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Heli Valkeinen

Physical Fitness, Pain and Fatigue in Postmenopausal Women with Fibromyalgia

Effects of Strength Training

JYVÄSKYLÄN YLIOPISTO

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UNIVERSITY OF JYVÄSKYLÄ

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ABSTRACT

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Finnish summary
Diss.

Fibromyalgia (FM) is a chronic non-inflammatory pain syndrome characterized mainly by widespread pain, fatigue and sleep disturbance. Its pathophysiology is still unknown and no curative treatment exists. Exercise training is usually recommended to persons with FM as one part of the treatment program; however, strength training has been studied very seldom in persons with FM. The purpose of this thesis was 1) to compare neuromuscular and aerobic performance, functional capacity, pain and fatigue between postmenopausal women with fibromyalgia (FMW) and healthy women (HW) and 2) to examine the acute responses of heavy-resistance fatiguing loading and the effects of regular strength training on neuromuscular performance, functional capacity, pain and fatigue. The age of the subjects was 50-70 years in two different study designs (study I: FMW n=23, HW n=11; studies II-IV: FMW n=26, HW n=10). Maximal muscle strength of different muscle groups was measured. Electromyographic activity of the lower leg muscles was recorded during the strength tests. The cross-sectional area of the quadriceps femoris was measured by magnetic resonance imaging and maximal oxygen uptake by the direct bicycle ergometer test. Functional capacity was assessed by 10-meter walking speed and 10-step stair-climbing time, and self-reported physical functional capacity by the Stanford Health Assessment Questionnaire. Pain and fatigue were assessed by the visual analog scale and quality-of-life by the RAND-36 questionnaire. For the strength training intervention women with FM (studies II-IV) were randomly assigned to a training (FMT; n=13) or a non-training control (FMC; n=13) group. HW served as the training controls. FMT and HW performed supervised progressive strength training twice a week for 21 weeks. To examine acute neuromuscular responses and exercise-induced muscle pain, a heavy-resistance fatiguing protocol was performed before and after the 21-week training period. The results showed that muscle strength of the lower extremities, work load and work time in the bicycle exercise test and functional capacity were lower in the postmenopausal FMW than in HW. Muscle strength in the upper body and maximal oxygen uptake did not differ between the groups. Heavy-resistance loading at week 0 and week 21 led to comparable decreases in maximal isometric leg extension force in FMT (25% and 26%) and HW (23% and 29%). The time course of exercise-induced muscle pain after the fatiguing loading was comparable between the groups. Strength training for 21 weeks improved the maximal muscle force of different muscle groups by 13-36% in FMT and by 24-37% in HW. Functional capacity improved in FMT, but remained unchanged in HW. No changes were observed in FMC. FMT reported a minor decreasing tendency in the FM symptoms and no adverse effects of the training were observed. The present study suggests that postmenopausal FMW may have decreased muscle strength, especially in the lower extremities. The acute neuromuscular responses and the time course of muscle pain after the fatiguing loading were comparable between the groups, suggesting normal fatiguing and recovery processes in FMT. The subjects were capable of improving their neuromuscular performance markedly by regular and progressive strength training and to carry the training out safely without exacerbation of symptoms. Therefore, individually tailored strength training is a recommendable exercise mode for postmenopausal women with FM.
Key words: fibromyalgia, physical fitness, strength training, pain, women, postmenopausal

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- There is a time for everything,
and a season for every activity under heaven –
Ecc 3:1

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Jyväskylä, September 2007

Heli Valkeinen

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles, which will be referred to in the text by their Roman numbers:

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II Valkeinen H, Häkkinen A, Hannonen P, Häkkinen K, Alén M. Acute heavy-resistance exercise-induced pain and neuromuscular fatigue in elderly women with fibromyalgia and in healthy controls. Effects of strength training. Arthritis Rheum 2006;54:1334-1339.

III Valkeinen H, Alén M, Hannonen P, Häkkinen A, Airaksinen O, Häkkinen K. Changes in knee extension and flexion force, EMG and functional capacity during strength training in older females with fibromyalgia and healthy controls. Rheumatology (Oxford) 2004;43:225-228.

IV Valkeinen H, Häkkinen K, Pakarinen A, Hannonen P, Häkkinen A, Airaksinen O, Niemitukia L, Kraemer WJ, Alén M. Muscle hypertrophy, strength development, and serum hormones during strength training in elderly women with fibromyalgia. Scand J Rheumatol 2005;34:309-314.

ABBREVIATIONS

ACR	American College of Rheumatology
BF	Biceps femoris muscle
CSA	Cross-sectional area
CV%	Coefficient of variation
DOMS	Delayed onset muscle soreness
EMG	Electromyography
FM	Fibromyalgia
FMC	Fibromyalgia control group
FMT	Fibromyalgia training group
GH	Growth hormone
HAQ	Health Assessment Questionnaire
HR_{max}	Maximum heart rate
HW	Healthy women
HWT	Healthy training women
IEMG	Integrated electromyography
MRI	Magnetic resonance imaging
QF	Quadriceps femoris
RAND-36	36-item health survey
RER	Respiratory exchange ratio
RM	Repetition maximum
VAS	Visual analog scale
VL	Vastus lateralis muscle
VM	Vastus medialis muscle
VO_{2max}	Maximal oxygen uptake
W_{max}	Maximal work load

CONTENTS

1 INTRODUCTION

The most common reason for seeking medical help among patients in Western societies is chronic pain (Gureje et al. 1998, Mäntyselkä et al. 2003) and one of the most common causes of chronic pain is fibromyalgia syndrome (FM) (White and Harth 2001). Chronic pain is estimated to affect on average 22% of primary care patients in different centres around the world (Gureje et al. 1998). The prevalence of FM varies between 0.5 to 5% in the general population (White and Harth 2001). In Finland the prevalence of FM has reported to be about 0.75%, which means over 50 000 patients (Mäkelä and Heliövaara 1991). It is most likely that the prevalence of FM has increased since the early 1990s, as the diagnosis of FM has become more familiar among physicians and the classification criteria have been changed since the study by Mäkelä and Heliövaara.

In the medical literature different muscle pain conditions have been described since the early 1800s. The names of such conditions have varied over the years - fibromyositis, myofascitis, myogelosis, muscular strain, muscular rheumatism, myofascial pain syndrome and psychogenic rheumatism being used among others (Jacobsen 1994, Wallace 1997). Sir William Gowers was the first to propose the term fibrositis, and around 1980 the term fibromyalgia was introduced (Wallace 1997). Since the 1980s attempts have been made to define fibrositis/fibromyalgia, the latest criteria being the American College of Rheumatology's (ACR) classification criteria of FM dating from 1990 (Yunus et al. 1981, Wolfe 1986a, Wolfe et al. 1990, Wessely and Hotopf 1999).

Fibromyalgia (Lat. fibra, fibre; Gr. mys, muscle; Gr. algos, pain; ia, condition) is a chronic non-rheumatic pain syndrome characterized by several different symptoms, such as widespread soft tissue pain, fatigue, sleep disturbance, morning stiffness, paresthesias, joint swelling, irritable bowel syndrome, headache, anxiety etc. (Yunus et al. 1981, 1988, Wolfe 1986b, Wolfe et al. 1990, 1995a, 1995b, 1997, Katz et al. 2006). Since the ACR's criteria were published (Wolfe et al. 1990), there has been continuous debate in the literature concerning the diagnosis of FM and its existence due to the fact that the criteria were not based on any objective findings (Forslind et al. 1990, Solomon and Liang 1997, Quintner and Cohen 1999, Ehrlich 2003a, 2003b, Hadler 2003, van Houdenhove 2003). This has also caused confusion in practice. In addition to FM several other syndromes exist with unexplained chronic pain and fatigue. These syndromes, such as chronic fatigue syndrome, myofascial pain syndrome and somatoform disorders, overlap with each other and also partly with FM (Schneider 1995, Clauw and Chrousos 1997, Clauw and Crofford 2003). Despite this criticism and also a suggestion that tender points should no longer be used as the essential criterion of FM in clinical use (Wolfe 2003), the ACR's criteria are still the most commonly used.

During the last two decades our knowledge about the effects of physical activity on health has increased enormously and exercise recommendations for the general healthy population (ACSM 1998b, Haskell et al. 2007) and also for healthy elderly people (ACSM 1998a, 2002) have been published with the aim of preventing risk factors for diseases and to enhance general health. At the same time it has been suggested that physical activity should be included more often in the prevention, treatment and rehabilitation programs of patients with different diseases and syndromes. However, more research is needed on the effectiveness, safety and suitability of different modes and dosages of physical activity (MSSE 2001).

Due to the unknown pathophysiology of FM treatments mainly concentrate on relieving subjects' symptoms (Goldenberg et al. 2004). Around 1975 it was noticed that deprivation of non-rapid-eye-movement sleep may be accompanied by the appearance of more musculoskeletal symptoms, such as pain, in sedentary persons than in physically fit persons (Moldofsky et al. 1975, Moldofsky and Scarisbrick 1976, McCain 1986). Most likely due to this finding physical activity, especially aerobic training was suggested, perhaps to the first time as a possible treatment for the fibrositis/fibromyalgia syndrome (Moldofsky et al. 1975, Moldofsky and Scarisbrick 1976, McCain 1986). However, the first randomized and controlled aerobic training study for these subjects was carried out not until themid-1980s (McCain 1986, McCain et al. 1988) and the first randomized and controlled 'pure' strength training study not until 2000 (Häkkinen et al. 2001a). Aerobic training has been shown to improve aerobic performance, tender point pain pressure threshold and pain (Busch et al. 2002, King et al. 2002, Valim et al. 2003, Assis et al. 2006), while strength training has been studied very seldom in subjects with FM (Busch et al. 2002).

The majority of the subjects with FM are women, and the highest prevalence of the syndrome has been found in 55-79-year-old women (Mäkelä and Heliövaara 1991, Wolfe et al. 1995b). However, the subjects in this age group have been studied least. In addition, it is known that most physical functions of the body decrease with increasing age and that this in turn will lead to decreased physical fitness. Therefore, in this thesis the focus is on *postmenopausal women with FM* (50-70 years old), while in the earlier studies the focus has mainly been in *premenopausal women with FM*.

Postmenopausal subjects with FM may have suffered from the symptoms for decades. Because the subjective symptoms of the syndrome, especially pain, have usually been localized in muscles, it is important to study whether this syndrome has an effect on muscle trainability. Thus, the first aim of this thesis was to compare different components of physical fitness, such as neuromuscular and aerobic fitness, between women with FM and healthy women in cross-sectional design (study I). Another purpose was to examine more specifically the effects of individual fatiguing loading exercise (acute responses) and regular strength training (long-term adaptations) on certain components of physical fitness, i.e. neuromuscular performance and functional capacity, and also on symptoms of FM, such as pain and fatigue, in a randomized controlled design (studies II-IV). In addition, the suitability and safety of strength training for postmenopausal women with FM is discussed.

2 REVIEW OF THE LITERATURE

2.1 Fibromyalgia

2.1.1 Symptoms, diagnosis, prevalence and demographics

Symptoms

The main symptom of FM is widespread pain in different parts of the body, especially in muscles and/or muscle-tendon insertions (Yunus et al. 1981, Wolfe et al. 1990). The intensity of pain can vary according to modulating factors such as stress, heat, and rest (Wolfe et al. 1990). The intensity of pain may be twice as high it is in subjects with rheumatoid arthritis (Viitanen et al. 1993). Subjects with FM often wake up feeling unrefreshed and thus, feel exhausted already in the morning (Wolfe et al. 1990, Moldofsky 2001). Depression and anxiety among other psychosomatic symptoms are also common in subjects with FM (Viitanen et al. 1993).

Subjects with FM may experience difficulties coping with different types of environmental stress and their symptoms may reflect those difficulties (Lorenzen 1994). The situation may lead to a vicious circle, where lack of coping skills may cause sleep disturbances, and fatigue may lead to decreased physical activity and poor physical fitness. This may again cause increased pain (Lorenzen 1994). Several subjects with FM are dissatisfied with their health (Wolfe et al. 1997) and they have limitations in their ability to work (Henriksson and Liedberg 2000, Henriksson et al. 2005) and manage everyday life activities (Henriksson 1994). Thus, the syndrome may strongly impair subjects' quality-of-life (Marques et al. 2005, Bennett et al. 2005, Bergman 2005).

Diagnosis

The current diagnosis of FM is based on the American College of Rheumatology's (ACR) classification criteria (Wolfe et al. 1990). The diagnosis is confirmed (Table 1), if a person has had widespread pain at least for three months and she/he has 11 or more tender points out of 18 specified points (Figure 1). At the moment the diagnosis is leaning to the number of tender points palpated with a recommended pressure of about 4 kg/cm^2 (Wolfe et al. 1990. Pain pressure threshold measured by dolorimetry has not been shown to be as sensitive a discriminator in identifying tender points as palpation (Wolfe et al. 1990).

Croft et al. (1994) have shown that people with chronic widespread pain do not necessarily have a high number of tender points and people with many tender points do not necessarily have chronic widespread pain. In people with chronic widespread pain tender points differ in their ability to predict FM and it is suggested, therefore, that perhaps all tender points do not equally merit inclusion in the criteria (White et al. 2000). However, a high number of tender points is associated with increased disability (Lundberg and Gerdle 2002) and distress in subjects with FM (Wolfe et al. 1997). Due to the widespread criticism it has been suggested that tender points should not be used as a diagnostic criteria in clinical practice (Wolfe 2003). However, no other surrogate criteria have yet been created.

Prevalence and demographics

Usually the onset of chronic pain in subjects with FM occurs in the 3rd or 4th decades of life (Yunus et al. 1981, Wolfe et al. 1995b) and increases over the years so that the highest prevalence of FM has been shown to be between the ages of 55 and 79 (Mäkelä and Heliövaara 1991, Wolfe et al. 1995b). In the adult population the prevalence of FM ranges from 0.6 to 10.5% (Mäkelä and Heliövaara 1991, Forseth and Gran 1992, Prescott et al. 1993, Wolfe et al. 1995b, White et al. 1999, Topbas et al. 2005). Remission of the symptoms is possible, but rare, and may favour a younger age (Pöyhiä et al. 2001, Fitzcharles et al. 2003). Prognosis of FM is unsatisfactory, although not life threatening (Wolfe et al. 1997). About 80-90% of the subjects with FM are females (Wolfe et al. 1995b), but it is also known among men (Yunus et al. 2000) and children (Yunus and Masi 1985, Buskila et al. 1995, Mikkelsson 1999). However, men with FM have fewer FM symptoms and tender points than women (Wolfe et al. 1995a, Yunus et al. 2000). Persons with FM may have lower income and education as well as higher rates of divorce than healthy persons (Wolfe et al. 1995b).

TABLE 1 The American College of Rheumatology 1990 criteria for the classification of fibromyalgia (modified from Wolfe et al. 1990).

For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied and widespread pain must have been present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.

1. History of widespread pain.
Defination. Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. "Low back" pain is considered lower segment pain.

2. Pain in 11 of 18 tender point sites on digital palpation.
Definition. Pain, on digital palpation, must be present in at least 11 of the following 18 tender point sites. Digital palpation should be performed with an approximate force of 4 kg. For a tender point to be considered "positive" the subject must state that the palpation was painful. "Tender" is not to be considered "painful".

Occiput: bilateral, at the suboccipital muscle insertions.
Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5-C7*.
Trapezius: bilateral, at the midpoint of the upper border.
Supraspinatus: bilateral, at origins, above the scapula spine near the medial border.
Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.
Lateral epicondyle: bilateral, 2 cm distal to the epicondyles.
Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle.
Greater trochanter: bilateral, posterior to the trochanteric prominence.
Knee: bilateral, at the medial fat pad proximal to the joint line.

*C5-C7 = three lowest vertebrae of the cervical spine.

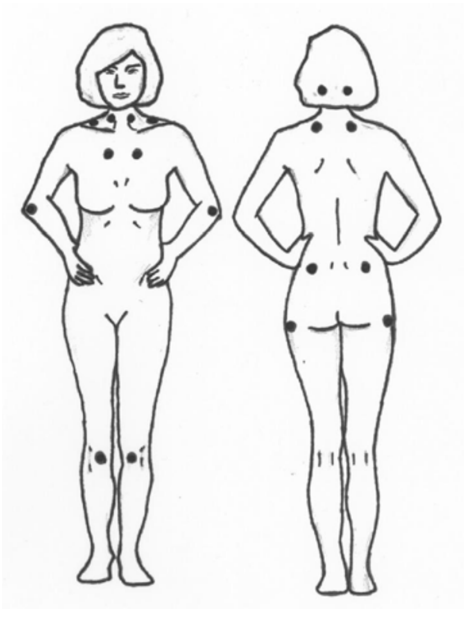

FIGURE 1 Locations of the tender points in fibromyalgia (modified from Wolfe et al. 1990).

2.1.2 Etiology

Despite extensive research, the pathophysiology of FM is still unknown and most likely it is complex and multidimensional (Clauw and Crofford 2003, Staud 2004, Mease 2005). Peripheral mechanisms, such as muscle structure and metabolism, have been studied, but no systematic pathophysiological findings have been discovered. Therefore, research has focused more and more on central mechanisms, such as pain processing, when looking for the causes of FM. However, the possible interactions between peripheral and central mechanisms are still unresolved (Staud 2004).

Peripheral mechanisms in fibromyalgia

Genetic factors may be involved in the etiology of FM (Pellegrino et al. 1989, Arnold et al. 2004). Factors, such as physical trauma, infections, emotional distress, endocrine disorders, and immune activation, may trigger symptoms of FM by activating peripheral nociceptors (Staud 2004). Since FM pain is mainly sensed in muscles, the muscle structure, function and metabolism have been extensively studied (Bartels and Danneskiold-Samsøe 1986, Bengtsson et al. 1986a, 1986b, Lund et al. 1986, Jacobsen et al. 1992, Jacobsen and Danneskiold-Samsøe 1992, Simms et al. 1994, Jubrias et al. 1994). Some researchers have concluded that there are muscle abnormalities in subjects with FM (Olsen and Park 1998, Park et al. 2000), while the opposite conclusions have also been drawn (Simms 1998). Recent studies have suggested that DNA fragmentation in muscle tissue has increased and the number and size of mitochondrias have changed in subjects with FM (Sprott et al. 2004). Also, the amount of intramuscular collagen in non-tender-point areas (e.g. vastus lateralis muscle) may be lower in subjects with FM than in healthy controls (Gronemann et al. 2004). This may lower the threshold for muscle micro-injuries as well as show non-specific signs of muscle pathology. These recent findings may indicate that abnormalities in muscles are possible; however, more research is needed to confirm the results.

Central mechanisms in fibromyalgia

The role of central mechanisms in maintaining symptoms, especially pain, continues to be controversial. First, disorder is possible in the central pain processing systems, such as in the dorsal horn of the spinal cord or hypothalamus (Graven-Nielsen and Arendt-Nielsen 2002, Price and Staud 2005). Secondly, it is also possible that ordinary stimuli in peripheral tissues may trigger symptoms of FM by activating peripheral nociceptors in muscles (Staud 2004). The stimulation may lead to the activation of pain sensation mechanisms in the central nervous system (Staud 2004) and cause abnormalities in pain processing (Graven-Nielsen and Arendt-Nielsen 2002, Price and Staud 2005). Continuous nociceptive stimulation from peripheral nociceptors may lead to hyperalgesia, allodynia and/or central sensitization. Hyperalgesia means a decreased threshold to nociceptive stimuli, such as heat, cold or pressure. In allodynia a patient feels pain following normally not-nociceptive stimuli. Central sensitization may be the result of prolonged and intensive activity by neurons of the dorsal horn of the spinal cord (Price and Staud 2005). In addition, temporal summation of secondary pain is transmitted through C-fibers to the dorsal horn of the spinal cord, which may lead to activation of N-methyl-D-aspartate receptors in the dorsal horn of the spinal cord. This process increases the firing rates of the nociceptive neurons and amplifies peripheral input (the phenomen also termed wind-up) (Staud 2004, Price and Staud 2005).

In addition, pain and other FM symptoms may be explained in part by several other possible changes in the central nervous system, such as disturbed regional cerebral blood flow, functions of the sympathetic nervous system and of the hypothalamic-pituitary-adrenal axis (Petzke and Clauw 2000, Mease 2005). Also some changes in hormone production, such as low concentrations of growth hormone, have been reported (Jones et al. 2007). Behavioural and psychological factors may also contribute to symptom maintenance (Gifford 1998, Mease 2005).

2.1.3 Treatment

The prevention and specific treatment of FM is impossible due to its unknown pathophysiology. Therefore, treatments mainly concentrate on relieving the symptoms. At the moment individually tailored medications, combined with patient education, exercise training and psychologically-based interventions, such as cognitive behavioural therapy, seem to be the most effective treatment for FM in the short-term (Rossy et al. 1999, Sim and Adams 2002, Goldenberg et al. 2004).

The main aim of pharmacotherapy is to decrease pain (Crofford 2004). Tricyclic antidepressants, particularly amitriptyline and cyclobenzaprine, have been shown to have the strongest evidence for short-term efficacy in FM (O'Malley et al. 2000, Crofford 2004, Goldenberg et al. 2004, Goldenberg 2007). They have moderate effects on sleep, overall well-being and pain severity, and a mild fatigue-decreasing effect (O'Malley et al. 2000). Serotonin reuptake inhibitors and serotonin-norepinehrine reuptake inhibitors, such as duloxetine and milnacipran, (Crofford 2004, Goldenberg 2007) as well as pregabalin (Crofford et al. 2005, Goldenberg 2007), which has analgesic and anticonvulsant activity, may have a modest effect on FM symptoms. Anti-inflammatory agents and sedatives or their combinations have only minimal effects on FM and their use is generally not recommended (Crofford 2004). In addition, sedatives may improve sleep, but their effect on pain is poor (O'Malley et al. 2000, Goldenberg et al. 2004). In summary, effective medications remain rather few and therefore, the treatment of subjects with FM should include also methods other than pharmacological treatment.

In cognitive behavioural therapy subjects with FM are taught skills to help them to manage pain and other symptoms, to handle anxiety, to improve coping behaviours and self-efficacy and to direct attention away from their symptoms (Rossy et al. 1999, Karjalainen et al. 2000, Sim and Adams 2002, Goldenberg et al. 2004). These skills are taught by relaxation methods, coping skills training (including skills for controlling thoughts, feelings, behaviour and physiologic responses), problem-solving techniques, and cognitive restructuring (Sandstrom and Keefe 1998). Although cognitive behavioural therapy and self-management therapies may have been described and used in different ways in different studies, these behavioural strategies have been used successfully in the treatment of FM subjects in combination with exercise training (Sandstrom and Keefe 1998). In randomized controlled studies exercise training has included walking training either in water or on land (Burckhardt et al. 1994, Gowans et al. 1999, Mannerkorpi et al. 2000, King et al. 2002, Cedraschi et al. 2004) or mixed training including both aerobic training, strength training and stretching (Buckelew et al. 1998, Redondo et al. 2004, Lemstra and Olszynski 2005).

The symptoms of FM, such as pain, fatigue and sleep problems, may easily lead to inactivity and, as a consequence of this, physical fitness may decrease (Mannerkorpi et al. 1994). Therefore, regular exercise is an essential component in the management of subjects with FM to maintain/improve physical fitness and to relieve symptoms (Goldenberg et al. 2004).

2.2 Physical fitness in women with fibromyalgia

Physical fitness is expressed as a set of attributes, which people can have or achieve and which relate to the ability to perform physical activity (Caspersen et al. 1985, Howley 2001). Fitness can be divided into skill-/performance-related physical fitness and health-related physical fitness (Caspersen et al. 1985, Bouchard and Shephard 1994, 77). Skill-/performance-related physical fitness is needed in optimal physical work or sport performance where the components of fitness, such as motor skills, maximal oxygen uptake, muscle strength and power, are essential (Bouchard and Shephard 1994, 81). Health-related physical fitness means “those components of fitness that are affected favorably or unfavorably by habitual physical activity and relate to health status" (Bouchard and Shephard 1994, 81). Physical components such as body composition, fat distribution, bone density, strength and endurance of muscles, heart and lung function, blood pressure, glucose and insulin metabolism, and blood lipoproteins, are used to describe health-related physical fitness (Caspersen et al. 1985, Bouchard and Shephard 1994, 81). In addition, the different components of health-related physical fitness should be on such a level that a person is able, for example to walk and lift, and to perform everyday tasks such as shopping and housework adequately in her/his own life (Rikli and Jones 1999).

Within a range determined by genetic factors, aging, physical inactivity, diseases and poor nutritional status weaken physical fitness (Bouchard and

Shephard 1994, 81), while well planned and safe exercise training and physical activity maintain and improve it (ACSM 1998b). In this review the term *physical fitness* is used to refer to overall physical condition of the body (includes both skill-/performance- and health-related context). *Health-related physical fitness* is used to emphasise the aspect of health.

2.2.1 Neuromuscular performance

Muscle mass

Neuromuscular performance is related to both neural and muscular structures and functions, which are essential to produce muscle force and power. Skeletal muscle is composed of fibers; these are usually divided into either slow-twitch or fast-twitch fibers according to their contractile and metabolic characteristics (Staron 1997). In force production fast-twitch fibers are important, because they generate energy by the short-term glycolytic system, contract faster and are able to produce more force and power than slow-twitch fibers (Staron 1997). A growth of muscle mass is a consequence of regular loading of the muscles and increased protein synthesis (Yarasheski 2003, Kraemer and Ratamess 2005). Protein synthesis is largely dependent on concentrations of anabolic hormones (e.g. testosterone, growth hormone and insulin-like growth factor-1). When the cross-sectional area (CSA) of the whole muscle is larger, maximal force production is also higher.

Muscle mass is at its largest at the age of 20 to 30 in both sexes and slowly starts to decrease with increasing age due to a decrease in the number of muscle fibers and size of individual fibers. Muscle mass declines about 1-2% annually after age 50 (Lexell et al. 1988, Janssen et al. 2000). In women around the age of 50, sex hormone production decreases due to the menopause. During this stage ovarian estrogen and progesterone production gradually decrease, leading to impaired protein synthesis and decreased muscle mass (Doherty 2003). The loss of muscle mass has shown to be larger in lower than upper body muscles (Janssen et al. 2000). In particular, the loss of fast-twitch fibers is fast and affects both maximal and explosive force production with increasing age (Häkkinen et al. 1998b, Deschenes 2004). This may lead to decreased functional capacity, such as in walking and balance (Daley and Spinks 2000).

Muscle mass in persons with fibromyalgia

Subjects with FM (n=11) have been shown to have over 60% fast-twitch fibers in the vastus lateralis muscle (Lindh et al. 1995) and a majority of slow-twitch fibers in the trapezius muscle (n=10) (Elert et al. 1992). Fiber distribution and fiber area did not differ between the subjects with FM and healthy controls, but the number of capillaries per square millimeter was lower in women with FM (Lindh et al. 1995). CSA of the quadriceps femoris (QF) muscle of middle-aged women with FM assessed by magnetic resonance imaging (MRI) was 58.5 cm^2 (mean age 50 years; n=16) (Nørregaard et al. 1995) and 57.0 cm^2 (mean age 38 years; n=11) (Häkkinen et al. 2002) and it has not been found to differ from that of healthy controls (Nørregaard et al. 1995, Häkkinen et al. 2002). Vestergaard-Poulsen et al. (1995) assessed the CSA of the tibialis anterior muscle by proton MRI and also found that CSA did not differ between subjects with FM (mean age 48 years; n=14) and healthy controls (mean age 50 years; n=12).

Several studies have suggested abnormalities in the muscle structure of subjects with FM. Bartels and Danneskiold-Samsøe (1986) suggested that there might be a network of reticular or elastic fibers connected to muscle fibers. Yunus et al. (1988) found slow-twitch fibers to be moth-eaten in appearance and to display myofibrillar lysis with glycogen and mitochondria deposition. Jacobsen et al. (1991b) suggested that the muscles of subjects with FM have 'rubber band' morphology. Some reviews have concluded that these muscle abnormalities are clear in FM (Olsen and Park 1998, Park et al. 2000, Le Goff 2006). In the review by Le Goff (2006) it was suggested that evidence exists for the disorganisation of Z bands and for abnormalities in the number and shape of mitochondria among other things. However, none of these abnormalities in the muscles of FM subjects have been confirmed in other studies (Simms 1998).

