

STUDIES IN SPORT, PHYSICAL EDUCATION AND HEALTH 60

Arja Häkkinen

Resistance Training in Patients with Early Inflammatory Rheumatic Diseases

Special Reference to Neuromuscular Function,
Bone Mineral Density and Disease Activity

Esitetään Jyväskylän yliopiston liikunta- ja terveystieteiden tiedekunnan suostumuksella
julkisesti tarkastettavaksi yliopiston Villa Ranan Blomstedt-salissa
maaliskuun 20. päivänä 1999 kello 12.

Academic dissertation to be publicly discussed, by permission of
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UNIVERSITY OF JYVÄSKYLÄ

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ISBN 951-39-0397-4
ISSN 0356-1070

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Jyväskylä University Printing House, Jyväskylä
and ER-Paino Ky, Lievestuore 1999

ABSTRACT

Häkkinen, Arja

Resistance training in patients with early inflammatory rheumatic diseases. Special reference to neuromuscular function, bone mineral density and disease activity.

Jyväskylä: University of Jyväskylä, 1999, 62p.

(Studies in Sport, Physical Education and Health,

ISSN 0356-1070; 60)

ISBN 951-39-0397-4

Diss.

The aim of the thesis was to examine the influences of dynamic resistance training on the neuromuscular system, bone mineral density (BMD), disease activity and working capacity in patients with chronic inflammatory arthritis (IA). Altogether 113 patients and 38 healthy subjects were involved in two cross-sectional surveys and two randomized interventional studies. The training programs lasted either 6 or 12 months and consisted of dynamic strength training and stretching. Maximal dynamic and isometric strength as well as rapid force development of the knee extensors, maximal isometric force of the trunk flexors and extensors and grip strength were recorded. The cross-sectional area of the knee extensors was measured by computerized tomography and BMD of femoral neck and lumbar spine by DXA bone densitometry. Disease activity, joint damage determined by X-rays and patients' functional capacity were assessed by Modified Disease Activity Score (DAS 28), Ritchie's and Larsen's articular indices and by Stanford Health Assessment Questionnaire (HAQ), respectively. Data on the use of disease-modifying drugs and corticosteroids were also recorded. The results of the cross-sectional studies showed that loss of muscle strength characteristics were visible during the first months after onset of IA, although the BMD of these newly diagnosed IA women remained within reference values for healthy subjects. Strength training led to significant increases in strength of the examined muscles in the training subjects without detrimental effects on disease activity, while the changes in BMD did not differ statistically significantly from those of the healthy controls. However, the strength gains were lost during a prolonged detraining period of 3 years. The physical loading of paid work was important in the development of joint destruction. Further, the study indicated that work, rather than disease-related factors are of central importance for the subsequent work disability and premature professional retirement of patients. In conclusion, the study demonstrated that dynamic strength training improved neuromuscular function but not BMD, and imposed no detrimental effects on disease activity in patients with chronic inflammatory arthritis.

Key words: Bone mineral density, detraining, disease activity, inflammatory arthritis, muscle strength, strength training, work disability.

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ABBREVIATIONS

ADL	activity of daily living
BMI	body mass index
BMD	bone mineral density
BMD _{fem}	femoral neck bone mineral density
BMD _{spine}	lumbar spine bone mineral density
CSA	cross sectional area
CT	computerized tomography
DAS 28	Modified Disease Activity Score (0-10 points)
DMARD(s)	disease modifying antirheumatic drugs
DXA	Dual X-ray absorptiometry
ESR	erythrocyte sedimentation rate
HAQ	Stanford Health Assessment Questionnaire (0-24 points)
Hb	hemoglobin
IA	inflammatory arthritis
IAP	intra-articular pressure
IP	interphalangeal joint
MCP	metacarpophalangeal (joint)
MET	metabolic equivalent unit value
MTP	metatarsophalangeal (joint)
PIP	proximal interphalangeal (joint)
PsA	psoriatic arthritis
RA	rheumatoid arthritis
RI	Ritchie's articular index (0-78 points)
1 RM	one repetition maximum
VAS	visual analogue scale (0-100 mm)

LIST OF ORIGINAL ARTICLES

This thesis is based on the following papers, which will be referred to by their Roman numerals I-VI.

