Acknowledgements

Before embarking on this scientific paper, I intend to direct your attention to those who have made it manageable for me. First, thanks to Karin Roeleveld for guidance through the entire process and a seemingly undying patience. Karin also wrote the MATLAB-scripts for extracting the needed data for strength and motor control analyses in collaboration with Ellen-Marie Bardal, thank you both! I am grateful to Paul-Jarle Mork and Ellen-Marie Bardal for coordinating and attending every training session. Finally, thanks to Håvard, Arild and Camilla for an excellent cooperation through the information gathering process. To the other students at the human movement science program I am grateful for 2 unforgettable years.

Abstract

Background: Earlier studies have demonstrated the potential of strength exercise for women with fibromyalgia in regulating central processes believed to be essential in the fibromyalgia etiology. Similar results have been presented for aerobic exercise in healthy sedentary women and healthy seniors. No previous study has been conducted on aerobic exercise and the effects on pain, strength and motor control for fibromyalgia, compared to matched control subjects.

Objective: To investigate the effects of a 12-week low to moderate aerobic exercise program on pain, strength, and motor control for 25 women with Fibromyalgia and 25 healthy controls, and to evaluate the possibility of global mechanisms affecting these factors.

Intervention: 12 weeks of supervised aerobic endurance on spinning ergometer bikes.

Main Outcome Measures: Pressure pain-thresholds (PPT) of the lower extremities and the neck area, voluntary strength of knee-extension, and arm abduction. Also, variation and frequency of variation of arm position during holding as properties of motor control.

Results: PPT was higher in CG than FMG for all measures ($p < 0.05$), and it was higher in the lower than upper body for both groups ($p < 0.001$). The CG was stronger than the FMG on both strength measures ($p < 0.05$). Frequency of variation of arm position showed group differences at baseline, but variation itself did not ($p < 0.05$). After the intervention period, the subjects showed increased lower body PPT ($p < 0.05$), a strong (> 20%) increase in knee extension strength ($p < 0.001$), and a minor (> 2%) increase in arm abduction strength ($p < 0.01$). There was also a similar change for both groups from baseline to post-intervention in the frequency of variation of arm position ($p < 0.05$).

Conclusions: Aerobic exercise has similar effects on strength, PPT and motor control for both groups. Cycling on spinning ergometer bikes is sufficient in improving strength of the lower extremities. There is no convincing indication that central factors are inhibiting the FMG in strength and position variation. The specific effects these factors have on frequencies of variation are uncertain. PPTs have no clear influence on strength or motor control for the FMG.

Key Words: Fibromyalgia, Aerobic exercise, Pain, Strength, Motor control.

Introduction

Fibromyalgia (FM) is a common musculoskeletal disorder with a population based prevalence ranging from 0.5 - 4 % in industrialized countries. It often leads to a sedentary lifestyle and is mostly found in women (Clauw & Crofford, 2003). The diagnostic criteria for FM are indications of pain in 11 out of 18 tender points when palpated and widespread pain in 3 out of 4 body quadrants for at least 3 months (Wolfe et al., 1990; Hassett et al., 2007). Related symptoms such as fatigue, muscle stiffness and weakness are common (Panton et al. 2006; Hasset et al. 2007). Lowered pain thresholds (hyperalgesia), painful response to normally non-painful stimuli (allodynia), sleep disturbance, irritable bowel, anxiety and depression are also common, but not diagnostic criteria for FM (Wolfe et al., 1990; Banic et al., 2004). In activities of daily living (ADL), reduced voluntary muscle strength and force control may be inhibiting for individuals with FM (Panton et al. 2006).

Due to the unknown etiology of FM, extensive research has been conducted on this subject. Recently, there have been a number of studies relating FM to a dysfunction in the autonomous nervous system (ANS) (Cohen et al. 2000; Martinez-Lavin, 2004; Sarzi-puttini et al. 2006). The ANS is an intricate network of higher brain-function which maintains homeostasis in the human body. Many bodily organs are regulated by antagonistic sympathetic/parasympathetic activity by the release of epinephrine or norepinephrine (Sarzi-puttini et al. 2006). The hypothesized dysfunction in FM is a disruption in homeostasis, characterized by sympathetic overactivity combined by a reduced parasympathetic reactivity. This keeps the body in suspense and unable to react adequately to stressors (Bengtsson & Bengtsson, 1988; Cohen et al. 2000; Martinez-Lavin, 2004; Sarzi-puttini et al. 2006). FM is also related to Hypothalamic pituitary adrenal axis (HPA axis) alterations described by abnormally low levels of cortisol and high levels of corticotrophin, further suggesting an inhibition of the stress-response system. HPA axis dysfunction is also related to depression and sleep disturbance, which is common in FM (Sarzi-puttini et al. 2006).

The central changes presented above may be related to motor control deficiencies in FM. It has previously been hypothesized that motor control deficiencies may be present for FM and that the origin is central (Casale et al. 2009). One factor that could affect the mechanisms of central motor control is nociceptive input. Even though motor control strategies are known to be affected by pain, the precise relationship remains uncertain (Arendt-Nielsen, L. Graven-Nielsen, T. 2008). For example, the integration of nociceptive input in the central nervous

system (CNS) resulting in a motor response is not specifically understood (Arendt-Nielsen, L. Graven-Nielsen, T. 2008; Sterling et al. 2001). Local nociceptive input from skeletal muscles may affect agonists and antagonists both ipsi- and contralaterally, which may give a greater impact of local pain on strategies of motor control (Arendt-Nielsen L. & Fallah D., 2009). Sterling et al. (2001) explain three theories on the association between pain and motor control; "the pain adaptation model", "the neuromuscular activation model" and "the vicious cycle model". The pain adaptation model describes adaptations to pain by increasing antagonist muscle activity during movement of painful limbs, causing aberrant movement patterns and difficulties in maintaining joint stability and control. The neuromuscular activation model describes delayed or inhibited synergistic functions in muscles controlling painful joints, resulting in altered patterns of neuromuscular activity and control. The vicious cycle model is characterized by pain leading to muscle hyperactivity through afferent influence on gamma motor neurons, which leads to "central sensitization", exhibited by increased excitability of alpha motor neurons. The result is stiffness of primary muscles. Muscle stiffness is in turn believed to increase metabolite production which further enhances the stiffness (Sterling et al. 2001). When "central sensitization" is established, it is thought that merely non-painful afferent input is needed to maintain the condition (Staud et al. 2009). No model of motor control and pain has been proven applicable to FM, but central sensitization is thought to maintain the painful sensations characterizing FM (Staud, 2002; Desmueles et al. 2003). In general, models of pain and motor control are difficult to attribute to chronic conditions since they are most prominently related to acute pain, but the phenomena described in these models are believed to persist into chronic conditions (Sterling et al. 2001). Though earlier research has described central motor control failure in FM, functional manifestations in motor tasks are limited to altered patterns of motor unit recruitment and reduced strength (Casale et al., 2009; Gerdle et al., 2010). Patients with chronic pain often have a normal range of movement despite of pain (Sterling et al. 2001). If central factors are the source of altered patterns of motor control in chronic conditions, a change at this level may be effective in normalizing motor control. Aerobic exercise (AE) has previously been related to central changes in autonomic function.

