis (P>0.06 for all comparisons).

Table 5. Pressure pain threshold (kPa) at pre-test, and post-test among patients with attendance rate above or equal to 60% (n=11).

	Pre test	Post test	Δ	*P**
Occiput R	226±73	196±93	-30	0.19
Occiput L	156±58	160±65	4	0.74
Supraspinatus R	220±67	225±65	5	0.88
Supraspinatus L	187±76	210±90	23	0.50
Trapezius R	157±53	194±79	37	0.26
Trapezius L	152±50	178±54	26	0.11
Quadriceps tendon L	292±180	292±136	0	1.00
Quadriceps tendon R	339±214	329±159	-10	0.85
Rectus femoris R	317±204	330±151	13	0.82
Rectus femoris L	305±152	324±172	19	0.66

Values are mean±SD
Paired samples t-test
Abbreviations: Δ= change, R = right side of the body, L = left side of the body

Discussion

The main finding of this study was that female FM patients had the same ability to enhance their aerobic fitness as age matched controls following a 12 week aerobic exercise program. However, a prerequisite to achieve these physiological benefits was to attend the scheduled exercise sessions on a regular basis (i.e. ≥60%, which equals 1.2 times each week or approximately 60 min per week). This was seen through an almost 10% increase in VO_2 and 26% increase in watt production at AT for the patients who exercised regularly, compared to a 2% decrease in VO_2 and 8% decrease in watt production at AT for the patients who attended less than 60% of the exercise sessions ($P \leq 0.05$ for both comparisons). Moreover, both the FM patients and controls who attended 60% or more of the scheduled exercise sessions improved their oxygen rate (ml/min/kg) by an average of roughly 10%, and the watt production at AT increased with an average of 26% for the FM patients and 17% for the controls, respectively. This increase in aerobic capacity indicates that the prescribed exercise intensity was adequate to facilitate a positive enhancement of the aerobic fitness in both patients and controls who attended a sufficient number of exercise sessions (≥60%). An exercise intensity below AT seems therefore to be sufficient to enhance aerobic fitness in sedentary FM patients, which is in accordance with Busch and co-workers (2008) recommendations, i.e., exercise prescribed for FM patients should be of low to moderate intensity to best reduce post exercise pain.

A significant difference in aerobic fitness characteristics between female FM patients and healthy matched sedentary controls were observed both prior to, and after the exercise program. This result is in accordance with previous findings by Valim and co-workers (2002), who reported inferior oxygen consumption and lower watt production at AT in female FM patients compared to healthy age-matched sedentary controls. The reason for the reduced aerobic capacity among FM patients is so far unknown, i.e., it can be a consequence of the illness, or it can be induced from deconditioning due to lower physical activity levels among FM patients. Both monitoring of physical activity (Kop et al., 2005), and self-reported levels of physical activity (Natvig et al., 1998; Bjørkgren et al., 2009) have failed to identify any evident difference in average physical activity among FM patients compared to healthy sedentary controls. However, the monitorial study by Kop and co-workers (2005) did find a significant lower amount of high intensity activity among FM patients compared to healthy controls. The importance of this reduced high intensity activity among the FM patients might be limited due to the findings done by van Santen and co-workers (2002b), who showed that

high intensity exercise are not superior in enhancing aerobic fitness in FM patients compared to exercise with low to moderate intensity.

Several studies have attempted to link the apparent reduced aerobic fitness among FM patients, compared to healthy controls, to the pathophysiology of the FM syndrome. Sahin and co-workers (2004) found evidence suggesting a lower maximal ventilation volume in FM patients compared to matched healthy controls, while Dinler and co-workers (2009) suggested that female FM patients may have a dysfunctional cardiopulmonary system compared to sedentary controls, due to longer recovery half times for oxygen turnover. Lindh and co-workers (1995) showed a lower capillary network in muscles of FM patients compared to healthy controls. A lower capillary density would give less oxygen delivery to working muscles, and in that way result in an earlier transition from aerobic to anaerobic energy utilization, thus inducing a premature AT in FM patients compared to healthy controls. However, lower maximal ventilation volume, longer recovery half times for oxygen turnover, and reduced capillary density might as well be a result from more sedentary behavior among FM patients compared to healthy subjects, and in that way not have a direct connection to the FM pathophysiology. The FM patients, who participated in a sufficient number of exercise sessions (≥60%) in this study, were equally exercisable as their matched healthy controls. This finding indicates that the reduced aerobic fitness found among the FM patients is mainly due to deconditioning from sedentary behavior, rather than a dysfunctional metabolic system.

