Preface

The study which this thesis is based on was carried out during the autumn of 2009 at the Norwegian University of Science and Technology (NTNU) in Trondheim. Writing took place during autumn 2009 and spring 2010.

Acknowledgements

I would like to thank my supervisor Karin Roeleveld at the Human Movement Sience Program at NTNU for her valuable advices and for writing Matlab scripts. I would also make use of the opportunity to say that she has been outstanding, especially when she used her vacation to help me with the last finish. Phd student Ellen Marie Bardal and my co-supervisor Paul Jarle Mork has contributed to the planning of this study, and coordinated and attended the training intervention, thank you both for that. Ellen Marie has also recruited subjects to the study and written matlab scripts in collaboration with Karin. In addition, I would like to thank my fellow students Knut R.W. Pettersen, Arild Hafstad and Håvard Brandsarbakken for cooperating with data collection. Finally, I would also like to thank all subjects who participated in the study.

ABSTRACT

Background: Fibromyalgia syndrome (FM) is associated with widespread pain over the entire body. Moreover, an impaired muscle function is frequently reported in FM patients. Several causes are supposed to cause these impairments, and causes can be multiply. However, the results are inconclusive. **Objective**: To investigate why women with FM have an impaired muscle function. **Material and methods:** Fifty women in the age 35-65 participated in an intervention study existing of 12 weeks indoor cycling. Twenty-five women with fibromyalgia (FM) and 25 women without FM (controls) were compared at baseline and post exercise. Outcome measures included pressure pain threshold (PPT), maximal voluntary contraction (MVC) force, rate of force development (RFD) and ipsilateral matching response. MVC, RFD and ipsilateral matching response was measured in shoulder abduction and knee extension. **Results**: Women with FM had significantly ($P<0.05$) lower PPT, MVC and RFD compared to healthy controls in both upper and lower body. Moreover, the pain ratio between upper and lower body was similar in both groups. After 12 weeks of indoor cycling both groups had a significant ($P<0.05$) increase in MVC and RFD in the knee extensors. Small changes in PPT might have occurred, but no significant ($P>0.05$) changes were present for groups separately. The women with FM and the healthy controls responded similar to the training. In the ipsilateral matching response there were no significant ($P>0.05$) differences between groups at baseline, and after 12 weeks training there were no significant ($P>0.05$) changes in either group. **Conclusion**: We suggest that impaired strength and RFD in women with FM is not due to pain. Lower extremities are more affected with impairments compared to upper body. In addition, our results suggest that possible disturbances in central mechanisms in women with FM do not inhibit training induced increase in strength and RFD. Moreover, it seems like pain have not resulted in impairments in proprioception in women with FM.

Key words: Fibromyalgia – women - pain- aerobic exercise- muscle performance- maximal voluntary contraction- MVC- Rate of force development- RFD- ipsilateral matching response- pressure pain threshold – PPT

CONTENTS

INTRODUCTION

Chronic musculoskeletal pain is common in the general population. In developed countries, chronic musculoskeletal pain is estimated to affect about 12 % of the adult population (Rohrbeck et al., 2007). Muscular-skeletal afflictions are in general the most important cause of morbidity, physical disability (Svalund, 2005) and sickness absence days in Norway (Andersen et al., 2009). In 2002, twenty-four percent of the population in Norway above 15 years had a muscular- skeletal affliction, according to themselves (Svalund, 2005). The fibromyalgia syndrome (FM) falls within the area of muscular-, skeletal-, connective tissue diseases (Norges fibromyalgi forbund, 2007). On world basis, FM affects about 2-4 % of the population (Wolfe et al., 1995; White et al., 1999). In Norway the prevalence is estimated to be similar (Forseth, 2008), and it is assumed that approximately 150.000 people in Norway are affected by the FM syndrome (Norges fibromyalgi forbund, 2007). FM is more frequent in females, and women represent about 85% of the population with FM (Nørregaard et al.,1994).

People with FM have widespread pain over the entire body and a high number of tender points in both upper and lower extremities. The pain is felt in the muscular tissue, skin, tendons and joints (Desmeules et al., 2003). Criteria for FM were not established until 1990, when the American College of Rheumatology made criteria for the classification of FM. These criteria were; pain in 11 of 18 tender points sites and a history of widespread pain[1]. Pain in these tender points is measured with pressure with an approximate force of 4 kg. The widespread pain must have been present for at least three months (Wolfe et al., 1990). However, the pathopyhsiology of the disease is poorly understood, and opinions are divided about central and peripheral mechanisms. A dysfunction in the autonomic nervous system in patients with FM is frequently reported (Hassett et al., 2007; Staud, 2008; Bradley, 2009). This dysfunction may contribute to enhanced pain and enhanced response to stressful events (Bradley, 2009). In addition it has been suggested that FM patients have a central dysfunction of the nociceptive modulating system in the central nervous system (Desmeules et al., 2003; Staud, 2006). Several authors have pointed out that FM patients develop central sensitization[2] (Bengtsson, 2002; Staud, 2006) and inadequate pain inhibition, and that peripheral tissue contributes to maintaining this state (Staud, 2006). Peripheral muscle tissue abnormalities have been proposed to be present in patients with FM (Pongratz & Späth,1998; Jacobsen,

[1] Pain in three sites qualifies as widespread pain. Some examples of three sites are; right shoulder, left buttock and thoracic spine (Wolfe et al, 1990).

[2] A lower threshold of activating nociceptors, and less stimuli is necessary before the brain percept pain (Woolf, 2004).

1998), while others report that the muscles of FM patients are alike those of healthy controls (Simms et al., 1994). However, there are no consistent findings regarding muscle tissue abnormalities in patients with FM (Staud, 2006). Whether there are both central and peripheral mechanisms causing the abnormal pain possessing is widely debated (Maquet et al., 2002). However, recent studies claim that the pathophysiolgy of FM is related to abnormalities of the central pain processing mechanisms, and not related to peripheral changes in the musculoskeletal system (Stahl, 2009).

In addition to chronic widespread pain, FM patients experience fatigue, sleep disturbance, morning stiffness, higher rates of headache, irritable bowel syndrome, and anxiety and depression (Wolfe et al, 1990). Patients with FM also have a lower pain threshold (Desmeules et al., 2003; Staud, 2006), and impaired muscle function compared to healthy controls (Elert et al., 1992; Lindh et al., 1995; Borman et al., 1999; Maquet et al., 2002; Bazzichi et al., 2009). Some of the muscle impairments found in FM patients are; decreased maximal voluntary strength (Jacobsen et al., 1991; Borman et al., 1999), decreased muscle endurance, and an inability to maximally activate muscles by voluntary command (Maquet et al., 2002). In addition, pain is suggested to impair the ability to rapid activate muscle force (Andersen et al., 2008), and to contribute to disturbances in proprioception (Matre et al., 2002; Visser & van Dieën, 2006).