Research on the effects of aerobic exercise (AE) on central levels has shown that autonomic function in healthy subjects can be changed, characterized by improved parasympathetic tone (Jurca et al., 2003; Okazaki et al., 2005). The proven benefits of exercise on autonomic function for FM are limited to results from a resistance exercise

program by Figueroa et al. (2008). AE interventions for FM have been beneficial for several other factors; reduced experienced pain, tender-point tenderness and tender-point count (Wigers, Stiles & Vogel, 1996;Richards & Scott, 2002; Valim et al. 2003; Gusi et al. 2006; Bircan et al. 2008), increased physical functioning, and quality of life (Gowans et al. 2004; Gusi et al. 2006). It is generally believed that long-term improvements in health-status from physical activity requires long-term adherence, since discontinuation is frequently related to a relapse of painful symptoms (Gowans et al. 2004; Wigers, Stiles & Vogel, 1996; Richards & Scott, 2002; Sarzi-Puttini et al. 2006). Furthermore, it is important not to demand too high intensity of AE for FM, since it may lead to increased experienced pain (Van Santen et al. 2002). Exercise combined with cognitive behavioral therapy seems to enhance the described effects (Rooks, 2007).

No previous study has investigated the link between AE and changes at central levels, or its effects on strength and motor control for FM. In the current study, it was suspected that changes in global mechanisms of FM could occur from AE.

The aim of this study was to investigate the effects of low to moderate AE for 12 weeks on pressure pain-thresholds, strength and motor control, and to evaluate the possibility of central mechanisms affecting these factors. It was hypothesized that a change at a central level would lead to increased pressure pain-thresholds, and that reduced pain would lead to improved motor control and strength for FM.

Outcomes will be measured in areas believed to benefit directly and indirectly from the prescribed exercise in order to support the hypothesis of effects on central levels from AE.

Subjects and Methods

The study was conducted as an intervention trial comparing a group of FM-patients (FMG) to a non-FM control group (CG) on effects from AE. Exclusion criteria were the following: High blood pressure, Endocrine/metabolic/neurological/circulatory and coronary-heart diseases, severe mental health conditions, high physical activity level, stroke and pregnancy.

Subjects were recruited through advertisement in the local newspaper and through the local FM-organization. The CG was mainly recruited from the faculty of the local university. All subjects were women, ranging from 40 – 65 years of age. The FMG and CG were

intentionally matched for age and BMI to provide comparable groups at baseline (Table 1.). A physician determined the FM diagnosis prior to the intervention.

Table 1. Baseline characteristics of the intervention groups

	FMG		CG	
N	25		25	
Age (years)	55.8 ± 6.8		51.8 ± 8.3	
Height (cm)	165 ± 6.1		168 ± 5.7	
Weight (kg)	Baseline: 78.70 ± 12.17*		Baseline: 71.14 ± 10.38*	
	Post: 74.75 ± 9.14	(N= 16)	Post: 71.30±10.90	(N= 20)
BMI	Baseline: 28.8 ± 4.13*		Baseline: 25.2 ± 3.52*	
	Post: 27.9 ± 3.54	(N= 16)	Post: 25.6 ± 3.60	(N= 20)

Descriptive data of FMG and CG presented with means and standard deviations. * = p-value <0.05, presented where the differences between groups are significant. N is presented for post-data.

Procedure

Height, weight, footedness and handedness for each subject were determined at baseline. Footedness was determined by the Waterloo footedness questionnaire (Elias, 1998) and handedness determined by the Edinburgh handedness inventory (Oldfield, 1971). Pressure pain-thresholds, strength and motor-control strategies for the dominant extremities were collected for each subject at baseline- and post-intervention.

The data collection was carried out in a structured manner focusing on a high degree of reproducibility, with the same procedure at baseline and post-intervention. The PPTs were measured initially. Afterwards the subjects underwent a position control task of the dominant leg, with a following 3 Maximal voluntary contractions of the same segment. Thereafter, the subjects did 4 position control tasks with both upper extremities; the measurement of position control was only done on the dominant side. Finally, 3 MVCs of the upper extremities were completed.

Pressure pain-thresholds

Pain levels were measured as the pressure pain-thresholds (PPT) of subjects. PPT measurements were done with a SBMEDIC algometer (type II, probesize: 1cm^2), determining PPT at ten specific sites on the days of testing. Measurements were done by placing the probe at predetermined points and increasing pressure by 40 Kilopascal/second (kPa/s) until subjects pushed a handheld trigger. Subjects were thoroughly instructed to push and release the trigger at the exact time they felt a painful sensation, kPa at pain-thresholds were thereby provided. Bilateral measurements at suboccipital muscle insertions, origin of supraspinatus, medial border of trapezius, rectus femoris muscle and tendon provided a somewhat objective indicator of subjects' PPT (fig 1.).

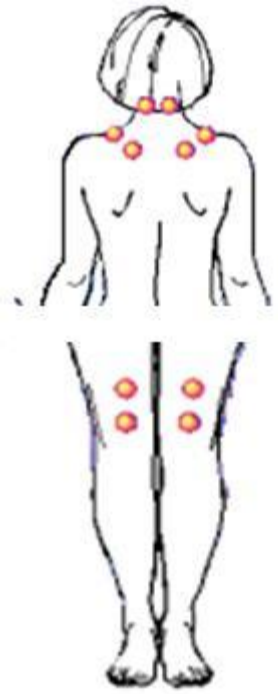

Fig 1. illustration of the selected points for pressure point threshold testing.