Regular participation in physical activity to improve aerobic fitness has been found to protect against development of cardiovascular diseases (Blair et al., 1996; Macera et al., 2003), and some types of cancer (Lee, 2003). Recently a prospective cohort study showed that widespread musculoskeletal pain is associated with increased mortality from cancer, and possibly cardiovascular diseases (McBeth et al., 2009). Since the major symptom of FM is widespread musculoskeletal pain, these findings are likely to apply to FM patients. In other words; FM patients are probably more at risk for cancer and cardiovascular related deaths than subjects without chronic widespread pain. Our study found on average a considerable lower aerobic fitness level among the FM patients compared to matched controls, similar results have also have been reported earlier (Valim et al., 2002). These findings emphasize that regular physical activity to improve aerobic fitness might be even more important for FM patients than healthy sedentary controls. Not only because of the observed lower aerobic fitness among FM patients in this study, but also due to their widespread musculoskeletal pain. A combination of these risk factors could generate a substantial higher risk of cancer

and cardiovascular related mortality among FM patients, compared to healthy subjects. Our exercise program generated on average a significant improvement in aerobic fitness among the FM patients who attended 60% or more of the scheduled exercise sessions. In other words, a minimum of approximately 60 min of exercise per week were on average enough to improve aerobic fitness among the FM patients. This is a relatively small amount of weekly exercise, and should therefore be endurable for most FM patients. In addition, only small changes in physical activity among sedentary females have been associated with a large reduction in mortality from cardiovascular diseases (Oguma & Shinoda-Tagawa, 2004). To sum up, it is important to motivate FM patients to carry out regular exercise, since only small amounts of weekly exercise seem to improve aerobic fitness which in turn would reduce mortality associated with cardiovascular diseases, and some types of cancer.

RPE level measured by the Borg scale had a tendency, though not significant (P=0.13 for patients, P=0.06 for controls), to be lower on a fixed watt load on the post-test compared to the pre-test for both controls and patients who attended 60% or more of the scheduled exercise sessions. This indicates that most subjects felt that a fixed watt load was easier to maintain after the exercise period compared to before the exercise intervention. Reduced RPE at a fixed watt load on post-test compared to pre-test is presumably a consequence of the increase in aerobic fitness experienced by patients and controls who attend 60% or more of the scheduled exercise sessions. This may also have positive effects on daily activities, i.e. lesser the feeling of fatigue which is one of the most prominent symptoms in FM patients.

In contrast to Nielens and co-workers (2000) and Cook and co-workers (2006), who found a difference in RPE between controls and FM patients, this study did not observed any difference between FM patients and healthy controls in Borg scores at AT either at pre- or post-test (P>0.40 for both comparisons). The reason for the inconsistent findings between this study and the previous conducted studies might be the difference at which intensity the RPE was measured. Nielens and co-workers calculated the Borg on 65% of maximum heart rate, while Cook and co-workers used ventilatory threshold instead of AT as basis for the assessment. Furthermore, the patients in the study by Cook and co-workers suffered from chronic fatigue syndrome in addition to FM. Thus it seems likely that the Borg scale is equally applicable to FM patients as healthy matched controls as a tool for assessing RPE at AT. However further research on a larger sample size are needed to confirm these results.

Pressure pain threshold (PPT) did not improve significantly among the FM patients from pre- to post test. This is in accordance with earlier findings (Gowans et al., 2001). The