Impaired muscle function in FM patients has been suggested to be a result of multiple causes. Pain, a sedentary lifestyle, factors related to FM, and age has, for instance, been proposed as possible explanations. Pain is one common explanation for impaired muscle function, and several experimental pain studies have been conducted to investigate the effect of pain on muscle function. For instance, studies have found that in the presence of chronic pain, the ability to rapidly activate painful and synergistic pain-free muscles are impaired (Andersen et al., 2008). However, the literature is divided concerning the effect pain has on muscle function. Some studies have found that muscle impairments is due to pain (Andersen et al., 2008; Matre et al., 2002), while others have reported that pain is not the cause (Borman et al., 1999). The differences in outcome between studies might be due to different tasks performed, and different muscles investigated. Graven-Nielsen & Arendt-Nielsen (2008) concluded that the specific motor task seems to determine the interaction between muscle pain and motor control.

The pathophysiology of the FM syndrome is as mentioned poorly understood, and it is possible that mechanisms concerning FM reflect the impaired muscle function. Both central and peripheral factors are put forward as possible reasons to impaired muscle function (and pain) in FM. Moreover, it has been suggested that lower maximal voluntary strength in FM patients seem to be a result of central rather than peripheral causes (Lund et al., 1991).

It has been suggested that FM patients are unfit (Borman et al., 1999; Bennett et al., 1989) and have a sedentary lifestyle. This might contribute to the impaired muscle function. However, the literature is in disagreement concerning this. Nørregaard et al., (1994) concluded in that decreased voluntary muscle strength in FM patients was due to de-conditioning, and that the absence of physical activity affected the muscles in a similar way as immobilization does. On the other hand, Maquet et al., (2002) suggested that the diminished muscle strength found in patients with FM was due to mechanisms independent from de-conditioning.

Impaired muscle strength and motor control is associated with a reduced ability to perform activities of daily living. Reduced knee extension strength is associated with gait disorders, falls, and loss of independence (Gusi et al., 2006). In addition, the ability to rapid activate muscles is important in many daily tasks e.g. during unexpected postural perturbations. Women with FM complain about problems performing simply daily tasks (Panton et al., 2006). Increased muscular strength, RFD, and proprioception can therefore be important factors contributing to a better physical functioning in daily life for these patients. Studies investigating the benefit of physical activity in FM patients were first conducted in the 80`. Exercise has shown to be efficacious in the treatment of FM, and sustained improvements in FM patients have been found after exercise interventions (Clauw, 2009).

The aim of this thesis was to investigate why women with FM have an impaired muscle function. Therefore we investigated the effect of a 12 week aerobic exercise (indoor cycling) on muscle function in women with FM in comparison to healthy controls. On the basis of possible central disturbances in patients with FM, we anticipated that aerobic training could lead to central changes in these patients. Thus, the muscular tests carried out, was based on the desire to investigate muscles in both upper and lower body. In other words, we investigated muscles with an assumed high amount of pain (upper body) and muscles with assumed less pain (lower pain). Three hypotheses to impaired muscle function were tested; (1) Pain, (2) sedentary lifestyle, (3) factors related to FM.

MATERIAL AND METHODS

Study design

This thesis is based on parts of the data derived from a larger intervention study concerning physical performance and autonomic dysfunction in women with FM. Fifty subjects underwent several tests at baseline and after a 12 week training period. This paper will only focus on some aspects from this study. Outcome measures used in this thesis includes; pressure pain threshold (PPT), ipsilateral matching response (proprioception), maximal voluntary contraction (MVC) force, and rate of force development (RFD). Baseline testing was performed within 3 weeks before exercise intervention, while post- testing was completed within 3 weeks after ended exercise intervention. The testing of each subject lasted for approximately 1 hour. At baseline 50 subjects participated (one patient group (N=25) and one control group (N=25)), and all subjects went through the same baseline and post- tests. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK). The remaining data from this intervention study is addressed elsewhere.

Subjects

Twenty-five women in the age 35-65 years with FM, and 25 age matched women without FM (controls) participate in the study. Subjects were recruited through advertisement in the local paper in the county of Sør-Trøndelag, Norway. Women with FM were also recruited through the local fibromyalgia association, and some controls were recruited by employees at NTNU. Besides having FM, the women with FM had to be free from other illnesses. Subjects were attempted to be matched for age, BMI and physical activity level. Therefore controls less than 35 years and over 65 years, which were lean or had a high level of physical activity, were excluded. All subjects went through a medical test, and signed a voluntary consent statement before participating in the study. Characteristics of the subjects are presented in table 1. At baseline patients had a significant higher weight and body mass index (BMI) compared to controls.

Table 1: Characteristics of the 50 subjects at baseline and the 36 subjects that participated at the post- test.

	Baseline		Post- test	
	PAS N=25	CON N=25	PAS N=16	CON N= 20
Age (years), mean (SD)	55. 8 (±6.8)	51.8 (±8.3)	54.9 (±7.2)	52.1 (±8.8)
Height (cm), mean (SD)	165 (±6.1)	168 (±5.7)		
Weight (kg), mean (SD)	*78.7 (±12.1)	*71.1 (±10.3)	74.7 (±9.1)	71.3 (±10.9)
BMI (kg/m^2), mean (SD)	*28.8 (±4.1)	*25.2 (±3.5)	27. 9 (±3.4)	25.6 (±3.6)
**Total MET-score, mean (N)	**1964 (20)	**2993 (22)		

Abbreviations: PAS, patients; CON, controls; SD, standard deviation; BMI, body mass index; MET-score, metabolic equivalent score.

*Significant difference between the two groups. $P < 0.05$

**number of participants differs from the other categories.

In addition to age, height, weight and BMI subjects' physical activity level at baseline was registered with a questionnaire. Physical activity (PA) was reported through the short (last 7 day recall) International physical activity questionnaire (IPAQ). Subjects' self- reported the frequency and duration of vigorous- and moderate PA, and walking for the last 7 days. This information was used to create metabolic equivalent (MET) scores for each intensity level. MET scores were calculated by the equation; intensity value x minutes x days (weekly MET score). The intensity values were; 8 for vigorous activity, 4 for moderate activity, and 3.3 for walking. Values from each intensity level were then added together to create a total MET score of PA. A mean score for each group was compared to see if there were any differences in PA level between the groups.