- I. Häkkinen A, Hannonen P, Häkkinen K 1995. Muscle strength in healthy people and in patients suffering from recent-onset inflammatory arthritis. *British Journal of Rheumatology* 34:355-60.
- II. Häkkinen A, Häkkinen K, Hannonen P 1994. Effects of strength training on neuromuscular function and disease activity in patients with recent-onset inflammatory arthritis. *Scandinavian Journal of Rheumatology* 23:237-42.
- III. Häkkinen A, Mälkiä E, Häkkinen K, Jäppinen I, Laitinen L, Hannonen P 1997. Effects of detraining subsequent to strength training on neuromuscular function in patients with inflammatory arthritis. *British Journal of Rheumatology* 36:1075-81.
- IV. Häkkinen A, Mälkiä E, Sokka T, Hannonen P 1998. A physically demanding occupation predicts premature retirement among patients with erosive arthritis. *Physiotherapy Theory and Practice* 14:13-22.
- V. Häkkinen A, Sokka T, Kotaniemi A, Paananen M-L, Mälkiä E, Kautiainen H, Hannonen P 1999. Muscle strength characteristics and central bone mineral density in women with recent-onset rheumatoid arthritis compared with healthy controls. *Scandinavian Journal of Rheumatology* 28:1-7.
- VI. Häkkinen A, Sokka T, Kotaniemi A, Kautiainen H, Jäppinen I, Laitinen L, Hannonen P. Dynamic strength training in patients with early rheumatoid arthritis increases muscle strength but not bone mineral density. Accepted for publication in *Journal of Rheumatology*.

ACKNOWLEDGEMENTS

This thesis owes much to several persons and organizations. The study was carried out in the Central Finland Health Care District, Jyväskylä, during the years 1991-1998 under three supervisors from three different scientific fields, thus showing the multidisciplinary nature of physiotherapy. It was not always easy to match the opinions of these three specialists; but however, I have tried to do my best.

I wish to thank Docent Pekka Hannonen MD, PhD, Head of the Department of Internal Medicine, Central Finland Health Care District, for his teaching in the field of clinical rheumatology and for creating an inspiring atmosphere in which to carry out scientific work. He also created the possibilities to conduct these studies in his department in the hospital.

I also wish to thank my two other supervisors from the University of Jyväskylä. Professor Esko Mälkiä PhD, from the Department of Health Sciences, has been my supervisor and advisor since my undergraduate years. He was always ready to help me, whenever I needed a specialist in the field of physiotherapy.

Professor Keijo Häkkinen PhD, from the Department of Biology of Physical Activity, has supported and critically advised me in the areas of exercise physiology and biomechanics and generally encouraged me throughout my studies.

I wish to express my warm gratitude to the reviewers of this thesis, Doctor Christina Stenström and Docent Kari Lehtinen, for their valuable comments on the manuscript.

There are several other persons who have contributed to my work. Irma Jäppinen and Liisa Laitinen of the Department of Physical Therapy and Marja-Leena Paananen and Leena Heinonen of the Department of Rheumatology 30 together with many others have done hours of additional work organizing the time-tables, guiding the patients and carrying out the measurements. I hope that we will be able to continue our multidisciplinary clinical work and studies in the future. Tuulikki Sokka MD clinically examined the patients, Hannu Kautiainen BA provided statistical expertise, and Antero Kotaniemi MD analyzed the bone mineral density results. I wish also express my gratitude to my superior, Iris Lampinen, for her encouragement and flexibility during the studies. I would also like to acknowledge the indefatigable cooperation of the patients, who complied so well with the demands of the study and thus, supported the research. Mr. Michael Freeman revised the English language of the thesis. Thank you all.