Muscle strength characteristics and EMG activity

(Maximal) muscle strength is defined as the (maximum) amount of force a muscle or muscle group can generate during a muscle contraction. Nerve impulses (action potentials), which originate from the central nervous system, are transmitted by motor neurons to muscles. When a nerve impulse reaches a muscle fiber, the impulse activates processes in the muscle myofibrils and sarcomeres, enabling myosin to form cross-bridges with actin. When several motor units are active at same time, although asynchronously, the formation of cross-bridges and their cyclic motion (overlap sliding of actin and myosin) in all the muscle sarcomeres and muscle fibers finally produce muscle contraction. The higher the firing frequency and recruitment of motor units, the more force is produced. This activation of motor units corresponds with muscle electric activity, which can be assessed on the skin by surface electromyography (EMG), the term EMG activity being commonly used to describe it (Hermens et al. 1999). Muscle strength is also affected by type of muscle contraction, which is categorized into isometric, concentric and eccentric actions. In addition to the type and amount of active motor units and type of muscle action, force production is also affected by muscle size, muscle length, joint angle and the speed of muscle contraction. Maximal force production demands quite a long time (about 2-5 seconds) for muscle contraction so that both fast- and slow-twitch muscle fibers can be fully activated. Explosive force production can be assessed by calculating the force produced during a certain time period, for example the first 100 or 500 ms of an isometric action (e.g. Häkkinen et al. 1998a).

In both sexes muscle strength reaches its peak values at about 30 years of age and remains almost unchanged until the 5th decade. The decline in strength between 50 and 60 years of age is quite mild, but accelerates after the age of 60 by about 1-2% yearly (Larsson et al. 1979, Frontera et al. 1991, Frontera et al. 2000). Older women (60-75 years, n=21) showed 23% less isometric knee extension force and 10% less elbow flexion force than younger (23-34 years; n=20) women in the cross-sectional study by Landers et al. (2001). When muscle strength has been compared between women in different age groups (n=74, age range 20-90), maximal isometric knee extension force and hand grip strength have been shown to decrease by 10% and by 8% between the age of 20 and 55 years (Samson et al. 2000). Hughes et al. (2001) followed the decrease of muscle strength in their longitudinal study and showed that isokinetic knee extension and flexion forces decreased by 14% and 16% per decade in women (n=68) whose age was about 60 years at the beginning of the study. However, the elbow flexor and extensor force declined by only about 2% per decade in the same study. These studies indicate that maximal muscle strength decreases with increasing age, but they also indicate that with increasing age the force production of the lower body declines more than that of the upper body (Samson et al. 2000, Hughes et al. 2001, Landers et al. 2001).

Another force production characteristic, explosive force, starts to decline about age 40, and most likely declines more rapidly than maximal strength (Häkkinen and Häkkinen 1991, Metter et al. 1997, Deschenes 2004). Age-related changes in the nervous system lead to a decreased number of motor neurons and for this reason the number of motor units, especially fast motor units also decreases (Vandervoort 2002). As the result of these changes, maximal voluntary activation of the muscles as well as the number and size of fast-twitch muscle fibers decrease with increasing age and these may earlier affect explosive than maximal force production (Häkkinen and Häkkinen 1991, Metter et al. 1997, Deschenes 2004).

Muscle strength characteristics and EMG activity in persons with fibromyalgia

Several cross-sectional studies have compared maximal muscle strength between subjects with FM and healthy controls. The cross-sectional studies in which study groups have only included women are presented in Table 2. These studies have shown that the maximal isokinetic and isometric muscle strength of the lower extremities is more often lower in premenopausal women with FM than in healthy women. However, Simms et al. (1994) and Häkkinen et al. (2000) did not observe differences in the strength of the lower extremities between the groups, as seen in Table 2.

Maximal muscle strength of the upper extremities and the trunk of women with FM compared to healthy controls have been studied much less. The studies presented in Table 2 found isokinetic and isometric muscle strength of the upper extremities in women with FM to be either lower or comparable with healthy control values. However, grip strength seemed to be lower in women with FM (Mengshoel et al. 1990, Verstappen et al. 1995, Maquet et al. 2002, Lund et al. 2003). In addition to the studies included in Table 2, a number of cross-sectional studies in which the subject groups have included both women and men have been published. In these studies isometric and isokinetic knee extension strength was lower in subjects with FM than in healthy controls (Bartels and Danneskiold-Samsøe 1986, Jacobsen and Danneskiold-Samsøe 1987), while no differences were observed between the groups in isometric muscle strength of the elbow flexors (Miller et al. 1996).

The lower maximal muscle strength in women with FM has been explained by impaired muscle function (Maquet et al. 2002) and reduced muscle microcirculation (Lund et al. 2003). Impaired muscle function, such as EMG activity of the vastus lateralis and hamstring muscles, has been reported to be reduced in women with FM, perhaps due to an impaired control mechanism at the supraspinal level (Lindh et al. 1994). However, a comparable relation between agonist-antagonist EMG activity and muscle strength has also been reported in these subjects (Häkkinen et al. 2000). Elert et al. (1992) found that, compared with controls, women with FM had a higher signal amplitude ratio in the trapezius muscle. Subjects with FM may, therefore, have greater inability to relax the muscles between muscle contractions. On the other hand, reduced strength of the knee extensors has been reported in subjects with FM despite a similar degree of central activation (Nørregaard et al. 1994a) and antagonist activation (Nørregaard et al. 1995) compared to healthy controls. Moreover, electrical muscle stimulation during the production of maximal voluntary isometric muscle strength has been used to test 'true' muscle strength subjects with FM. These studies found that subjects with FM were not always able to produce maximal muscle force voluntarily; instead that the 'true' maximal force was produced during voluntary contraction stimulated by electrical stimulation (Jacobsen et al. 1991a, Lindh et al. 1994, Nørregaard et al. 1995).

As the above results indicate, clear muscle abnormalities have not been found in the muscles of subjects with FM. Researchers have suggested that these subjects' lower maximal muscle strength could be caused by a lower degree of effort (Nørregaard et al. 1997, Lindh et al. 1994), fear of pain (Jacobsen et al. 1991a, Lindh et al. 1994, Henriksson et al. 1996) or physical inactivity (Nørregaard et al. 1994a, 1995, Vestergaard-Poulsen et al. 1995, Borman et al. 1999). On the basis of the results of these cross-sectional studies can be concluded that maximal isokinetic and isometric muscle strength in lower extremities is lower in women with FM than in healthy controls. The results for maximal muscle strength in the upper body are conflicting and thus further research on this issue is needed. In addition, the reasons for lower maximal muscle strength are unclear, while explosive force production has been studied very little in subjects with FM, again indicating the need for further experimental research work.

TABLE 2 Muscle strength of women with FM compared to that of healthy women in cross-sectional studies*.

Study	Number of subjects	Age[#] (years)	Muscle strength tests	Strength results
Mengshoel et al. 1990	FMW 26 HW 26	43 (21-62) ?	Grip strength	Lower in FMW (40%)
Jacobsen et al. 1991a	FMW 20 HW 20	49 (5) 47 (5)	Isokinetic KE (different knee angles), isometric KE[##]	All lower in FMW (~45%)
Jubrias et al. 1994	FMW 11 HW 10	40 (30-54) 34 (19-43)	1RM of wrist flexors	Dominant arm lower in FMW (21%) Nondominant arm: no differences
Lindh et al. 1994	FMW 25 HW 22	40 (6) 39 (8)	Isometric, concentric KE (different knee angles)[##], isometric, concentric KF	KE (44-50%) and KF (47-55%) lower in FMW
Nørregaard et al. 1994a	FMW 20 HW 21	48 (10) 49 (6)	Isometric KE[##]	Lower in FMW (~30-40%)
Simms et al. 1994	FMW 13 HW 13	40 (6) 34 (11)	Isometric ankle dorsiflexion, isometric contraction of upper trapezius	No differences
Nørregaard et al. 1995	FMW 16 HW 14	49 (10) 50 (7)	Isokinetic, isometric KE[##], isometric KF[##], isokinetic, isometric ankle dorsiflexion[##], isokinetic, isometric ankle plantarflexion[##]	KE (~30%), KF (~38%) and plantarflexion (~44-55%) lower in FMW; dorsiflexion no differences
Verstappen et al. 1995	FMW 87 HW 52	45 (9) 44 (7)	Arm pull strength, grip strength	Both lower in FMW (~20%)

(continues)

TABLE 2 (continues)

Study	Number of subjects	Age# (years)	Muscle strength tests	Strength results
Vestergaard-Poulsen et al. 1995	FMW 14 HW 12	48 (9) 50 (7)	Isometric ankle dorsiflexion	Lower in FMW (23%)
Henriksson et al. 1996	FMW 19 HW 37	36 (10) 38 (10)	Isometric strength of several different muscle groups	All lower in FMW (12-38%)
Nørregaard et al. 1997	FMW 181 HW 126	47 (39-54)$ 53 (36-68)$	Isokinetic KE and KF and isokinetic elbow extension and flexion	All lower in FMW (20-30%)
Borman et al. 1999	FMW 24 HW 15	30 (6) 31 (8)	Isokinetic KE and KF with angular velocities of 60°/s and 180 °/s	No differences, except KE 60°/s lower in FMW (18%)
Häkkinen et al. 2000	FMW 11 HW 12	39 (6) 37 (5)	1RM of bilateral leg extension, isometric bilateral leg extension, isometric unilateral KF	No differences
Maquet et al. 2002	FMW 16 HW 85	43 (9) 35 (13)	Grip strength and isokinetic KE and KF	All lower in FMW (~40%)
Lund et al. 2003	FMW 9 HW 9	45 (34-52)$ 45 (25-59)$	Grip strength	Lower in FMW (49%)
Panton et al. 2006	FMW 29 HW 12	46 (7) 44 (8)	Grip strength and isokinetic KE and KF	Grip strength: no differences, KE and KF lower in FMW (~20-40%)

*Published 1985-2007, participants women only, healthy women as a control group, cross-sectional study design.
FMW = women with fibromyalgia; HW = healthy women; KE = knee extension; KF = knee flexion; 1RM = one repetition maximum
# mean(SD) or mean(range); ##twitch interpolation technique; $median age; ? = not reported

2.2.2 Aerobic performance

Aerobic performance means the body's ability to sustain prolonged and dynamic exercise. The best indicator of this is maximal oxygen uptake (VO_{2max}). This is a level "in which oxygen consumption plateaus or increases only slightly with additional increases in exercise intensity" (McArdle et al. 2004, 162). VO_{2max} can be measured as maximal or submaximal by ergometer tests, such as on a treadmill and cycle ergometer, using different test protocols. During direct testing the respiratory gases of the test person are measured and the test is performed until exhaustion or a symptom-limited maximum. During indirect testing respiratory gases are not measured and VO_{2max} is estimated by the test results using different formulae. Exercise is quantified and standardized in terms of work capacity (maximal work load = W_{max}) and/or power output (Jones and Carter 2000). Intensity of aerobic exercise, or work performed, is linearly related to oxygen uptake and heart rate, except in very low and very intensive aerobic exercise. To meet the increased oxygen demand of physically active tissues, blood flow increases due to the higher heart rate and/or stroke volume, and energy production remains on the aerobic level. If the intensity of exercise increases up to exhaustion, energy is produced more and more by glycolysis (anaerobic energy production), resulting in lactate accumulation until finally the individual is unable to continue the performance due to fatigue. Thus, to maintain aerobic performance and to meet the increased demand for oxygen of the active tissues, the capacity of the long-term energy system as well as those of the pulmonary, cardiovascular and neuromuscular systems should work well. However, several factors, such as heredity, gender, age, diseases, body size and composition, mode of exercise, economy of movement and state of training etc., affect VO_{2max} (Jones and Carter 2000, McArdle et al. 2004, 202, 235).

VO_{2max} is highest around the age of 20 in both men and women and declines those after from 3% to 6% per decade in the 20s and 30s and accelerates so that in the 70s the decline is over 20% per decade (Hawkins and Wiswell 2003, Fleg et al. 2005). This decline is a result of a decrease in maximal heart rate, cardiac output and stroke volume (Weiss et al. 2006); however, peripheral blood flow also decreases due to a decreased number of capillaries (Proctor et al. 2004). In addition, a progressive decline in mitochondrial function may impair the energy metabolism of the skeletal muscles and thus aerobic performance (Dirks et al. 2006).

Aerobic performance in persons with fibromyalgia

Aerobic performance has been measured with both direct and indirect tests in women with FM compared to healthy women (Table 3). *Direct tests* by treadmill have shown VO_{2max} to be lower in women with FM than in healthy controls (Valim et al. 2002), while direct tests by cycle ergometer have shown lower (Lund et al. 2003) or similar (Bennett et al. 1989, Simms et al. 1994) values in women with FM compared to controls. An estimated VO_{2max} using *indirect cycle* *ergometer tests* has not differed between FM and control groups (Mengshoel et al. 1990, 1995) or it has been lower in women with FM (Nørregaard et al. 1994b). In addition, in the study where the groups included both men and women VO_{2max} did not differ between the subjects with FM and healthy controls (Sietsema et al. 1993).

However, lower maximal heart rate (van Denderen et al. 1992, Nørregaard et al. 1994b, Verstappen et al. 1995, Valim et al. 2002, Lund et al. 2003) and/or lower W_{max} (van Denderen et al. 1992, Nørregaard et al. 1994b, Verstappen et al. 1995, Lund et al. 2003) have been reported during aerobic tests in women with FM. Among the studies which have reported maximal heart rate, only Simms et al. (1994) did not observe differences between FM and control groups. A lower heart rate in the aerobic test may indicate impaired sympathetic activity (van Denderen et al. 1992), while lower W_{max} may be a result of physical inactivity (Bennett et al. 1989, van Denderen 1992), or a lower level of motivation or pain (Verstappen et al. 1995), which have also been mentioned as reasons for low muscle strength in women with FM. On the other hand, pain intensity has not been shown to be related to physical limitation (Valim et al. 2002).

The results of VO_{2max} in the studies presented in Table 3 are conflicting due to the different study populations and test protocols used, which makes it difficult, therefore, to draw conclusions on whether aerobic performance in women with FM is lower or comparable with that of healthy controls or whether it is a result of FM or reduced physical activity (Bennett et al. 1989, van Denderen 1992). However, lower maximal heart rate and W_{max} have been reported frequently in women with FM.

TABLE 3 Aerobic performance of women with FM compared to that of healthy controls in cross- sectional studies*.

Study	Number of sybjects	Age[#] (years)	Aerobic performance test	Maximal oxygen uptake $(ml \cdot min^{-1} \cdot kg^{-1})$	Other results
Bennett et al. 1989	FMW 25 HW 25	41 (2) 42 (2)	Bicycle; direct test until exhaustion (15 W increase in 1 min)	FMW 22, HW 22; ns.	
Mengshoel et al. 1990	FMW 26 HW 26	43 (21-62) ?	Bicycle; indirect test according to Åstrand	FMW 34, HW 36; ns. (estimated)	
van Denderen et al. 1992	FMW 10 HW 10	41 (18-50) 41 (18-50)	Bicycle; indirect test until exhaustion (30 W increase in every 3 min)	?	Wmax lower in FMW[&] HRmax lower in FMW[&]
Nørregaard et al. 1994b	FMW 15 HW 15	49 (44-54) 50 (46-54)	Bicycle; indirect test until exhaustion (20-30 W increase in every 3 min)	FMW 22, HW 30[&] (estimated)	Wmax lower in FMW[&] HRmax lower in FMW[&]
Simms et al. 1994	FMW 13 HW 13	40 (6) 34 (11)	Bicycle; direct test until exhaustion (15 W increase in every 1 min)	FMW 30, HW 32; ns.	HR_{max}; ns.
Mengshoel et al. 1995	FMW 37 HW 20	34 (21-42)[$] 31 (22-44)[$]	Bicycle; indirect test according to Åstrand	Estimated; ns.	
Verstappen et al. 1995	FMW 87 HW 52	45 (9) 44 (7)	Bicycle; indirect test until exhaustion	?	Wmax lower in FMW[&] HRmax lower in FMW[&]
Valim et al. 2002	FMW 50 HW 50	41 (9) 41 (8)	Treadmill; direct test	FMW 26, HW 31[&]	HRmax lower in FMW[&]
Lund et al. 2003	FMW 9 HW 9	45 (34-52)[$] 45 (25-59)[$]	Bicycle; direct test until exhaustion	FMW 24, HW 36[&] (median values)	Wmax lower in FMW[&] HRmax lower in FMW[&]

*Published 1985-2007, participants women only, healthy women as a control group, cross-sectional study design.
FMW = women with fibromyalgia; HW = healthy women; W = watt; Wmax = maximal work load; HRmax = maximal heart rate
[#] mean(SD) or mean(range); [$]median age; [&]statistically significant between the groups; ns. = not significant; ? = not reported

2.2.3 Functional capacity and quality-of-life

The World Health Organization has developed an International Classification of Functioning, Disability and Health, known as the ICF (WHO 2001, 3-25). In this classification the terms 'functioning' and 'disability' are the two main terms. Functioning encompasses all body functions, activities and participation, while disability covers impairments, activity limitations and restrictions on participation (WHO 2001, 3-25). Diseases and lifestyle habits as well as inactivity may cause changes in body structures and functions, such as decreased muscle strength and aerobic performance (Rikli and Jones 1999). As a consequence of these changes activities in the area of mobility and self-care may become difficult, i.e. a person faces activity limitations. In ICF the term 'mobility' includes activities such as 'walking short distances' and 'climbing' (e.g. climbing steps), while the term 'self-care' includes activities such as 'washing oneself' and 'dressing' (WHO 2001, 144-152). In this thesis short walking and stair-climbing tests and a Health Assessment Questionnaire (HAQ) were used to assess functioning and disability. However, these terms are not used here, because they are very broad and overlapping. Therefore, the term *functional capacity* has been used to describe both measured and self-reported results of the functional capacity tests. The term *mobility* is used, when only walking tests are referred to and *self-reported functional capacity* refers only to the HAQ index. In the original studies (I-IV) the term used is *functional performance* or *physical functional capacity*.

Functional capacity can be assessed by different tests or self-reported by questionnaires. The ability to move is essential to maintain independent living for as long as possible over the life course (Daley and Spinks 2000, Guralnik and Ferrucci 2003). Several tests have been developed to evaluate mobility, such as walking and stair climbing tests (Guralnik and Ferrucci 2003). In short walking tests walking time/speed is measured, while in longer walking tests, such as the 6-min test, aerobic performance is estimated (Guralnik and Ferrucci 2003). Both walking and stair-climbing tests require muscle strength and muscle co-ordination in the lower extremities as well as good balance, both of which are pronounced during maximal and rapid performances in daily life. With increasing age, however, limitations on functional capacity increase, especially in women (Daley and Spinks 2000, Visser et al. 2005, Sainio et al. 2006). For example, walking speed in healthy women aged 55-64 and 65-74 was 1.6 and 1.4 m/s, respectively, in a cross-sectional study of 8028 persons aged over 30 (Sainio et al. 2006). In the younger age group 11% and in the older age group 31% of women had a walking speed of less than 1.2 m/s, which is the speed required to cross the street during the green light in Finland (Sainio et al. 2006). The corresponding numbers for self-reported difficulties in climbing one flight of stairs were 11% and 25%.

Functional capacity and quality-of-life in persons with fibromyalgia

The results of short walking and stair-climbing tests have not been reported in women with FM (Mannerkorpi and Ekdahl 1997). A stair-climbing test was part of the Continuous Scale-Physical Functional Performance Test in the study by Panton et al. (2006). The test included 16 everyday household tasks, and the results of stair-climbing time as well as of all the other tests were lower in the premenopausal women with FM (n=29; mean age 46 years) than healthy controls (n=12). In the study by Henriksson et al. (1996) self-reported difficulty in performing common motor tasks was assessed on a four-graded ordinal scale in women with FM (n=19; mean age 36 years). Climbing stairs was "much more difficult" or "impossible to perform" for 53%, running 100 m for 74% and carrying bags with 5 kg for 84% of the participants.

Mannerkorpi and Ekdahl (1997) summarized different methods of assessing functional limitation and disability, and the reliability and validity of the tests used in studies among subjects with FM. Functional limitation has been measured, for example, by the chair-test, step-test and 6-min walking test, and disability, for example, by the HAQ, the Arthritis Impact Measurement Scale and the Fibromyalgia Impact Questionnaire. Neither the test-retest reliability of functional tests and reliability nor the validity of the HAQ have been reported in subjects with FM (Mannerkorpi and Ekdahl 1997, Wolfe et al. 2000). In women with rheumatoid arthritis (n=100; mean age 62 years) a higher (worse) HAQ index was associated with lower walking time and lower muscle strength (Häkkinen et al. 2006). This may indicate that early intervention strategies are important to maintain muscle strength and functional capacity especially in older women.

Disabilities in daily activities also decrease the quality-of-life of older people (Guralnik and Ferrucci 2003). Several subjects with FM are dissatisfied with their health (Wolfe et al. 1997), and experience limitations in their working ability (Henriksson and Liedberg 2000, Henriksson et al. 2005) and managing their everyday life activities (Henriksson 1994, Henriksson et al. 1996). In chronic pain syndromes, such as FM, a linear relationship has seldom been found between the impairment and disability, as several other factors - psychological, emotional, social and cultural - affect the situation. However, all these together with chronic pain may strongly impair quality-of-life in subjects with FM (Marques et al. 2005, Bennett et al. 2005, Bergman 2005).

2.3 Strength training recommendations

Physical activity is defined as "a body movement produced by muscle action that increases energy expenditure" (Bouchard and Shephard 1994, 77-88) and it can be divided into leisure-time and occupational physical activity (Bouchard and Shephard 1994, 77-88). One form of leisure-time physical activity is exercise training. During exercise training planned, structured and repetitive bodily movements are performed to improve or maintain one or more components of physical fitness (Bouchard and Shephard 1994, 77-88). Exercise training is divided into two main categories - aerobic and strength training. In this thesis the term *exercise training* is used to describe physical exercise in general. Where a more precise specification of exercise is needed, the terms *aerobic training*, *strength training* and, as needed, other specific terms are used. The terms '*health-related physical activity*' (Laitakari et al. 1996) and '*health-enhancing physical activity*' (Vuori et al. 1994, 1996) have also become current, when there is a special need to emphasise the effects of physical activity on health.

2.3.1 General principles in strength training

The goals of exercise training include maintaining current physical fitness or improving it, preventing risk of having certain diseases, and maintaining or improving working and functional capacity (Taylor et al. 2004). Despite such different goals the general principles of exercise training are similar and equally valid in both strength and aerobic training. Training should change the homeostasis of the body by exceeding ordinary everyday load. Training frequency, intensity and/or duration have to change progressively so that physical fitness can be improved (the principles of progression and overload). In addition, the training has to focus on the characteristics (e.g. muscle strength) and/or systems of the body (e.g. neuromuscular) which are the object of improvement (the principle of the specificity of training). Training should be varied and applied individually according to the physical fitness and health status of the trainee to avoid over-training and possible adverse effects of training (the principle of individuality). Moreover, if the training done is not progressive, or is performed too seldom, at too low an intensity or is totally stopped, all the changes in the body due to the training are reversible (principle of reversibility).

For healthy adults the ACSM (1998b) recommends strength training, which should be progressive, individualized, and loads all the major muscle groups of the body 2-3 times/week. As the intensity and/or total volume of the training increase, greater the strength gains will be achieved (ACSM 1998b, Rhea et al. 2003). Dynamic resistance exercises are recommended as they best mimic everyday activities and risk for injuries, and muscle soreness may be lower than in isometric strength training (ACSM 1998b). In addition, the ACSM (1998b) also recommends aerobic training to be performed 3-5 times/week at an intensity of 55/65%-90% of maximum heart rate (40/50%-85% of maximum oxygen uptake reserve) and with a session duration of 20-60 min (continuous or intermittent).

By different strength training protocols it is possible to improve muscle endurance and explosive and maximal strength. To achieve improvements in these different aspects of muscle performance, a training program can be modified by varying the exercises, amount of load, number of sets and repetitions as well as the lengths of the rest intervals between sets (Häkkinen

1994, ACSM 2002). Untrained individuals are recommended to start strength training at low intensity (40-50% 1RM) and with a high number of repetitions (15-20 or more) in each set (Häkkinen 1994, ACSM 2002). This type of training mainly increases muscle endurance, although it may also increase muscle strength in previously untrained individuals during the first weeks of the training period due to improved neural activation. When the training intensity varies between 50-80% 1RM with 6-15 repetitions, it is known as hypertrophic strength training (Häkkinen 1994). This mode of training improves muscle mass, but it also improves maximal strength. Intensities over 80% 1RM are performed with a few repetitions and will mainly improve maximal muscle strength. Explosive muscle strength, i.e. rapid force production, improves when every repetition is performed at high speed. The intensity of the explosive type of training will be about 40-60% 1RM with a few repetitions in previously untrained individuals (Häkkinen 1994). The use of different training regimens varies according to the sport event (e.g. long-distance running vs. high jump vs. shot put) and the purpose of training. For health-related physical fitness muscle endurance and hypertrophic-type strength training are recommended, but improvement of explosive strength would also be important for maintaining mobility (ACSM 2002).

2.3.2 Strength training principles in fibromyalgia

Physical exercise has been recommended for persons with FM not only to improve overall physical fitness and functional capacity, but also to relieve symptoms. Several reviews have summarised the exercise recommendations for these subjects (Offenbächer and Stucki 2000, Mannerkorpi and Iversen 2003, Gowans and deHueck 2004, Mannerkorpi 2005, Busch et al. 2002, Pedersen and Saltin 2006), but little information of the suitability of strength training on subjects with FM exists (Busch et al. 2002, Mannerkorpi and Iversen 2003). Jones and Clark (2002) propose a very light-intensive strength training, which focuses mainly on muscle endurance instead of maximal strength. In addition, eccentric exercises should be avoided due to increased pain (Jones and Clark 2002, Gowans and deHueck 2004), enough pauses should be included between sets (Gowans and deHueck 2004) and strength training for the lower and upper extremities should be performed in separate sessions (Gowans and deHueck 2004). It is important to emphasise that these suggestions are based on the authors' personal opinions, and only a few studies and even fewer randomised controlled trials (Table 4) have examined the effects of progressive strength training in subjects with FM. Therefore, more research is needed on the effects of this training mode on neuromuscular performance and FM symptoms (Mannerkorpi and Iversen 2003).

Special attention should be paid to motivation as well as compliance with exercise needs in persons with FM (Offenbächer and Stucki 2000, Jones and Clark 2002, Mannerkorpi 2005). It is also important to monitor subjectively perceived pain and modify the exercise, if needed, as the high-intensity exercise can increase self-reported pain in persons with FM compared to low-intensity exercise (van Santen et al. 2002). Further, other possible adverse effects of exercise, such as disruption of sleep and neuroendocrine stress reaction, should be avoided (Clark et al. 2001, Jones and Clark 2002).

2.4 Effects of strength training in women with fibromyalgia

2.4.1 Neuromuscular performance

Acute neuromuscular and hormonal responses

In healthy individuals an intensive strength training session causes acute neuromuscular and metabolic responses in the body. It leads to an acute decrease in muscle strength due to neuromuscular fatigue (Gandevia 2001, Westerblad and Allen 2002). Maximal isometric leg extension strength decreased in healthy 50-year-old women (n=7) by 31% and in 70-year-old women (n=8) by 14% after fatiguing loading (leg press exercise with 5 sets of 10 RM and recovery of 2 min between the sets) (Häkkinen 1995). Average integrated EMG activity (IEMG) of the QF muscles also decreased in both groups, although not systematically in women at the age of 50. Due to the anaerobic nature of the loading protocol, blood lactate concentration increased in both the 50- and 70-year-old women. These increases were associated with decreases in maximal force. However, such changes are largely dependent, among other factors, on the loading, its intensity, length of recovery periods, and amount of muscle mass used.

Acute hormonal changes due to an exhaustive bout of strength training are important in eliciting muscle strength gains and hypertrophy due to changes in protein synthesis. Loading protocols with sufficient intensity and the volume of resistance exercise as well as a large amount of muscle mass contribute to greater increases in both testosterone and growth hormone (GH) concentrations. The magnitude of the acute GH response to a single strength training session is minor in women compared to men and decreases largely with increasing age (Häkkinen and Pakarinen 1995). Accordingly, two recent reviews have concluded that the acute effects of a strength training session on total and free testosterone and GH are quite minor in older healthy women (Consitt et al. 2002, Kraemer and Ratamess 2005). In the study by Häkkinen et al. (2001b) one group of healthy women at the mean age of 64 (n=10) performed a heavy-resistance loading protocol (leg press exercise with 5 sets of 10 RM) before and after a 21-week strength training period. The results showed that the serum concentrations of total and free testosterone did not change during the exercise bout either pre- or post-training. However, a statistically significant elevation in GH, although rather minor in magnitude, was observed during the post-training loading. The concentration of the main catabolic hormone, cortisol, has been shown to increase during a strength training bout in healthy women, but the findings are not consistent (Consitt et al. 2002, Kraemer and Ratamess 2005).