Strength

Maximum strength was determined by performing three maximum voluntary contractions (MVC) with both arms, and the dominant leg. Maximum strength was determined as the highest level of force produced from three repetitions. During MVC of the leg, subjects were placed in a chair, with straps over the waist, nondominant thigh and shoulder in order to limit movement to the segments involved in the task. The dominant leg was placed by an attachment to a dynamometer (fig.2). Subjects were instructed to "kick and hold as much force as you can against the pillow on the attachment for 5 seconds". Subjects could hold on to the strap over the nondominant shoulder if they wished during the MVC.

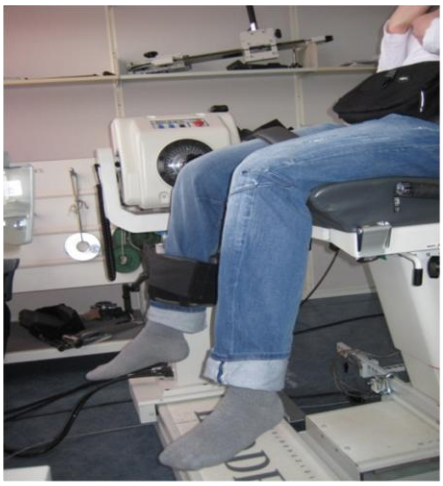

Fig 2. Setup for knee-extension MVC. The dominant leg was fastened to an attachment in a dynamometer.

Arm strength was measured by fastening straps proximally to the radiohumeral joint while sitting in a chair (fig. 3). The straps were attached to force-transducers (Interface inc. Scottsdale, Arizona). During MVC of the arms, the subjects were provided with a footrest. Subjects were instructed to abduct their arms as hard as they could for 5 seconds. They were instructed to use their neck-musculature as little as possible, since the measurements were intended to measure the medial section of the deltiodeus muscle.

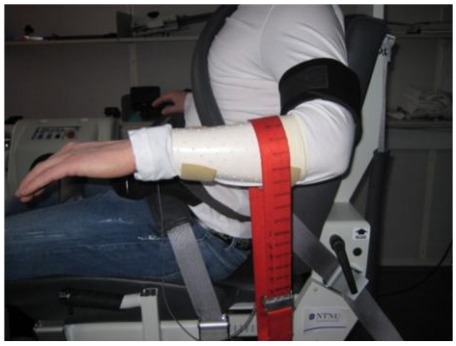

Fig 3. Setup for arm-abduction MVC, red straps were attached to force transducers.

Position control

A position control task was used to measure motor control. Subjects were instructed to hold their arms in an abduction of 45 degrees for 45 seconds. The position fluctuation was determined by an accelerometer attached laterally on the most horizontal area of the humerus by double-sided adhesive tape (fig 4). The arm-task was done 4 times, first with no external load, then with external loads of 0.5, 1, and 2kg attached proximally to the radiohumeral joint (Fig 4.).

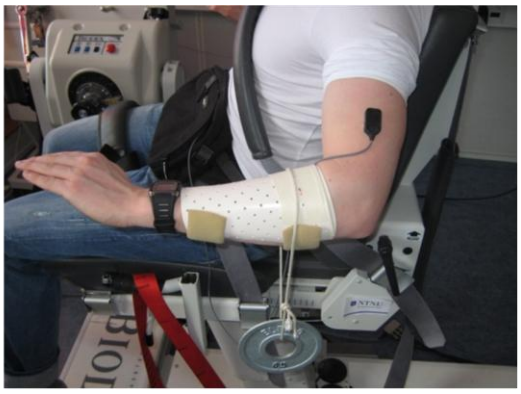

Fig 4. Setup for motor-control tasks. Arms in 45° abduction. Accelerometer placed laterally on the overarm, weights hanging proximal to the radiohumeral joint..

Visual feedback gave continuous information about the extremity's position on a 19" screen placed approximately 100cm in front of the subjects, allowing them to adjust their arm during the task in order to find the position they were instructed to hold.

The position was illustrated by a solid white line on a black background in the middle of the screen. Subjects were instructed to "cover the white line as well as possible with the green signal". "The green signal" was feedback from the accelerometer relative to the extremity`s position. If they were not able to see the white line, one of the researchers would point it out for them at the beginning of the task.

Visually, the task started on the left side of the screen, the signal would travel along the screen for 45 seconds at a speed of approximately 0.5cm/second. When the signal had reached the right side, the task was finished and subjects were given a 60 second break.

The same protocol was performed for gathering data on a position-holding in knee extension with the dominant leg. The data was not reliable because of noise distorting the accelerometer-signal; the information is thus not included in this thesis.

Exercise intervention

The exercise intervention lasted for 12 weeks and consisted of low to moderate intensity of aerobic endurance exercise. Subjects went through a cycling exercise program in groups on spinning ergometer bikes twice a week lasting for 45-50 minutes. Each session consisted of 6-7 minutes of warm-up on a spinning ergometer bike, then 4-5 periods lasting about 7 minutes with moderate intensity. Each period was followed by approximately 2 minutes of low intensity breaks. The intensity of the exercise session was increased gradually through the weeks of exercise.

Data analysis and statistics

MATLAB for windows (The Mathworks, Nattick, USA; version 2009a) was used on the continuous force- and position-data in order to produce parametric data for statistical analyses. The force-data was processed through a 6 Hz low pass filter before extracting maximum values. In position control data the first 10 seconds of the tasks were excluded since subjects used this time to attain the desired position. The standard deviation of acceleration (SDa) was then extracted for the remaining 35 seconds for each task, and is used in analyses as the absolute position variation. Thereafter, the percentage of total energy in the frequencies of 5-7 Hz (Lfs) and 8-12 Hz (Hfs) was extracted by power spectrum analysis. This provided 2 variables used to describe frequencies of variation. Lfs represented position variation of spinal control, while Hfs represented variation of supraspinal control (Takanokura & Sakamoto, 2001).

Mean PPT from each measurement site on the upper body was calculated into a single variable representing mean upper body PPT (uPPT). The same was done for lower body PPT (lPPT).

The MVC data from the upper extremities was calculated into a single variable by adding the mean values from both arms.

Statistical testing was done by SPSS (version 17.0 SPSS Inc., Chicago, IL, USA). Depending on Shapiro-wilk tests, which provided information on whether or not there was a normal distribution, parametric or nonparametric tests were run. A general linear model with repeated measurements (GLM) was applied for studying test effects, group effects and

interaction effects. An independent samples t-test was used to compare groups, while a paired t-test was utilized to study test-effects.

Two nonparametric tests were applied. Group comparisons at baseline and post-intervention were done by a Mann-Whitney u-test. A Wilcoxon signed ranks test was used to determine test-effects and compare outcomes across groups from baseline to post-intervention.