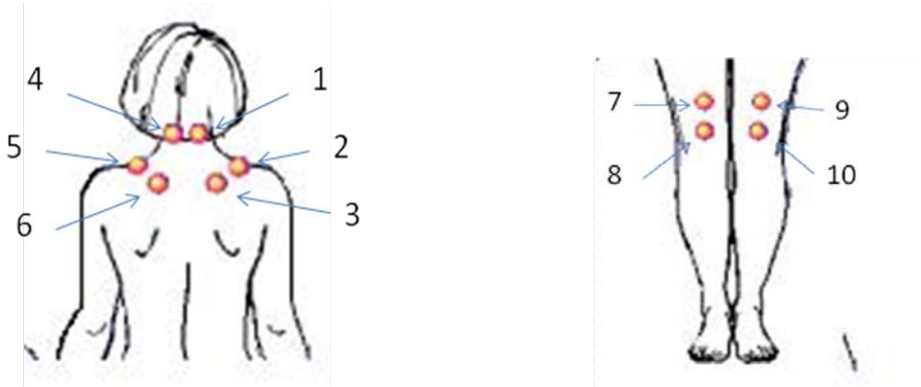
Equipment and test procedure

As mentioned, this thesis is based on data from a larger intervention study. This section describes the test procedure and equipment (in the same order as tested) used for PPT, ispsilateral matching response, and MVC. Initial to these tests, subjects' dominant arm and leg was determined with validated self reporting forms. Forms used were the "Edinburgh Handedness Inventory" (Elias et al., 1998) and the "Waterloo footedness questionnaire" (Oldfield, 1971).

Pressure pain threshold (PPT)

PPT was assessed with a digital algometer (Somedic algometer type II, SB MEDK Electronics, Solna, Sweden) with a probe size of 1.0 cm^2. PPT measures were obtained on 10 sites of the body, 6 in the neck area and 4 in the thighs. Measure points are illustrated in figure 1, and were measured at; m.occiput (near the base of the scull at suboccipital insertion), m.supraspinatus (origin of supraspinatus at the upper medial scapula corner), m.trapezius (in the middle of the trapezius belly), quadriceps femoris tendon (proximal to patella in seated position) and m.rectus femoris (approximately 7-8 cm proximal to the measure point of quadriceps femoris tendon).

Subjects were seated in a chair while the test was performed. A continuous pressure was applied with the algometer on each measure point, with an increasing application rate of 40 kPa/s. Subjects were instructed to push a button on the algometer when they felt that the pressure applied, went from a pressure to a sensation of pain. It was emphasized that the subjects should press the button before it was really painful, and that it was the change-over from pressure to pain that was the target. The number that appeared on the algometer when subjects pressed the button was used as the pressure pain threshold. The sequence of measures is illustrated in figure 1.



A. B.

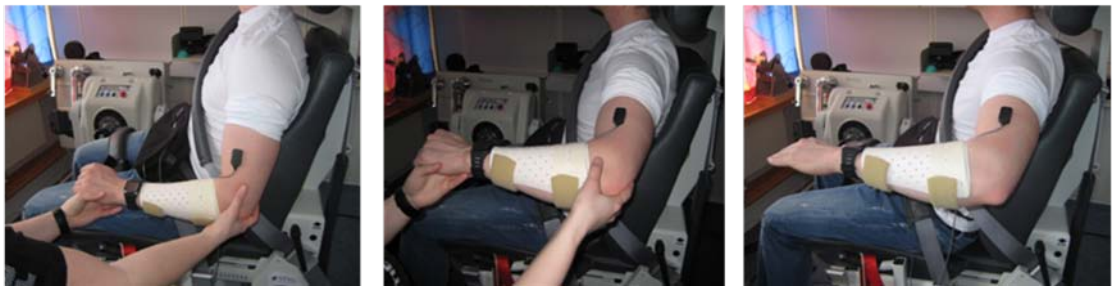
Figure 1: Schematic illustration of the measuring points of the pressure pain threshold, in upper (A) and lower body (B). Numbers illustrates the sequence of the measures.

Ipsilateral matching response

Ipsilateral matching response is used to measure the ability to reproduce a target position, and is frequently used in studies investigating proprioception (Hurley et al., 1998). To measure the angle of the knee and arm during the ipsilateral matching response task, a 3D accelerometer (Accelerometer Biosignal Sensor, Delsys Inc, Boston, MA, USA) was used as a goniometer. One accelerometer was attached to the subjects' dominant leg (distal to tibia) (Figure 2B) and one accelerometer to the subjects` dominant arm (lateral on the upper arm, placed on the most vertical location of the upper arm when the arm was hanging down along the body) (figure 2A). The accelerometer data were recorded on a computer, and sampled at 1000Hz (Delsys Bagnoli EMG system, Delsys Bagnoli-16 EMG system and Delsys universal input unit, Delsys Inc., Boston, MA, USA). Subjects were seated in a Biodex chair (BIODEX System 3 Pro, Biodex Medical Systems, Shirley, NY, USA) during the test, with their knee in ~ 90° angel, and their back rested against the back of the chair (Figure 2). Subjects were strapped with belts over their dominant thigh, over the waist, and across their upper body, to minimize hip, pelvic and lower trunk movement.

Ipsilateral matching response was measured using an open kinetic chain and active limb positioning (figure 2). The test was performed on knee extension and shoulder abduction in one trial each. The knee extension was performed unilateral on the dominant leg, and the shoulder abduction was performed unilateral in the passive part (instructor moving subjects limb), and bilateral in the active part (subject reproducing movement). In order to exclude the visual support, subjects were instructed to close their eyes during the task. Passive positioning by the examiner was performed by extending the limb, at ~ 10°/sec, from the starting position (knee extension: 90° in the knee, and shoulder abduction: 0° in the shoulder joint and 90° in the elbow joint) to target position (knee extension: ~ 120°, and shoulder abduction ~ 45°) (figure 2). Subjects maintained the position for 5 s without physical contact from the examiner in order to identify the target position. Subsequent to this, the examiner replaced the limb to the start position. After a 15 s pause subjects were instructed to actively reproduce the test position, and hold the position for 5 s. On the command from the examiner, subjects returned their limb to the initial position. The absolute difference in degrees between the test position and the reproduced position is reported as ipsilateral matching response.

A



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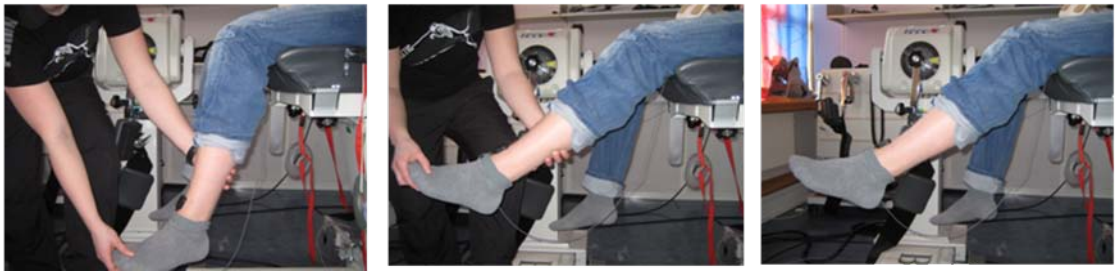


Figure 2: Procedure for ipsilateral matching response in shoulder abduction (A) and knee extension (B). On figure A and B the location of the accelerometer (black rectangle) is shown. The white cuff on figure A was to minimize the pressure of the force transducer straps in the MVC task.