Acute neuromuscular and hormonal responses in persons with fibromyalgia

Acute neuromuscular and hormonal responses to a strength training session have been reported in only a few studies in premenopausal women with FM (Häkkinen et al. 2000, 2002). Häkkinen et al. (2000) in their cross-sectional study reported the acute neuromuscular responses of premenopausal women with FM (mean age 39 years; n=11) and healthy women (mean age 37 years; n=12) during a heavy-resistance fatiguing loading (leg press exercise with 5 sets of 10 RM). The fatiguing loading led to similar decreases in maximal and explosive muscle strength and maximal IEMG activity of the isometric leg extensors as well as marked increases in blood lactate concentrations in both women with FM and healthy controls. In addition, both groups also reported similar delayed onset muscle soreness (DOMS) response, showing the highest muscle pain on the first and second day after the acute loading.

Serum concentrations of total and free testosterone and GH in premenopausal women with FM and in healthy women were investigated during the above-mentioned heavy-resistance fatiguing loading session before and after the 21-week strength training period (Häkkinen et al. 2002). The concentrations of total and free testosterone did not change in either group during the loading either before or after the training period. However, an acute increase was observed in the concentration of GH immediately at the end of the fatiguing loading before and after the 21-week training period in both groups, the relative changes between the loadings remained the same. In addition, in women with FM the time duration of the GH response lengthened, becoming significant not only at post, but also at 15 and 30 minutes post-training after the 21-week training period due to decreased inter individual variation in the acute GH response at week 21. This short-term increase in GH may have some clinical meaning, such as a decrease in pain, in the hormonal functions of subjects with FM, as it has shown that GH concentration may fall in subjects with FM (Jones et al. 2007). Except for the those by Häkkinen et al. (2000, 2002), no other studies have simulated single strength training sessions and studied acute changes in neuromuscular and hormonal responses in women with FM.

Long-term neuromuscular and hormonal adaptations

Long-term neuromuscular (Häkkinen 1994, Kraemer et al. 1996, Yarasheski 2003, Fry 2004, Hunter et al. 2004, Latham et al. 2003, Macaluso and De Vito 2004, Gabriel et al. 2006, Duchateau et al. 2006) as well as hormonal (Consitt et al. 2002, Kraemer and Ratamess 2005) adaptations to strength training have been extensively studied in healthy adults and several reviews have been published. Muscle strength improves largely during the initial weeks of strength training mainly due to alterations in the neural regulation of muscular activity (Häkkinen and Komi 1983, Fry 2004, Duchateau et al. 2006). Around week 8-12 adaptations of muscle structure, e.g. hypertrophy, are also observed due to the increased in size of the muscle fibers. Progressive strength training in previously untrained individuals can lead to marked increases in their maximal and explosive muscle strength, CSA and EMG activity irrespective of age or gender. However, the magnitude of these changes is largely related to the physical fitness of participants and the strength training program used (Häkkinen 1994, Kraemer et al. 1996, Fry 2004).

In healthy women regular strength training may slightly increase basal concentrations of testosterone. Long-term changes in basal GH-concentration have not been observed after strength training and findings on cortisol concentrations have been inconsistent (Häkkinen et al. 2001b, Consitt et al. 2002, Kraemer and Ratamess 2005):

Long-term neuromuscular and hormonal adaptations in persons with fibromyalgia

Table 4 lists the strength training studies conducted with a randomised controlled design which have reported on muscle strength in premenopausal women with FM. Isometric and isokinetic muscle strength increased by several per cent after 12 weeks (Jones et al. 2002, Kingsley et al. 2005) and 21 weeks of strength training (Häkkinen et al. 2001a, 2002) in women with FM. The increases were comparable with those of healthy controls (Häkkinen et al. 2001a, 2002). Also, the change in muscle IEMG activity of the women with FM was comparable with that of healthy women and co-activation of the antagonists did not change during the training period (Häkkinen et al. 2001a, 2002). Studies indicate that adaptations of the neuromuscular system to strength training in premenopausal women with FM are comparable to those in healthy controls (Häkkinen et al. 2001a, 2002) and that women with FM are able to perform training without any adverse effects (Jones et al. 2002).

Only one study, Häkkinen at al. (2002), has examined basal serum hormone concentrations of total testosterone, free testosterone and GH in premenopausal women with FM and healthy controls during a 21-week strength training period. The authors reported no systematic changes in any hormone concentrations in either group, while the CSA of the QF increased by 7% in the women with FM and by 9% in the healthy women during the 21-week strength training period. According to the authors this indicates that the subjects with FM were able to retain the capacity for training-induced hypertrophy despite the disease (Häkkinen et al. 2002).

On the basis of the studies presented in Table 4 it can be concluded that regular strength training leads to notable increases in muscle strength in premenopausal women with FM. However, the number of randomised controlled studies is limited and further studies are needed.

TABLE 4 Randomised controlled strength training studies in women with FM*.

Study	Number of subjects	Mean age (years)	Training program	Training intensity	Strength results	Changes in symptoms
Häkkinen et al. 2001a, 2002	FMT 11 HT 12 FMC 10	39 37 37	FMT and HT: 21 weeks, 2/wk, 60 min/x, 2-6 sets of 5-12 reps FMC: No training	40% - 80% 1RM	FMT: Isom LE +27%$^{\#}$, 1RM LE +23%$^{\#}$, Isom KE +18%$^{\#}$, Isom KF +13%$^{\#}$ HT: Isom LE +37%$^{\#}$, 1RM LE +28%$^{\#}$, Isom KE +22%$^{\#}$, isom KF +26%$^{\#}$	VAS: neck pain ↓$^{\#}$, general pain ↓ ns. in FMT VAS: fatigue ↓$^{\#}$ in FMT
Jones et al. 2002	FMT 34→28 FMC 34→28	49 46	FMT: Strength training 12 weeks, 2 x/wk, 60 min/x, 1 set of 4-5 to 12 reps FMC: Stretching 12 weeks, 2 x/wk, 60 min/x	Low	Isokin KE, KF, shoulder in/external rotation increased in FMT$^{\#}$	VAS-pain, myalgic score, TP ↓$^{\#}$ in FMT
Kingsley et al. 2005	FMT 15→8 FMC 14→12	45 47	FMT: 12 weeks, 2 x/wk, 30 min/x, 1 set of 8-12 reps FMC: No training	40% - 80% 1RM	1RM chest press +8%$^{\#}$, 1RM LE +21%$^{\#}$	Myalgic score, TP ↓ ns.

*Published 1985-2007, participants women only, control group, randomized controlled trial.
FMT = Fibromyalgia training group; FMC = Fibromyalgia control group; HT = Healthy training group; reps = repetitions; 1RM = One repetition maximum
FMT 34→28 = drop-outs; Isom = Isometric; Isokin = Isokinetic; LE = Leg extension; KE = Knee extension; KF = Knee flexion
VAS = visual analogue scale; TP = Tender points; ns. = not significant; #statistically significant change; ↓ = decreased

2.4.2 Functional capacity

Functional capacity and strength training

Strength training has been shown to improve muscle strength, but this improvement will not necessarily lead to large improvements in walking speed in healthy elderly women due to differences in level of functional capacity level prior to the intervention (Daley and Spinks 2000, Latham et al. 2003, Lopopolo et al. 2006). Latham et al. (2003) concluded in their systematic review that strength training has a modest beneficial effect on walking speed. In particular, habitual (i.e. self-selected speed) walking speed improves due to strength training, while fast walking speed (i.e. maximal speed) seems not to improve in healthy women (Lopopolo et al. 2006). In their non-controlled study Symons et al. (2005) examined the effect of different strength training modes (maximal isokinetic eccentric-only, maximal isometric-only and maximal isokinetic concentric-only) on stair ascent and descent time. After the 12-week training period all the strength training modes showed a positive influence on stair ascent and descent time, but walking speed did not change in the 73-year-old women studied (n=12). However, in the randomized controlled study by Kalapotharakos et al. (2005) heavy- and moderate-intensity strength training for 12 weeks led to similar improvements in walking speed (30% vs. 33%) and stair-climbing time (14% vs. 13%) in healthy inactive older adults (aged 60-74 years; n=10-12). This finding supports the conclusions of Latham et al. (2003), while Lopopolo et al. (2006) concluded that a higher training intensity may more likely to improve walking speed than lower intensity. No benefits of strength training have been found on self-reported physical disability in healthy older adults (Latham et al. 2003).

Functional capacity and strength training in persons with fibromyalgia

In women with FM the effect of strength training on functional capacity has been assessed with different methods. Kingsley et al. (2005) used the Continuous-Scale Physical Functional Performance test, which is based on ordinary routine tasks, such as carrying an object, floor sweeping etc. It also included tests of stair-climbing and 6-minute walking distance. The results were presented as a total score or as scores of different domains. Mobility of upper-body strength domain improved after strength training in the premenopausal women with FM (n=15) when compared to the control group (n=14) in an intention-to-treat analysis. According to the authors the study provided evidence that increased muscle strength after strength training can improve the tasks of normal daily living in which strength is needed.

Self-reported functional capacity of women with FM has been examined by the Arthritis Self-Efficacy Scale after a 12-week (Jones et al. 2002) and by the HAQ after a 21-week (Häkkinen et al. 2001a) strength training period. The Arthritis Self-efficacy Scale contains 20 items concerning different tasks, such as walking 100 feet on level ground in 20 seconds. Certainty that one can perform a task is measured on a scale of 10 (very uncertain) to 100 (very certain) in 10-point increments. Neither functional capacity (walking), measured by the Arthritis Self-Efficacy Scale (Jones et al. 2002), nor the HAQ index improved in either the training or control groups after the intervention, due to the minor level of disability present already at the beginning of the study (Häkkinen et al. 2001a). However, the changes in the HAQ index correlated positively with the changes in pain and in general health, indicating a decrease in perceived physical disability in the training group (Häkkinen et al. 2001a).

In strength training studies the focus has generally been on the measurement of neuromuscular performance in women with FM. Assessments of tested and self-reported functional capacity have been inconsistent. Therefore, no conclusions about the effects of strength training on functional capacity in women with FM can be drawn.

2.4.3 Pain and fatigue

Pain and exercise in general

Pain is a normal protection mechanism and physiological reaction of the body to a dangerous painful stimulus. Pain can be categorized in several ways, i.e. nocisepthic, neuropathic (specific, when the origin of pain is known) and idiopathic (non-spesific, when the origin of pain is not known) pain, acute and chronic pain, central and peripheral pain as well as pain according to a cause, such as cancer pain (Carr and Goudas 1999, Turk and Okifuji 1999). Regulation of the sensation of pain is a combination of physiological changes in the pain perception system and behavioural and psychological factors. If, for example, a person is concentrating on something else or is in a competition situation, these may activate pain inhibition systems and by different transmitters decrease pain intensity (Turk and Okifuji 1999). Some mechanical stimuli, such as exercise, may also attenuate pain sensation (Koltyn 2000). In addition, perception of pain is a very subjective experience and, therefore, pain threshold as well as pain intensity vary greatly between individuals (Carr and Goudas 1999, Turk and Okifuji 1999). Due to the subjective nature of pain a precise and objective measurement of pain is difficult (Turk and Okifuji 1999, Williams et al. 2004).

Exercise, which exceeds the normal habitual intensity of physical activity in an individual, will lead to acute exercise-induced pain in the muscles so engaged. This pain is termed as delayed onset muscle soreness (DOMS), because it is usually sensed most intensively one or two days after exercise (Cheung et al. 2003). When the same exercise is repeated, the DOMS will not occur as intensively as earlier. The etiology of DOMS is not clear and several hypotheses have been suggested, such as lactic acid accumulation, muscle spasm, connective tissue damage, muscle cell damage, inflammation and the enzyme efflux (Cheung et al. 2003). Most likely the phenomen is explained by a combination of two or more factors (Cheung et al. 2003). It is also common to feel pain during exercise. Most often this pain is induced by very intensive anaerobic performance, resulting in acute and local muscle oxygen deficiency and blood lactate accumulation. This pain usually disappears immediately after termination of the performance.

Exercise could be suggested as a method for treating pain in patients with chronic pain and in healthy individuals, as it has been shown to attenuate pain perception (Koltyn 2000, 2002). In this case the term exercise-induced hypoalgesia should be used (Koltyn 2002). Cross-sectional studies in a group of healthy adults showed that an acute bout of aerobic exercise performed on a treadmill (Hoffman et al. 2004) and on a cycle ergometer (Koltyn et al. 1996) attenuated pain perception for 5 to 15 minutes after exercise. Also, a single bout of strength training has been shown to modify the sensation of pain (Bartholomew et al. 1996, Koltyn and Arbogast 1998). In the study by Bartholomew et al. (1996) the participants (body-builders and regularly training males) were allowed to perform a self-selected exercise for 20 minutes and, in a control setting, they rested quietly for 20 minutes. After the exercise bout, pain tolerance increased significantly compared to resting. A comparable result was reported by Koltyn and Arbogast (1998), where sitting quietly was compared to strength training consisted of 45 minutes of lifting three sets of ten repetitions at 75% 1RM. In addition, high-intensity exercise (60-75% VO_{2max} or over) has been reported most consistently to cause hypoalgesia after exercise (Koltyn 2002). According to a randomized controlled trial regular aerobic exercise may have an effect on the management of chronic pain up to about six months in FM (Wigers et al. 1996), but more studies are needed to identify the optimal dose of exercise required to produce hypoalgesia (Koltyn 2002). In addition, there is a need for studies which examine the effect of strength training on possible exercise-induced hypoalgesia.

Mechanisms underlying exercise-induced hypoalgesia are not well understood. An analgesic response after exercise, caused by the involvement of the endogenous opioid system, has most often been suggested as an explanation (Koltyn 2000). It has also been suggested that interaction might occur between the pain modulatory and cardiovascular systems, as individuals with elevated resting blood pressure have reduced sensitivity to noxious stimuli compared to individuals with lower resting blood pressure (Koltyn et al. 2001, Koltyn and Umeda 2006). Exercise causes elevation of blood pressure during exertion. This has shown to be connected with changes in pain perception, and therefore, it is possible that these two systems, pain modulation and cardiovascular responses, take part in exercise-induced hypoalgesia (Koltyn and Umeda 2006).

Fatigue and exercise in general

Like pain, fatigue is also defined in several ways. It may be defined as neuromuscular fatigue, which can be divided into neural fatigue and muscular fatigue. Muscular fatigue may be divided further into decreased muscle strength or decreased muscle endurance. Fatigue after aerobic performance means reduced aerobic capacity (i.e. reduced aerobic endurance). In addition to the above-mentioned definitions a healthy person can feel general fatigue or tiredness due to mental or physical stress. This general fatigue or tiredness is also common non-specific symptom in several diseases and syndromes, such as FM (Wolfe et al. 1990). Difficult fatigue is also a central symptom in chronic fatigue syndrome, which may overlap with FM (Clauw and Chrousos 1997). It was found that persons with chronic fatigue syndrome who were treated by exercise therapy were less fatigued than controls (Edmonds et al. 2004), suggesting that exercise may have beneficial effects on general fatigue. Thus, improving physical fitness may improve the capacity to tolerate fatigue. Also, changes in self-reported mood and well-being after exercise may decrease the feeling of fatigue (Brosse et al. 2002, Barbour and Blumenthal 2005).

Pain, fatigue and strength training in persons with fibromyalgia

In the strength training studies, presented in Table 4, subjective perceived pain in women with FM has been assessed by a visual analog scale or/and the number of tender points. In all studies the pain showed a decreasing trend, but only Jones et al. (2002) and Kingsley et al. (2005) reported a significant decrease in pain. A pain shows great interindividual variation (Häkkinen et al. 2002) and, therefore, the clinical relevance of the decreasing pain can not be objectively determined. It has to taken into consideration that the reasons for drop-out have been various (Jones et al. 2002, Kingsley et al. 2005); especially high attrition rate (47%) was reported in the study by Kingsley et al. (2005). However, all studies presented in Table 4 concluded that strength training does not exacerbate pain in premenopausal women with FM. Fatigue measured by a visual analog scale (VAS) has also been reported to decrease after a period of strength training (Häkkinen et al. 2001a, 2002).

3 PURPOSE OF THE STUDY

Subjects with FM are mainly women and the highest prevalence of the syndrome is among women aged 55 to 79 years. Despite this women with FM aged 55 and over have been studied the least. With increasing age most physical functions of the body decrease and this in turn leads to a decrease in physical fitness. Moreover, many postmenopausal women with FM may have suffered from symptoms for decades and may, therefore, have a low level of fitness. Because subjective symptoms of FM, especially pain, have mainly been localized in muscles, it is important to study whether the syndrome has an effect on different aspects of physical fitness. Thus, *the first hypothesis was that the physical fitness of postmenopausal women with FM would be lower than that in age-matched healthy controls.*

Strength training consists of single consecutive training sessions, which cause acute neuromuscular and metabolic responses in the body. When strength training sessions are repeated regularly, acute changes in the body will lead to long-term training adaptations with beneficial effects on functional capacity. In addition, strength training may attenuate pain perception, a phenomenon is known as exercise-induced hypoalgesia. However, only a few randomised controlled trials of regular strength training have been conducted in women with FM and, therefore, more information is needed about the suitability (adherence) and safety of strength training in these subjects, especially postmenopausal women with FM. The *second hypothesis was that the symptoms of FM would affect the trainability of the muscles in postmenopausal women with FM with the result that they may not be able to improve their neuromuscular functions and functional capacity by regular progressive strength training as much as healthy controls.*

Thus, the general aim of this doctoral thesis was to compare neuromuscular and aerobic performance, functional capacity, pain and fatigue between postmenopausal women with FM and healthy women and to examine the acute responses of heavy-resistance fatiguing loading and the effects of regular strength training on neuromuscular performance, functional capacity, pain and fatigue in postmenopausal women with FM and healthy controls.

More specifically, the aims of this thesis can be expressed as follows:

To compare postmenopausal women with FM aged between 50 to 70 years and age-matched healthy women with respect to

- physical fitness (neuromuscular and aerobic performance, walking speed, stair-climbing time and self-reported functional capacity) (I);
- acute physiological responses (neuromuscular performance, blood lactate concentration and DOMS) to heavy-resistance fatiguing loading before and after a 21-week strength training period (II); and
- the effects of a 21-week strength training program on muscle strength and EMG activity of knee extensors and flexors as well as walking speed and stair-climbing time (III).

To examine, in postmenopausal women with FM, randomized into training and control groups,

- the effects of a 21-week strength training program on muscle strength, EMG activity and CSA of knee extensors and flexors (III, IV); and
- the effects of strength training on walking speed and stair-climbing time as well as subjectively perceived pain and fatigue (III).

4 MATERIALS AND METHODS

4.1 Subjects and study design

Inclusion and exclusion criteria

This thesis consists of two different study populations – one in study I and the other in studies II-IV, both of which included women with FM and age-matched healthy women. The subjects were all women due to the fact that most subjects with FM are women. The inclusion criteria were age 50-70 years, female gender, having FM as defined according to the 1990 ACR's classification criteria (Wolfe et al. 1990) and being physically capable to participate in normal daily activities. The exclusion criteria were cardiovascular disease, diabetes, or any other diseases which may have interfered with musculoskeletal functions, earlier injuries or operations in the joints, or difficulties in adhering to training according to the study plan. Regular strength and aerobic training during the previous year before the study was also an exclusion criterion. The subjects were allowed to continue their light aerobic physical activities such as walking and biking 1-3 times per week in the manner they were accustomed to before the intervention. Healthy women fulfilled the same entrance criteria except for the diagnosis of FM.

Subjects

Study I: During 2002 an informative letter of invitation to the study was sent to 180 postmenopausal women with FM via the Rheumatoid Arthritis Association of Central Finland and the out-patient clinic (Fig. 2). Seventy-one women were willing to participate, but 33 of them were excluded on the basis of the exclusion criteria. The rheumatologist examined 38 volunteers, and at this stage 8 women were excluded according to the entrance criteria. Before the measurements another 7 women refused to participate in the study for personal reasons. Thus 23 women fulfilled the entrance criteria of the study (Table 5).

The healthy women were a subgroup of volunteers who had participated in the larger research project in 2004 (data not published). They were recruited by flyers from the city of Jyväskylä. Thirty-nine women were recruited and 24 of them were invited to a medical examination prior to inclusion in the present study (Fig. 2). Ten of them were excluded on the basis of exclusion criteria and three of them were unwilling to participate to the study. Thus, eleven healthy women served as control subjects in study I (Table 5).

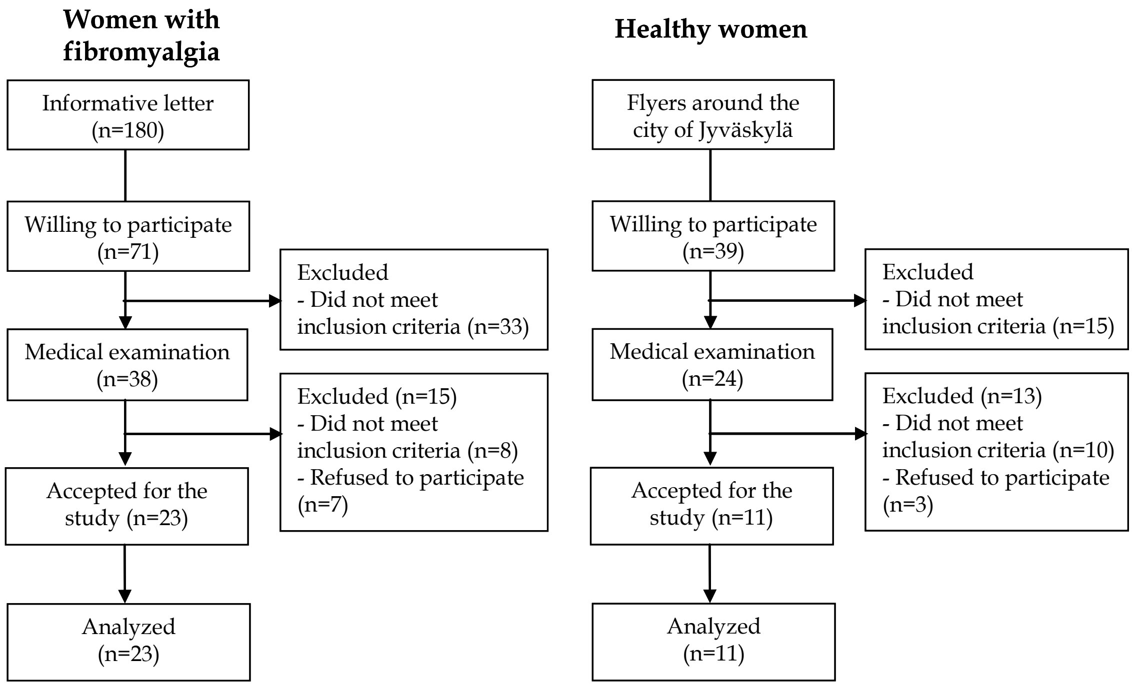

FIGURE 2 Flow-chart of the cross-sectional study (Study I).

TABLE 5 Age and anthropometric characteristics (mean, SD) of the subject groups in studies I–IV.

	Age (years)	Height (cm)	Weight (kg)	BMI
Study I				
FMW (n=23)	58.0 (2.4)	1.62 (0.05)	71.5 (9.9)	27.4 (3.5)
HW (n=11)	58.3 (4.7)	1.63 (0.05)	67.7 (8.1)	25.6 (3.0)
Studies II-IV				
FMT (n=13)	60.2 (2.5)	1.59 (0.04)	66.4 (8.8)	25.6 (3.0)
FMC (n=13)	59.1 (3.5)	1.62 (0.05)	69.7 (9.7)	26.5 (2.6)
HWT (n=10)	64.2 (2.7)	1.60 (0.06)	70.5 (6.1)	27.5 (1.9)

FMW = Fibromyalgia women; HW = Healthy women; FMT = Fibromyalgia training women;
FMC = Fibromyalgia control women; HWT = Healthy training women
BMI = Body mass index

Studies II-IV: During 2000 an informative letter was sent to 100 postmenopausal women with FM, who had visited the out-patient clinic (Fig. 3). Sixty subjects agreed to participate. Twenty volunteers were excluded on the basis of the exclusion criteria and the remaining 40 volunteers were examined by the rheumatologist. At this stage 14 women were excluded due to unwillingness to comply with the study protocol or the exclusion criteria. The 26 women who were accepted fulfilled the ACR's criteria for FM and after inclusion were randomly allocated by draw into a training (FMT, n=13) and a non-training control (FMC, n=13) group (Table 5).

In studies II and III the healthy women were those who had participated in the earlier research project in 1998 (Häkkinen et al. 2001b). They were recruited by flyers from the city of Jyväskylä. Forty-six healthy women stated their willingness to participate in the study and 26 of them were invited for a medical examination (Fig. 3). Fifteen of them were excluded on the basis of the exclusion criteria and, thus, 11 healthy women were accepted as controls (Table 5). In study IV no healthy women were included.

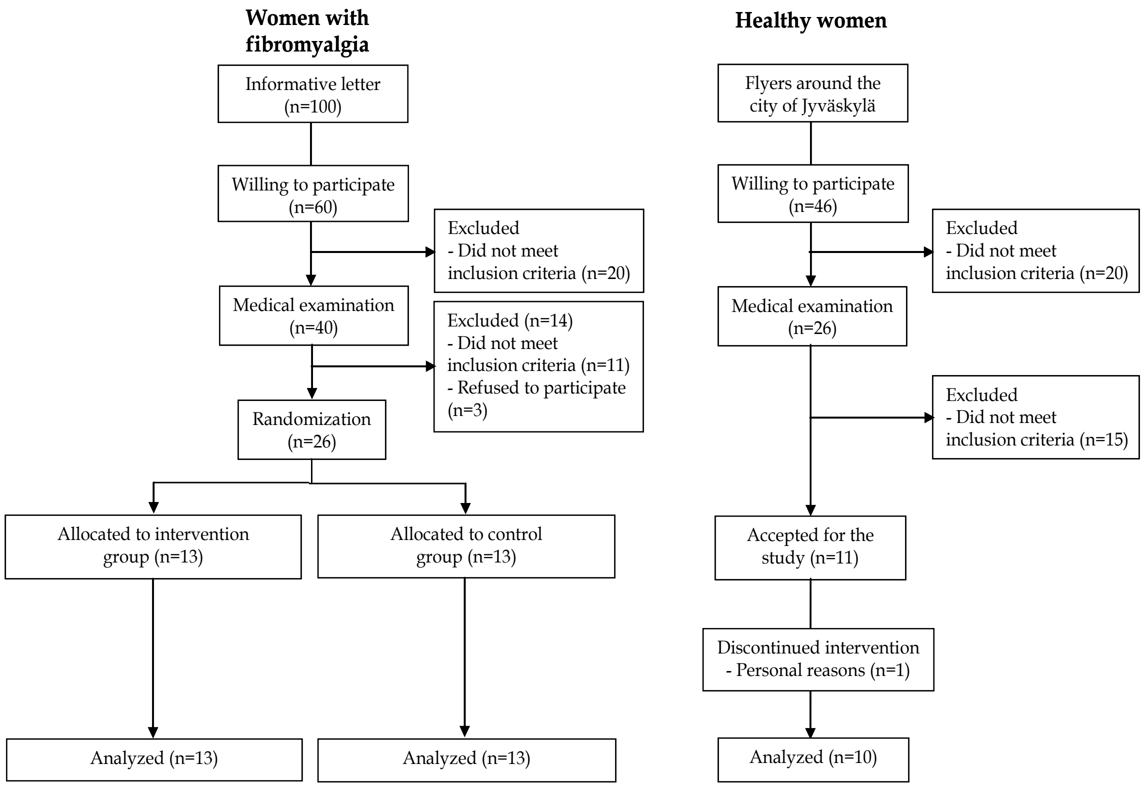

FIGURE 3 Flow-chart of the randomized controlled study (Studies II-IV).

Study design

Study I was a cross-sectional-study and studies II-IV were randomized controlled trials. In Study I the overall physical fitness of the women with FM was compared to that of healthy controls. Neuromuscular responses caused by acute fatiguing loading before and after a 21-week strength training period was examined in Study II, and the effects of regular strength training for 21-week were examined in Studies III and IV. All subjects were measured twice before the training period (at week -2 and 0) to increase the reliability of the baseline measurements, and again at week 21. In addition, at weeks 7 and 14 strength and functional capacity tests were administered to the FMT and healthy training groups to monitor their improvement during the training period. The training groups performed the supervised training program twice a week (II-IV). The subjects and the measurer were not blinded for the intervention.

Ethical aspects

The studies were conducted according to good clinical and scientific practice. All subjects were carefully informed both orally and in written form about the study design and potential risks involved and they all gave their written consent prior to initiation of the study. The study was approved by the Ethics Committee of the Central Hospital of Jyväskylä.

4.2 Measurements

4.2.1 Neuromuscular performance (I-IV)

General measurement instructions

Before the muscle strength measurements all subjects did a warm-up for 10 minutes (bicycle ergometer and stretching exercises). After checking the settings and repeating the instructions, each strength test started with 3-4 warm-up trials at submaximal level. After the warm-up trials at least three maximal isometric trials were measured for each subject and the best result (N, Newton) was taken for the statistical analysis. The subject was asked on a verbal command to produce maximal force as rapidly as possible during 3 – 5 seconds. There was a 1-min rest period between trials. In concentric leg extension action maximal force (kg) was reached within 3-5 trials. One of the two measurers was the same in all the muscle strength tests.