average improvement in PPT, though not significant (P>0.06 for all comparisons), were larger when all the patients were included compared to when only the patients with attendance rates above or equal to 60% were analyzed. This suggests that there were no correlation between exercise volume and change in PPT status. Sabbag and co-workers (2007) found an increase in aerobic fitness among FM patients after the first 3 months of their 1 year exercise intervention, but did not observe any changes in PPT. However, a significant improvement in average PPT was found after 9 months. These findings indicate that a 12 week or 3 month exercise intervention might be adequate to improve aerobic fitness, but on the other hand too short to facilitate any significant positive enhancement of PPTs in FM patients. A recent study by McVeigh and co-workers (2007) investigated the fluctuation of PPT at the 18 tender point sites defined by the American College of Rheumatology. Their results indicate a stability of PPT throughout a period of 28 days. Thus a fluctuation would not likely be the reason for the lack of change in PPT throughout the exercise program. However, PPT is also a subjective evaluation of pain, and day to day variation in mood or presence of comorbidities might influence the result. Changes in PPT following aerobic exercise interventions seems inconsistent, the reason for this inconsistency might be due to the variation in severity of the illness in each FM patient, which in turn reflects the heterogeneity among the FM patients. This makes it important to individually tailor exercise programs for each FM patients, to best reduce pain (Mannerkorpi & Iversen, 2003). A greater understanding of the pathophysiology behind FM, combined with a larger sample, in a long term aerobic exercise program might produce better understanding of how PPT can be altered.

There are several limitations to this study. Our study only included subjects that participated in none or low levels of leisure time exercise activities. Since the selection was done on the basis of self-reported physical exercise, it might be that some of the subjects did not consider activities they practiced as physical exercise. For instance; walking the dog for an hour each day might not be perceived as physical exercise by some of the subjects, however compared to a person who is completely sedentary this will probably count as physical exercise. Therefore some self-reporting bias may have occurred, furthermore causing a disparity in aerobic fitness between the FM patients and the controls.

High attrition rates in exercise intervention among FM patients are not uncommon (Mengshoel et al., 1992; Rooks et al., 2002). This study was not an exception, with as many as one third (33 %, n=8) of the patients dropping out from the exercise program. In addition, 5 patients did not attend sufficient exercise sessions (i.e. ≥60%) to generate the increase in

aerobic fitness associated with this exercise program. Leaving only 46% (n=11) of the patients completing a sufficient number of exercise sessions throughout the 12 weeks. Mannerkorpi and Iversen (2003) emphasized the need for an individual tailored exercise program for FM patients, due to the heterogeneity of this patient group. This study succeeded in individualizing the exercise intensity for each patient, which in turn excluded the possibility of too high exercise intensity, and in that way reduced the likelihood of attrition on the basis of too strenuous intensity (van Santen et al., 2002b). Still 2 patients dropped out because they felt a worsening of their symptoms. Another issue is the choice of spinning as exercise method. Since this study only consisted of spinning sessions, it might be that this type of exercise did not appeal to all of the patients due to the presence of comorbidities, this may in turn be a reason for the reduced adherence among the patients to the exercise program. Furthermore, this study did not include any educational component towards the management of FM, and inclusion of such a component may have increased the adherence to the exercise program among the patients (Hauser et al., 2009). On the other hand, it is well documented that FM patients suffer from a range of additional symptoms other than pain (Clauw, 1995; Epstein et al., 1999), and since 5 patients gave other diseases as reason for their drop outs, it seems likely that interference from other disease might be an important reason for the high attrition rates experienced in this intervention.

In conclusion, this study indicate that female FM patients can improve their aerobic fitness to the same extent as healthy sedentary controls following a 12 week aerobic exercise program with low to moderate intensity. This is important since low to moderate exercise intensity are associated with less post-exercise pain in FM patients compared to high intensity exercise. Furthermore, a substantial lower aerobic fitness was observed among the FM patients compared to the healthy controls. The reduced aerobic fitness is more likely to be a result from more sedentary behavior rather than a dysfunctional metabolic system, due to the similar progress in aerobic fitness between FM patients and healthy controls. However, further research is needed on the level of physical activity among FM patients compared to healthy controls, especially monitorial studies. Furthermore, a better understanding of the FM pathophysiology could also contribute to a wider understanding of the reduced aerobic fitness in FM patients.

Literature

Abeles, A. M., Pillinger, M. H., Solitar, B. M., & Abeles, M. (2007). Narrative review: the pathophysiology of fibromyalgia. *Annals of Internal Medicine, 146(10),* 726-734.

Arnold, L. M., Hudson, J. I., Hess, E. V., Ware, A. E., Fritz, D. A., Auchenbach, M. B., Starck, L. O., & Keck Jr, P. E. (2004). Family study of fibromyalgia. *Arthritis & Rheumatism, 50(3),* 944-952.

Bengtsson, A. (2002). Editorial: the muscle in fibromyalgia. *Rheumatology, 41(7),* 721-724.