Analyses were performed in a stepwise manner. First, group differences at baseline and post-intervention were tested. Then group differences in alterations from baseline to post-intervention were tested. Third, both groups were combined in the same analyses to determine if there were test effects.

Attrition

10 subjects from FMG and 5 subjects from CG withdrew from the exercise program. The main reasons were health problems unattributable to the intervention, or personal issues, 2 subjects reported worsening of FM symptoms related to the intervention. Nevertheless, one of the withdrawn subjects from the FMG who had a low participation percentage was available for post-intervention testing, leaving 16 FMG-subjects and 20 CG-subjects for statistical analyses. The criteria for significant findings were $p \leq 0.05$ for all tests.

Ad hoc testing

The mean percentage of exercise participation was low (60.36 % for FMG and 70.6 % for CG), therefore it was hypothesized that those who participated the most would have the greatest strength, PPT and position control improvements. In order to determine the effects of more or less exercise participation, subgroups within CG and FMG according to participation percentage were created. The cut-off point was 75% (approximately 9 weeks) of the total exercise period. Subjects in the FMG who participated less than 75% were put in a subgroup of low participation (FMG_{LP}, N = 8) while those who participated more than 75% were placed in a subgroup of high participation (FMG_{HP}, N = 8). The same criteria was made for CG_{LP} (N = 4) and CG_{HP} (N = 15). Results from analyses of these groups were called “exercise effects”. The statistical tests were either a Paired samples T-test or a Wilcoxon signed ranks test depending on the normal distribution obtained from a shapiro wilk test.

It was believed that subjects within the FMG who had the greatest increase in PPT would have reduced levels of experienced pain. This was believed to be a factor for performing better than in voluntary strength and position control tasks. To test this, the FMG was divided into two groups of the largest/smallest increase in PPT (PPT+, N = 8 / PPT-, N =

8) to determine if changes in PPT gave different results in strength or position control than the initial analyses on the FMG. The statistical testing was done by a Mann-Whitney U-test and a Wilcoxon signed ranks test, since a Shapiro wilk test found no normally distributed data.

Results

Pressure pain-thresholds

CG had 68.6 % higher mean uPPT and 53.2 % higher mean lPPT than FMG at baseline, post-intervention uPPT was 49.5 % higher, lPPT was 54.4 % higher, all group differences were significant (Mann-Whitney U test $p < 0.05$) (fig 5). Mean lPPT was significantly higher than mean uPPT within both groups at baseline and post-intervention (wilcoxon signed ranks test $p < 0.001$) (fig 5).

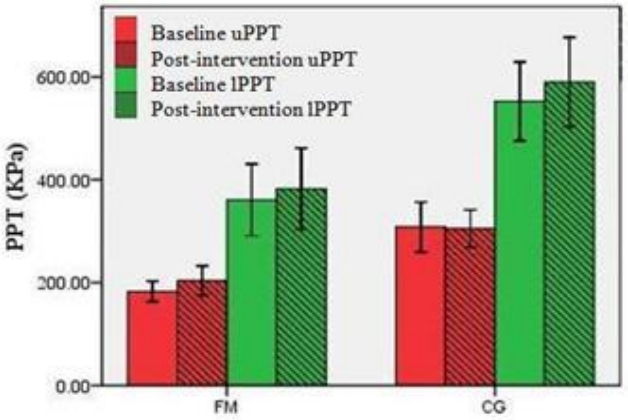

Fig 5. Baseline and post-intervention mean PPT for FMG and CG. Columns represent baseline and post-intervention PPT (KPa). Error-bars represent 95 % CI

The ratio between mean uPPT and lPPT was not significantly different between groups at baseline or post-intervention (Mann-Whitney U-test $p > 0.3$) and did not change from baseline to post-intervention in any group (Wilcoxon signed ranks test $p > 0.2$). No groups showed significant alterations in mean uPPT or lPPT from baseline to post intervention (Wilcoxon signed ranks test $p > 0.1$), but there was a test effect for increased lPPT when both groups were combined (Wilcoxon signed ranks test $p < 0.05$).

When subgroup-analyses according to exercise-participation were performed, there were no systematic differences indicating an exercise-effect within FMG or CG. The only significant finding was that FMG_{LP} had significant increase in lPPT (Wilcoxon signed ranks test $p = 0.05$). All other p-values within subgroups were > 0.1.

Strength

A GLM with test number as a repeated measure, showed significant differences in knee-strength between groups ($p < 0.001$). The CG had 33.4 % higher MVC than the FMG at baseline. The same measure was 23.3 % higher than the FMG post-intervention (fig 6 A.). The GLM showed a significant increase in knee-strength from baseline to post-intervention for both groups ($p < 0.001$). CG increased MVC by 22 % (absolute change = 32.5 Nm), FMG increased by 32 % (absolute change = 35.3Nm). No interactions were found ($p > 0.4$).

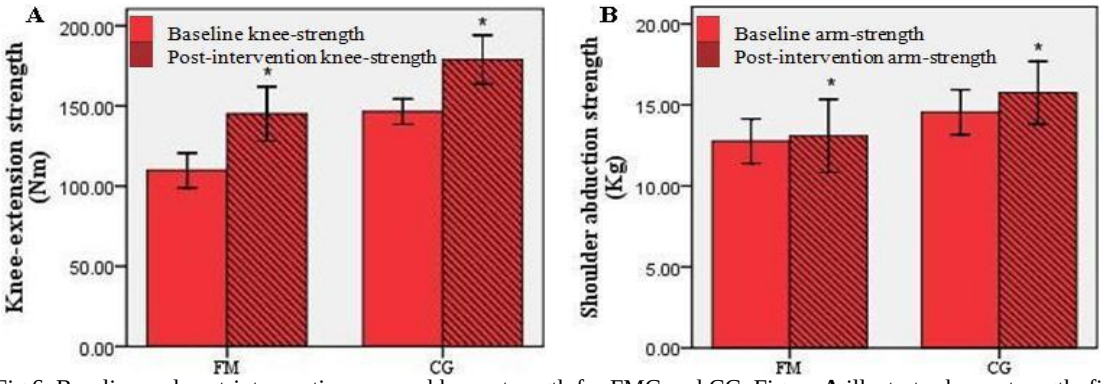

Fig 6. Baseline and post-intervention arm and knee-strength for FMG and CG. Figure **A** illustrates knee-strength, figure **B** illustrates arm-strength. Columns represent strength (Kg for arm, Nm for knee). Error bars represent 95% CI. * Indicates significant strength increase within groups at $p < 0.05$ level.