Maximal isometric voluntary contraction (MVC) force

MVC was measured in knee extension and shoulder abduction. Subjects were seated in a Biodex chair while performing both knee extension and shoulder abduction. During the MVC`s subjects received visual feedback on a computer screen. Each MVC lasted for 5 second and was performed 3 times for both knee extension and shoulder abduction. There was a 60 second pause between each contraction. During the MVCs, the instructor verbally motivated subjects to generate as much force as they could. For standardization, the same instructor performed all verbal information and tried to use the exact words, tone and sound level to all subjects.

To measure MVC in the knee extensor, a dynamometer (BIODEX System 3 Pro, Biodex Medical Systems, Shirley, NY, USA) was used. The knee extension trial was performed unilateral on the dominant leg. The centre of rotation of the dynamometer was adjusted to fit the centre of rotation in subjects' knee, and the test position was set to ~90° angel in the knee (figure 3A). MVCs in the shoulder abduction were measured using force transducers (Interface Inc, Scottsdale, Arizona, USA). The shoulder abduction trial was performed bilateral to avoid cheating (e.g. by leaning towards the opposite direction). Shoulder abduction was performed with a 45° angel in the shoulder and 90° elbow, with palms facing

down (figure 3B). To find the correct angel in shoulders and elbows, a manual goniometer (MSD Europe BVBA, Londerzeel, Belgium) was used. Since the shoulder abduction method permitted several degrees of freedom, subjects were instructed how to perform a shoulder abduction, without cheating (e.g. by elevating the neck or using m.biceps), and subjects were corrected if they were doing it wrong.

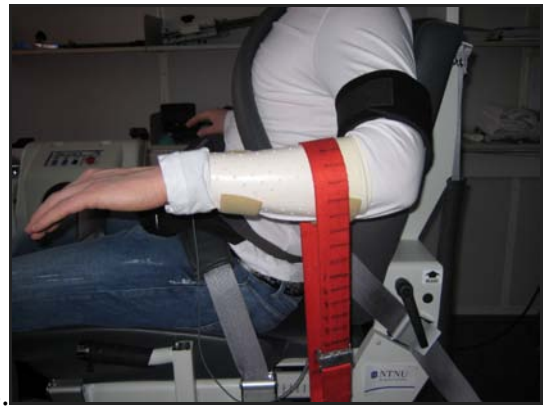
A.  B. 

Figure 3: Procedure of maximal isometric voluntary contraction (MVC) in leg extension (A) and shoulder abduction (B).The white cuff in picture B was to minimize the pressure by the strap while performing the MVC.

Training intervention

The training intervention consisted of indoor cycling (spinning) twice a week, over a 12 week period. For practical reasons subjects were divided into two mixed groups, and went through the same programme. Each training session lasted for 45- 60 minutes and was lead by an instructor. All subjects received a heart rate monitor (Polar electro, Finland) to control the intensity during the exercise. Prior to the training intervention subjects performed a lactate threshold test (for procedure read Hafstad, 2010) on an ergometer cycle. In addition, heart rate was measured during the test. Based on these tests the training intensity was set for each subject individually. The intensity was, moderate, up to 75% of estimated maximal heart rate (220-age). The exercise consisted of several intervals, where the main target was to achieve the intensity mentioned above, and a few intervals was carried through with intensity up to 85% of estimated maximal heart rate.

Data analyses

In order to carry out parametric variables for statistical analyses, the force and accelerometer data from both baseline and post- test were analyzed using Matlab software (The Math Works, Natick, MA, USA) version 7.8.0.(R2009a),

Force data

The Biodex dynamometer data and force transducer data from the MVC trials were calibrated from volt to Nm/Kg using linear regression. Initial to testing, offset was removed to avoid drift/conduction in the force transducers. The force data was lowpass filtered at 6 Hz with a butterworth filter. The highest peak force from all three MVC trials for each task (dominant leg, dominant/ non-dominant arm) over the entire time period (5 sec) was taken for the analysis. The force signal was sampled at 1000Hz and recorded on a computer. Outcome variables were kg for shoulder abduction and Nm for leg extension. To get RFD values, the entire force curve from the MVC was differentiated to a new curve. From this RFD curve, the highest value was taken out as the absolute RFD (Nm^{-1} and Kg^{-1}).

Accelerometer data

The accelerometer data from the ipsilateral matching response trial was lowpass filtered at 2 Hz to remove acceleration due to movement (gravity was the variable we wanted to look into). The gravitation force was used to calculate angel by using the mathematical inverse trigonometric function acos. Outcome variable was difference in degrees between target position and reproduced angel (figure 4).

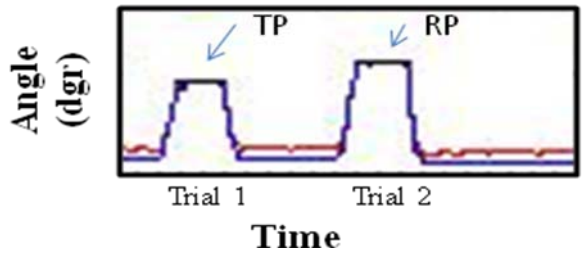


Figure 4: Illustration of detected data from the ipsilateral matching response task. The figure shows target position (TP) where the instructor lead the limb into position, and the reproduced position (RP) where the subject performed the task active. The difference in degrees between TP and RP were used as outcome variable for the ipsilateral matching response task.

Statistical analyses

Statistical analyzes were performed using the Statistical package for the Sosial Sciences (SPSS statistics 17.0). All MVC data were normal distributed (Shapiro-wiik), and parametric tests were used. A two- way analysis of variance (ANOVA) with repeated measures was assessed to determine differences within and between groups before training and after 12 weeks of training. In addition, to compare groups in specific MVC parameters at baseline and post- test, independent t-tests were performed.

Data from PPT, RFD and the ipsilateral matching response task, violated the normal distribution (Shapiro-wiik), and non-parametric test were assessed. To examine if there were any differences at baseline and post- test between groups, Mann-Whitney U test was used. Changes from baseline to post- test were assessed with a Wilcoxon test. Where significant results were noted, delta values were calculated to determine if there were any difference in alteration between groups. Results are reported as mean values for parametric statistics and median values for non-parametric statistics, and a 95% confidence interval (CI) are displayed. Statistical significance was set at $P \leq 0.05$.

RESULTS

The main purpose of this thesis was to compare women with FM (PAS) and healthy controls (CON). And due to this, the main analyses compare PAS and CON. Further on, sub analyses were obtained to investigate if changes were dependent on training participation. Since there was a high variance in training participation in the study, subjects were divided into sub divisions by percentage training participation. Since the main analyses showed no significant difference in changes between women with FM and the controls, sub divisions consisted of a mix of women with FM and controls. The division was; subjects who participated in lee than 75% (low training group, LTG, N=12) and more than 75% (high training group, HTG, N=24) of the training sessions. Subjects who did not participate in the post- test were excluded in the sub analyses. The sub analyses are presented under the headline "low training group vs high training group" in the following chapter.