Concentric muscle force

Maximal bilateral concentric leg extension force (II, IV) was measured using a David 210 dynamometer (horizontal leg press; David Fitness and Medical Ltd., Outokumpu, Finland). The subject was in a seated position with the hip at an angle of 110° and the knee at 70°. On a verbal command, the subject performed a concentric leg extension starting from the flexed knee position of 70°. One-repetition-maximum (1RM) of the leg extensors (hip, knee, and ankle extensors) was determined by increasing the load after every trial until the subject was unable to perform an extension action. The highest load (kg) with full knee extension was accepted as the result (Häkkinen et al. 1998a). The coefficient of variation (CV%) between the control and baseline measurements was 9.9% in the women with FM (n=24).

Isometric muscle force

Maximal isometric bilateral leg extension force and force-time variables (I, II, IV) were measured on an electromechanical dynamometer (horizontal leg press). In this test, the subjects sat with the hip and knee joints at 110° and 107°, respectively, and the feet were placed against a force plate (Häkkinen and Komi 1983, Häkkinen et al. 1998a). On a verbal command, the subject performed a maximal leg extension action. The CV% for maximal strength between the control and baseline measurements was 18.3% in the women with FM (n=23).

Maximal isometric unilateral force and force-time variables of the right knee extensors and flexors (I, III) were measured using a David 200 dynamometer (David Fitness and Medical Ltd., Outokumpu, Finland). The subject was in a seated position with the hip and knee joints at 110° and 107°, respectively. On a verbal command, the subject performed, first maximal unilateral knee extension actions and, after changing the settings, knee flexion actions (Häkkinen et al. 1998b). The CV% for knee extension and flexion between the control and baseline measurements were 17.7% and 11.6%, respectively, in the women with FM (n=24) and 11.7% and 13.7% in the healthy women (n=10).

Maximal isometric force of the right elbow flexors (I) was measured using a dynamometer (Metitur Ltd., Jyväskylä, Finland) (Rantanen et al. 1994) The subject was in a seated position. Her upper arm was aligned with the trunk and the elbow angle was 90°. The wrist was in a neutral position and fixed by a belt. The subject was asked on a verbal command to produce maximal force (kg) as rapidly as possible.

Grip strength (I) was measured using a hand grip dynamometer. The subject sat with her lower arm resting on a table with the elbow joint at 90° and the upper arm was alignment with the trunk. First, the grip strength of the right hand was measured, followed by that of the left hand. The best result of both hands (mean of the left and right hands) was taken for the statistical analysis. The CV% between the control and baseline measurements was 22.3% for both hands in the women with FM (n=23) and 12.1% in the healthy women (n=10).

Maximal isometric force of the trunk extensors and flexors (I) was measured using a dynamometer (Digitest Ltd, Muurame, Finland) (Viitasalo et al. 1977). During the extension action the subject stood with the force plate against her upper back. The upper edge of the force plate was at the level of the spine of the scapula and a belt was tightened around the hip at the level of the spina iliaca anterior superior. During the flexion action the force plate was against her upper chest – upper edge under the clavicle - and her hip was attached again supported by the belt. The subject pushed the force plate with her upper body with a maximal voluntary isometric action. At least 3 trials were recorded, and the highest peak force (kg) was taken for the analysis.

The force signal of isometric bilateral leg extension, unilateral knee extension and flexion as well as unilateral elbow flexion actions were recorded on a computer and thereafter digitized and analysed with a Codas TM computer system (Data Instruments, Inc., Akron, OH, USA). The force-time analysis on the absolute scale included calculation of the average force (N) produced during the first 500 ms of the action to assess explosive force production (Häkkinen et al. 1998b). The highest forces produced by the hand grip and trunk extension and flexion actions were recorded from the display on an amplifier.

Electromyographic activity

Electromyographic (EMG) activity of the right vastus lateralis (VL), vastus medialis (VM) and biceps femoris (BF) muscles were recorded during the maximal bilateral concentric and isometric leg extension, unilateral knee extension and flexion actions and during the maximal right elbow flexion action from the long head of the biceps brachii (BB) and the triceps brachii (TB) (I-IV). Bipolar (20 mm interelectrode distance) surface EMG recording (Beckman miniature-sized skin electrodes 650437, Illinois, USA) was employed. The electrodes were placed longitudinally on the muscles as determined by the SENIAM procedure (Hermens et al. 1999). The positions of the electrodes were marked on the skin by small ink tattoos to ensure the same location in each test over the 21-week experimental period (Häkkinen and Komi 1983).

The EMG signals were recorded telemetrically (Glonner, Biomes 2000, Münich, Germany), amplified and digitized at a sampling frequency of 1000 Hz by an on-line computer system. After this the EMG was full-wave rectified, integrated (IEMG in µV · s), and time normalized for 1 s in the following phases: a) in the concentric action for the entire range of motion, b) in the isometric actions for the initial phase of the contraction, up to 500 ms (0-500 ms), and c) for the maximal peak force phase of the isometric actions (500-1500 ms) to calculate maximal IEMG (Häkkinen et al. 1998a, 1998b). In order to calculate the antagonist coactivation percentage for the BF muscle during the extension action, the following formula was used: IEMG of the BF during the extension divided by the IEMG of the BF during the flexion, all multiplied by 100 (Häkkinen et al. 1998b, 2000).

Muscle mass

The CSA (cm^2) of the right QF muscle (IV) was measured with magnetic resonance imaging (MRI; Magnetom Vision 1.5 T, Kuopio, Finland; sequence SE T1: TR/TE 550/17 ms, slice thickness 10mm) before and after the 21-week strength training period. Fifteen axial scans of the thigh interspaced by a distance of 1/15 length of the femur (Lf) were obtained from the level of 1/15 to 15/15 Lf for assessing the CSA of QF from the whole thigh. The Lf was measured as the distance from the bottom of the lateral femoral condyle to the lower corner of the femur head. The CSA of the whole QF was measured from slices 3/15 to 12/15 (slice 3 near the knee joint) by tracing manually along the border of the QF. Muscle CSA was measured from FMT and FMC, but not in the healthy women.

4.2.2 Aerobic performance (I)

Maximal oxygen uptake (VO_{2max}) was measured by using a bicycle ergometer (Tunturi Electronic Ergometer 980E, Tunturi Ltd., Turku, Finland) under a physician's supervision. The test began with a 3-minute warm-up at an intensity of 50 W. After that the intensity was increased by 20 W every second minute until exhaustion. The highest load reached during the test was taken as the maximal work load (W_{max}). Heart rate was measured using an electrocardiograph. Blood pressure was measured before, during and after the test to monitor cardiovascular risks. Oxygen uptake was monitored continuously by the breath-and-breath method using the Vmax229 analysator (SensorMedics, Yorba Linda, CA, USA). VO_{2max} was reached when the measured VO_2 reached a plateau or started to decrease, respiratory exchange ratio (RER) was over 1.0, heart rate was +/-10 beats from the predicted maximum and/or the subject felt that she had reached her maximal level and wanted to stop the test. Capillary blood samples were taken from the fingertip at two-minute intervals for lactate analysis. Samples were deproteinized with perchloric acid and lactate concentration was analyzed using an enzymatic method (BioMeriux, Mercy l'Etoile, France) and measured using a Shimadzu CL 720 spectrophotometer (Kyoto, Japan).

4.2.3 Functional capacity (I, III)

Maximal walking speed (m/s) and time (s) for 10 m and the time (s) to climb 10 steps without hand-rails were measured by photo cells. The shortest time out of three attempts in each measurement was used in the analyses. The CV% of walking time for 10 m and stair-climbing time between the control and baseline measurements were 6.8% and 8.2%, respectively, in the women with FM (n=24) and 7.5% and 8.8% in the healthy women (n=10).

Self-reported functional capacity was assessed using the Stanford Health Assessment Questionnaire (HAQ) (Fries et al. 1980) before and after the strength training period. Daily physical function was divided into eight categories, each of which consisted of two or three activities. In each category the scale ranged from 0 (able without difficulty) to 3 (not able). Thus the maximum HAQ score possible was 24. This was divided by the number of categories (8) to form a disability index, which also ranged between 0 and 3.

4.2.4 Pain and fatigue (I-III)

Pain and general fatigue, the two most commonly reported subjectively perceived FM symptoms, were assessed on a 100 mm VAS (Dixon and Bird 1981) for all subjects during the week immediately before and after the intervention period. On the VAS 0 mm means 'no pain' and 100 mm 'the worst possible pain'. Exercise-induced muscle pain after heavy-resistance fatiguing loading was also assessed by the VAS.

4.2.5 Quality-of-life (I)

A Finnish version of RAND-36 questionnaire (Hays et al. 1993, Aalto et al. 1999) was used to assess general health and quality-of-life in Study I. RAND-36 contains 36 items, measuring eight aspects of health: physical functioning, social functioning, role limitations physical, role limitations emotional, mental health, vitality, bodily pain and general health perception. Change in perceived health over the last year is measured with one item. All raw scale scores are linearly converted to a percentage (0-100) scale, with higher scores indicating higher levels of functioning or well-being.

4.2.6 Measurements of acute responses during the heavy-resistance fatiguing loading protocol (II)

The heavy-resistance fatiguing loading protocol included the bilateral dynamic leg press exercise on the David 210 dynamometer (David Fitness and Medical Ltd., Outokumpu, Finland) using the initial position of the 1RM test (Häkkinen et al. 2001b). The loads were individually adjusted (the initial load was 75% 1RM) during the course of the session due to fatigue so that each subject would be able to perform 10 repetitions per set for a total of 5 sets (5 x 10 RM). If the load became too heavy, the subject was assisted slightly during the last 1-3 repetitions of the set, while she maintained her maximum performance and the required number of repetitions was reached. 2-min recovery time was allowed between sets. Before the loading and after every set isometric leg extension force was measured by the electromechanical dynamometer, as described above. In addition, the EMG of the VL and VM muscles were recorded to follow changes in EMG activity and strength due to fatigue. Before the loading at least three maximal isometric trials were measured, but after every set only one trial was performed and analysed. The 'average load/set' was calculated by the following formula: [(1st set kilograms x 10 repetitions) + (2nd set kg x 10 reps) + … + (5th set kg x 10 reps) / 5 sets].

The fatiguing loading protocol also included assessment of blood lactate concentration and of exercise-induced muscle pain, known as DOMS. Blood lactate concentration was analysed from blood samples taken from the fingertip before the loading, immediately after the 3rd and the last set as well as 15 and 30 min after the loading. DOMS was assessed by a 100 mm visual analog scale (VAS) one day before the loading, on the loading day and on six successive days (day 1, day 2 etc.) after the loading. The loading was performed by the lower extremities and the subjects were asked to report feelings of pain, especially pain in their lower body muscle groups, such as low back, buttocks and legs.

4.3 Strength training program (II-IV)

The strength training took place twice a week for 21 weeks and was conducted in small groups of 4-8 persons. All the training sessions lasted from 60 to 90 minutes and were supervised by three students from the Departments of Health Sciences and Biology of Physical Activity. Every training session started with warm-up exercises for ten minutes, such as bicycling and stretching, continued with strength training for 45-60 minutes, and ended with ten-minute stretching.

This strength training was specifically planned to improve neuromuscular performance. Although the major muscle groups under investigation were the leg extensors and flexors, the so-called whole-body training system was used to provide balanced gains in strength for the other muscle groups as well. Each training session included two exercises for the knee extensors (the bilateral leg press exercise and the bilateral or unilateral knee extension exercise on the David 200 dynamometer) and four to five other exercises for the other main muscle groups of the body. Other exercises were the seated bench press and/or the triceps push-down and/or biceps curl and/or lateral pull-down exercise for the upper body; the sit-up exercise for the trunk flexors and/or another exercise for the trunk extensors; and the bilateral/unilateral knee flexion exercise and/or leg adduction/abduction exercise. The loads were individually determined during the training sessions throughout the 21-week training period according to the maximum-repetition method. The subjects kept an exercise diary to record the loads used in the training (Häkkinen et al. 1998a).

During the first 7 weeks the subjects trained with loads of 40 to 70% of the 1RM (Table 6). Subjects performed 8-20 repetitions per set completing 2-4 sets of each exercise. The loads were 60 to 70% of the maximum by week 11 and 60 to 80% by week 14. In the two exercises for the leg extensors the subjects performed 3-6 sets and in the other exercises they performed 2-4 sets with 5-12 repetitions. During the last 7 weeks of training (weeks 15-21), the subjects performed 4-6 sets with loads of 60 to 80% of the 1RM in the two exercises for the leg extensors and 2-4 sets with the same loads as in the other exercises (Häkkinen et al. 1998a).

The strength training program was a combination of heavy-resistance and "explosive" strength training. The heavy-resistance training was executed according to the normal principles of strength training, as described above. In addition about 20% of the total of the leg extensor exercises with light loads was performed according to the principle of explosive strength training from week 8 onwards (Table 6). This means that these repetitions were executed as explosively as possible (rapid muscle actions) (Häkkinen et al. 1998a). Explosive-type strength training was included in the program for improving force production characteristics, which are important in maintaining mobility.

TABLE 6 Progression of the strength training program. The trained muscle groups are presented in the text above.

	Maximal force		Explosive force	
Week	Intensity	Sets	Intensity	Sets
1-4	40-60% RM*	2-4		
5-7	50-70% RM*	2-4		
8-11	60-70% RM*	2-6	40-50% RM**	2
12-14	60-70-80% RM*	2-6	50% RM**	2
15-18	60-70-80% RM*	2-6	40-50% RM**	2
19-21	70-80% RM*	2-6	50% RM**	2

*RM = repetition maximum during maximal force; Repetitions: 40%=15-20, 50%=12-15, 60%=10-12, 70%=8-10, 80%=5-8

**RM = repetition maximum during explosive force: Repetitions: 40%=10-12, 50%=8-10

4.4 Statistical methods

Standard statistical methods were used to calculate means, standard deviations (SD) and 95% confidence intervals (95% CI). Normality of the variables was analyzed by the Kolmogorov-Smirnov test. The differences between the groups were tested by Student's t-test for unpaired samples in the cross-sectional design (I) and at the baseline in the longitudinal designs (II, IV). At the baseline in study III the differences between the groups were tested by the analysis of variance (Oneway-ANOVA). Quality-of-life variables were analysed by the Mann-Whitney non-parametric test. After the 21-week training the differences between the groups and the changes within the groups were analyzed by analysis of variance with repeated measures (ANOVA) and probability adjusted (Bonferroni) t-tests were used for pairwise comparison where appropriate. The SPSS statistical program (SPSS, Chicago, IL, USA) was applied. The $p<0.05$ criterion was used.

5 RESULTS

5.1 Descriptive data

The anthropometric data on the subjects is presented in Table 5 in chapter 4.1. The anthropometric results did not differ between the study groups. The FM diagnosis had been made on average (SD) 6.6 (4.8) years earlier in Study I and 7.6 (4.1) years earlier in Studies II-IV. At the time of entry in the study, an average of 16.4 (1.6) and 16.1 (1.9) palpable tender points were found in Study I and in Studies II-IV, respectively. Individually tailored FM medications are presented in Table 7. The training subjects with FM completed 95% and healthy training controls 99% of the all planned strength training sessions, and no injuries or other adverse effects caused by the training were recorded. All subjects, except one healthy woman (Studies II-IV) were able to complete the scheduled training.

TABLE 7 Regular medications of the postmenopausal women with FM in the present study.

	Study I	Studies II-IV	
	FM n=23	FMT n=13	FMC n=13
Medications			
Analgesics	14 (62%)	5 (38%)	5 (38%)
Muscle relaxants	8 (35%)	6 (46%)	4 (31%)
Antidepressants	14 (62%)	7 (54%)	7 (54%)
Hormone replacement therapy	14 (62%)	12 (92%)	9 (69%)

5.2 Physical fitness in postmenopausal women with fibromyalgia (I)

Various aspects of physical fitness were compared between the postmenopausal women with FM and healthy controls in cross-sectional study I (Table 8). Neuromuscular performance differed between these study groups, especially in the lower extremities. Women with FM had lower maximal isometric force values in all the measured muscle groups of the lower extremities than did the healthy women ($p<0.05$). Knee and leg extension forces as well as knee flexion force in the women with FM were 82%, 68% and 84%, respectively, of those of the healthy controls. In addition, explosive muscle strength during the initial 500 ms of the isometric knee extension action was lower in the women with FM than in the controls ($p<0.001$). However, differences were not observed between the study groups (ns.) in the maximal forces of the upper body and trunk muscle groups.

The antagonist co-activation of the biceps femoris muscle during the extension actions was calculated. The coactivation of the biceps femoris during the bilateral leg extension ($p=0.008$) and unilateral knee extension ($p=0.009$) actions were higher in the women with FM than in the healthy controls (Table 8).

Aerobic performance was lower in the postmenopausal women with FM than in the healthy controls. The women with FM had lower maximal work time ($p=0.013$), workload (W_{max}; $p=0.013$), heart rate ($p=0.001$) and blood lactate concentration ($p=0.006$) at the end of the test. No significant difference between the groups was observed in maximal oxygen uptake (VO_{2max}) (Table 8).

Also maximal walking time ($p=0.044$), stair-climbing time ($p=0.001$) and the HAQ index ($p<0.001$) were lower in the women with FM (Table 8), but maximal walking speed (m/s) did not quite reach statistical significance ($p=0.078$). Moreover, the women with FM reported significantly more ($p<0.001$) general pain and fatigue assessed by VAS compared to the healthy women (Table 8). The quality of life assessed by RAND-36 was significantly worse in the postmenopausal women with FM than the healthy women in all dimensions except mental health and vitality (Table 8).

TABLE 8 Results of various aspects of physical fitness, functional capacity, pain, fatigue and quality-of-life in the postmenopausal women with FM (FMW) and the age-matched healthy women (HW).

	FMW		HW		
	n	Mean (95% CI)	n	Mean (95% CI)	p-value[#]
Maximal muscle force					
Isometric bilateral leg extension (N)	23	1285 (1128 to 1442)	11	1898 (1671 to 2125)	<0.001
Isometric unilateral knee extension (N)	23	414 (373 to 455)	11	502 (442 to 561)	0.019
Isometric unilateral knee flexion (N)	23	197 (180 to 215)	11	235 (209 to 260)	0.019
Isometric unilateral elbow flexion (N)	23	162 (147 to 177)	11	186 (165 to 208)	0.066
Isometric grip strength (kg)	23	35 (33 to 38)	11	35 (31 to 38)	0.821
Isometric trunk extension (kg)	23	53 (47 to 59)	11	54 (46 to 63)	0.684
Isometric trunk flexion (kg)	23	42 (38 to 46)	11	42 (36 to 49)	0.903
Explosive muscle force					
Isometric knee extension (N)	23	169 (127 to 211)	11	305 (245 to 366)	0.001
Antagonist co-activity					
During isometric leg extension (%)	20	25 (20 to 30)	11	14 (7 to 20)	0.008
During isometric knee extension (%)	21	29 (23 to 36)	10	13 (4 to 23)	0.009
Maximal aerobic capacity					
VO_2 ($ml \cdot min^{-1} \cdot kg^{-1}$)	23	21 (19 to 22)	11	22 (20 to 24)	0.173
RER	23	1.14 (1.10 to 1.17)	11	1.44 (1.39 to 1.50)	< 0.001
Work load (W)	23	130 (120 to 139)	11	151 (137 to 164)	0.013
Work time (min)	23	9.57 (9.02 to 10.54)	11	12.06 (10.43 to 13.27)	0.013
HR (beat/min)	23	158 (153 to 163)	11	174 (166 to 181)	0.001
LA (mmol/l)	23	7.1 (6.4 to 7.9)	11	9.1 (8.0 to 10.2)	0.006
Functional capacity					
Walking speed (m/s)	23	2.1 (2.0 to 2.2)	11	2.3 (2.1 to 2.4)	0.078
Walking time (s)	23	4.7 (4.5 to 5.0)	11	4.4 (4.1 to 4.7)	0.044
10-step stair-climbing (s)	23	3.7 (3.5 to 3.8)	11	3.2 (3.0 to 3.4)	0.001
HAQ-index (scale 0-3)	23	0.5 (0.4 to 0.6)	11	0.01 (-0.2 to 0.2)	<0.001
Symptoms by VAS (0-100 mm)					
General pain	23	44 (36 to 52)	11	6 (-6 to 18)	<0.001
Fatigue	23	49 (41 to 57)	11	24 (12 to 35)	0.001
Quality-of-life by RAND-36*					
General health perception	23	48 (41 to 55)	11	74 (64 to 84)	< 0.001
Physical functioning	23	66 (59 to 73)	11	93 (83 to 104)	< 0.001
Social functioning	23	81 (73 to 89)	11	95 (84 to 107)	0.034
Mental health	23	78 (72 to 84)	11	82 (73 to 91)	0.447
Vitality	23	56 (49 to 63)	11	66 (56 to 77)	0.125
Bodily pain	23	47 (40 to 53)	11	85 (76 to 95)	< 0.001
Physical role limitations	23	51 (36 to 66)	11	93 (71 to 115)	0.002
Emotional role limitations	23	57 (40 to 73)	11	85 (60 to 109)	0.040

VO_{2max} = maximal oxygen uptake; RER = respiratory exchange ratio; HR = heart rate; LA = blood lactate; HAQ = Stanford Health Assessment Questionnaire; VAS = Visual Analog Scale

*RAND 36-Item Health Survey; See scale from the text. [#]FMW vs. HW

5.3 Effects of strength training

5.3.1 Baseline results

At the baseline, before the 21-week strength training period, the study groups did not differ from each other in maximal and explosive muscle force of the lower extremities (Table 9). However, the difference between FMT and HWT in knee extension force reached almost statistical significance (p=0.055). The antagonist coactivation of the biceps femoris during the extension actions and CSA of the QF did not differ between the groups. In functional capacity, HWT had faster stair-climbing time than FMT (p=0.002) and FMC (p=0.002), but walking speed and time did not reach statistical significance. No other differences were observed at the baseline.

TABLE 9 Baseline results of neuromuscular performance, functional capacity and pain and fatigue in three study groups (FMT = Fibromyalgia training group; FMC = Fibromyalgia control group; HWT = Healthy training women).

	FMT		FMC		HWT	
	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
Maximal muscle force						
Concentric bilateral leg extension (kg)	13	93 (80 to 106)	12	98 (85 to 111)		x
Isometric bilateral leg extension (N)	13	1121 (924 to 1318)	12	1178 (974 to 1383)		x
Isometric unilateral knee extension (N	13	403 (339 to 467)	12	414 (362 to 465)	10	498 (441 to 555)
Isometric unilateral knee flexion (N)	13	223 (190 to 256)	12	240 (215 to 265)	10	210 (168 to 252)
Explosive muscle force						
Isometric knee extension (N)	13	223 (173 to 273)	12	227 (185 to 270)	10	272 (196 to 348)
Antagonist co-activity						
During isometric leg extension (%)	9	29 (19 to 39)	11	24 (14 to 33)		x
During isometric knee extension (%)	8	39 (31 to 48)	10	28 (14 to 42)	10	24 (18 to 31)
Muscle mass						
CSA of quadriceps femoris (cm^2)	13	49 (45 to 53)	13	46 (43 to 50)		x
Functional capacity						
Walking speed (m/s)	12	1.8 (1.7 to 1.9)	12	1.8 (1.7 to 1.9)	10	2.0 (1.9 to 2.1)
Walking time (s)	12	5.5 (5.2 to 5.8)	12	5.5 (5.2 to 5.8)	10	5.0 (4.8 to 5.3)
10-step stair-climbing (s)	12	3.6 (3.4 to 3.8)[#]	12	3.6 (3.4 to 3.8)[##]	10	3.1 (2.9 to 3.3)
HAQ-index (scale 0-3)	13	0.5 (0.2 to 0.8)	13	0.4 (0.2 to 0.7)		x
Symptoms by VAS (0-100 mm)						
General pain	13	38 (26 to 49)	13	40 (29 to 51)		x
Fatigue	13	47 (36 to 61)	13	50 (38 to 62)		x

CSA = Cross-sectional area; HAQ = Stanford Health Assessment Questionnaire; VAS = Visual Analog Scale
[#]Statistically significant difference between FMT and HWT; [##]Statistically significant difference between FMC and HWT
x = Not measured in the present study

5.3.2 Changes in neuromuscular performance (III, IV)

Maximal muscle strength and IEMG-activity (III, IV)

The effects of the 21-week strength training period on the neuromuscular performance of the lower extremities were compared between the training women with FM (FMT) and healthy training women (HWT) as well as between FMT and the non-training control women with FM (FMC). First, the results between FMT and HWT are summarized. The relative changes in the knee extension and flexion forces after the 21-week strength training period did not differ significantly between the training groups (ns.) (Fig. 4). In FMT and HWT the training led to increases of 32% ($p<0.001$) and 24% ($p<0.001$) in maximal knee extension force and 13% ($p<0.05$) and 24% ($p<0.01$) in maximal knee flexion force. Fig. 5 shows the individual changes in the subjects' knee extensor force.

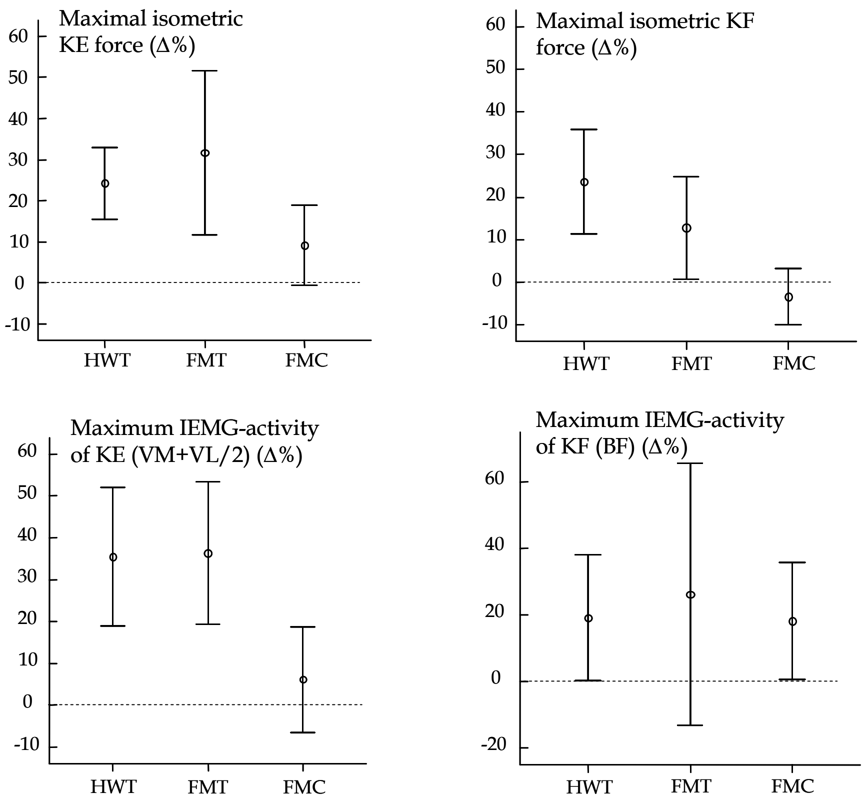

FIGURE 4 Relative changes (mean, 95% CI) in maximal isometric unilateral knee extension (KE) and knee flexion (KF) forces as well as maximum mean IEMG activity of vastus medialis (vm) and lateralis (vl) muscles during the KE action and maximum IEMG activity of biceps femoris (bf) muscle during the KF action after the 21-week experimental period. HWT = Healthy training women; FMT = Fibromyalgia training women; FMC = Fibromyalgia non-training women.