A GLM with test number as repeated measures revealed significant group differences in arm-strength ($p = 0.049$). CG had 13.3 % higher MVC than FMG at baseline, the difference increased to 19.8 % post-intervention. There was also a significant test effect in arm strength from baseline to post-intervention ($p < 0.01$) (fig 6 B). The increase was 8.3 % for CG (absolute change = 1.2Kg) and 2.3% for FMG (absolute change = 0.3Kg). No interactions were found ($p > 0.6$).

There were no significant findings in analyses of subgroups according to exercise participation for arm strength (wilcoxon signed ranks test $p = 0.075$ for FMG_{LP}, $p > 0.1$ for other subgroups), indicating no exercise-effect. There was a significant increase in knee-strength for all subgroups (Paired samples t-test $p < 0.01$) except for CG_{LP} ($p = 0.067$).

The subgroups of PPT+/PPT- had no significant differences in arm- or knee-strength at any measurement time (Mann-Whitney U test $p > 0.06$ for knee-strength, $p > 0.5$ for arm strength). A wilcoxon signed ranks test found no significant increase in arm-strength ($p > 0.1$), but a significant increase in knee-strength for both PPT-/PPT+ ($p < 0.05$).

Position control

There were no systematic significant group differences at baseline or post intervention for Standard-deviation of acceleration (SDa) (fig 7) (Mann-Whitney U-test $p > 0.2$. However, $p = 0.053$ for task 4 post-intervention), or a test-effect (Paired samples t-test $p > 0.4$). Wilcoxon signed ranks test found a decrease in SDa in task 4 from baseline to post-intervention for the CG ($p < 0.05$) (fig 7).

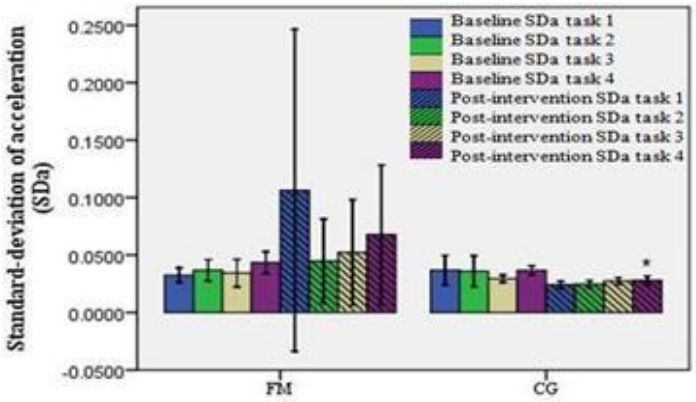

Fig 7. Baseline and post-intervention SDa for FMG and CG. Error bars represent 95% CI. * = significant baseline to post alterations at $p < 0.05$ level

A Mann-Whitney U test revealed a significantly higher percentage of position-variation in Lfs and a corresponding lower percentage in Hfs in all tasks for FMG compared to CG at baseline ($p < 0.05$) (fig 8 A and B). Post intervention significant group differences were; a higher percentage of Lfs in task 1 for FMG, and a higher percentage of Hfs in task 4 for CG (Mann-Whitney U-test $p < 0.05$). There was a test effect in the following frequency-bands: decrease of Lfs in tasks 1-4, increase in Hfs in tasks 1-3 (Paired samples t-test $p < 0.05$).

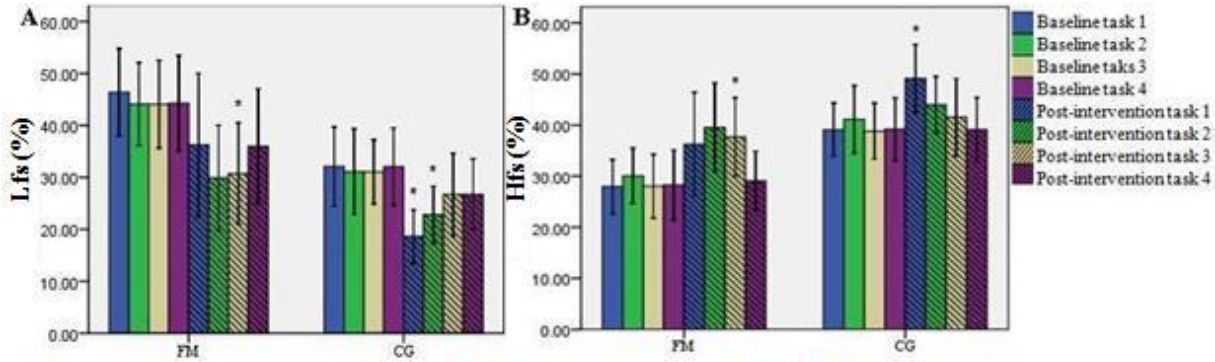

Figure 8. Baseline and post-intervention data-distribution from position control tasks for FMG and CG. Figure **A** represents percentage of total energy in low frequencies of 5 - 7 Hz (Lfs), figure **B** represents percentage of total energy in high frequencies of 8 - 12 Hz (Hfs). Each column represents one task. Error bars represent 95% CI. * = significant baseline to post alterations within groups at $p < 0.05$ level.

The CG had a significant increase in Hfs in task 1, and a decrease in Lfs in tasks 1 and 2 from baseline to post-intervention (fig 8 A and B) (Wilcoxon signed ranks test $p < 0.05$). The FMG increased significantly in Hfs in task 3 and decreased in Lfs in task 3 (fig 8 A and B) (Wilcoxon signed ranks test $p < 0.05$).

When subgroups according to exercise participation were considered, a Wilcoxon signed ranks test found a significant increase from baseline to post-intervention in Hfs task 3 for FMG_{LP} ($p < 0.05$). The same test found a decrease in Lfs task 1, an increase in Hfs task 1 and a decrease in SDa task 4 for CG_{HP} ($p < 0.05$).

PPT- showed significantly higher SDa than PPT+ in task 1 at baseline (0.039 +- 0.016 VS 0.023 +- 0.0046) (Mann-Whitney U-test $p < 0.05$, other measures were $p > 0.1$). Post-intervention measurements found no significant differences between PPT+/PPT- (Mann-Whitney U-test $p > 0.1$). Baseline to post-intervention testing showed a significant decrease in Lfs in task 4 for PPT+, while Hfs in task 3 increased in PPT- (Wilcoxon signed ranks test $p < 0.05$, other measures were $p > 0.06$).