Fifty subjects (25 PAS and 25 CON) were included in the baseline analyses. Thirty-six subjects (16 PAS and 20 CON) participated in the post- test, and they were all included in the analysis except from one patient who was excluded in the MVC (shoulder abduction) analysis due to statistical reasons (outlier), and in the RFD (shoulder abduction) analysis because of test failure. Characteristics of the participants are presented in table 1 in the methods chapter. There was no significant difference in age, height and physical activity level between the groups. The FM patients were significantly heavier and had a higher BMI than the controls at baseline. This difference was not present at post- test.

Drop out

Fourteen subjects dropped out of the study, 9 patients (2 reported worse symptoms during training, 7 due to personal reasons and other illnesses), and 5 controls (4 due to personal reasons, 1 because of other illnesses).

Participation and intensity during training intervention

Thirty- six subjects participated on the post- test, and the average training participation was 76%. Nine patients and 15 controls participated in >75% of the training sessions (HTG), and the average participation was 92% in this group. In the <75% training group (LTG) there were 7 patients and 5 controls, and the average training participation was 43%. Subjects in the HTG

had an average BORG[3] score of 13.4, and an average percentage of estimated (220 - age) maximal heart rate of 76.7% during the training sessions. The average intensity in the HTG was equally distributed between patients and controls.

Pressure pain threshold (PPT)

All six individual measuring points from the PPT measure in the upper body were added together and divided by six, to create a mean value for the PPT upper body. In addition, a mean value for measuring points in the lower body was created. Since the individual measuring points did not show any different statistical outcome, these mean values for upper and lower body was created in order to reduce the number of performed statistical tests.

Figure 5 shows PPT in upper and lower body in both PAS and CON, at baseline and post-test. PAS had significantly lower PPT score in upper body compared to CON both at baseline ($P<0.001$) and post- test ($P<0.001$). However there were no significant changes in PPT from baseline to post- test either in the PAS ($P= 0.266$) or CON ($P=0.411$) group, or both groups combined ($P=0.182$). PAS had an average increase in PPT upper body by 16% (but reduced median), while the CON had an increase of 9%. There was no significant difference in percentage increase between groups.

PAS had significant lower PPT in the lower body compared to CON both at baseline ($P=0.001$) and post- test ($P=0.001$). All subjects as one group showed a significant increase in PPT in the lower body ($P=0.021$). However, there was no significant increase in either PAS ($P=0.136$) or CON ($P= 0.100$) separately. On average, PAS had a 16% increase in PPT lower body and CON had a 14% average increase.

[3] The BORG RPE (rate perceived exertion) scale measures perceived exertion, on a scale of 6-20, where 6 is very little exertion and 20 is very hard exertion.

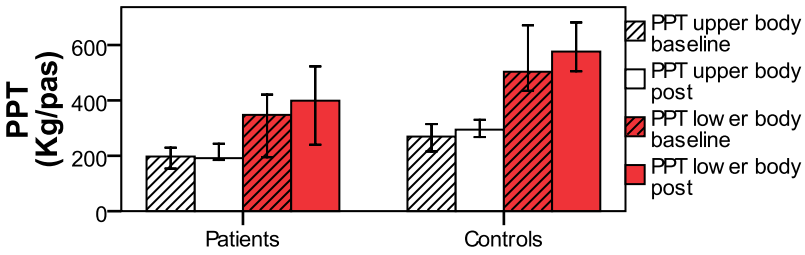


Figure 5: Pressure pain threshold (PPT) in upper and lower body, in patients (left) and controls (right), at baseline (striped bars) and post- test (filled bars). Bars represent median values in Kg/pas and a 95% confidence interval (CI).

Ratio values between upper and lower body were calculated in both groups. A Mann-Whitney U test revealed no significant difference in ratio between PAS and CON either at baseline (P=0.930) or post- test (P=0.329). In addition, there were no significant changes in ratio from baseline to post- test in either group (PAS P=0.266, CON P=0.411).

PPT: Low training group (LTG) vs high training group (HTG)

There were no significant differences between the LTG and HTG in PPT in upper and lower body at baseline or post- test. There was no significant increase in upper body in either groups (LTG P= 0.060, HTG P= 0.841). In PPT in lower body both groups displayed an average increase, however there was only a significant (P= 0.023) increase in the LTG (HTG P= 0.346).

Maximal voluntary isometric strength (MVC)

At baseline and post- test PAS had a lower average shoulder abduction strength compared to CON, both in dominant (10% lower) and non-dominant arm (15 % lower) (figure 6). However, there was only a significant difference in non- dominant arm, both at baseline (P=0.029) and post- test (P=0.018), where CON were stronger.

All subjects taken together as one group had an increase in shoulder abduction strength from baseline to post- test, in both dominant arm (P= 0.01) and non-dominant arm (P=0.012). However, there was no significant increase in either PAS or CON group separately. There were no significant changes in percentage increase between groups, either in dominant (PAS 14 %, CON 15% increase) or non-dominant arm (both groups 14% increase), from baseline to post- test.

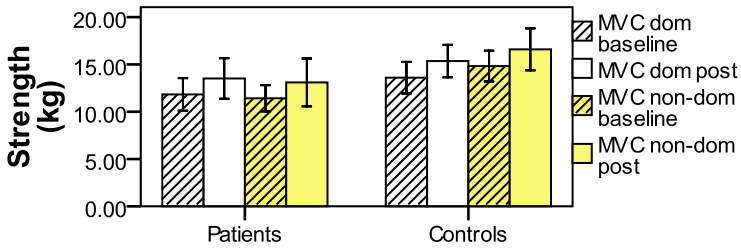


Figure 6: Shoulder abduction strength (MVC kg) in dominant and non-dominant arm, at baseline and post- test in patients (left) and controls (right). Bars represent mean values and a 95% CI.

Figure 7 represents results from knee extension strength for PAS and CON at baseline and post- test. CON were 25% (P<0.000) stronger than PAS in isometric knee extension strength at baseline, and 19% (P=0.004) stronger at post- test. Both groups had a significant increase in isometric knee extension strength from baseline to post- test (PAS P= 0.001, CON P< 0.000). However there was no significant (P= 0.617) difference in absolute increase between the two groups. On the other hand, PAS had a significantly higher (P=0.017) percentage increase in knee extension strength compared to CON (PAS 37% increase and CON 22% increase).