Blair, S. N., Kampert, J. B., Kohl III, H. W., Barlow, C. E., Macera, C. A., Paffenbarger, R. S., & Gibbons, L. W. (1996). Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all cause mortality in men and women. *The Journal of American Medical Association, 276(3),*205-210.

Bjørkgren, K., Wallander, M. A., Johansson, S., & Svardsudd, K. (2009). General symptom reporting in female fibromyalgia patients and referents: a population-based case-referent study. *BMC Public Health, 9(402).*

Busch, A. J., Schachter C. L., Overend, T. J., Peloso P. M, & Barber K. A. (2008). Exercise for treating fibromyalgia syndrome. *Journal of Rheumatology, 35(6),* 1130-1144.

Clauw, D. J. (1995) The pathogenesis of chronic pain and fatigue syndromes, with special reference to fibromyalgia. *Medical Hypotheses, 44(5),* 369-378.

Cook, D. B., Nagelkirk, P. R., Poluri, A., Mores, J., & Natelson, B. H. (2006). The influence of aerobic fitness and fibromyalgia on cardiorespiratory and perceptual responses to exercise in patients with chronic fatigue syndrome. *Arthritis & Rheumatism, 54(10),* 3351-3362.

Dinler, M., Diracoglu, D., Kasikcioglu, E., Sayli, O., Akin, A., Aksoy, C., Oncel, A., & Berker, E. (2009). Effect of aerobic exercise training on oxygen uptake and kinetics in patients with fibromyalgia. *Rheumatology International, 30(2),* 281-284.

Edwards, R. R. (2005). Individual differences in endogenous pain modulation as a risk factor for chronic. *Neurology, 65(3),* 437-443.

Epstein, S. A., Kay, G., Clauw, D., Heaton, R., Klein, D., Krupp, L., Kuck, J., Leslie, V., Masur, D., Wagner, M., Waid, R., & Zisook, S. (1999). Psychiatric disorders in patients with fibromyalgia: a multicenter investigation. *Psychosomatics, 40(1),* 57–63.

Giske, L., Vøllestad, N. K., Mengshoel, A. M., Jensen, J., Knardahl, S., & Røe, C. (2008). Attenuated adrenergic responses to exercise in women with fibromyalgia – a controlled study. *European Journal of Pain, 12(3),* 351-360.

Goffaux, P., de Souza, J. B., Potvin, S., & Marchand, S. (2009). Pain relief through expectation supersedes descending inhibitory deficits in fibromyalgia patients. *Pain, 145(1-2),* 18-23.

Gowans, S. E., DeHueck, A., Voss, S., Silaj, A., Abbey, S. E., & Reynolds, W. J. (2001). Effect of a randomized, controlled trial of exercise on mood and physical function in individuals with fibromyalgia. *Arthritis Care & Research, 45(6),* 519-529.

Grant, S., Aitchison, T., Henderson, E., Christie, J., Zare, S., McMurray, J., & Dargie, H. (1999). A comparison of the reproducibility and the sensitivity to change of visual analogue scales, Borg Scales, and Likert Scales in normal subjects during submaximal exercise. *Chest, 116(5),* 1208–1217.

Harkness, E. F., Macfarlane, G. J., Nahit, E., Silman, A. J., & McBeth, J. (2004). Mechanical injury and psychosocial factors in the work place predict the onset of widespread body pain: a two-year prospective study among cohorts of newly employed workers. *Arthritis & Rheumatism, 50(5),* 1655-1664.

Hauser, W., Bernardy, K., Arnold, B., Offenbacher, M., & Schiltenwolf, M. (2009). Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials. *Arthritis & Rheumatism, 61(2),* 216-224.

Kop, W. J., Lyden A., Berlin, A. A., Ambrose, K., Olsen, C., Gracely R. H., Williams, D. A., & Clauw, D. J. (2005). Ambulatory monitoring of physical activity and symptoms in fibromyalgia and chronic fatigue syndrome. *Arthritis & Rheumatism, 52(1),* 293-303.

Kurtze, N., & Svebak, S. (2001). Fatigue and patterns of pain in fibromyalgia: correlations with anxiety, depression, and co-morbidity in a female county sample. *British Journal of Medical Psychology, 74(4),* 523-537.