Discussion

The main findings when comparing groups in from this study, were lower pressure pain-thresholds and strength in the shoulders and knee in the FMG compared to the CG. There were also differences in frequency-bands of position-variation, while the absolute variations were similar in both groups. Though pressure pain-thresholds in the FMG were lower than in the CG, the ratio between upper and lower extremity thresholds was not different between groups, indicating that both groups had the same distribution in this measure, but the FMG had a generally lowered threshold.

The main intervention effects were similar strength increases in knee-extension and arm-abduction in both groups. There were also similar increases in pressure pain-thresholds and position control outcomes for both groups after training. When both groups were combined, a test-effect for increased pressure pain-thresholds in the lower extremities was found. There were test effects showing a decrease of total energy in low frequency-bands in tasks 1-4 and an increase in high frequency bands in tasks 1-3. The results indicate that groups had similar effects from exercise. Additionally, the study found no results indicating that more or less exercise participation, or changes in pressure pain-thresholds had specific effects on the primary outcome variables.

The supposed role of central factors on fibromyalgia pain (Cohen et al. 2000; Martinez-Lavin, 2004; Sarzi-Puttini et al. 2006) and the effects of pain on motor control (Sterling et al. 2001) lead to the assumption that a regulation in central processes from AE could result in reduced pain and thereby improved motor control and strength.

The increase in knee extension strength for both groups was above the 20 % minimum criteria of change attributable to an exercise program (Dvir, 2003). The FMG had a slightly higher relative increase than the CG (FMG increased by 32 %, CG increased by 22 %). Low levels of physical fitness has been associated with women with FM (Panton et al. 2006; Hasset et al. 2007), therefore, women in the FMG may have been more susceptible to physiological changes from exercise. This may explain the higher relative increase compared to the CG. On the other hand, a low level of physical activity was a requirement for study-entry, which should have left a CG without a particularly high physical activity level. Hence, the low resistance-loads in spinning-cycling were most likely adequate to improve strength in the lower extremities for both groups. Central regulations in both groups of subjects from exercise has been shown before (Jurca et al. 2003; Okazaki et al. 2005; Figueroa et al. 2008), but such effects from AE on FM are still not proven. Though strength increase from strengthening exercise is common for FM (Häkkinen et al. 2002; Kingsley et al. 2005; Figueroa et al. 2008), such results has not been shown before from AE. Also, strength increase attributable to central regulations has not been found before. However, the strength increase of the upper extremities may have been of a different origin than the increase in lower extremity strength, which most likely could be attributed to the AE. At the same time, the specific factor leading to the upper extremity strength increase could not be identified. The relative change in strength was similar in both groups, and the only common denominator for both groups was participation in the same exercise program. The CG increased slightly more (8.3 % for the CG, 2.3 % for the FMG), indicating that no effect on this level was specific for the FMG. The effects were small, and may be associated to the degrees of freedom available in the task. The arm abduction task was not as mechanically restrained as the knee-extension tasks. A slight inward rotation of the shoulder or supination of the forearm could allow for recruitment of other muscles. This should not be the case, since the instructions of the task were thorough. Nevertheless, subjects had some variations in their performance. However, arms are typically used for stabilizing the body during spinning, which may have been the basis for their slight strength increase.

The increased level of low frequency band variation for the FMG at baseline indicated a differing strategy for maintaining a position over time compared to the CG. This difference seemed to be stable and not in associated with the external loads during tasks. The CG had a greater contribution from high frequency bands during the position control tasks. According to Takanokura & Sakamoto (2001), this could indicate that the frequency of variation in the

FMG was more of spinal origin, while the variation in the CG was more of central origin. If the frequency band-distributions from the CG were to represent normal motor control, the FMG seemed to have a reduced central contribution at baseline. However, the post-intervention results for the FMG showed changes towards the baseline levels of the CG in all frequency bands. The similar tendency of change in both groups for position control data indicated that the FMG had the same effects as the CG, and had come closer to "normal" levels after exercise. The fact that this change was in the upper extremity, which had not been exercised, indicates that central processes had been changed. Also, the presented change had taken place despite of fairly stable PPT-values. This is in conflict with the initial assumption that reduced PPT would predict improved position control. The analyses of PPT+/PPT- groups showed no convincing results on this matter, except for PPT- who had a high absolute variation in task 1 at baseline. No other results argued for systematic differences between PPT+/PPT-.

The study intended to compare a similar position control task of the dominant lower extremity to the upper extremity. As presented earlier, the data collected was not reliable and was therefore not included for this thesis.

The present study is the first to evaluate the relationship between AE and central changes for FM, the addition of an exercising healthy control group is also different from other studies. It was suspected that central regulations comparable to those found in earlier studies could occur from AE. The results from Okazaki et al. (2005) and Jurca et al. (2003) indicated the potential of AE in regulating autonomic function in general, while Figueroa et al. (2008) showed that such changes could occur from strengthening exercise for FM. A study by Brandsarbakken (2010) on the same subjects as in this study found no ANS dysfunction in the FMG. There may be a possibility that our FMG had no ANS dysfunction, and that the effects from exercise may be attributable to improved physical functioning. Nevertheless, "central sensitization" or an altered HPA-axis may be present (Sarzi-Puttini et al. 2006; Staud et al. 2009) and may be affecting strength and position control.

A lack of effects on central levels can not be confirmed, since we have no measure on the ANS, HPA axis or a measure of central sensitization. For the same reason, the hypothesis that alterations at a central level may have taken place cannot be rejected. The increase in arm strength and changes in position control-properties may be indicators of some change. Nevertheless, an MVC increase of 2.3 % (FMG) and 8.3 % (CG) in arm abduction is not of

any physiological relevance when concerning strength increase from exercise (Dvir, 2003). Nevertheless, there is currently no clear cut-off available to determine what increases in strength can be attributed to central changes. Additionally, there is no firm evidence that improved central functioning will necessarily result in improved strength.