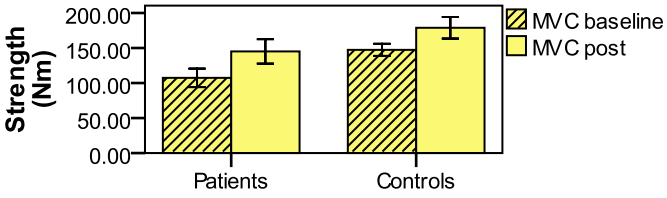


Figure nr 7: Knee extension strength (MVC). Bars represent mean values in Newton meters (Nm) and a 95% CI. Patients on the left and controls at the right. Striped bars represent baseline strength and filled bars represent post strength.

MVC: Low training group vs high training group

LTG and HTG were compared to examine the effect of the training intervention.

There were no significant differences in shoulder abduction strength in either dominant or non-dominant arm at either baseline or post- test between LTG and HTG. Both groups had an increase in shoulder abduction strength in dominant and non-dominant arm. However, there was no significant (P=0.436) difference in increase in shoulder abduction strength from baseline to post- test between LTG and HTG.

HTG was stronger than LTG in knee extension at baseline and post- test. However, there were no significant differences between the groups either at baseline (P=0.631) or post- test

(P=0.748). Both groups had an increase in knee extension strength from baseline to post- test, but there was no significant (P=0.677) difference between LTG and HTG.

Further analyses on the average values indicated no differences between PAS and CON in the training intensity effect.

Rate of force development (RFD)

At baseline CON had significant (P=0.024) higher RFD values in non- dominant arm compared to PAS (figure 8). None of the two groups had a significant alteration in RFD in non-dominant arm from baseline to post- test (PAS P= 0.101, CON P= 0.852). CON had higher values in RFD dominant arm both at baseline and post- test. However, there was no significant difference between the two groups either at baseline (P=0.101) or post- test (P=0.172). There were no significant changes in either PAS (P=0.096) or CON (P=0.502) group from baseline to post- test.

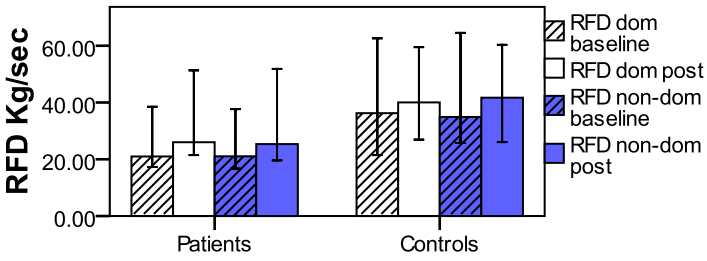


Figure 8: Rate of force development (RFD kg/sec) in shoulder abduction at baseline (hatched bars) and after 12 weeks indoor cycling (open bars). Median values and a 95 % CI are presented.

Figure 9 shows median values in RFD knee extension for PAS and CON at baseline and post-test. At baseline (P=0.008) and post- test (P= 0.046) CON had significant higher RFD knee extension values compared to PAS. Both groups had a significant increase in RFD knee extension from baseline to post- test (PAS P= 0.036, CON P= 0.030). PAS displayed an average percentage increase of 49% and the CON an average percentage increase of 25%. However, there was no significant (P=0.484) difference in increase between the two groups.

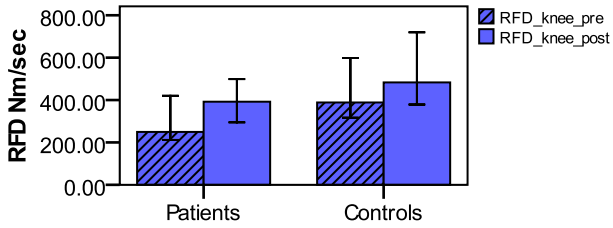


Figure 9: Rate of force development (RFD Nm/sec) in knee extension before (hatched bars) and after (open bars) 12 weeks indoor cycling. Bars represent median values for patients (left) and controls (right). A 95% CI is displayed.

RFD: Low training group vs high training group

There were no significant differences at baseline or post- test between the LTG and the HTG in either of the RFD variables. In RFD dominant and non- dominant arm there was no significant alterations from baseline to post- test in either group. Both groups had an increase in RFD knee from baseline to post- test. However there was only a significant (P=0.024) increase in the HTG.

Ipsilateral matching response

Figure 10 displays deviation (in degrees) from target position, in the ispsilateral matching response task, for shoulder abduction and knee extension. PAS had a higher deviation at both baseline and post- test in shoulder abduction and knee extension compared to CON. However there were no significant differences between groups. Both groups had an increased deviation from baseline to post- test, but there were no significant changes in either group.

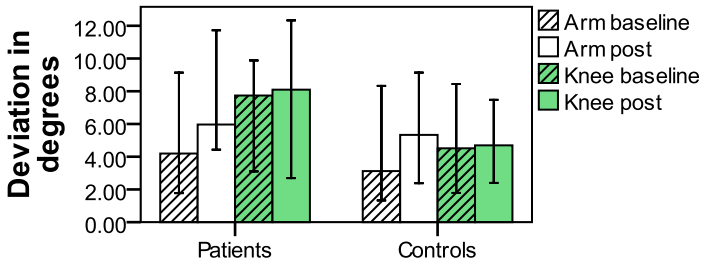


Figure 10: Differences at baseline and changes from baseline to post- test in ipsilateral matching response were non-significant. Figure shows median values and a 95% CI. Values are presented as deviation in degrees from target position.

Ipsilateral matching response: Low training group vs high training group

There were no significant differences between the LTG and the HTG at baseline or post- test in shoulder abduction or knee extension matching response. There were no significant changes from baseline to post- test in either group.

DISCUSSION

The main aim of this thesis was to investigate why women with FM have an impaired muscle function. Therefore, we investigated changes in muscle function and PPT before and after a 12 week aerobic exercise, between women with FM and healthy controls. Based on our results, three hypotheses to impaired muscle function in women with FM were tested as possible explanations; (1) Pain (2) sedentary lifestyle (3) factors related to FM. Both muscles with an assumed high amount of pain (upper limb) and muscles with less pain (lower limb) were investigated. In the following, it will be discussed how and why our results suggest that impaired muscle strength and impaired RFD in women with FM is not due to pain. In addition, our results indicate that the upper limb is not more influenced than the lower limb, either by pain or muscle impairments, in women with FM. In fact, our results point in the direction of higher muscle impairment in the lower limb. The discussion will start with a short presentation of which muscle impairments that were present in women with FM, and which changes occurred after training. The ipsilateral matching response results were non-significant and are discussed in a separate paragraph.

Impaired muscle function in FM

Our study revealed several differences at baseline between women with FM and healthy controls. Women with FM had lower PPT in both upper and lower body, lower maximal voluntary strength and lower RFD in non-dominant arm and knee, compared to the healthy controls. These findings are in agreement with other studies which have found lower PPT (Mikkelsson et al., 1992; Lorenz, 1998; Desmeules et al., 2003; Petzke et al., 2003; Gracely et al., 2003; Staud, 2006), lower maximal strength (Nørregaard et al., 1994; Jacobsen, 1998; Maquet et al., 2002; Gusi et al., 2006; Panton et al., 2006), and lower RFD (Andersen et al., 2008) in patients with FM, compared to healthy controls.