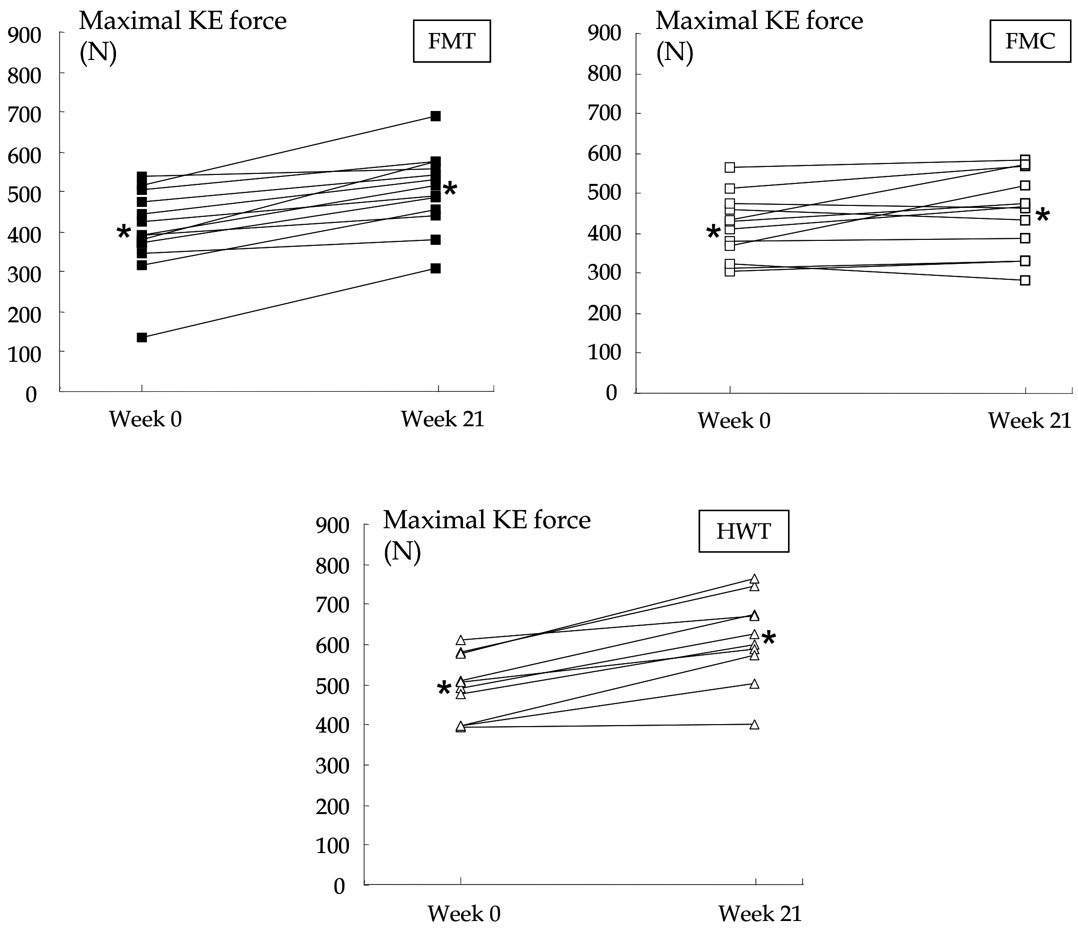

FIGURE 5 Individual results for maximal isometric unilateral knee extension force (N) in postmenopausal women with FM and healthy controls after the 21-week experimental period. The * represents mean value of the whole group. FMT = Fibromyalgia training women; FMC = Fibromyalgia non-training women; HWT= Healthy training women.

Moreover, the relative changes in the maximum mean IEMG activity of the VL and VM muscles during the knee extension action as well as the maximum IEMG activity of the biceps femoris muscle during the knee flexion action did not differ between FMT and HWT after the training period (Fig. 4). The training led to notable increases in the IEMG activity of the knee extensors in both groups ($p<0.001$; FMT 36%; HWT 36%), while the IEMG activity of the knee flexors increased in HWT (19%; $p<0.05$), but remained statistically non-significant in FMT (26%) due to large individual variation. The relative change in the antagonist co-activation during knee extension did not differ between the groups (ns.; FMT 4%; HWT 4%). The improvements in muscle strength and IEMG activity were observed throughout the training period without any plateaus in both FMT and HWT (Fig. 6).

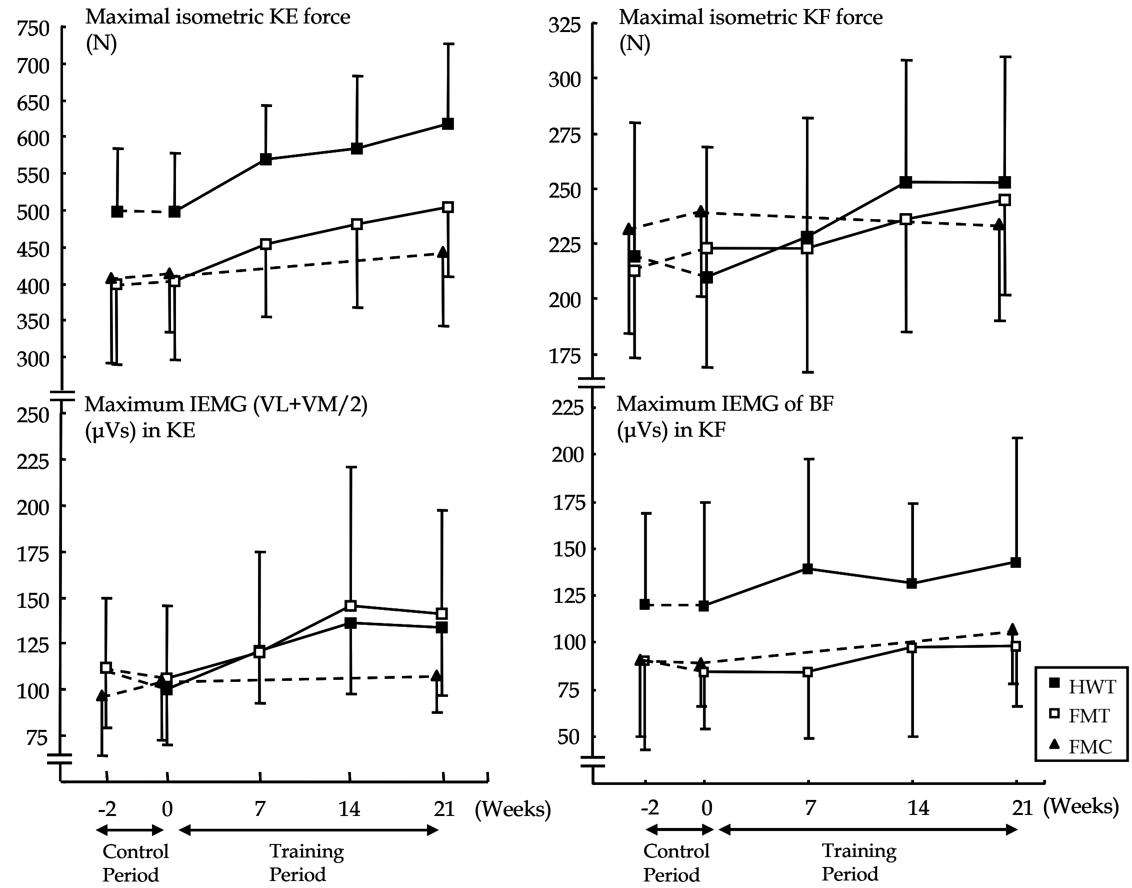

FIGURE 6 Maximal isometric knee extension (KE) and knee flexion (KF) forces (absolute values; mean±SD) as well as mean IEMG activity of vastus medialis (VM) and lateralis (VL) muscles during KE action and IEMG activity of biceps femoris (BF) muscle during KF action during the control and the 21-week experimental period. HWT = Healthy training women; FMT = Fibromyalgia training women; FMC = Fibromyalgia non-training women.

Next, the maximal muscle strength and IEMG activity results after the 21-week intervention period are summarized for FMT and FMC. In FMT maximal muscle strength ($p<0.001$ - 0.05) (Figs. 4 and 7) and the IEMG activity of the measured muscles ($p<0.01$ – 0.05) (Figs. 4 and 7) of the lower extremities, except for the IEMG activity of the knee flexors (ns.), improved significantly compared to FMC. For example, the improvements in maximal concentric and isometric leg extension forces were 33% ($p<0.05$) and 36% ($p<0.05$) in FMT, while the corresponding changes in FMC were 4% and 4% (ns.). Also the IEMG activity of the leg extensors of FMT in concentric action increased by 57% ($p<0.05$) and in isometric action by 47% ($p<0.05$). In FMC the change in IEMG activities were minor (14%; ns.) in both actions, although the increase in maximal average IEMG activity during concentric action reached statistical significance ($p<0.05$). The increases in leg extension actions were observed throughout the training period without any plateaus in FMT compared to FMC (Fig. 8).

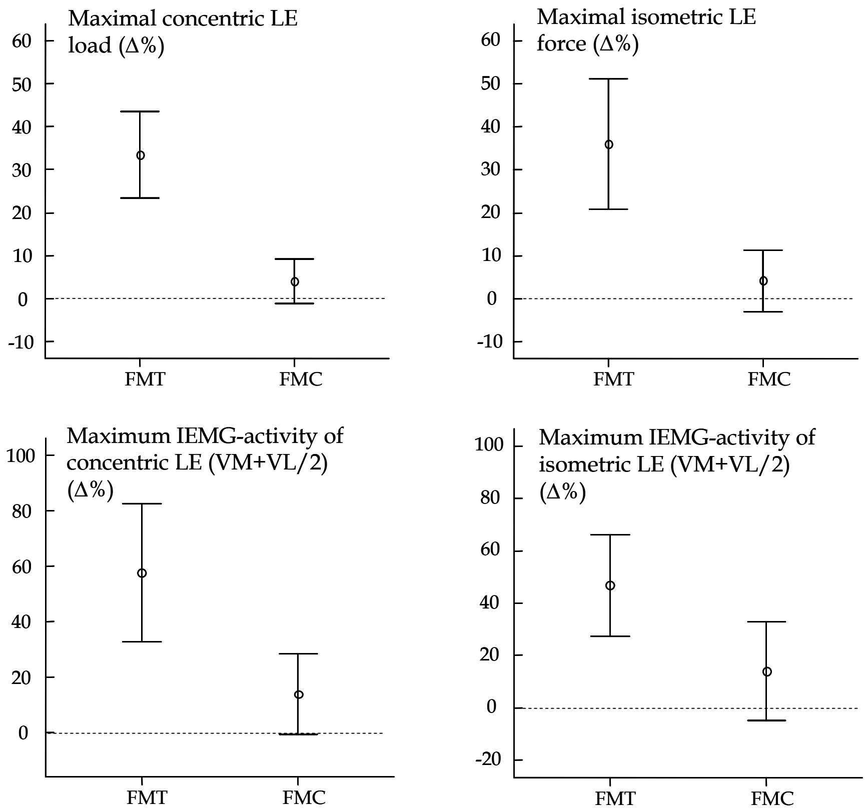

FIGURE 7 Relative changes (mean, 95% CI) in maximal concentric and isometric bilateral leg extension (LE) forces as well as mean IEMG activity of vastus medialis (VM) and lateralis (VL) muscles during LE actions after the 21-week experimental period. FMT = Fibromyalgia training women; FMC = Fibromyalgia non-training women.

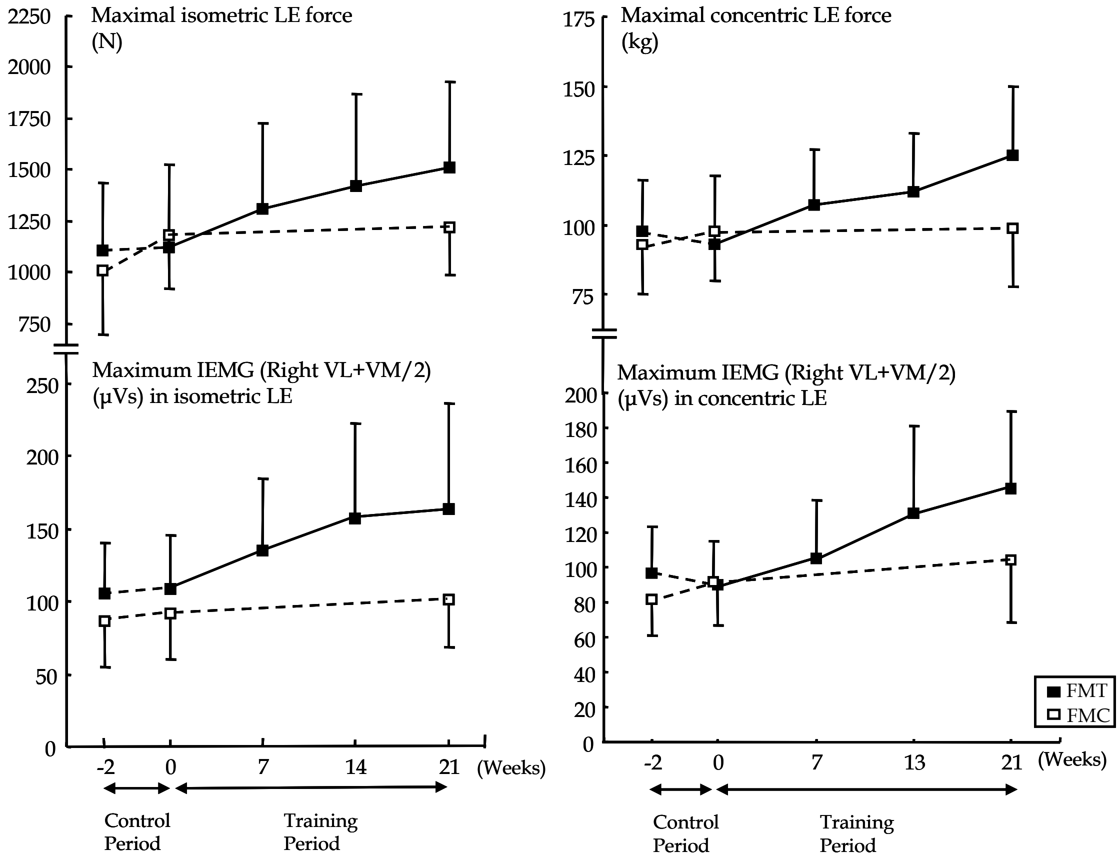

FIGURE 8 Maximal isometric and concentric leg extension (LE) forces (absolute values; mean±SD) as well as mean IEMG activity of vastus medialis (VM) and lateralis (VL) muscles during the actions during the control and the 21-week experimental period. FMT = Fibromyalgia training women; FMC = Fibromyalgia non-training women.

Explosive muscle strength (III, IV)

The relative changes between FMT and HWT in the average explosive force of isometric knee extension action did not quite reach statistical significance ($p=0.068$). However, explosive force increased in both groups (FMT $p<0.001$; HWT $p<0.01$) (Fig. 9). Also, the explosive force of isometric leg extension increased in FMT ($p<0.01$), while no changes were observed in FMC (Fig. 9). Therefore, FMT differed significantly from FMC in the average explosive force of the isometric leg ($p=0.016$) and knee ($p<0.001$) extension actions.

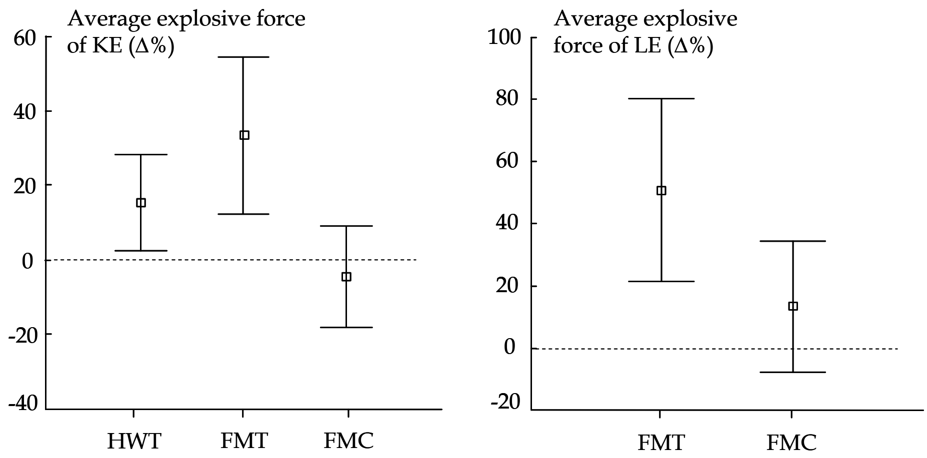

FIGURE 9 Relative changes (mean, 95% CI) in explosive isometric knee extension (KE) and leg extension (LE) forces during the initial 500 ms of the actions after the 21-week experimental period. HWT = Healthy training women; FMT = Fibromyalgia training women; FMC = Fibromyalgia non-training women.

Muscle CSA (IV)

In Fig. 10 the changes in CSA of the QF are shown in FMT and FMC. The mean CSA of the QF was largest at slice 9, being 48.7 (95%CI: 44.9-52.6) cm^2 in FMT and 46.4 (95%CI: 42.5-50.3) cm^2 in FMC at baseline (ns.). The mean relative increase in the QF (mean of all MRI slices) was 5.3% (95%CI: 3.0-7.6%) in FMT and 0.9% (95%CI: -1.4-3.2%) in FMC. These changes differed significantly between the groups ($p=0.011$). Larger increases in the muscle CSA of FMT were observed at the mid-thigh slices, as shown in the Fig. 10, while in FMC the CSA remained statistically unchanged. The individual changes in muscle CSA in FMT and FMC are shown in Fig. 11.

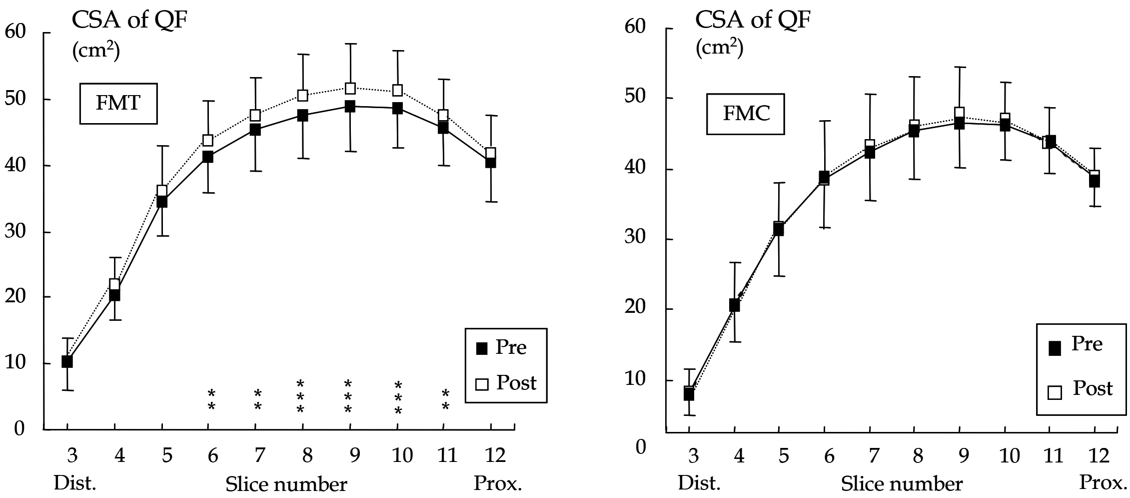

FIGURE 10 Cross-sectional area (CSA) of the quadriceps femoris (QF) muscle (cm²; mean±SD) in the women with fibromyalgia before and after the 21-week experimental period. FMT = Fibromyalgia training women; FMC = Fibromyalgia non-training women. ** p<0.01; *** p<0.001.

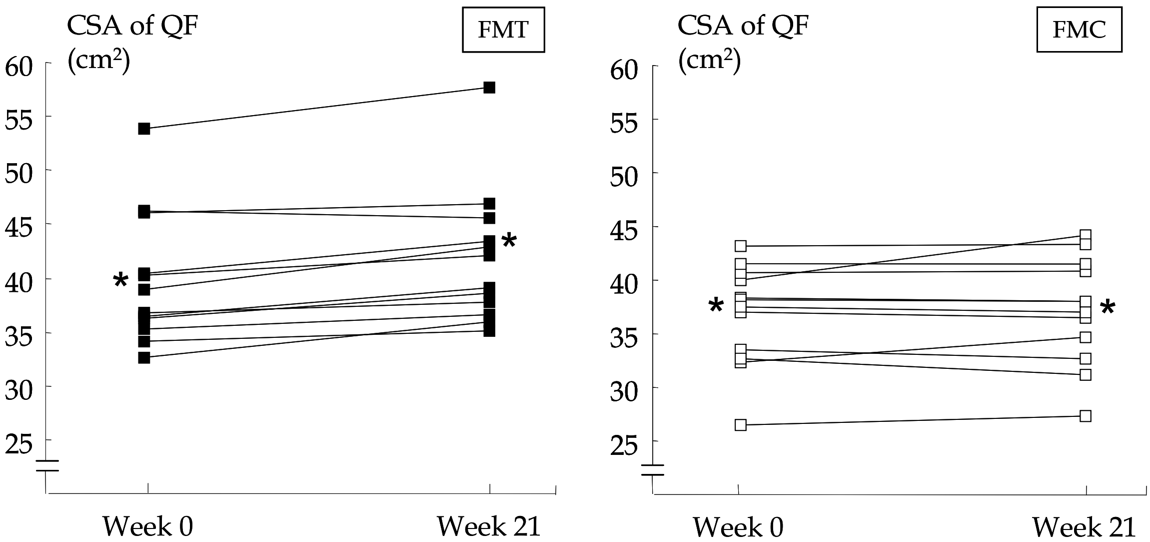

FIGURE 11 Individual results for total cross-sectional area (CSA) of quadriceps femoris (QF) muscle (cm²; sum of all slices) in the women with fibromyalgia before and after the 21-week experimental period. The * represents mean value of the whole group. FMT = Fibromyalgia training women; FMC = Fibromyalgia non-training women.

5.3.3 Changes in functional capacity (III)

The relative changes in maximal walking speed and stair-climbing time did not differ between FMT and HWT after the 21-week strength training period. In FMT mobility improved in both tests ($p<0.05$), but remained statistically unchanged in HWT (Fig. 12). The change in stair-climbing time differed significantly between FMT and FMC (p<0.05), but no differences were observed in maximal walking speed. In FMC maximal walking speed also improved (p<0.01).

The self-reported HAQ index improved significantly during the training in FMT (from 0.5±0.4 to 0.3±0.2; p<0.01) as compared to FMC (from 0.4±0.5 to 0.5±0.5; ns.).

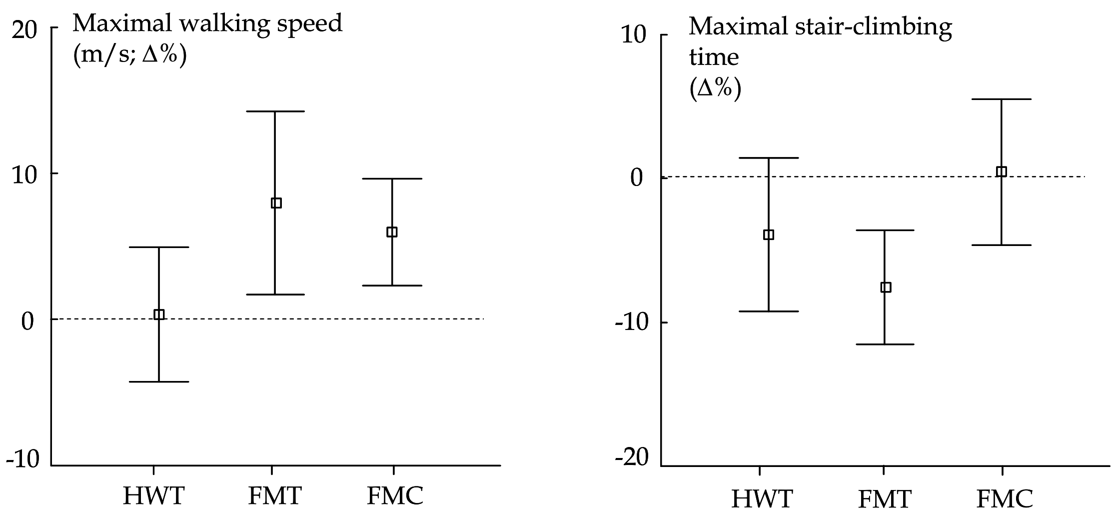

FIGURE 12 Relative changes (mean, 95% CI) of maximal walking speed and stair-climbing time after the 21-week experimental period. HWT = Healthy training women; FMT = Fibromyalgia training women; FMC = Fibromyalgia non-training women.

5.3.4 Changes in pain and fatigue (III, IV)

Symptoms of FM were assessed only in the women with FM. The study period did not lead to any significant differences in perceived general pain in muscles or in fatigue between FMT and FMC. However in FMT, the symptoms showed a minor decreasing, although not statistically significant, tendency. In Fig. 13 the individual results for perceived pain and fatigue during the intervention period are presented in FMT and FMC. Individual variation in both groups was large, as some subjects reported increased pain and fatigue over the study period, while some reported clear decreases. However, none of the training subjects reported any adverse effects of the strength training. In addition, the number of tender points in FMT decreased from 16.5±1.8 to 14.6±2.5 (p<0.05), but no changes were observed in FMC.

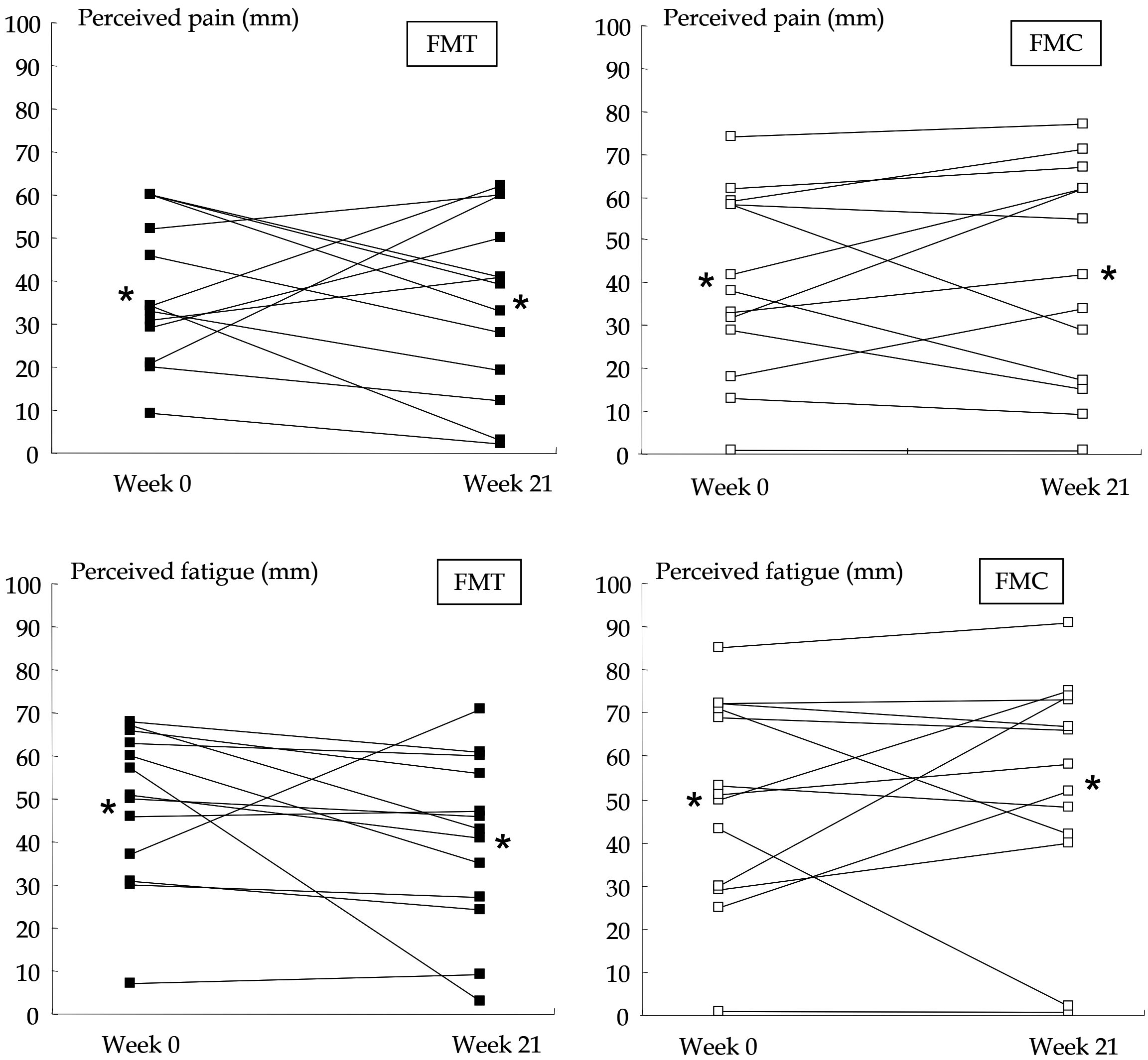

FIGURE 13 Individual results for perceived general pain in muscles and fatigue measured by the Visual Analog Scale (mm) in the women with fibromyalgia after the 21-week experimental period. The * represents mean value of the whole group. FMT = Fibromyalgia training women; FMC = Fibromyalgia non-training women.

5.4 Acute responses to the heavy-resistance fatiguing loading: effects of strength training (II)

Maximal muscle strength and IEMG activity

At week 0 the average load/set (during bilateral leg extension) was lower in FMT than in HWT (805 vs. 943 kg; $p<0.05$), but at week 21 no differences was observed between the groups (1128 vs. 1189 kg; ns.). The average load/set increased in FMT by 41±16% ($p<0.001$) and in HWT by 26±8% ($p<0.001$).