Even though there is some evidence arguing for central changes, the most prominent results seem to be of local origins attributable to the exercise (ref. increases in pressure pain-thresholds and strength in the lower extremity). Moreover, the similar effects on pressure pain-thresholds in both groups argue against the assumption that AE can reduce pain through a regulation at a central level. Reduced pain levels from exercise has previously been related to FM (Wigers, Stiles & Vogel, 1996;Richards & Scott, 2002; Valim et al. 2003; Gusi et al. 2006; Bircan et al. 2008) and healthy controls (Bircan et al. 2008). We found results argumenting that AE can increase local pressure pain-thresholds in trained muscles, which may be useful for individuals experiencing day-to-day pain or merely sedentary individuals in general. Additionally, the FMG had only a slight increase in pressure pain-thresholds after the exercise period, while their knee extension strength was comparable to the strength of the CG at baseline. This argues against pain causing reduced strength. The same tendency of change after exercise was shown in position control properties, also in contrast to the initial assumption that pain would predict poor position control in FM. In general, the FMG had the same effects from training as the CG, despite lower pressure pain-thresholds.

The comparable effects from training of the FMG from this study adds to the literature stating that women with FM are equally trainable compared to controls (Gusi et al. 2006; Häkkinen et al. 2001; Häkkinen et al. 2002). There have not been previous studies on AE showing effects on strength for FM. The specific contribution from the present study regarding strength was that AE is sufficient to increase strength for women with FM and healthy controls. The strength increase may improve the ability to perform activities of daily living such as gardening. This may be especially useful for the FMG, when considering that muscle weakness is common for this group (Panton et al. 2006). The results strengthen the potential of AE in improving aspects of FM, and may suggest cycling as an alternative to strengthening exercise. In addition, the attrition rate from this study suggests that even low- to moderate intensity exercise may be overwhelming for sedentary women with FM.

Models of pain motor control are hard to apply, since they are composed of a complex set of phenomena which are mostly observed in acute pain. The heterogeneity of the FM

condition leaves any single model hard to attribute beyond individuals with FM. The difference between groups in position control at baseline may be a manifestation of the delayed or inhibited synergistic functions described by the neuromuscular activation model. The synergistic alterations are believed to produce altered control of neuromuscular activity (Sterling et al. 2001), reducing joint stability. This may have been the cause of group differences in frequency of variation at baseline. The pain-adaptation model seems to be non-applicable to the FMG. This model describes unusual movement patterns caused by muscle pain, which was not observed in the position control tasks. The differing distribution of frequency bands may be caused by the presence of "central sensitization", sensitizing of alpha motor neurons, it may also be a result of a sensitized fusimotor system as described in the vicious cycle model (Sterling et al. 2001).

Similar protocols investigating motor control as the one in this study may provide a basis for identifying motor alterations in FM objectively. Thereby, specific motor control deviations can be found beyond those describing aberrant movements. The only general consensus seems to be that muscle activation and recruitement may be changed in the presence of pain (Sterling et al. 2001). It is suspected that prolonged muscular activity may be the source of pain in the first place.

In conclusion, the effects from AE on position control, pain and strength from low to moderate exercise were similar for the FMG and CG. This adds to the existing literature stating the equal trainability of women with FM compared to healthy controls. New findings are that aerobic exercise is sufficient to improve strength, and it seems to change the frequency of position variation for both groups. Merely low doses of low- to moderate intensity AE is needed to achieve these effects. Changes in pressure pain-thresholds do not influence strength or position control changes. Also, women with FM seem to have a distribution of upper and lower body pressure pain-thresholds comparable to healthy women, but a generally lowered threshold. There is no absolute truth to the proposed central deficiencies in FM, and models of motor control and pain are hard to attribute to this condition. The strengthening of muscles and normal responses to exercise in this study leads to an assumption that muscles of women with fibromyalgia are normal.

The results are not sufficient to prove or disprove effects of AE on global mechanisms for FM, or the effects of global mechanisms on strength, pain or motor control. More research is needed on this area for FM, as it may lead to substantial benefits for this group of subjects.

Limitations of the study

The selection of subjects was based on self-reported physical activity levels, which may have lead to under-reporting, depending on what subjects regarded as physical activity. There was no non-exercising FM group for outcome comparisons; such a group may have provided a basis to describe specific changes for the FMG. Also, the pressure pain-thresholds may not be sufficient in measuring fibromyalgia-pain. Measurements on all 18 tender points may have created a better understanding of the impact AE may have had on the experienced pain in fibromyalgia. The MVC protocol of arm-abduction in this study has many degrees of freedom, enabling many muscles to contribute; a more restricted MVC task may have been more reliable. Also, the missing data on position control for the dominant leg limited the analyses of aerobic exercise and its effects on position control.

References

Arendt-Nielsen, L. Graven-Nielsen, T. (2008) Muscle pain: sensory implications and interaction with motor control. *Clinical Journal of Pain,* 24, (4), pp 291 – 298.

Arendt-Nielsen L. & Fallah D., (2009) Motor control adjustments in musculoskeletal pain and the implications for pain recurrence. *Pain,* 142, pp. 171-172

Banic B., Petersen-Felix S., Andersen OK., Radanov BP., Villiger PM., Arendt-Nielsen L., Curatolo M. (2004) Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. *Pain,* 107, (1-2), pp. 7–15.

Bengtsson M., & Bengtsson A. (1988) Regional sympathetic blockade in primary fibromyalgia. *Pain*, 33, (2), pp. 161-167.

Bircan Ç., Seide A. K., Akgün B., El, Ö. & Alper S. (2008) Effects of strengthening versus aerobic exercise program in fibromyalgia. *Rheumatology international*, 28, (6), pp. 527-532.

Brandsarbakken (2010) Effects of aerobic exercise on autonomic function and pain in women with fibromyalgia. *Masters thesis, NTNU.*

Casale R., Sarzi-Puttini P., Atzeni F., Gazzoni M., Buskila D., Rainoldi A. (2009) Central motor control failure in fibromyalgia: a surface electromyography study. *BMC Musculoskeletal Disorders,* 10, (78), pp. 1-9.

Cohen H., Neumann L., Shore M., Amir M., Cassuto Y., Buskila D. (2000) Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. *Seminars in Arthritis and Rheumatism,* 29, (4), pp. 217-227.

Clauw D. J., Crofford L. J., (2003) Chronic widesat baselinead pain and fibromyalgia: what we know, and what we need to know. *Best Practice & Research Clinical Rheumatology*, 17, (4), pp. 685 – 701.

Craig C. L., Marshall A. L., Sjöström M., Bauman A. E., Booth M. L., Ainsworth B. E., Pratt M., Ekelund U., Yngve A., Sallis J. F., Oja P. (2003) International physical activity questionnaire: 12-country reliability and validity. *Medicine and science in sports and exercises,* 35, (8), pp. 1381-1395.