Finally, I wish to express my gratitude to my daughters Maija, Liisa and Leena for their understanding and love. You three together with my husband Keijo took the responsibility for many daily practical matters, but have not allowed me to forget the challenges of every day life.

This study was supported by grants from the Central Finland Health Care District and from the Yrjö Jahnesson Foundation, Finland.

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ABSTRACT

ABBREVIATIONS

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1 GENERAL INTRODUCTION

The impact of arthritis on the individual is multidimensional and various rehabilitation programs have consequently been developed for these patients (Pincus et al. 1984, Nicholas 1994, Nordström et al. 1996). The long-term outcome varies from a minimal loss of function to shortened life expectancy (Cobb et al. 1953, Mutru et al. 1985, Myllykangas-Luosujärvi et al. 1995). Although rheumatoid arthritis (RA) patients represent only 8% of all patients with musculoskeletal diseases, they consume 40% of all hospital days used by this patient group, making RA a very expensive sickness (Yelin & Felts 1990). Several studies conducted worldwide have shown that more than a half of patients become work disabled during the first 10 years of the disease (Mäkisara & Mäkisara 1982, Kaarela et al. 1987, Yelin et al. 1987, Allaire et al. 1996, Mau et al. 1996). To date, not a single preventable risk factor for RA is known and hence, since the cause of disease remains unknown, it can not be cured. Therefore, due to the limited resources available, it seems that efforts should be targeted to preventive rehabilitation at the early phases of disease.

Ever since figures such as Hippocrates, Aurelianus and Plinynt the treatment of inflammatory arthritis (IA) has focused on pain release by heat or cold and by rest (Short 1959). John Hunter in 1835 stated that "nothing can promote the contraction of a joint so much as motion before the disease is removed" (Partridge and Dutchie 1963). Passive treatment methods (bed rest, immobilization, physical modalities) were recommended even as late as at the 1970s (Ropes 1961, Gault and Spyker 1969, Mills et al. 1971, Nicholas & Ziegler 1977, Smith & Polley 1978, Alexander et al. 1983). Since then the treatment philosophy has taken a more active direction and exercise forms which put little stress on the joints, such as various motion exercises and non-weight-bearing isometric exercises, have been advocated (Baker 1953, Swezey 1974, Jivoff 1975). Historically, dynamic exercises of an intensity capable of improving muscle strength and aerobic capacity were thought to enhance pain and disease activity, and to provoke joint damage. During the last two decades, several

studies have concluded that dynamic exercise is effective and safe in patients with RA and does not seem to aggravate arthritis with respect either to clinical disease activity or to radiological progression (Ekblom et al. 1975, Lyndberg et al. 1988, Minor et al. 1989, Ekdahl et al. 1990, Stenström et al. 1991, Hansen et al. 1993).

A number of studies conducted on this subject have not been randomized according to the review of van der Ende et al. (1998). In most of these studies the duration of the disease has also been rather long (10-15 years). By this time the extent of joint damage as well as loss of muscle strength and functional capacity has already become very considerable. However, much less information is available on neuromuscular performance and disability in the early stages of the disease. The present study was designed to address the following questions: Do patients with newly diagnosed inflammatory arthritis have decreased muscle strength and/or BMD compared with healthy subjects? How does prolonged strength training followed by detraining effect neuromuscular function, BMD, disease activity and the capacity to work in these patients?