Before the loading the initial maximal isometric leg extension force was measured and was found to be lower in FMT than HWT both at week 0 and week 21 (p=0.022 and p=0.004). The loading led to a significant decrease in maximal isometric leg extension force in both groups (Fig. 14). At week 0 the decrease was 25% in FMT and 23% in HWT (both p<0.001), and thus the difference between the groups was not significant. At week 21 the decreases were 26% and 29% in FMT and HWT (p<0.001), and the difference between the groups was significant (p<0.01). However, the percentage change in IEMG activity (pre vs. post) during the loading at weeks 0 and 21 did not differ between or within the groups (Fig. 14).

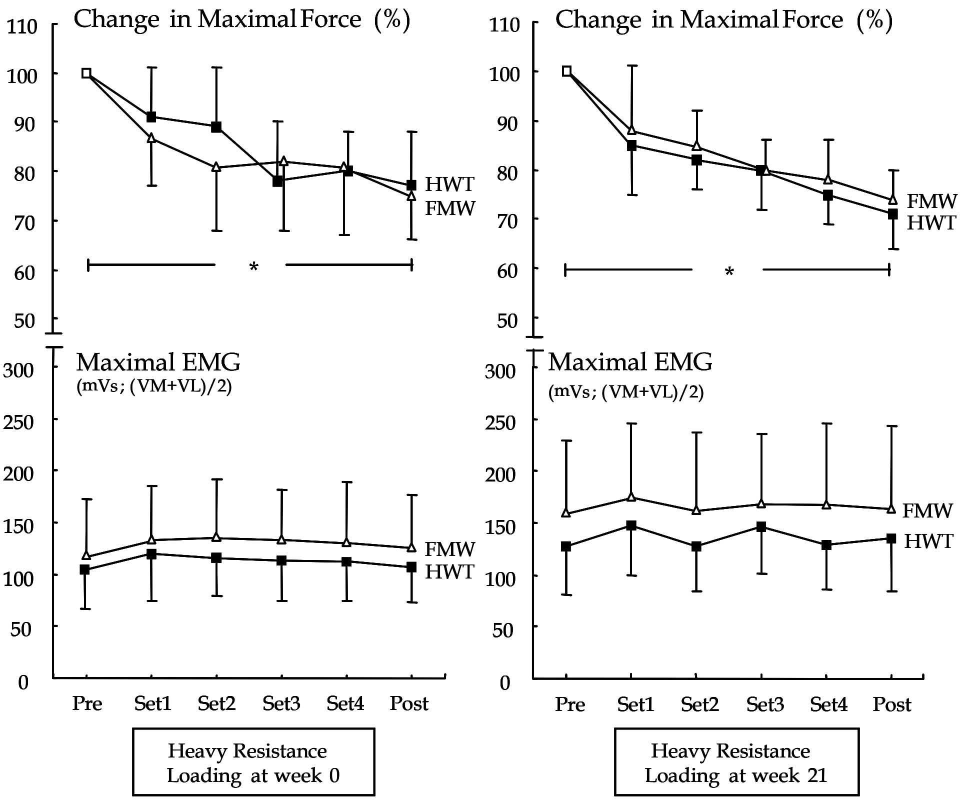

FIGURE 14 Acute relative changes in maximal isometric force and acute changes in maximal mean IEMG activity of the vastus medialis (VM) and lateralis muscles (VL) during the heavy-resistance loading in the postmenopausal women with fibromyalgia (FMW; Δ) and the healthy controls (HWT; ■) at the beginning (week 0) and at the end (week 21) of the 21-week strength training period (*no interaction between the groups, but the changes within both groups p<0.001).

Blood lactate concentration

At week 0 and 21 the relative increases in blood lactate concentration did not differ between the groups, but the increases were significant within the groups (p<0.001) (Fig. 15). In both groups the highest value of blood lactate was reached at the end of the loadings (post-value). At week 0 the blood lactate concentration recovered to the pre-loading level during the 30-minute recovery period, while at week 21 it remained elevated in both groups ($p<0.01$). Blood lactate increases were lower at week 0 than at week 21 during the loading in both groups ($p<0.05$ in FMT and $p<0.001$ in HWT).

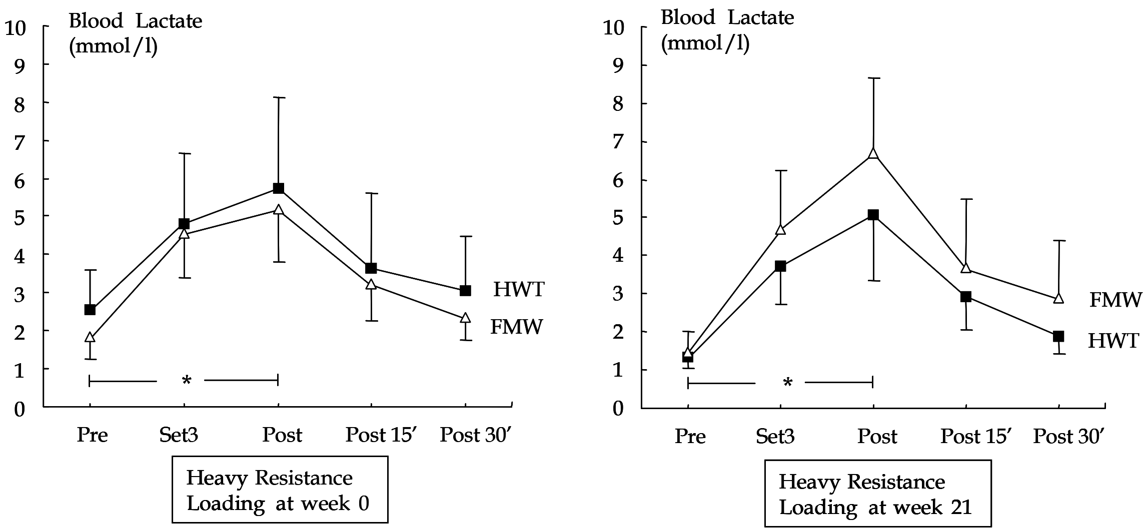

FIGURE 15 Blood lactate concentration before, during and after the heavy-resistance loading in the postmenopausal women with fibromyalgia (FMW; Δ) and the healthy controls (HWT; ■) at week 0 and at week 21 (*no interaction between the groups, but changes within both groups $p<0.001$).

Exercise-induced muscle pain

FMT reported more exercise-induced muscle pain (the average pain value of all the measured days) than HWT at week 0 and 21 ($p<0.05$) (Fig. 16). At week 0 the DOMS reaction differed between the groups ($p=0.015$), but no differences were observed at week 21 ($p=0.558$). In addition, both groups reported the highest DOMS during day 1 and day 2 after the loading ($p<0.05$). However, an interesting result was that after the 21-week strength training period both groups reported lower DOMS during day 1 and day 2 at week 21 than at week 0 ($p<0.05$).

Finally, when the percentage changes in the acute loadings before (at week 0) and after (at week 21) the strength training period were compared, no differences were observed in average load/set, isometric force, IEMG activity, blood lactate or pain between the groups (all interactions ns.).

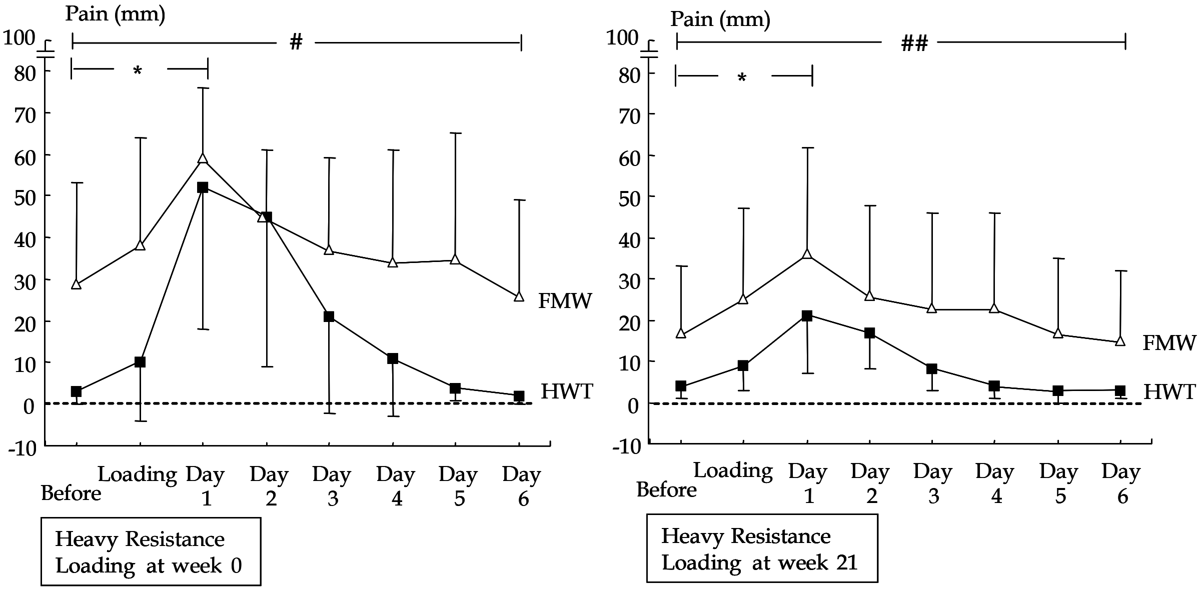

FIGURE 16 Exercise-induced muscle pain (measured by visual analog scale) before the loading, on the loading day and during the six days after the heavy resistance loading in the postmenopausal women with fibromyalgia (FMW; Δ) and the healthy controls (HWT; ■) at week 0 (#interaction between the groups p=0.015; *changes within both groups p<0.05) and at week 21 (##no interaction between the groups; *changes within both groups p<0.05).

6 DISCUSSION

6.1 Physical fitness in postmenopausal women with fibromyalgia

Neuromuscular performance (I)

The focus of the earlier training studies with women with FM has been on younger premenopausal age groups. This present study offers, therefore, novel information on the physical fitness and trainability of postmenopausal women with FM in the age group 50-70 years. Previous FM studies have reported on the muscle strength of the lower extremities and concluded that muscle strength is lower in premenopausal women with FM than in healthy controls (Table 2). The results of the present measurements (Study I) showed that the muscle strength of the extensors in the lower extremities differed between the groups. On the basis of these and earlier results it is possible to conclude that muscle strength in the lower extremities is lower in women with FM than in healthy controls.

However, the results of measurements of the muscle strength of the upper extremities between women with FM and healthy controls have been far more inconsistent in earlier studies (Table 2), except for grip strength which seemed to be lower in the women with FM (Mengshoel et al. 1990, Verstappen et al. 1995, Maquet et al. 2002, Lund et al. 2003). In the present study, the isometric muscle strength of upper body and trunk muscle groups did not differ between the groups. These results may support earlier findings in healthy adults that maximal force production may not decline with increasing age in the upper body muscle groups as much as it does in those of lower body (Hughes et al. 2001, Landers et al. 2001). It is possible that postmenopausal women with FM and healthy women use their upper body muscle groups rather similarly during normal daily activities and, therefore, maintain their muscle strength level. However, this assumption was not assessed in the present study.

If muscle strength is lower in the lower extremities in postmenopausal women with FM than in healthy women, then several possible explanations can be suggested. In the present study muscle activation was measured by the IEMG activity of the muscles during the strength tests and expressed as percentages of the co-activation of the biceps femoris muscle during the bilateral leg extension and unilateral knee extension actions. The result showed that the co-activation of the biceps femoris muscle during the extension was higher in the women with FM than in the healthy controls. This may indicate that co-ordination of these muscles has been disturbed and may partly impair maximal force production.

The mean CSA of QF has been shown to vary from 57 to 58.5 cm^2 in premenopausal women with FM and to be comparable to that of healthy women (Nørregaard et al. 1995, Häkkinen et al. 2002). In the present study the mean CSA of QF in postmenopausal women with FM was about 47 cm^2. This may indicate an age-related decrease in muscle mass (Lexell et al. 1988, Janssen et al. 2000), but it could also be a consequence of physical inactivity. However, we did not measure the CSA of QF in the healthy women and, therefore, it is impossible to conclude whether the lower CSA of QF explained the differences in muscle strength between the study groups.

Several earlier studies on premenopausal women with FM have suggested that physical inactivity could explain the low muscle strength found in women with FM (Nørregaard et al. 1994a, 1995, Vestergaard-Poulsen et al. 1995, Borman et al. 1999). This assumption may partly explain the muscle strength of the lower extremities. However, assessment of physical activity is difficult, because regular exercise training and work as well as physical activity in the everyday chores have effects on physical fitness and, therefore, all these areas should be assessed carefully. In addition, it is essential assess the intensity of physical activity. Unfortunately, physical activity was measured incompletely in the present study as also quite often in the earlier studies. Thus, the effects of physical activity or inactivity on muscle strength in postmenopausal women with FM should be examined carefully in further studies.

It has been also suggested that fear of pain could explain lower muscle strength in women with FM (Jacobsen et al. 1991a, Lindh et al. 1994, Henriksson et al. 1996, Maquet et al. 2002). Fear of pain already before a movement is known as expected pain (pain catastrophising) (Lamé et al. 2005). This means that a person believes that something bad will happen, such as an increased in pain due to the movement or exercise. This could be supported by the results of some earlier studies of electrical muscle stimulation. These studies have shown that maximal muscle force produced voluntarily has been at submaximal level in the subjects with FM and the real maximal force has been produced only during voluntary contraction stimulated by electrical stimulation. Therefore, the subjects with FM may produce a lower degree of effort due to pain or expected pain (Jacobsen et al. 1991a, Lindh et al. 1994, Nørregaard et al. 1995). Fear of pain may also lead to avoidance of intensive physical activity (Edwards et al. 2006). However, in the present study the participants were encouraged during the measurements to perform their voluntary maximal actions. Despite this it is also possible that the women with FM, at least to some extent, felt fear of pain, which may have had an effect on their strength results.

Aerobic performance (I)

The results of this study showed that W_{max}, work time, maximal heart rate and blood lactate concentration in the aerobic test were lower in the women with FM than in the healthy controls. However, absolute and relative VO_{2max} did not differ between the groups. This unexpected result may raise the question of whether the women with FM reached their real maximum in the test. According to the results for maximal heart rate and RER, the maximum level was reached in both groups.

Aerobic performance is dependent on the function of the cardiovascular system; however, muscular fitness is also important, since muscles perform actions and their oxidative capacity, therefore, should also be as good as possible. In this study aerobic performance was measured by a maximal cycle ergometer test, which especially places the loading on the thigh muscles (i.e. m. quadriceps femoris). In earlier studies W_{max} has been lower in women with FM than in healthy controls (van Denderen et al. 1992, Nørregaard et al. 1994b, Verstappen et al. 1995, Lund et al. 2003). These studies, however, have not reported the muscle strength of the lower extremities in the same subjects. Thus, it remains unclear whether individuals with larger muscle strength of the lower extremities would have attained higher W_{max} and a longer work time than individuals with less muscle strength. In the present study we observed weak correlations (Study I) between W_{max} and work time with the knee extension and flexion forces in women with FM, but not in healthy women. This may indicate that the strength of the leg muscles may be a factor limiting W_{max} in subjects with FM, when they perform a maximal test on a cycle ergometer; however, this needs further study.

Individuals with better aerobic fitness and higher W_{max} usually also have higher blood lactate concentration at the end of the test than individuals with lower aerobic fitness. A high lactate concentration indicates an efficient anaerobic muscle metabolism and good ability to endure unpleasant feelings of fatigue and pain due to increased blood lactate accumulation in the muscles. In the earlier studies capillary lactate concentration has not been reported during a direct aerobic test in women with FM. Nørregaard et al. (1994b) performed an indirect cycle ergometer test in premenopausal women with FM and healthy controls. They did not observe a difference in maximal capillary lactate concentration between the groups, although median W_{max} was lower in the women with FM. In the present study both maximal lactate concentration and W_{max} remained lower in the postmenopausal women with FM than in the healthy controls, which may indicate that the women with FM had impaired anaerobic muscle metabolism. It is also possible that they felt muscle pain

(Verstappen et al. 1995) more than the controls, and this led them to stop the test. However, Valim et al. (2002) did not observe any relationship between aerobic capacity and pain level during the treadmill test, as evaluated by the bodily pain scale of SF-36 and the Fibromyalgia Impact Questionnaire. This suggested that intensity of pain was not related to physical limitation. In the present study this remains unanswered.

Previous studies have mainly reported lower maximal heart rate in women with FM than controls during aerobic tests (van Denderen et al. 1992, Nørregaard et al. 1994b, Verstappen et al. 1995, Valim et al. 2002, Lund et al. 2003). Lower heart rate may indicate that the subjects with FM have lower aerobic fitness compared to controls; however, it may also indicate impaired regulation of the autonomic sympathetic nervous system in women with FM due to the FM syndrome (van Denderen et al. 1992). The present result was well in line with the earlier ones as the maximal heart rate was also lower in our postmenopausal women with FM. However, this needs further research, as a lower heart rate may be a consequence of FM or it may indicate nothing more than normal large inter-individual variation.

Direct tests by cycle ergometer have found VO_{2max} to be lower in premenopausal women with FM (Lund et al. 2003) or comparable with the values for healthy controls (Bennett et al. 1989, Simms et al. 1994). In the present study VO_{2max} was low in both groups; however, according to Shvartz and Reibold's (1990) reference values it was within the average levels. However, an unexpected result was that VO_{2max} did not differ between the postmenopausal women with FM and healthy controls despite the lower W_{max} and lower maximal heart rate in the subjects with FM. Since VO_{2max} and heart rate increase linearly with increasing W_{max} our result is difficult to explain. One possible explanation could be that healthy subjects were able to perform anaerobic work for longer than the subjects with FM. In the subjects with FM, on the other hand, VO_{2max} could have increased more, but the limiting factor was their weak muscle performance or perhaps unpleasant feeling of pain in their leg muscles (Nørregaard et al. 1994b). A further explanation could be that impaired regulation of the autonomic sympathetic nervous system may have affected both lung and heart functions in the postmenopausal women with FM. In addition, it is possible that the postmenopausal women with FM were more sensitive to feelings of fatigue and interrupted the test earlier than the controls. Unfortunately, perceived exertion (Borg scale) was not asked during the test, which would have made it possible to estimate whether the subjects had performed the aerobic test up to their subjective maximum. However, more research is needed to conclude whether VO_{2max} is different in postmenopausal women with FM compared to healthy women.

Functional capacity and quality-of-life (I)

In the present study maximal stair-climbing time and walking time were lower in the postmenopausal women with FM compared to healthy women, but walking speed did not quite reach statistical significance. However, walking speed was 2.0 m/s in the subjects with FM and 2.2 m/s in the healthy controls. This is clearly faster than in the study by Sainio et al. (2006), in which walking speed was less than 1.2 m/s in 11% of their samples of healthy women aged 55-64 (age group mean 1.6 m/s). In addition, none of our participants had difficulties in stair-climbing, while in Sainio et al. (2006) 11% of the women reported difficulties climbing one flight of stairs. Our results may indicate that the postmenopausal women with FM were in 'good' physical condition and, given the inclusion and exclusion criteria, a possibly rather selected group. However, the results of short walking and stair-climbing tests have not been reported earlier in subjects with FM.

The scale of the self-reported HAQ index runs from 0 (good functional capacity) to 3 (several disabilities). In our women with FM the index was 0.5 and in the healthy controls only 0.01. Although the functional capacity of the women with FM was lower than that of the healthy controls, the results indicate that both groups had, in fact, good functional capacity. Despite the good HAQ index in our study, some other studies have reported that subjects with FM may have difficulties managing everyday life activities (Henriksson et al. 2005). Our study supports this, as most of the items of the RAND-36 questionnaire showed that quality-of-life was significantly lower than in the subjects with FM than the healthy controls. The women with FM were, however, able to manage everyday chores without difficulties. Thus, our subjects may have been in better physical condition than those in earlier FM studies (e.g. Richards and Scott 2002).

6.2 Effects of strength training in postmenopausal women with fibromyalgia

Neuromuscular performance

Acute neuromuscular responses. In this study (II) the acute responses of neuromuscular functions were tested during the fatiguing loading before and after the 21-week strength training period. The loading was deliberately made more strenuous than in normal strength training, but was nevertheless planned to simulate a typical training exercise session. The loading before the training period led to a decrease of 25% in leg extension force in the postmenopausal women with FM. The decrease was also comparable with that in the present age-matched healthy controls (23%) as well as with that in the healthy 50-year-old women (31%) in the earlier study by Häkkinen (1995). After the 21-week strength training period the fatiguing loading was performed again and the decreases in leg extension force were comparable with the decreases at week 0 in both groups. The training period led to significant increases in muscle strength and, therefore, the absolute force level was higher after the training than before it. This also led to increased load in every set, which may in turn increase the subjects' ability to tolerate physical loading everyday life as well. In addition to neuromuscular changes, GH concentration may also slightly increase after every strength training session (Häkkinen and Pakarinen 1995, Häkkinen et al. 2002). In women with FM this change in GH concentration might be important, as GH concentration may have been lowered in women with FM and it may be partly connected to symptoms of FM (Jones et al. 2007).

The acute decrease in muscle strength is a result of decreased neural activation of the working muscles as well as increased blood lactate concentration due to fatiguing loading. In healthy women (50 years) (Häkkinen 1995) and in women with FM (38 years) (Häkkinen et al. 2000) fatiguing loading led to a decrease in the average IEMG activity of the quadriceps femoris muscle. In the present study the percentage change in IEMG activity (pre vs. post) during the loading at week 0 and 21 did not differ between the groups or within the groups, indicating similar responses to fatiguing loading. It is interesting that neural activation did not decrease, although muscle strength decreased. One explanation could be that to maintain the required muscle force, despite the increase in blood lactate concentration and fatigue, neural activation has to increase by the recruiting of new motor units and increasing the firing frequency of working motor units (Crewther et al. 2006). In this study the blood lactate concentration increased due to loading in both groups, showing normal anaerobic energy metabolism also in the women with FM. This result was, however, contrary to that observed in the aerobic test in our cross-sectional study (I), which was discussed earlier. Owing to these different results obtained from different tests, anaerobic energy metabolism in women with FM needs further study.

Long-term neuromuscular adaptations. It is well documented that regular and progressive strength training leads to increases in muscle strength due to increased EMG activity and CSA of the trained muscles (Häkkinen 1994, Latham et al. 2003, Fry 2004). These improvements would not be possible if there were impairments in hormonal responses and/or neuromuscular functions due, for example, to disease. It has been proposed that women with FM cannot perform intensive strength training, because FM and its symptoms, especially pain, could worsen. Therefore, only few strength training studies have been conducted in these subjects. However, all the training studies presented in Table 4 indicated that premenopausal women with FM were able to perform strength training and that their neuromuscular long-term adaptations were comparable with those of healthy women. The present results (III, IV) are also well in line with the earlier ones. In our study the training led to a 32% increase in maximal knee extension force in the postmenopausal women with FM and 24% in the healthy women. In both groups the IEMG activity of the leg extensors increased by 36%. Moreover, the explosive force of the leg muscle groups also improved in the women with FM, confirming further that the adaptations of the neuromuscular functions were comparable between the study groups. Also the development of hypertrophy in the trained muscles indicated that the structural changes in the women with FM were normal, although the changes in hormones, such as GH concentrations, have not been systematic (Häkkinen et al. 2002, Jones et al. 2007). Häkkinen et al. (2002) found that the CSA of QF increased by 7% in middle-aged women with FM and by 9% in healthy women during a 21-week strength training period. In our study the CSA of QF increased by 5% in the postmenopausal women with FM. Therefore, it can be concluded that women with FM did not have impaired neuromuscular functions and the trainability of their muscles remained normal despite a history of FM of several years.

Functional capacity

Strength training has a modest beneficial effect on walking speed in healthy older individuals (Latham et al. 2003). Lopopolo et al. (2006) concluded that self-selected walking speed improved in healthy individuals due to strength training, while maximal speed did not. In the present study (III) functional capacity improved in all the tests in the women with FM, while no improvements were observed in the healthy women; this was most likely due to the better results of the latter already at the baseline. The improvements in the women with FM could partly be a result of increased maximal, and especially explosive, muscle strength of the leg muscles. Although the HAQ index was good already at the beginning of the study in the women with FM, further minor improvements were, however, observed both in the HAQ index and walking speed after the regular strength training period.

Pain and fatigue

Acute, intensive and uncommon physical activity, compared to normal activities, usually leads to exercise-induced muscle pain (DOMS). When exercise is repeated regularly, muscle pain usually decreases and finally disappears. In the present study (II) heavy-resistance fatiguing loading caused a comparable DOMS phenomenon between the postmenopausal women with FM and the healthy controls. DOMS attenuated at the end of 21-week training, indicating normal responses in the women with FM. However, in subjects with chronic pain, such as FM, acute strong pain, i.e. DOMS, may cause interruption of exercise training soon after its commencement. In clinical work it would be especially important to distinguish chronic pain and pain induced by physical activity. It has been suggested that neuromuscular changes in subjects with FM could be a consequence of decreased physical activity, not FM itself (Vøllestad and Mengshoel 2005) and, therefore, it would be essential to note the effects of pain on the activity level as well as the length of recovery periods, when designing exercise prescriptions for these subjects (Vlaeyen and Linton 2000, de Gier et al. 2003).

Of more interest than DOMS is the possibility of exercise-induced hypoalgesia as a consequence of regular training. However, the effects of exercise on attenuating the general pain are not totally clear, as the mechanisms underlying exercise-induced hypoalgesia are not well understood (Koltyn 2000). Earlier randomized controlled studies have all shown that regular strength training in premenopausal women with FM may attenuate subjectively perceived general pain (Häkkinen et al. 2001a, 2002, Jones et al. 2002, Kingsley et al. 2005). Our present results (III, IV) partly support this finding, since the individual results for pain (Fig. 13) showed a large inter-individual variation. Both strength and aerobic training seem to have some positive effects on general pain (Busch et al. 2002). One explanation for a decrease in general pain after training, could be possible changes in the endogenous opioid system (Koltyn 2000) or interactions between the pain modulatory and cardiovascular responses (Koltyn et al. 2001, Koltyn and Umeda 2006). However, more research on these is needed. In particular, there is a need for studies in which pain is followed for at least several months to assess whether the strength training effects are maintained over the long-term, if the training is continued regularly or if the training is stopped.

Exercise training has been shown to decrease fatigue in subjects with chronic fatigue syndrome (Edmonds et al. 2004). Changes in self-reported mood and well-being after exercise may also decrease the perception of fatigue (Brosse et al. 2002, Barbour and Blumenthal 2005). The present results indicate that fatigue tended to diminish also in the postmenopausal women with FM after regular strength training. This finding was well in line with the earlier studies in premenopausal women with FM (Häkkinen et al. 2001a, 2002). Fatigue may decrease due to improved overall physical fitness or to improvement in mood and social relationships during training, and, therefore it is difficult to conclude whether training alone affects fatigue.

6.3 Strength training in fibromyalgia

Knowledge on the suitability of strength training in subjects with FM has been scarce (Mannerkorpi and Iversen 2003, Busch et al. 2002). The present training intervention was carried out by performing a 21-week strength training program in postmenopausal women with FM. The program was planned so that it fulfilled the general principles of exercise training. In particular, the progression of training intensity was carefully structured. Training intensity was mainly between 60-80% 1RM, which increased muscle mass; however, in these previously untrained women with FM maximal muscle strength improved as well. In addition, about 20% of the total amount of training was planned to be explosive training, in which the concentric phase of the exercise action was performed as explosively as possible. The postmenopausal women with FM were able to perform this explosive training without any problems or adverse effect.

In the present study the training was dynamic and it was performed for all the main muscle groups of the body. Dynamic training enables increased blood flow in the muscles and does not cause muscle pain (DOMS) as much or as easily as eccentric exercises may do, at least at the beginning of training

(Jones and Clark 2002, Gowans and deHueck 2004). As the main problem in FM is pain in the muscles, strength training should start carefully so as to avoid extra pain as much as possible. For this reason it is important to explain clearly to the trainees the difference between FM pain and DOMS so as to minimize interruption of the training. It is also possible to emphasize that regular strength training leads to muscle adaptation and may even attenuate pain perception, as the DOMS results showed after fatiguing loading. In the present study the subjects trained in small groups and pairs. This could be an important way of motivating subjects to continue regular training and also avoid drop-out (Jones et al. 2004). These subjects with FM should be encouraged to exercise despite general FM pain, as the results showed that pain is not exacerbated due to training, and the subjects' ability to tolerate loading (most likely also in everyday life) improved. However, if FM pain worsens due to training, the exercise program should be modified. At first, it would be best to decrease the intensity or duration of the exercise sessions, while maintaining normal training frequency. If the pain persists, then decreased frequency would also be essential. However, it is important to remember that if the goal of the training is improve muscle strength, the training frequency should be higher than if the goal is only to maintain the existing level of muscle strength. However, the general principle should be normal strength training, as FM does not restrict training and there are no prohibited movements.