Desmeules J. A., Cedraschi C., Rapiti E., Baumgartner E., Finckh A., Cohen P., Dayer P., Vischer T. L. (2003) Evidence of central sensitization in patients with fibromyalgia. *Arthritis and Rheumatism*, 48, (5), pp. 1420-1429.

Dvir, Z. (2003) How much is necessary to indicate a real improvement in muscle function? A review of modern methods of reproducibility analysis. *Isokinetics and Exercise science,* 11, (1), pp. 49-52.

Elias J. L., Bryden M. P., Bulman-Fleming M. B. (1998) Footedness is a better predictor than is handedness of emotional lateralization. *Neuropsychologia,* 36, (1), pp. 37-43.

Figueroa A., Kingsley J., McMillan V., Panton L. (2008). Resistance exercise training improves heart rate variability in women with fibromyalgia. *Clinical Physiology and Functional Imaging,* 28, (1), pp. 49-54.

Gerdle B., Grönlund C., Karlsson S. J., Holtermann A., Roeleveld K. (2010) Altered neuromuscular control strategies of the trapezius muscle in fibromyalgia. *BMC Musculoskeletal Disorders,* 11, (42), pp. 1-8.

Gowans E. S., deHuek A., Voss S., Silaj A., Abbey S. E. (2004) Six-month and one-year followup of 23 weeks of aerobic exercise for individuals with Fibromyalgia. *Arthritis care & research,* 51,(6), pp. 890 – 898.

Gusi N., Tomas-Carus P., Häkkinen A., Häkkinen K. & Ortega-Alonso A. (2006) Exercise in waist-high warm water decreases pain and improves health-related quality of life and strength in the lower extremities in women with fibromyalgia. *Arthritis and Rheumatism,* 55, (1), pp. 66-73.

Häkkinen, A., Häkkinen, K., Hannonen, P. & Alen, M. (2001) Strength training induced adaptations in neuromuscular function of premenopausal women with fibromyalgia: comparison with healthy women. *Annals of the Rheumatic Diseases,* 60, (1), pp. 21 – 26.

Häkkinen, A., Pakarinen, A., Hannonen, P., Häkkinen, A., Airaksinen, O., Valkeinen, H. & Alen, M. (2002) Effects of strength training on muscle strength, cross-sectional area, maximal electromyographic activity, and serum hormones in premenopausal women with fibromyalgia. *Journal of Rheumatology,*29,(6), pp.1287-95.

Hassett, A. L., Radvanski, D. C., Vaschillo, E. G., Vaschillo, B., Sigal, L. H., Karavidas, M. K., Buyske, S. & Lehrer, P. M. (2007) A pilot study of the efficacy of heart rate variability (HRV) biofeedback in patients with fibromyalgia. *Applied Psychophysiology & Biofeedback,* 32, (1), pp. 1-10.

Jurca R., Church T. S., Morss G., Jordan A., Earnest C. (2003) Eight weeks of moderate-intensity exercise training increases heart rate variability in sedentary postmenopausal women. *American heart journal,* 147, (5), pp. e8-e15.

Kingsley J. D., Panton L. B., Toole T., Sirithienthad P., Mathis R., McMillan V. (2005) The Effects of a 12-Week Strength-Training Program on Strength and Functionality in Women With Fibromyalgia. *Archives of physical medicine and rehabilitation,* 86, (9), pp. 1713 – 1721.

Martinez-Lavin, M. (2004) Fibromyalgia as a sympathetically maintained pain syndrome. *Current pain and headache reports,* 8, (5), pp. 385 – 389.

Okazaki K., Iwasaki K., Prasad A., Palmer M., Martini E., Fu Q., Arbab-Zadeh A., Zhang R., Levine B. (2005) Dose-response relationship of endurance training for autonomic circulatory control in healthy seniors. *Journal of applied physiology,* 99, pp. 1041-1049.

Oldfield, R. C. (1971) The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia,* 9, (1), pp. 97-113

Panton L., Kingsley J., Toole T., Cress M., Abboud G., Sirithienthad P., Mathis R., McMillan V. (2006) A comparison of physical function performance and strength in women with fibromyalgia, age- and weight-matched controls, and older women who are healthy. *Physical therapy,* 86, (11), pp. 1479 – 1488.

Richards, S. C., Scott, D., L. (2002) Prescribed exercise in people with fibromyalgia: parallel group randomized controlled trial. *Boston Medical Journal.* 325 (7357):185.pp. 1-4.

Rooks D. S., Gautam S., Romeling M., Cross M. L., Stratigakis D., Evans B., Goldenberg D. L., Iversen M. D., Katz J. N. (2007) Group exercise, Education, and Combination Self-management in Women With Fibromyalgia, A randomized trial. *Archives of internal medicine,* 167(20) pp. 2192-2200.

Sarzi-Puttini, P., Atzeni, F., Diana, A., Doria, A., Furlan, R. (2006) Increased neural sympathetic activation in Fibromyalgia syndrome. *Annals New York academy of sciences,* 1069 pp. 109 – 117.

Staud R. (2002) Evidence of involvement of central neural mechanisms in generating fibromyalgia pain. *Current Rheumatology Reports*, 4, pp. 299–305

Staud, R., Nagela S., Robinson M. E., Price D. D. (2009) Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: a randomized, double-blind, placebo-controlled study. *Pain,* 145, (1), pp. 96 – 104.

Sterling, M., Gwendolen J. & Wright, A. (2001) The effect of musculoskeletal pain on motor activity and control. *The journal of pain*, l 2, (3), pp. 135 – 145.

Takanokura M., Sakamoto K. (2001) Physiological tremor of the upper limb segments. *European journal of applied physiology*, 85, (3-4), pp. 214-225.

Valim, V., Olivieira, L., Suda, A., Silva, L., de Assis, M., Neto, T. B., Feldman, D., Natour, J. (2003) Aerobic fitness effects in Fibromyalgia. *The journal of rheumatology,* 30, (5), pp. 1060 –1069.

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

Wigers, H. S., Stiles, T. C. & Vogel, P.A. (1996) Effects of Aerobic Exercise versus Stress Management Treatment in Fibromyalgia. A 4.5 year prospective study. *Scandinavian Journal of Rheumatology,* 25,(2), pp. 77 – 86.

Wolfe F. et al. (1990) The American College of Rheumatology 1990 Criteria For The Classification of Fibromyalgia, Report Of The Multicenter Criteria Committee. *Arthritis and Rheumatism,* 33, (2), pp.160 – 172.