Training induced changes

After 12 weeks of indoor cycling, our results revealed similar changes in all variables in the women with FM and the healthy controls. Significant increases were found in maximal isometric strength and RFD in the knee extensors. In addition, a significant increase in PPT in the lower body (thigh) was found for all subjects taken together as one group. There might have been small changes in the upper body, but no significant changes were noted within groups.

Possible reasons to impaired strength and RFD in FM

There were as mentioned three hypotheses we wanted to test as possible explanations for impaired strength and RFD in women with FM, and in the following these hypotheses will be discussed.

Is impaired strength and RFD caused by pain?

In addition to lower PPT, women with FM were weaker than the controls. In average they were 10-15 % weaker in the shoulder abductors (both dominant and non-dominant), and 25% weaker in the knee extension. The same tendency was present for the RFD. These findings implies that the women with FM had more diminished strength and RFD in the muscles with the highest PPT, than the muscles with the lowest PPT. Therfore, our results suggest that lower strength and RFD is not due to lower pain threshold, and therefore not pain. This is in disagreement with some studies, which have proposed that pain could impair muscle strength, the ability to activate muscles on voluntary command, and the ability to rapidly activate muscles (Andersen et al., 2008). However, some studies agree on our suggestion that pain is not the cause to impaired muscle function (Borman et al., 1999).

Further on, our assumption that pain is not the reason to muscle impairments can be supported by the fact that strength and RFD increased more than the PPT after 12 weeks training, and that there were similar training induced changes in women with FM and healthy controls. Women with FM had a mean increase of 16% in PPT in the lower body, a mean increase of 37% in knee extension strength, and a mean increase of 49% in RFD in the knee, while controls showed 14% increase in PPT, 22% increase in MVC, and 25% increase in RFD. Thus, women with FM and healthy controls had a similar percentage increase in PPT lower body, while the increases in strength and RFD were higher in women with FM. This suggests that the women with FM still had a low PPT, while they had a large increase in strength and RFD. Since the increases in strength and RFD were independent from the increase in PPT, we can suggest that impaired strength and RFD in women with FM is not due to pain. In addition, the similar change shown in women with FM as in healthy controls, states that the women with FM responded in the same degree as the healthy subjects, and therefore the pain did not restrain strength and RFD increase in these patients.

Even though we have suggested that pain is not a reason to impaired strength and RFD, fear of pain could have resulted in the lower strength and RFD in women with FM seen at baseline. Studies have shown that patients with FM complain about fatigue and pain during exercise and physical tests (Maquet et al., 2002), and that they are afraid of performing rapid movements in fear of pain. This fear of increased pain could not only impair the ability of rapid force capacity of painful muscles, but also synergistic pain free muscles, and thereby impair muscle force capacity (Andersen et al., 2008). It might have been that women with FM were afraid of increased pain at baseline test, while they during the training intervention acquired a higher training tolerance, and thereby dared to make a higher effort at post- test. However these assumptions are guessing, and outside of the scope of this paper, and are not further discussed.

Is impaired strength and RFD caused by a sedentary lifestyle?

A sedentary lifestyle can contribute to impairments in strength and RFD. In our study the healthy controls were attempted to be matched in physical activity level, and at baseline there were no differences in self reported activity level. However, the aerobic cycling test at baseline revealed a significant difference in aerobic capacity between the women with FM and the healthy controls (Hafstad, 2010), implying that there might have been differences in activity level. It is possible that the women with FM have over- reported their activity level while the healthy controls have under-reported their activity level. If the healthy controls actually were more active by e.g. walking to the store or cycling to work, it could be one explanation for the large differences in muscle performance at baseline. However, based on the fact that the self reported activity level was similar in the two groups, but the physiological performance was significantly different, it is possible that the muscle impairments are due to poor physical capacity or factors concerning the FM syndrome rather than sedentary lifestyle.

Is impaired strength and RFD caused by the FM syndrome?

So far, we have suggested that impaired muscle strength and RFD is not caused by pain, but may be related to reduced physical capacity, fear of pain, a result of a sedentary lifestyle, or physiological disturbances caused by the FM syndrome. Both central and peripheral mechanisms are introduced in the literature as possible sources to impaired muscle function in FM patients. Jacobsen (1998) suggested that both peripheral and central mechanisms may contribute to impaired muscle function and pain in FM. Central mechanisms refer to

disturbance in the central nervous system, and peripheral mechanisms refer to abnormalities in muscle tissue found in patients with FM.

A central dysfunction in the autonomic nervous system (Staud, 2006, 2008), and a dysfunction in the pain processing system by central sensitization (Bengtsson, 2002; Desmeules et al., 2003; Staud, 2006) are often seen in FM patients. Due to this we hypothesized that the 12 weeks of indoor cycling could lead to central changes in the autonomic system, and thereby increased muscle performance in the entire body in the women with FM. However, our results displayed local changes in the muscles used during the cycling. Significant changes in the lower body were found, while there were no significant changes in the upper body. This indicates that we cannot confirm our hypothesis. Moreover, the improvements in PPT were small while the RFD and strength gain was large. Thus, the local improvements in strength and RFD in the knee extensors, and non-significant improvements in the arms, indicates that central mechanisms might not be the cause of impaired strength and RFD. However, it might be that the relationship between local impairments and central mechanisms does not have a clear *vice versa* relationship. Therefore, it might be possible that the central mechanisms are causing the impairments, but not inhibiting the strength improvements. However, this is only speculations, and due to our results we cannot for sure reject central mechanisms as a possible cause to impaired muscle strength and RFD.

Abnormalities in the muscle tissue were also suggested as a possible contributor to impairments. However, due to our results we can only speculate if there is a relation. We did not carry out muscle biopsies, and due to this we actually do not know what happened local in the muscle tissue. For instance, Borman (1999) suggested that muscles impairments could be due to impairment in the capacity and utilization of oxygen in the muscles. Nevertheless, based on our results, we cannot suggest if there are pathological mechanisms that are causing muscle impairments, or which mechanisms contributing.

Lower extremities more affected than upper extremities

Patients with FM report more pain in the upper extremities. This is in agreement with the lower PPT in the upper body compared to the lower body, found in patients with FM (present study. However, both the women with FM and the healthy controls had lower PPT in the upper body compared to the lower body. Moreover, we did not find any difference in pain

ratio between upper and lower body between patients and controls. These findings indicate that the women with FM do not have more pain in the upper body compared to healthy subjects.