The present study showed that both maximal and explosive muscle strength of the knee extensors improved markedly in the postmenopausal subjects with FM. Therefore, it can be concluded that this type of normal and progressive strength training is suitable to women with FM. In addition, subjects with FM are most likely able to obtain the same positive health benefits, such improved muscle strength, mass and co-ordination, by strength training as healthy individuals, and thus this mode of exercise can be recommended to the subjects with FM. However, aerobic training, which is also an essential part of overall training, should not be forgotten. Aerobic training has been studied more than strength training in these subjects and it is also a suitable mode of training for subjects with FM (Busch et al. 2002). Both training modes are important and should be recommended. If necessary, with careful testing of different aspects of physical fitness and careful interpretation of the results, the training can be focused either on strength or aerobic exercise according to need.

6.4 Methodological considerations

Cross-sectional study (I)

The strengths of the present cross-sectional study were several measurements of different aspects of physical fitness and the older age of the women with FM (postmenopausal) than has been the case in earlier studies. The neuromuscular measurements used in the present study are commonly used in exercise physiology and biomechanical research. The reliability of the muscle strength results is enhanced, when attention is paid to the proper calibration of the measuring equipment, and it is ensured that preparatory instructions and measuring technique are always the same for all subjects. However, a common problem in a population with FM is that despite careful preparation and encouragement during the tests it is possible that the subjects will not perform a maximal effort in the test due to fear of pain and/or lack of motivation. This has also been considered in some earlier studies (e.g. Verstappen et al. 1995, Miller et al. 1996) and it may explain, at least partly, the conflicting results on physical fitness in patients with FM. The measurement of EMG activity is known to be influenced by several factors, such as skin preparation, thickness of adipose tissue etc., and therefore, the results of EMG activity should always be interpreted with caution.

Also, the aerobic test is commonly used as a measurement of maximal oxygen uptake. During the test, the subjects had to breathe through a face mask, which may have felt slightly uncomfortable and thus may have had an effect on the results. As it has been mentioned earlier, the subjects were most likely in quite good physical condition, which may partly explain the good results obtained in the functional capacity tests. Pain and fatigue are subjectively perceived feelings and their objective measurement is difficult.

The main limitation is that the study was a cross-sectional design with small sample sizes and that the healthy women were measured a couple of years later than the women with FM. Although on both occasions the measurement equipment was the same, the instructions were identical and also one of the measurers was the same individual, it is possible that the measurements include an element of systematic measurement bias. In addition, our subjects were volunteers, which means that they were most likely more active and well-motivated than the population in general and also interested in the issue in question. For this reason, it is possible that the present sample of postmenopausal women with FM were healthier and more physically active than persons with FM usually are. However, it was not possible to assess these factors, because the current ACR's criteria for FM do not classify persons with FM into subgroups. In spite of this, sampling bias should be taken into consideration, when discussing the results. Also, individually tailored medication used for FM symptoms may have had some limiting effects on physical performance in the women with FM.

Randomized controlled strength training study (II-IV)

The main strength of the present intervention was the randomized controlled study design, in which the women with FM were randomly assigned to either the training or control group to ensure that the groups would be as similar as possible. However, the measurers and the subjects were not blinded for the intervention, which may have an effect on the results. On the other hand, one of the two measurers was always the same individual. Having the healthy subjects as a training control group, strengthened the study design and was essential to control for other effects besides training. They had, however, participated in a similar intervention study two years earlier, which may have had an effect on the measurements and training performed despite the fact that the study design was same in both years. In addition, the inclusion and exclusion criteria of the study were strictly set and those factors especially, which may have had an effect on neuromuscular performance, were carefully checked.

Previously, few randomized strength training studies have been carried out in premenopausal women with FM and thus there was a need for information as to whether prolonged strength training is suitable for postmenopausal women with FM. Thus, the age of the subjects and the length of the training period (21 weeks) can be considered strengths of the study. In addition, the strength training intervention was carefully planned according to the general principles of training and it was supervised. The low drop-out rate and lack of side-effects can also be regarded as strengths. Additionally, performing heavy-resistance fatiguing loading before and after the training period yielded important knowledge about acute neuromuscular responses and DOMS in these subjects and the possible modulating effect of strength training.

The above discussion of the reliability of neuromuscular and functional capacity measurements also holds for in the intervention study. Moreover, the reproducibility of measurements is essential if reliable results are to be obtained, when the measurements are repeated several times during the intervention. In this study the coefficient of variation (CV%) was used to measure the reproducibility of the measurements (see chapter 4.2 Measurements). The large CV% in women with FM may be explained by possible pain sensations during the measurements or by fear of pain. It may also indicate how difficult it is for them to produce maximal effort, as they are probably used to avoiding maximal and explosive trials in everyday life. The CV% was lower in the walking tests, perhaps because the tests simulate normal action very well.

Despite its several strengths, this study also has limitations. The main limitation was the small sample size and lack of adequate power calculations before the study. However, the present sample sizes were most likely large enough for main outcome variables of the muscle strength and CSA analyses, as the gains in these characteristics after regular and progressive strength training have earlier been found to be substantial. Therefore, to demonstrate a mean increase in muscle strength of 25% in the training group and 5% in the control group with a SD of 10% (Häkkinen et al. 2002) with a power of .80 and α of 0.05, four patients per group would have been needed. Further, to demonstrate a mean increase of 6% in CSA of QF during the training period in the training group and 2% in the control group with SD 3% (Häkkinen et al. 2002) would have required nine patients per group. However, due to the larger inter-individual variation the power of the study is insufficient in the other measurements. Second, both the women with FM and healthy controls were volunteers (see discussion above) and they were allowed to use individually tailored medication. Also a closer inquiring into previous physical activity should have been made. The lack of strength assessments for weeks 7 and 14 in the control group of women with FM made a comparison-of-effects training profile in relation to time impossible between the training and control groups. The FM symptoms, and especially pain, should have been assessed more frequently during the training period so as be able to monitor them according to increasing training intensity and duration. On the basis of these strengths and limitations the results of the cross-sectional and the intervention studies can be generalized mainly to postmenopausal women with FM who are physically in rather good condition.

6.5 Practical implications and future research

This study showed that neuromuscular performance in particular may decrease in postmenopausal women with FM due to either FM syndrome or decreased physical activity. Therefore, more attention should be focused on this aspect of physical fitness in subjects with FM. The notable increases in muscle strength and mass as well as the improvements in functional capacity due to the regular and progressive strength training are clinically relevant to prevent loss of these characteristics with increasing age. Especially important was the finding that pain showed a decreasing trend after strength training; this could be used as a factor to motivate women with FM to exercise regularly.

Previous studies have shown that aerobic exercise is an effective and safe mode of training for women with FM. The present study showed that strength training is also a suitable mode of training for these subjects. Therefore, general exercise recommendations can be applied to postmenopausal women with FM to prevent risk factors of common diseases, such as type II diabetes and metabolic syndrome, and to enhance general health. In clinical work and real life subjects with FM may have perhaps other diagnoses, such as high blood pressure, depression, osteoarthritis, and/or difficult symptoms of FM, which means that the use of strength training should be tailored even more individually. Otherwise there are no obstacles, except motivation of subjects with FM to exercise regularly and perhaps also lack of knowledge of primary care to applying and to including this training mode in health promotion programs targeted at postmenopausal women with FM.

There are several possible topics for further research on FM and exercise training. First, overall physical fitness should be studied more broadly so that it would be possible to observe changes in different aspects of physical fitness. One interesting question and a cause of continuous speculation is whether lower muscle strength is a result of lower physical activity or not in subjects with FM. Therefore, physical activity should be examined more carefully by follow-up studies. The dose-response relationship of strength training (as well as other training modes), and especially the effects of different intensities of training, on different aspects of physical fitness and functional capacity in FM need more investigation. One important effect of strength training might be its attenuating effect on FM pain, but it is not known whether the effect would be larger or lower in the subjects with FM, if they continued regular training several years. Finally, there is a need to study the effects and suitability/feasibility of different training modes alone or together with coping strategies and patient education.

7 PRIMARY FINDINGS AND CONCLUSIONS

The primary findings of the present study can be summarized as follows:

1) In postmenopausal women with FM (aged 50-70) muscle strength of the lower extremities was lower than in healthy women. This finding may partly explain the lower functional capacity as well as lower work load and work time in the bicycle exercise test in women with FM. Muscle strength in the upper body and maximal oxygen uptake were comparable with those of healthy women.

2) Acute neuromuscular responses and the time course of DOMS after the fatiguing loading in women with FM were comparable with the values in healthy women suggesting normal fatiguing and recovery processes in postmenopausal women with FM.

3) Progressive and regular strength training led to marked improvement in muscle strength, EMG activity and CSA of the lower extremities in postmenopausal women with FM comparable to the values in healthy controls, indicating the similar trainability of the measured muscles in both groups.

4) Progressive and regular strength training slightly improved functional capacity in postmenopausal women with FM.

5) Progressive strength training does not exacerbate, but may even slightly attenuate perceived pain and fatigue in postmenopausal women with FM.

6) Strength training is an effective, suitable and safe mode of training for postmenopausal women with FM.

In conclusion, the present study suggests that postmenopausal women with FM may have decreased muscle strength, especially in the lower extremities. However, the subjects are able to recover from fatiguing loading normally and are capable of considerably improving their neuromuscular performance remarkably by regular and progressive strength training and to carry it out safely without exacerbation of symptoms or sustaining any injuries. Another clinically important conclusion is that subjects with FM may gain the same positive performance- and health-related effects from strength training as healthy subjects. Therefore, individually tailored strength training is a recommendable mode of exercise for postmenopausal women with FM.

YHTEENVETO

Fyysinen kunto, kipu- ja väsymysoireet ja säännöllisen voimaharjoittelun vaikutukset menopaussi-iän ohittaneilla fibromyalgiaa sairastavilla naisilla

Fibromyalgia (FM) on krooninen kipuoireyhtymä, jonka syytä ei tiedetä. Se aiheuttaa useita oireita, joista keskeisimpiä ovat kipu eri puolilla kehoa, väsymys ja univaikeudet. Suurin osa sairastuneista on naisia. Yleisin sairastumisikä on alle 50 vuotta, mutta koska FM paranee vain harvoin, sairaus on tavallisin 55-79–vuotiailla. Oireyhtymän hoito keskittyy oireiden lievittämiseen lääkityksen, liikunnan ja erilaisten kognitiivisten käyttäytymisterapioiden avulla. Liikunnan merkitystä korostetaan, koska sen avulla sairastuneiden fyysistä kuntoa voidaan ylläpitää ja parantaa. Tavallisimmin FM:a sairastaville on suositeltu aerobista liikuntaa, koska voimaharjoittelun on ajateltu pahentavan oireita. Voimaharjoittelututkimuksia on tehty FM:an sairastuneille vain muutamia eikä menopaussi-iän ohittaneita naisia ole tutkittu juuri lainkaan.

Tämän tutkimuksen tarkoituksena oli selvittää FM:a sairastavien menopaussi-iän ohittaneiden naisten fyysistä kuntoa, hermo-lihasjärjestelmän (neuromuskulaarisia) välittömiä vasteita uuvuttavaan kuormitukseen ja säännöllisen voimaharjoittelun vaikutuksia hermo-lihasjärjestelmän suorituskykyyn, liikkumiskykyyn sekä oireisiin ja verrata niitä terveiden naisten tuloksiin. Tutkimus koostui kahdesta erillisestä tutkimusjoukosta, joissa molemmissa tutkittavien naisten ikä oli 50-70 –vuotta. Ensimmäisessä tutkimusjoukossa oli FM:a sairastavia naisia 23 ja terveitä naisia 11, joilta tutkittiin poikkileikkausasetelmalla fyysistä kuntoa. Toisessa tutkimusjoukossa osallistujia oli vastaavasti 26 ja 10 ja heiltä tutkittiin säännöllisen 21 viikkoa kestävän voimaharjoittelun vaikutuksia hermo-lihasjärjestelmän suoritus-kykyyn.

Poikkileikkausasetelmassa tutkittavien kestävyyskunto mitattiin polkupyörä-ergometritestillä maksimaalisen hapenottokyvyn määrittämiseksi. Maksimaalista lihasvoimaa ala- ja yläraajojen sekä vartalon lihaksista mitattiin dynamometreillä. Voimatestien aikana alaraajojen lihaksista mitattiin myös lihasten sähköistä aktiivisuutta (elektromyografia, EMG). Lisäksi liikkumiskykyä tutkittiin 10 m:n kävelynopeudella ja 10 porrasaskelman nousuajalla sekä itsearvioitua toimintakykyä Stanford Health Assessment -kyselyllä (HAQ). FM:n oireista kipua ja väsymystä arvioitiin 10 cm:n Visual Analog Scale –janalla (VAS) ja elämän laatua RAND-36 –kyselyllä.

21 viikon kuntosaliharjoittelua varten toisen tutkimusjoukon FM:a sairastavat naiset satunnaistettiin harjoittelu- (n=13) ja kontrolliryhmään (n=13). Myös terveiden naisten ryhmä harjoitteli. Harjoitteluryhmät toteuttivat ohjattua ja progressiivista voimaharjoittelua säännöllisesti kaksi kertaa viikossa 21 viikon ajan. Voimaharjoittelun vaikutuksia tutkittiin maksimaaliseen lihasvoimaan, EMG-aktiivisuuteen ja reisilihasten poikkipinta-alaan sekä em. liikkumiskykyyn ja oireisiin. Ennen ja jälkeen harjoittelujakson harjoitteluryhmiltä

tutkittiin myös yksittäisen intensiivisen voimaharjoitus-kuormituksen (jalkojen ojennus; 5 sarjaa 10 toiston maksimikuormalla) aiheuttamia akuutteja vaikutuksia elimistössä mittaamalla lihasvoimaa ja EMG-aktiivisuutta alaraajojen lihaksista sekä veren maitohappopitoisuutta ja voimakkaan kuormituksen aiheuttamaa lihaskipureaktiota.

Poikkileikkausasetelman tulokset osoittivat, että menopaussi-iän ohittaneilla FM:a sairastavilla naisilla on alaraajoissa heikompi lihasvoima kuin terveillä naisilla, mutta yläraajojen ja vartalon lihasvoimissa ei ollut havaittavissa eroa. Kestävyyskuntotestissä työkuorma oli alempi ja työaika lyhyempi FM:a sairastavilla naisilla kuin terveillä, mutta maksimaalisessa hapenottokyvyssä ei ollut eroa ryhmien välillä. FM:a sairastavilla naisilla oli lisäksi hieman heikompi liikkumiskyky, he raportoivat enemmän oireita ja heillä oli huonompi elämän laatu kuin terveillä naisilla.

Säännöllinen progressiivinen 21 viikon voimaharjoittelu johti huomattavaan lihasvoiman ja lihasten sähköisen aktiivisuuden lisääntymiseen FM:a sairastavilla naisilla ja nämä muutokset olivat täysin verrattavissa terveiden naisten vastaaviin tuloksiin. FM:a sairastavilla naisilla myös reisilihasten poikkipinta-ala kasvoi ja liikkumiskyky kehittyi merkitsevästi harjoittelun seurauksena. FM:n oireet, erityisesti kipu, väheni hieman harjoittelujakson aikana.

Intensiivinen voimaharjoituskuormitus aiheutti lihasvoiman merkittävän laskun ja veren maitohappopitoisuuden nousun kuormituksen aikana sekä FM:a sairastavilla että terveillä naisilla ennen ja jälkeen voimaharjoittelujakson. Lihaskipu kuormittavan suorituksen jälkeen lisääntyi samalla tavoin molemmilla ryhmillä ollen suurimmillaan 1. ja 2. päivänä kuormituksen jälkeen. FM:a sairastavat naiset raportoivat yleisen kiputason (FM-kipu) sekä kuormitukseen liittyvän lihaskivun alentuneen harjoittelujakson jälkeen verrattuna harjoittelujaksoa edeltävään tilanteeseen. Intensiivinen kuormitus osoitti, että FM:a sairastavat naiset pystyvät tarvittaessa koviinkin ponnistuksiin ja että, kuormituksesta palautuminen tapahtuu samoin terveisiin naisiin verrattuna.

Johtopäätöksenä voidaan todeta, että menopaussi-iän ohittaneilla FM:a sairastavilla naisilla näyttäisi olevan alentunut lihasvoima erityisesti alaraajoissa. FM:a sairastavat naiset voivat kuitenkin kehittää voimantuotto-ominaisuuksiaan huomattavasti säännöllisellä voimaharjoittelulla. Voimaharjoittelun todettiin olevan turvallista näille henkilöille eikä se aiheuttanut oireiden pahentumista tai vammoja. Sekä intensiivisen kuormituksen akuutit muutokset että säännöllisen pitkäaikaisen voimaharjoittelun aiheuttamat muutokset elimistössä osoittivat, että FM:a sairastavilla naisilla hermo-lihasjärjestelmän toiminnot ovat täysin verrattavissa terveiden naisten vastaaviin muutoksiin. FM:sta ja sen aiheuttamista oireista huolimatta lihasten harjoitettavuus on säilynyt normaalina. Lisäksi harjoittelu vähensi hieman FM:lle tyypillisiä lihaskiputuntemuksia. Yksilöllisesti annosteltu voimaharjoittelu on siis turvallinen, tehokas ja käyttökelpoinen liikuntamuoto menopaussi-iän ohittaneille FM:a sairastaville naisille.

REFERENCES

Aalto AM, Aro AR, Teperi J. RAND-36 as a measure of Health-Related Quality of Life. Reliability, construct validity and reference values in the Finnish general population. Helsinki:Stakes, Research Reports 101, 1999.

ACSM. American College of Sports Medicine: Position Stand. Exercise and physical activity for older adults. Med Sci Sports Exerc 1998a;30:992-1008.

ACSM. American College of Sports Medicine: Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. Review. Med Sci Sports Exerc 1998b;30:975-991.

ACSM. American College of Sports Medicine: Position Stand. Progression models in resistance training for older adults. Med Sci Sports Exerc 2002;34:364-380.

Arnold LM, Hudson JI, Hess EV, Ware AE, Fritz DA, Auchenbach MB, Starck LO, Keck PE. Family study of fibromyalgia. Arthritis Rheum 2004;50:944-952.

Assis MR, Silva LE, Alves AM, Pessanha AP, Valim V, Feldman D, Neto TL, Natour J. A randomized controlled trial of deep water running: clinical effectiveness of aquatic exercise to treat fibromyalgia. Arthritis Rheum 2006;55:57-65.

Barbour KA, Blumenthal JA. Exercise training and depression in older adults. Neurobiol Aging 2005;26 Suppl 1:119-123.

Bartels EM, Danneskiold-Samsoe B. Histological abnormalities in muscle from patients with certain types of fibrositis. Lancet 1986;1:755-757.

Bartholomew JB, Lewis BP, Linder DE, Cook DB. Post-exercise analgesia: replication and extension. J Sports Sci 1996;14:329-334.

Bennett RM, Clark SR, Goldberg L, Nelson D, Bonafede RP, Porter J, Specht D. Aerobic fitness in patients with fibrositis. A controlled stufy of respiratory gas exchange and ^{133}xenon clearance from exercising muscle. Arthritis Rheum 1989;32:454-460.

Bennett RM, Schein J, Kosinski MR, Hewitt DJ, Jordan DM, Rosenthal NR. Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/acetaminophen. Arthritis Care Res 2005;53:519-527.

Bengtsson A, Henriksson K, Larsson J. Muscle biopsy in fibromyalgia: light microscopical and histochemical findings. Scand J Rheumatol 1986a;15:1-6.

Bengtsson A, Henriksson KG, Larsson J. Reduced high-energy phosphate levels in the painful muscles of patients with primary fibromyalgia. Arthritis Rheum 1986b;29:817-821.

Bergman S. Psychosocial aspects of chronic widespread pain and fibromyalgia. Disabil Rehabil 2005;27:675-683.

Borman P, Celiker R, Hascelik Z. Muscle performance in fibromyalgia syndrome. Rheumatol Int 1999;19:27-30.

Bouchard C, Shephard RJ. Physical activity, fitness, and health: the model and key concepts. In Bouchard C, Shephard RJ, Stephens T (eds.), Physical activity, fitness and health: international proceedings and consensus statement. Champaign, IL: Human Kinetics Publishers, 1994;77-88.

Brosse AL, Sheets ES, Lett HS, Blumenthal JA. Exercise and the treatment of clinical depression in adults: recent findings and future directions. Review. Sports Med 2002;32:741-760.

Buckelew SP, Conway R, Parker J, Deuser WE, Read J, Witty TE, Hewett JE, Minor M, Johnson JC, Van Male L, McIntosh MJ, Nigh M, Kay DR. Biofeedback/Relaxation training and exercise interventions for fibromyalgia: a prospective trial. Arthritis Care Res 1998;11:196-209.

Burckhardt CS, Mannerkorpi K, Hedenberg L, Bjelle A. A randomized, controlled clinical trial of education and physical training for women with fibromyalgia. J Rheumatol 1994;21:714-720.

Busch A, Schachter CL, Peloso PM, Bombardier C. Exercise for treating fibromyalgia syndrome. The Cochrane Database Syst Rev 2002;3: CD003786. [Updated March 2006]

Buskila D, Neumann L, Hershman E, Gedalia A, Press J, Sukenik S. Fibromyalgia syndrome in children – an outcome study. J Rheumatol 1995;22:525-528.

Carr DB, Goudas LC. Acute pain. Lancet 1999;353:2051-2058.

Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep 1985;100:126-131.

Cedraschi C, Desmeules J, Rapiti E, Baumgartner E, Cohen P, Finckh A, Allaz AF, Vischer TL. Fibromyalgia: a randomised, controlled trial of a treatment programme based on self management. Ann Rheum Dis 2004;63:290-296.

Cheung K, Hume PA, Maxwell L. Delayed onset muscle soreness. Treatment strategies and performance factors. Review. Sports Med 2003;33:145-164.

Clark SR, Jones KD, Burckhardt CS, Bennett RM. Exercise for patients with fibromyalgia: risks versus benefits. Review. Curr Rheum Rep 2001;3:135-146.

Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 1997;4:134-153.

Clauw DJ, Crofford LJ. Chronic widespread pain and fibromyalgia: what we know, and what we need to know. Best Pract Res Clin Rheumatol 2003;17:685-701.

Consitt LA, Copeland JL, Tremblay MS. Endogenous anabolic hormone responses to endurance versus resistance exercise and training in women. Sports Med 2002;32:1-22.

Crewther B, Cronin J, Keogh J. Possible stimuli for strength and power adaptation: acute metabolic responses. Review. Sports Med 2006;36:65-78.

Croft P, Schollum J, Sillman A. Population study of tender point counts and pain as evidence of fibromyalgia. Br Med J 1994;309:696-699.

Crofford LJ. Pharmaceutical treatment options for fibromyalgia. Curr Rheumatol Rep 2004;6:274-280.

Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, Young JP Jr., LaMoreaux LK, Martin SA, Sharma U, and the Pregabalin 1008-105 Study Group. Pregabalin for the treatment of fibromyalgia syndrome. Results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:1264-1273.

Daley MJ, Spinks WL. Exercise, mobility and aging. Review. Sports Med 2000;29:1-12.

van Denderen JC, Boersma JW, Zeinstra P, Hollander AP, van Neerbos BR. Physiological effects of exhaustive physical exercise in primary fibromyalgia syndrome (PFS): is PFS a disorder of neuroendocrine reactivity? Scand J Rheumatol 1992;21:35-37.

Deschenes MR. Effects of aging on muscle fibre type and size. Review. Sports Med 2004;34:809-824.

Dixon S, Bird H. Reproducibility along a 10 cm visual analogue scale. Ann Rheum Dis 1981;40:87-89.

Dirks AJ, Hofer T, Marzetti E, Pahor M, Leeuwenburgh C. Mitochondrial DNA mutations, energy metabolism and apoptosis in aging muscle. Review. Ageing Res Rev 2006;5:179-195.

Doherty TJ. Aging and sarcopenia. J Appl Physiol 2003;95:1717-1727.

Duchateau J, Semmler JG, Enoka RM. Training adaptations in the behaviour of human motor units. J Appl Physiol 2006;101:1766-1775.

Edmonds M, McGuire H, Price J. Exercise therapy for chronic fatigue syndrome. Cochrane Database Syst Rev 2004;3:CD003200. [Updated May 2006]

Edwards RR, Bingham CO, Bathon J, Haythornthwaite JA. Catastrophizing and pain in arthritis, fibromyalgia and other rheumatic diseases. Arthr Care Res 2006;55:325-332.

Ehrlich GE. Fibromyalgia, a virtual disease. Editorial. Clin Rheumatol 2003a;22:8-11.

Ehrlich GE. Pain is real; Fibromyalgia isn't. Editorial. J Rheumatol 2003b;30:1666-1667.

Elert JE, Rantapää-Dahlqvist SB, Henriksson-Larsen K, Lorentzon R, Gerdle BUC. Muscle performance, electromyography and fibre type composition in fibromyalgia and work-related myalgia. Scand J Rheumatol 1992;21:28-34.

Fitzcharles MA, Costa DD, Pöyhiä R. A study of standard care in fibromyalgia syndrome: a favourable outcome. J Rheumatol 2003;30:154-159.

Fleg JL, Morrell CH, Bos AG, Brant LJ, Talbot LA, Wright JG, Lakatta EG. Accelerated longitudinal decline of aerobic capacity in healthy older adults. Circulation 2005;112:674-682.

Forseth K, Gran JT. The prevalence of fibromyalgia among women aged 20-49 years in Arendal, Norway. Scand J Rheum 1992;21:74-78.

Forslind K, Fredriksson E, Nived O. Does primary fibromyalgia exist? Br J Rheumatol. 1990;29:368-370.

Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-145.

Frontera WR, Hughes VA, Lutz KJ, Evans WJ. A cross-sectional study of muscle strength and mass in 45- to 78-yr-old men and women. J Appl Physiol 1991;71:644-650.

Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R. Aging of skeletal muscle: a 12-yr longitudinal study. J Appl Physiol 2000;88:1321-1326.

Fry AC. The role of resistance exercise intensity on muscle fibre adaptations. Review. Sports Med 2004;34:663-679.

Gabriel DA, Kamen G, Frost G. Neural adaptations to resistive exercise: mechanisms and recommendations for training practices. Sports Med 2006;36:133-149.

Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev 2001;81:1725-1789.

de Gier M, Peters ML, Vlaeyen JWS. Fear of pain, physical performance, and attentional processes in patients with fibromyalgia. Pain 2003;104:121-130.

Gifford L. Pain, the tissues and the nervous system: a conceptual model. Physiotherapy 1998;84:27-36.

Goldenberg DL. Pharmacological treatment of fibromyalgia and other chronic musculoskeletal pain. Best Pract Res Clin Rheumatol 2007;21:499-511.

Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. JAMA 2004;92:2388-2395.

Gowans SE, deHueck A, Voss S, Richardson M. A randomized, controlled trial of exercise and education for individuals with fibromyalgia. Arthritis Care Res 1999;12:120-128.

Gowans SE, deHueck A. Effectiveness of exercise in management of fibromyalgia. Review. Curr Opin Rheumatol 2004;16:138-142.

Graven-Nielsen T, Arendt-Nielsen L. Pheripheral and central sensitization in musculoskeletal pain disorders: an experimental approach. Curr Rheumatol Rep 2002;4:313-321.

Gronemann ST, Ribel-Madsen S, Bartels EM, Danneskiold-Samsöe B, Bliddal H. Collagen and muscle pathology in fibromyalgia patients. Rheumatology 2004;43:27-31.

Guralnik JM, Ferrucci L. Assessing the building blocks of function. Utilizing measures of functional limitation. Am J Prev Med 2003;25:112-121.

Gureje O, von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization study in primary care. JAMA 1998;280:147-151.

Hadler NM. "Fibromyalgia" and the medicalization of misery. Editorial. J Rheumatol 2003;30:1668-1670.

Haskell WL, Lee I-M, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health. Updated recommendation for adults from the American College of Sports

Medicine and the American Heart Association. Circulation 2007;116:000-000. DOI: 10.1161/CirculationAHA.107.185649.

Hawkins S, Wiswell R. Rate and mechanism of maximal oxygen consumption decline with aging: implications for exercise training. Rewiev. Sports Med 2003;33:877-888.

Hays RD, Sherbourne CD, Mazel RM. The RAND 36-item health survey 1.0. Health Economics 1993;2:217-227.

Henriksson CM. Longterm effects of fibromyalgia on everyday life. A study of 56 patients. Scand J Rheumatol 1994;23:36-41.

Henriksson KG, Bäckman E, Henriksson C, de Laval JH. Chronic regional muscular pain in women with precise manipulation work. Scand J Rheumatol 1996;25:213-223.