Lawrence, R. C., Felson, D. T., Helmick, C. G., Arnold, L. M., Choi, H., Deyo, R. A., Gabriel, S., Hirsch, R., Hochberg, M. C., Hunder, G. G., Jordan, J. M., Katz, J. N., Kremers, H. M., & Wolfe, F. (2008). Estimates of the prevalence of arthritis and other rheumatic conditions in the United States – Part II. *Arthritis & Rheumatism, 58(1),* 26-35.

Lee, I-M. (2003). Physical activity and cancer prevention – data from epidemiologic studies. *Medicine & Science in Sports & Exercise, 35(11),* 1823-1827.

Lindh, M., Johansson, G., Hedberg, M., Henning, G. B., & Grimby, G. (1995). Muscle fiber characteristics, capillaries and enzymes in patients with fibromyalgia and controls. *Scandinavian Journal Rheumatology, 24(1),* 34-37.

Macera, C. A., Hootman, J. M., & Sniezek, J. E. (2003). Major public health benefits of physical activity. *Arthritis & Rheumatism, 49(1),* 122-128.

Mannerkorpi, K., & Iversen, M. D. (2003). Physical exercise in fibromyalgia and related syndromes. *Best Practice & Research Clinical Rheumatology, 17(4),* 629–647.

McBeth, J., Symmons, D. P., Silman, A. J., Allison, T., Webb, R., Brammah, T., & Macfarlane, G. J. (2009). Musculoskeletal pain is associated with a long-term increased risk of cancer and cardiovascular-related mortality. *Rheumatology, 48(1),* 74-77.

McVeigh, J. G., Finch, M. B., Hurley, D. A., Basford, J. R., Sim, J., & Baxter G. D. (2007). Tender point count and total myalgic score in fibromyalgia: changes over a 28-day period. *Rheumatology International, 27(11),* 1011-1018.

Medbøe, J. I., Mamen, A., Olsen, O. H., & Evertsen, F. (2000). Examination of four different instruments for measuring blood lactate concentration. *Scandinavian Journal of Clinical and Laboratory Investigation, 60(5),* 367-380.

Meiworm, L., Jakob, E., Walker, U. A., Peter, H. H., & Kreul, J. (2000) Patients with fibromyalgia benefit from aerobic endurance exercise. *Clinical Rheumatology, 19(4),* 253-257

Mengshoel, A. M., Komnæs, H. B., & Førre, Ø. (1992). The effects of 20 weeks of physical fitness training in female patients with fibromyalgia. *Clinical and Experimental Rheumatology, 10(4),* 345-349.

Meyer, B. B., & Lemley, K. J. (2000). Utilizing exercise to affect the symptomology of fibromyalgia: a pilot study. *Medicine & Science in Sports & Exercise, 32(10),* 1691-1697.

Natvig, B., Bruusgaard, D., & Eriksen, W. (1998). Physical leisure activity level and physical fitness among women with fibromyalgia. *Scandinavian Journal of Rheumatology, 27(5),* 337-341.

Nielens, H., Boisset, V., & Masquelier, E. (2000). Fitness and perceived exertion in patients with fibromyalgia syndrome. *The Clinical Journal of Pain, 16(3),* 209-213.

Oguma, Y., & Shinoda-Tagawa, T. (2004). Physical activity decreases cardiovascular disease risk in women: review and meta-analysis. *American Journal of Preventive Medicine, 26(5),* 407-418

Panton, L. B., Kingsley, J. D., Toole, T., Cress, M. E., Abbound, E., Sirithienthad P., Mathis, R., & McMillan, V. (2006). A comparison of physical functional performance and strength in women with fibromyalgia, age- and weight-matched controls, and older women who are healthy. *Physical Therapy, 86(11),* 1479-1488.

Pillemer, S. R., Bradley, L. A., Crofford, L. J., Moldofsky, H., & Chrousos, G. P. (1997). The neuroscience and endocrinology of fibromyalgia. *Arthritis & Rheumatism,40(11),* 1928-1939.

Pongratz, D. E., & Späth, M. (1998). Morphologic aspects of fibromyalgia. *Zeitschrift für Rheumatologie, 57(suppl 2),* 47-51.

Price, D. D., & Staud, R. (2005). Neurobiology of fibromyalgia syndrome. *Journal of Rheumatology, 32 (Suppl 75),* 22-28.

Richards, S. C. M., & Scott, D. L. (2002). Prescribed exercise in people with fibromyalgia: parallel group randomised controlled trial. *British Medical Journal, 325(7357),* 185.