Possible reasons explaining training induced changes

The greatest difference in strength and RFD at baseline between women with FM and healthy controls was present in the knee extensors. Moreover, the greatest training induced changes were also present in the knee extensors. Consequently, this suggests that the increase in strength and RFD in the knee extensors is due to local adaptations in the muscles. The subjects in the study had a low physical capacity prior to the study, and it is reasonable to assume that only a little training (cycling) was necessary to gain strength in the knee extensors. Strength training on untrained healthy subjects has resulted in strength increase due to neural adaptations (Häkkinen et al., 2001). Thus, the local changes seen in the present study might also be due to neural adaptations. However, based on our results the physiological mechanisms behind the improvements cannot be proven or eliminated here, and is not further discussed.

One possible explanation for why women with FM had a higher percentage increase in strength and RFD might be due to their physical fitness prior to the training intervention. At baseline, the women with FM had lower performance in almost all parameters compared to controls. Hence, less training might have been needed to increase their physical performance. Other studies support the fact that women with FM respond in the same degree as healthy subjects after a training intervention. In a study using strength training it has been shown that women with FM had normal muscle function and similar degree of trainability in the voluntary neuromuscular characteristics of muscles as in healthy subjects (Valkeinen et al., 2004; Valkeinen et al., 2006).

Proprioception in FM

Studies show that pain can lead to impaired proprioception (Matre et al., 2002), which will lead to less precise motor control and increased co-activation of muscles (Visser & van Dieën, 2006). In our study we were not able to prove this assumption, as there were no significant changes in ipsilateral matching response between groups at baseline. Therefore, lower PPT in women with FM and no significant difference in ipsilateral matching response between groups, indicates that pain in these patients have not resulted in impaired proprioception.

However, even if our study failed to show significant differences, the tendency for the ipsilateral matching response was similar as for strength and RFD. Our results suggest that women with FM had a higher deviation from the target position in the matching response test in the knee extension. This pattern was not present in the shoulder abduction. At post- test, the tendency seemed to be that the matching response decreased compared to baseline.

Our failure to demonstrate differences between women with FM and healthy controls can also be due to the test protocol. We measured the ipsilateral matching response in one trial, and at one target position. Studies investigating proprioception differs a lot in methodology, and even within studies. Differences consist of; numbers of trial used, how a body part is positioned as a target, if the same or the contralateral limb is positioned to match, different combinations of passive and active positioning, and different equipment (e.g. differences between methods in the studies by Sandlund et al., 2006; Gandevia et al., 2006; Smith et al., 2009; Fuentes & Bastian, 2010; Gay et al., 2010). For instance, some studies use motorized equipment where the subjects` limb is relaxed in the instrument, which can reduce the ability cheat. In our study, an instructor guided the subjects' limb into target position. It might be that it is harder to totally relax when a person is holding the limb, compared to a steady machine. Therefore, it can be that the subjects moved their limb together with the instructor in the passive part of the task. Further on, this could have lead to that the target position was easier to reproduce, and therefore the results found. However, the test condition was similar to all subjects, and we did not find any significant difference between groups.

It is widely debated if training can lead to improvements in proprioception. In earlier years the term proprioceptive training has been used. This kind of training has for instance been proven to prevent recurrent ankle strains (Verhagen et al., 2004; Hupperets et al., 2009), and to attenuate age-related position sense decline (Ribeiro & Oliveira, 2009). Contrary, Ashton-Miller et al., (2001) suggested that training could lead to increased coordination and balance, but not improvements in proprioception. The absence of improvements in ispsilateral matching response in our study might also be due to the type of training. It is possible that the training has to be so-called proprioception training, and that improvements are dependent on the task performed. However, further research investigating proprioception is needed, and conduction of a standardized method is needed.

Drop out and changes dependent on training participation

Seventy-two percent of the subjects completed the study (36 of 50 subjects). The dropout rate of 28% is smaller than reported in other group interventions done on FM patients (Rooks et al., 2002; Mengshoel et al., 1992). However these two studies had an exercise intervention whit a longer duration (20 weeks) than our study (12 weeks). The main reason for dropout in our study was to personal reasons and illnesses (not fm related).

Participation is critical to the success of an exercise intervention. Of the 36 subjects who completed the study, there was an average participation of 72% during the 12 week cycling intervention. This level of participation is smaller compared to other studies, which reported a compliance of 81% during a 20 week intervention (Rooks et al., 2002) and 86% compliance during a 12 week intervention (Gowans et al., 1999).

Our sub analyzes showed that the changes in strength were not dependent on training participation. However changes in PPT and RFD were dependent on training participation. Changes in PPT were greater in the subjects who participated in fewest sessions (average participation of 42%), while the increase in RFD was dependent on a high training participation (average 92%). These results were not important regarding the aim of this thesis, and are therefore not further discussed.

Limitations and further research

The MVCs in shoulder abduction was measured with force transducers, and consequently with a strap around the subjects forearm. This lead to several degrees of freedom, making it easy to cheat, and the instructions to the subjects were crucial to correct the execution of the task. It could have been that some of the subjects did not correctly perform the shoulder abduction by using other muscles (e.g. elevating the neck or using m.biceps instead of using the deltoid muscle). This was of course commented by the instructor if it was evident.

In our study subjects were not told to generate force as rapid as they could, but only to generate as much force as they could during the 5 second MVC task. This might have affected the total values of the RFD, but it cannot explain the difference between patients and controls. It is possible that the lower RFD at baseline in the patients is due to a different strategy to achieve maximal strength compared to the healthy controls

Self reporting physical activity is a very subjective measure and is dependent on each subjects' opinion of what physical activity is. One person can count every little movement as physical activity, while others only report more vigorous activities as e.g. organized training session etc.

In addition, MET scores were used to calculate physical activity level. In reality MET is a measure of energy expenditure based on body mass and height (Jette et al., 1990). We did not account for body mass and height in our study, but calculated a MET score from minutes/ hours spent on walking, moderate activity and vigorous activity, where these three intensities was replaced with numbers. Based on this, we assume that our calculations were good enough to compare groups in our study. However, we do not recommend using the values on MET in this study to compare with other MET calculations in other studies.

Our results indicated that muscle impairments in women with FM are not caused by pain. However, the reasons to impairments are yet to be addressed, and further research is needed to find out what is causing muscle impairments in these patients.

CONCLUSION

In conclusion, the present results suggest that impaired muscle strength and RFD in women with FM is not due to pain. Moreover, our results indicate that the lower limb is more affected by muscle impairments, even though the lower limb had the highest PPT. Moreover, our results showed that local adaptations in the knee extensors occurred after 12 weeks indoor cycling. Therefore, our results weaken the suggestion that a possible central change has occurred after training, and suggest that central mechanisms behind FM did not inhibit local changes in the muscles. Additionally, we suggest that impairments might be related to multiple factors as; low physical capacity, fear of pain, sedentary lifestyle, and other factors concerning the FM syndrome. There was a tendency for impaired proprioception in the knee extensors in women with FM compared to healthy subjects, however the results were non-significant. Thus, we suggest that pain in FM has not yet resulted in impaired proprioception in these patients.

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