Henriksson C, Liedberg G. Factors of importance for work disability in women with fibromyalgia. J Rheumatol. 2000;27:1271-1276.

Henriksson CM, Liedberg GM, Gerdle B. Women with fibromyalgia: work and rehabilitation. Review. Disabil Rehabil 2005;27:685-695.

Hermens HJ, Freriks B, Merletti R, Stegeman D, Blok J, Rau G, Disselhorst-Klug C, Hägg G. European recommendations for surface electromyography. Results of the SENIAM project. Roessingh Research and Development, 1999.

Hoffman MD, Shepanski MA, Ruble SB, Valic Z, Buckwalter JB, Clifford PS. Intensity and duration threshold for aerobic exercise-induced analgesia to pressure pain. Arch Phys Med Rehabil 2004;85:1183-1187.

van Houdenhove B. Fibromyalgia: a challenge for modern medicine. Editorial. Clin Rheumatol 2003;22:1-5.

Howley ET. Type of activity: resistance, aerobic and leisure versus occupational physical activity. Med Sci Sports Exerc 2001;33(6 Suppl.):S364-S369.

Hughes VA, Frontera WR, Wood M, Evans WJ, Dallal GE, Roubenoff R, Fiatarone Singh MA. Longitudinal muscle strength changes in older adults: influence of muscle mass, physical activity, and health. J Gerontol A Biol Sci Med Sci 2001;56:B209-B217.

Hunter GR, McCarthy JP, Bamman MM. Effects of resistance training on older adults. Review. Sports Med 2004;34:329-348.

Häkkinen A, Häkkinen K, Hannonen P, Alen M. Force production capacity and acute neuromuscular responses to fatiguing loading in women with fibromyalgia are not different from those of healthy women. J Rheumatol 2000;27:1277-1282.

Häkkinen A, Häkkinen K, Hannonen P, Alen M. Strength training induced adaptations in neuromuscular function of premenopausal women with fibromyalgia: comparison with healthy women. Ann Rheum Dis 2001a;60:21-26.

Häkkinen A, Kautiainen H, Hannonen P, Ylinen J, Mäkinen H, Sokka T. Muscle strength, pain, and disease activity explain individual subdimensions of the Health Assessment Questionnaire disability index, especially in women with rheumatoid arthritis. Ann Rheum Dis 2006;65:30-34.

Häkkinen K. Neuromuscular adaptation during strength training, aging, detraining, and immobilization. Crit Rev Phys Rehabil Med 1994;6:161-198.

Häkkinen K. Neuromuscular fatigue and recovery in women at different ages during heavy resistance loading. Electromyogr Clin Neurophysiol 1995;35:403-413.

Häkkinen K, Häkkinen A. Muscle cross-sectional area, force production and relaxation characteristics in women at different ages. Eur J Appl Physiol 1991;62:410-414.

Häkkinen K, Kallinen M, Izquierdo M, Jokelainen K, Lassila H, Mälkiä E, Kraemer WJ, Newton RU, Alén M. Changes in agonist-antagonist EMG, muscle CSA, and force during strength training in middle-aged and older people. J Appl Physiol 1998a;84:1341-1349.

Häkkinen K, Alén M, Kallinen M, Izquierdo M, Jokelainen K, Lassila H, Mälkiä E, Kraemer WJ, Newton RU. Muscle CSA, force production, and activation of leg extensors during isometric and dynamic actions in middle-aged and elderly men and women. J Aging Phys Act 1998b;6:232-247.

Häkkinen K, Komi PV. Changes in neuromuscular performance in voluntary and reflex contraction during strength training in man. Int J Sports Med 1983;4:282-288.

Häkkinen K, Pakarinen A. Acute hormonal responses to heavy resistance exercise in men and women at different ages. Int J Sports Med 1995;16:507-513.

Häkkinen K, Pakarinen A, Kraemer WJ, Häkkinen A, Valkeinen H, Alen M. Selective muscle hypertrophy, changes in EMG and force, and serum hormones during strength training in older women. J Appl Physiol 2001b;91:569-580.

Häkkinen K, Pakarinen A, Hannonen P, Häkkinen A, Airaksinen O, Valkeinen H, Alén M. Effects of strength training on muscle strength, cross-sectional area, maximal electromyographic activity, and serum hormones in premenopausal women with fibromyalgia. J Rheumatol 2002;29:1287-1295.

Jacobsen S. Chronic widespread musculoskeletal pain – the fibromyalgia syndrome. Dan Med Bull 1994;41:541-564.

Jacobsen S, Danneskiold-Samsøe B. Isometric and isokinetic muscle strength in patients with fibrositis syndrome. Scand J Rheumatol 1987;16:61-65.

Jacobsen S, Wildschiodtz G, Danneskiold-Samsoe B. Isokinetic and isometric muscle strength combined with transcutaneous electrical muscle stimulation in primary fibromyalgia syndrome. J Rheumatol 1991a;18:1390-1393.

Jacobsen S, Bartels EM, Danneskiold-Samsøe B. Single cell morphology of muscle in patients with chronic muscle pain. Scand J Rheumatol 1991b;20:336-343.

Jacobsen S, Danneskiold-Samsoe B. Dynamic muscular endurance in primary fibromyalgia compared with chronic myofascial pain syndrome. Arch Phys Med Rehabil 1992;73:170-173.

Jacobsen S, Jensen KE, Thomsen C, Danneskiold-Samsoe B, Henriksen O. ^{31}P magnetic resonance spectroscopy of skeletal muscle in patients with fibromyalgia. J Rheumatol 1992;19:1600-1603.

Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. J Appl Physiol 2000;89:81-88

Jones AM, Carter H. The effect of endurance training on parameters of aerobic fitness. Sports Med 2000;29:373-386.

Jones KD, Burckhardt CS, Clark SR, Bennett RM, Potempa KM. A randomized controlled trial of muscle strengthening versus flexibility training in fibromyalgia. J Rheumatol 2002;29:1041-1048.

Jones KD, Clark SR. Individualizing the exercise prescription for persons with fibromyalgia. Review. Rheum Dis Clin N Am 2002;28:419-436.

Jones KD, Burckhardt CS, Bennett JA. Motivational interviewing may encourage exercise in persons with fibromyalgia by enhancing self efficacy. Arthritis Rheum. 2004;51:864-867.

Jones KD, Deodhar P, Lorentzen A, Bennett RM, Deodhar AA. Growth hormone perturbations in fibromyalgia: a review. Semin Arthritis Rheum 2007. doi:10.1016/j.semarthrit.2006.09.006.

Jubrias SA, Bennett RM, Klug GA. Increased incidence of a resonance in the phosphodiester region of ^{31}P nuclear magnetic resonance spectra in the skeletal muscle of fibromyalgia patients. Arthritis Rheum 1994;37:801-817.

Kalapotharakos VI, Michalopoulos M, Tokmakidis SP, Godolias G, Gourgoulis V. Effects of a heavy and a moderate resistance training on functional performance in older adults. J Strength Cond Res 2005;19:652-657.

Karjalainen KA, Hurri H, Jauhiainen M, Koes BW, Malmivaara A, Roine R, van Tulder M. Multidisciplinary rehabilitation for fibromyalgia and musculoskeletal pain in working age adults. The Cochrane Database Syst Rev 2000;2:CD001984. [Updated March 2006]

Katz RS, Wolfe F, Michaud K. Fibromyalgia diagnosis. A comparison of clinical, survey, and American College of Rheumatology Criteria. Arthritis Rheum 2006;54:169-176.

King SJ, Wessel J, Bhambhani Y, Sholter D, Maksymowych W. The effects of exercise and education, individually or combined, in women with fibromyalgia. J Rheumatol. 2002;29:2620-2627.

Kingsley JD, Panton LB, Toole T, Sirithienthad P, Mathis R, McMillan V. The effects of a 12-week strength-training program on strength and functionality in women with fibromyalgia. Arch Phys Med Rehabil 2005;86:1713-1721.

Koltyn KF. Analgesia following exercise. A review. Sports Med 2000;29:85-98.

Koltyn KF. Exercise-induced hypoalgesia and intensity of exercise. Review. Sports Med 2002;32:477-487.

Koltyn KF, Arbogast RW. Perception of pain after resistance exercise. Br J Sports Med 1998;32:20-24.

Koltyn KF, Garvin AW, Gardiner RL, Nelson TF. Perception of pain following aerobic exercise. Med Sci Sports Exerc 1996;28:1418-1421.

Koltyn KF, Trine MR, Stegner AJ, Tobar DA. Effect of isometric exercise on pain perception and blood pressure in men and women. Med Sci Sports Exerc 2001;33:282-290.

Koltyn KF, Umeda M. Exercise, hypoalgesia and blood pressure. Sports Med 2006;36:207-214.

Kraemer WJ, Fleck SJ, Evans WJ. Strength and power training: physiological mechanisms of adaptation. Exerc Sports Sci Rev 1996;24:363-397.

Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. Review. Sports Med 2005;35:339-361.

Laitakari J, Vuori I, Oja P. Is long-term maintenance of health-related physical activity possible? An analysis of concepts and evidence. Health Educ Res 1996;11:463-477.

Lame IE, Peters ML, Vlaeyen JWS, von Kleef M, Patijn J. Quality of life in chronic pain is more associated with beliefs about pain than with pain intensity. Eur J Pain 2005;9:15-24.

Landers KA, Hunter GR, Wetzstein CJ, Bamman MM, Weinsier RL. The interrelationship among muscle mass, strength, and the ability to perform physical tasks of daily living in younger and older women. J Gerontol A Biol Sci Med Sci 2001;56:B443-B448.

Larsson L, Grimby G, Karlsson J. Muscle strength and speed of movement in relation to age and muscle morphology. J Appl Physiol 1979;46:451-456.

Latham N, Anderson C, Bennett D, Stretton C. Progressive resistance strength training for physical disability in older people. The Cochrane Database Syst Rev 2003;2:CD002759. [Updated August 2005]

Le Goff P. Is fibromyalgia a muscle disorder? Review. Joint Bone Spine 2006;73:239-242.

Lemstra M, Olszynski WP. The effectiveness of multidisplinary rehabilitation in the treatment of fibromyalgia. A randomized controlled trial. Clin J Pain 2005;21:166-174.

Lexell J, Taylor CC, Sjostrom M. What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. J Neurol Sci 1988;84:275-294.

Lindh MH, Johansson GA, Hedberg M, Grimby GL. Studies on maximal voluntary muscle contraction in patients with fibromyalgia. Arch Phys Med Rehabil 1994;75:1217-1222.

Lindh M, Johansson G, Hedberg M, Henning G-B, Grimby G. Muscle fiber characteristics, capillaries and enzymes in patients with fibromyalgia and controls. Scand J Rheumatol 1995;24:34-37.

Lopopolo RB, Greco M, Sullivan D, Craik RL, Mangione KK. Effect of therapeutic exercise on gait speed in community-dwelling elderly people: a meta-analysis. Phys Ther 2006;86:520-540.

Lorenzen I. Fibromyalgia: a clinical challenge. J Internal Med 1994;235:199-203.

Lund N, Bengtsson A, Thorborg P. Muscle tissue oxygen pressure in primary fibromyalgia. Scand J Rheumatol 1986;15:165-173.

Lund E, Kendall SA, Janerot-Sjoberg B, Bengtsson A. Muscle metabolism in fibromyalgia studied by P-31 magnetic resonance spectroscopy during aerobic and anaerobic exercise. Scand J Rheumatol 2003;32:138-145.

Lundberg G, Gerdle B. Tender point scores and their relations to signs of mobility, symptoms, and disability in female home care personnel and the prevalence of fibromyalgia syndrome. J Rheumatol 2002;29:603-613.

Macaluso A, De Vito G. Muscle strength, power and adaptations to resistance training in older people. Review. Eur J Appl Physiol 2004;91:450-472.

Mannerkorpi K. Exercise in fibromyalgia. Curr Opin Rheumatol 2005;17:190-194.

Mannerkorpi K, Burckhardt CS, Bjelle A. Physical performance characteristics of women with fibromyalgia. Arthritis Care Res 1994;7:123-129.

Mannerkorpi K, Ekdahl C. Assessment of functional limitation and disability in patients with fibromyalgia. Scand J Rheumatol 1997;26:4-13.

Mannerkorpi K, Iversen MD. Physical exercise in fibromyalgia and related syndromes. Review. Best Pract Res Clin Rheumatol 2003;17:629-647.

Mannerkorpi K, Nyberg B, Ahlmen M, Ekdahl C. Pool exercise combined with an education program for patients with fibromyalgia syndrome. A prospective, randomized study. J Rheumatol 2000;27:2473-2481.

Maquet D, Croisier JL, Renard C, Crielaard JM. Muscle performance in patients with fibromyalgia. Joint Bone Spine 2002;69:293-299.

Marques AP, Ferreira EAG, Matsutani LA, Pereira CAB, Assumpcao A. Quantifying pain threshold and quality of life of fibromyalgia patients. Clin Rheumatol. 2005;24:266-271.

McArdle WD, Katch FI, Katch VL. Exercise physiology: energy, nutrition and human performance. 5. ed. Baltimore: Lippincot Williams & Wilkins, 2004; 162, 202, 235.

McCain GA. Role of physical fitness training in the fibrositis/fibromyalgia syndrome. Am J Med 1986;(Suppl. 3A) 81:73-77.

McCain GA, Bell DA, Mai FM, Halliday PD. A controlled study of the effects of a supervised cardiovascular fitness training program on the manifestations of primary fibromyalgia. Arthritis Rheum 1988;31:1135-1141.

Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. J Rheumatol 2005;32 Suppl. 75:6-21.

Mengshoel AM, Forre O, Komnaes HB. Muscle strength and aerobic capacity in primary fibromyalgia. Clin Exp Rheumatol 1990;8:475-479.

Mengshoel AM, Vollestad NK, Forre O. Pain and fatigue induced by exercise in fibromyalgia patients and sedentary healthy subjects. Clin Exp Rheumatol 1995;13:477-482.

Metter EJ, Conwit R, Tobin J, Fozard JL. Age-associated loss of power and strength in the upper extremities in women and men. J Gerontol A Biol Sci Med Sci 1997;52:B267-B276.

Mikkelsson M. One year outcome of preadolescents with fibromyalgia. J Rheumatol 1999;26:674-682.

Miller TA, Allen GM, Gandevia SC. Muscle force, perceived effort and voluntary activation of the elbow flexors assessed with sensitive twitch interpolation in fibromyalgia. J Rheumatol 1996;23:1621-1627.

Moldofsky H. Sleep and pain. Sleep Med Rev 2001;5:387-398.

Moldofsky H, Scarisbrick P. Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. Psychosom Med 1976;38:35-44.

Moldofsky H, Scarisbrick P, England R, Smythe H. Musculoskeletal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. Psychosom Med 1975;35:341-351.

MSSE 2001. Dose-response issue concerning physical activity and health: an evidence-based symposium. Med Sci Sports Exerc 2001;33(6 Suppl):S345-S641.

Mäkelä M, Heliövaara M. Prevalence of primary fibromyalgia in the Finnish population. BMJ 1991;303:216-219.

Mäntyselkä PT, Turunen JHO, Ahonen RS, Kumpusalo EA. Chronic pain and poor self-rated health. JAMA 2003;290:2435-2442.

Nørregaard J, Bülow PM, Danneskiold-Samsøe B. Muscle strength, voluntary activation, twitch properties and endurance in patients with fibromyalgia. J Neurol Neurosurg Psychiatry 1994a;57:1106-1111.

Nørregaard J, Bülow PM, Mehlsen J, Danneskiold-Samsøe B. Biochemical changes in relation to a maximal exercise test in patients with fibromyalgia. Clin Physiol 1994b;14:159-167.

Nørregaard J, Bülow PM, Vestergaard-Poulsen P, Thomsen C, Danneskiold-Samsøe B. Muscle strength, voluntary activation and cross-sectional muscle area in patients with fibromyalgia. Br J Rheumatol 1995;34:925-931.

Nørregaard J, Bülow PM, Lykkegaard JJ, Mehlsen J, Danneskiold-Samsøe B. Muscle strength, working capacity and effort in patients with fibromyalgia. Scand J Rehab Med 1997;29:97-102.

Offenbächer M, Stucki G. Physical therapy in the treatment of fibromyalgia. Review. Scand J Rheumatol 2000;29 Suppl 113:78-85.

Olsen NJ, Park JH. Skeletal muscle abnormalities in patients with fibromyalgia. Am J Med Sci 1998;315:351-358.

O'Malley PG, Balden E, Tomkins G, Santoro J, Kroenke K, Jackson JL. Treatment of fibromyalgia with antidepressants. A meta-analysis. J Gen Intern Med 2000;15:659-666.

Panton LB, Kingsley JD, Toole T, Cress ME, Abboud G, Sirithienthad P, Mathis R, McMillan V. A comparison of physical functional performance and strength in women with fibromyalgia, age- and weight-matched controls, and older women who are healthy. Phys Ther 2006;86:1479-1488.

Park JH, Niermann KJ, Olsen N. Evidence for metabolic abnormalities in the muscles of patients with fibromyalgia. Curr Rheumatol Rep 2000;2:131-140.

Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. Scand J Med Sci Sports 2006;16 Suppl. 1:3-63.

Pellegrino MJ, Waylonis GW, Sommer A. Familial occurrence of primary fibromyalgia. Arch Phys Med Rehabil. 1989;70:61-63.

Petzke F, Clauw DJ. Sympathetic nervous system function in fibromyalgia. Curr Rheumatol Rep 2000;2:116-123.

Prescott E, Kjoller M, Jacobsen S, Bulow PM, Danneskiold-Samsoe B, Kamper-Jorgensen F. Fibromyalgia in the adult Danish population: A prevalence study. Scand J Rheumatol 1993;22:233-237.

Price DD, Staud R. Neurobiology of fibromyalgia syndrome. J Rheumatol 2005;32 Suppl. 75:22-28.

Proctor DN, Koch DW, Newcomer SC, Le KU, Smithmyer SL, Leuenberger UA. Leg blood flow and VO_2 during peak cycle exercise in younger and older women. Med Sci Sports Exerc 2004;36:623-631.

Pöyhiä R, Costa DD, Fitzcharles MA. Pain and pain relief in fibromyalgia patients followed for three years. Arthritis Care Res 2001;45:355-361.

Quintner JL, Cohen ML. Fibromyalgia falls foul of a fallacy. Lancet 1999;353:1092-1094.

Rantanen T, Era P, Heikkinen E. Maximal isometric strength and mobility among 75-year-old men and women. Age Aging 1994;23:132-137.

Redondo JR, Justo CM, Moraleda FV, Velayos YG, Puche JJ, Zubero JR, Hernandez TG, Ortells LC, Pareja MA. Long-term efficacy of therapy in patients with fibromyalgia: a physical exercise-based program and a cognitive-behavioral approach. Arthritis Rheum 2004;51:184-192.

Rhea MR, Alvar BA, Burkett LN, Ball SD. A meta-analysis to determine the dose response for strength development. Med Sci Sports Exer 2003;35:456-464.

Richards SC, Scott DL. Prescribed exercise in people with fibromyalgia: parallel group randomised controlled trial. BMJ 2002;325:185-188.

Rikli RE, Jones CJ. Development and validation of a functional fitness test for community-residing older adults. J Aging Phys Act 1999;7:129-164.

Rossy LA, Buckelew SP, Dorr N, Hagglund KJ, Thayer JF, McIntosh MJ, Hewett JE, Johnson JC. A meta-analysis of fibromyalgia treatment interventions. Ann Behav Med 1999;21:180-191.

Sainio P, Koskinen S, Heliövaara M, Martelin T, Härkänen T, Hurri H, Miilunpalo S, Aromaa A. Self-reported and test-based mobility limitations in a representative sample of Finns aged 30+. Scand J Pub Health 2006;34:378-386.

Samson MM, Meeuwsen IB, Crowe A, Dessens JA, Duursma SA, Verhaar HJ. Relationships between physical performance measures, age, height and body weight in healthy adults. Age Ageing 2000;29:235-242.

Sandstrom MJ, Keefe FJ. Self-management of fibromyalgia: the role of formal coping skills training and physical exercise training programs. Arthritis Care Res 1998;11:432-447.

van Santen M, Bolwijn P, Landewe R, Verstappen F, Bakker C, Hidding A, van Der Kemp D, Houben H, van der Linden S. High or low intensity aerobic fitness training in fibromyalgia: does it matter? J Rheumatol 2002;29:582-587.

Schneider MJ. Tender points/fibromyalgia vs. trigger points/myofascial pain syndrome: a need for clarity in terminology and differential diagnosis. J Manip Physiol Ther 1995;18:398-406.

Shvartz E, Reibold RC. Aerobic fitness norms for males and females aged 6 to 75 years: a review. Aviat Space Environ Med 1990: 61: 3-11.

Sietsema KE, Cooper DM, Caro X, Leibling MR, Louie JS. Oxygen uptake during exercise in patients with primary fibromyalgia syndrome. J Rheumatol 1993;20:860-865.

Sim J, Adams N. Systemic review of randomized controlled trials of nonpharmacological interventions for fibromyalgia. Clin J Pain 2002;18:324-336.

Simms RW. Fibromyalgia is not a muscle disorder. Am J Med Sci 1998;315:346-350.

Simms RW, Roy SH, Hrovat M, Anderson JJ, Skinar G, LePoole SR, Zerbini CA, de Luca C, Jolesz F. Lack of association between fibromyalgia syndrome and abnormalities in muscle energy metabolism. Arthritis Rheum 1994;37:794-800.

Solomon DH, Liang MH. Fibromyalgia: scourge of humankind or bane of a rheumatologist's existence? Editorial. Arth Rheum 1997;40:1553-1555.

Sprott H, Salemi S, Gay RE, Bradley LA, Alarcon GS, Oh SJ, Michel BA, Gay S. Increased DNA fragmentation and ultrastructural changes in fibromyalgia muscle fibres. Ann Rheum Dis 2004;63:245-251.

Staron RS. Human skeletal muscle fiber types: delineation, development and distribution. Can J Appl Physiol 1997;22:307-327.

Staud R. Fibromyalgia pain: do we know the source? Curr Opin Rheumatol 2004;16:157-163.

Symons TB, Vandervoort AA, Rice CL, Overend TJ, Marsh GD. Effects of maximal isometric and isokinetic resistance training on strength and functional mobility in older adults. J Ger Med Sci 2005;60A:777-781.

Taylor AH, Cable NT, Faulkner G, Hillsdon M, Narici M, Van Der Bij AK. Physical activity and older adults: a review of health benefits and the effectiveness of interventions. Review. J Sports Sci 2004;22:703-725.

Topbas M, Cakirbay H, Gulec H, Akgol E, Ak I, Can G. The prevalence of fibromyalgia in women aged 20-64 in Turkey. Scand J Rheumatol 2005;34:140-144.

Turk DC, Okifuji A. Assessment of patients' reporting of pain: an integrated perspective. Lancet 1999;353:1748-1788.

Valim V, Oliveira LM, Suda AL, Silva LE, Faro M, Neto TL, Feldman D, Natour J. Peak oxygen uptake and ventilatory anaerobic threshold in fibromyalgia. J Rheumatol 2002;29:353-357.

Valim V, Oliveira L, Suda A, Silva L, de Assis M, Barros NT, Feldman D, Natour J. Aerobic fitness effects in fibromyalgia. J Rheumatol 2003;30:1060-1069.

Vandervoort AA. Aging of the human neuromuscular system. Review. Muscle Nerve 2002;25:17-25.

Verstappen FTJ, van Santen-Hoeufft HMS, van Sloun S, Bolwijn PH, van der Linden S. Fitness characteristics of female patients with fibromyalgia. J Musculoskeletal Pain 1995;3:45-58.

Vestergaard-Poulsen P, Thomsen C, Norregaard J, Bulow P, Sinkjaer T, Henriksen O. 31P NMR spectroscopy and eletcromyography during exercise and recovery in patients with fibromyalgia. J Rheumatol 1995;22:1544-1551.

Viitanen JV, Kautiainen H, Isomäki H. Pain intensity in patients with fibromyalgia and rheumatoid arthritis. Scand J Rheumatol 1993;22:131-135.

Viitasalo J, Viljamaa K, Komi PV. Dynamometers for measurements of isometric trunk and leg force. Research reports from Department of Biology of Physical Activity 22, University of Jyväskylä, 1977.

Visser M, Goodpaster BH, Kritchevsky SB, Newman AB, Nevitt M, Rubin SM, Simonsick EM, Harris TB, for the Health ABC Study. J Gerontol Med Sci 2005;60A:324-333.

Vlaeyen JWS, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain 2000;85:317-332.

Vøllestad NK, Mengshoel AM. Relationships between neuromuscular functioning, disability and pain in fibromyalgia. Disabil Rehabil 2005;27:667-673.

Vuori I, Oja P, Paronen O. Physically active commuting to work – testing its potential for exercise promotion. Med Sci Sports Exerc 1994;26:844-850.

Vuori I, Oja P, Ståhl T. Promoting of health-enhancing physical activity. Development of a European strategy, network and action program. Report of the meeting on promotion of health-enhancing physical activity. A preparatory European meeting. European commission, Tampere, Finland, April 12-14, 1996.

Wallace DJ. The fibromyalgia syndrome. Ann Med 1997;29:9-21.

Weiss EP, Spina RJ, Holloszy JO, Ehsani AA. Gender differences in the decline in aerobic capacity and its physiological determinants during the later decades of life. J Appl Physiol 2006;101:938-944.

Wessely S, Hotopf M. Is fibromyalgia a distinct clinical entity? Historical and epidemiological evidence. Baillieres Clin Rheumatol 1999;13:427-436.

Westerblad H, Allen DG. Recent advances in the understanding of skeletal muscle fatigue. Curr Opin Rheumatol. 2002;14:648-652.

White KP, Harth M. Classification, epidemiology, and natural history of fibromyalgia. Curr Pain Headache Rep 2001;5:320-329.

White KP, Speechley M, Harth M, Ostbye T. The London Fibromyalgia Epidemiology Study: the prevalence of fibromyalgia syndrome in London, Ontario. J Rheumatol 1999;26:1570-1577.

White KP, Harth M, Speechley M, Østbye T. A general population study of fibromyalgia tender points in noninstitutionalized adults with chronic widespread pain. J Rheumatol 2000;27:2677-2682.

WHO. ICF: International classification of functioning, disability and health. Geneva: World Health Organization 2001; 3-25, 144-152.

Wigers SH, Stiles TC, Vogel PA. Effects of aerobic exercise versus stress management treatment in fibromyalgia. Scand J Rheumatol 1996;25:77-86.

Williams DA, Gendreau M, Hufford MR, Groner K, Gracely RH, Clauw DJ. Pain assessment in patients with fibromyalgia. A consideration of methods for clinical trials. Clin J Pain 2004;20:348-356.

Wolfe F. Development of criteria for the diagnosis of fibrositis. Am J Med 1986a;81:99-104.

Wolfe F. The clinical syndrome of fibrositis. Am J Med 1986b;81:7-14.

Wolfe F. Stop using the American College of Rheumatology Criteria in the clinic. Editorial. J Rheumatol. 2003;30:1671-1672.

Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain GA, Reynolds WJ, Romano TJ, Russell IJ, Sheon RP. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multi-center criteria committee. Arthritis Rheum 1990;33:160-172.

Wolfe F, Ross K, Anderson J, Russell IJ. Aspects of fibromyalgia in the general population: sex, pain threshold and fibromyalgia symptoms. J Rheumatol 1995a;22:151-156.

Wolfe F, Ross K, Anderson J, Russell IJ, Herbert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995b;38:19-28.

Wolfe F, Anderson J, Harkness D, Bennett RM, Caro XJ, Goldenberg DL, Russell IJ, Yunus MB. Health status and disease severity in fibromyalgia. Arthritis Rheum 1997;40:1571-1579.

Wolfe F, Hawley DJ, Goldenberg DL, Russell IJ, Buskila D, Neumann L. The assessment of functional impairment in fibromyalgia (FM): Rasch Analyses of 5 functional scales and the development of the FM Health Assessment Questionnare. J Rheumatol. 2000;27(8):1989-1999.

Yarasheski KE. Exercise, aging, and muscle protein metabolism. Review. J Gerontol A Biol Sci Med Sci. 2003;58:M918-M922.

Yunus MB, Masi AT. Juvenile primary fibromyalgia syndrome. A clinical study of thirty-three patients and matched normal controls. Arthritis Rheum 1985;28:138-145.

Yunus M, Masi AT, Calabro JJ, Miller KA, Feigenbaum SL. Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls. Semin Arthritis Rheum 1981;11:151-171.

Yunus MB, Kalyan-Raman UP, Kalyan-Raman K. Primary fibromyalgia syndrome and myofascial pain syndrome: clinical features and muscle pathology. Arch Phys Med Rehabil 1988;69:451-454.

Yunus MB, Inanici F, Aldag JC, Mangold RF. Fibromyalgia in men: comparison of clinical features with women. J Rheumatol 2000;27:485-490.