Rooks, D. S., Silverman, C. B., & Kantrowitz, F. G. (2002). The effects of progressive strength training and aerobic exercise on muscle strength and cardiovascular fitness in women with fibromyalgia: a pilot study. *Arthritis Care & Research, 47(1),* 22-28.

Russell, I. J. (1995). Abnormal laboratory findings related to pain and fatigue in fibromyalgia. *Journal of Musculoskeletal Pain, 3(2),* 59-65.

Sabbag, L. M. d. S., Pastore, C. A., Junior, P. Y., Miyazaki, M. H., Goncalves, A., Kaziyama, H. H. S., & Battistella, L. R. (2007). Effects of physical conditioning over patients with fibromyalgia. *Revista Brasileira de Medicina do Esporte, 31(1),* 5-8.

Sahin, G., Ulubas, B., Calikoglu, M., & Erdogan, C. (2004). Handgrip strength, pulmonary function tests, and pulmonary muscle strength in fibromyalgia syndrome: is there any relationship? *Southern Medical Journal, 97(1),* 25-29.

Saunders, A. C., Feldman, H. A., Correia, C. E., & Weinstein D. A. (2005). Clinical evaluation of a portable lactate meter in type I glycogen storage disease. *Journal of Inherited Metabolic Disease, 28(5),* 695-701.

Sjödin, B., and Jacobs, I. (1981). Onset of blood lactate accumulation and marathon running performance. *International Journal of Sports Medicine, 2(1),* 23-26.

Valkeinen, H., Häkkinen, A., Alen, M., Hannonen, P., Kukkonen-Harjula, K., & Häkkinen, K. (2008). Physical fitness in postmenopausal women with fibromyalgia. *International Journal of Sports Medicine, 29(5),* 408-413.

Valim, V., Oliveira, L. M., Suda, A. L, Silva, L. E., Faro, M., Neto, T. L. B., Feldman, D., & Natour, J. (2002). Peak oxygen uptake and ventilatory AT in fibromyalgia. *Journal of Rheumatology, 29(3),* 353-357.

van Santen, M., Bolwijn, P., Landewe, R., Verstappen, F., Bakker, C., Hidding, A., van der Heijde, D., Houben, H., & van der Linden, S. (2002b). High or low intensity aerobic fitness training in fibromyalgia: does it matter? *Journal of Rheumatology, 29(3),* 582-587.

White, K. R., Carette, S., Harth, M., & Teasell R. W. (2000). Trauma and fibromyalgia: is there an association and what does it mean? *Seminars in Arthritis & Rheumatism, 29(4),* 200-216.

Wilson, H. D., Robinson, J. P., & Turk, D. C. (2009). Toward the identification of symptom patterns in people with fibromyalgia. *Arthritis & Rheumatism , 61(4),* 527–534.

Wolfe, F., Smythe, H. A., Yunus, M. B., Bennett, R. M., Bombardier, C., Goldenberg, D. L., Tugwell, P., Campbell, S. M., Abeles, M., Clarck, P., Fam, A. G., Farber, S. J., Fiechtne J. J., Franklin, C. M., Gatter, R. A., Hamaty, D., Lessard, J., Lichtbroun, A. S., Masi, A. T., McCain, G. A., Reynolds, W. J., Romano, T. J., Russell, I. J., & Sheon, R. P. (1990). The American college of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. *Arthritis & Rheumatism, 33(2),* 160-172.

Wolfe, F., Ross, K., Anderson, J., & Russell, I. J. (1995). Aspects of fibromyalgia in the general population: sex, pain threshold, and fibromyalgia symptoms. *Journal of Rheumatology, 22(1),* 151-156.

Wolfe, F., Anderson, J., Harkness, D., Bennett, R. M., Caro, X. J., Goldenberg, D. L., Russell, I. J., & Yunus, M. B. (1997). Health status and disease severity in fibromyalgia: results of a six-center longitudinal study. *Arthritis & Rheumatism, 40(9),* 1571-1579.

Wood, P. B., Patterson II, J. C., Sunderland, J. J., Tainter, K. H., Glabus, M. F., & Lilien, D. L. (2007). Reduced presynaptic Dopamine activity in fibromyalgia syndrome demonstrated with positron emission tomography: a pilot study. *The Journal of Pain, 8(1),* 51-58.