2 REVIEW OF THE LITERATURE

2.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) was first described as a variant of gouty arthritis by J.A. Landre-Beauvais in 1800. The term "rheumatoid arthritis" was coined by Garrod in 1858, and The American Rheumatism Association made this nomenclature official in 1941 (Short 1959). RA has a worldwide distribution and is not selective by race or ethnic group. The prevalence of RA is 0.5-1.0% in the adult population in most Western countries (Gran 1987). Three-quarters of patients are females. In the classical series of RA patients collected during 1930-36, the mean age at the onset of the disease was 32 years for males and 37 years for females (Short 1959). A recent study in Finland showed that the mean age of diagnosis of RA increased by 7.6 years from 1975 (50.2 years) to 1990 (57.8 years) (Kaipiainen-Seppänen et al. 1996).

RA is a disease of autoimmune origin. Despite extensive investigation, the etiology of the disease is unclear and no definite cure is available. RA may manifest a variety of symptoms and signs, such as morning stiffness, joint pain, tenderness and swelling of the joints, fatigue, weight loss and anemia. However, persistent synovitis and the subsequent destruction of cartilage and bony structures of joints are the characteristic clinical features of RA. Extra-articular signs, such as rheumatoid nodules, vasculitis and serositis are also found in a proportion of patients. The diagnosis of RA is based on the classification criteria established by the American Rheumatism Association in 1958 and revised by the American College of Rheumatology in 1987 (American Rheumatism Association 1958, Arnett 1988).

2.2 Psoriatic arthritis

Moll and Wright (1973) defined psoriatic arthritis (PsA) as psoriasis associated with inflammatory arthritis and usually a negative test for rheumatoid factor. Patients with severe psoriasis have arthritis more frequently than those with mild psoriasis (O'Neill & Silman 1994). It still is a common belief, however, that there exist forms of PsA which lack the detailed classification criteria that are available for many other rheumatic diseases (Laurent 1985, Bennet 1993, O'Neill & Silman 1994). Prevalence of PsA is estimated to be about 0.1% (Laurent 1985, Falk & Vandbakk 1993). The mean age at onset in a recent epidemiological study was 46.8 years and the male:female ratio 1.3:1 in Finland in 1990 (Kaipiainen-Seppänen 1996).

2.3 Radiographic erosions in rheumatoid arthritis

Because RA may be manifest by a variety of symptoms and signs, the assessment of clinical disease activity is notoriously difficult. At present there is no single test, which can be reliably used to establish disease activity. Thus, a number of subjective (morning stiffness, pain), semiobjective (various articular indices) and objective (laboratory tests, X-rays) measurements are used in monitoring the activity of the disease. Of these, radiological signs of joint damage in the hands and feet demonstrate the effect of synovial inflammation on cartilage and subchondral bone, and can be regarded as an irreversible biological endpoint (Genant 1985, van Zeben et al. 1994).

2.3.1 Scoring of the radiographic erosions in rheumatoid arthritis

Destruction of the joint in RA may occur in any synovial joint, but there is a predilection for small peripheral joints and wrists (Martel et al. 1965, De Carvalho & Graudal 1980, Scott et al. 1984, Möttönen 1988). The rate of destruction is most rapid during the first 1-2 years of the disease (Fuchs et al. 1989, Plant et al. 1994, Jonsson et al. 1996). The X-ray examination of the hands and feet offers a quantification of the cumulative effects of local and systemic inflammation and is a part of the diagnostic procedure. It is also used in therapeutic trials to monitor the course of the disease and the efficacy of treatment. Several scoring methods have been developed of which the most commonly used today are the Larsen and Sharp methods (Larsen et al. 1977, Sharp 1989).

2.3.2 Effect of loading on the joints

Healthy joints have negative resting intra-articular pressure (IAP) (Jayson & Dixon 1970a), while in rheumatic synovitis IAP is raised. During exercise IAP

exceeds the capillary perfusion pressure, causing hypoxia (Mapp et al. 1995, Gaffrey et al. 1995). IAP also increases in extreme positions of the joint, during muscle contraction and in loaded exercises (Edward et al. 1964, Eying and Murray 1964, Jayson & Dixon 1970b, Gaffrey et al. 1995).

Physical loading is said to be related to increased joint destruction in RA (Castillo et al. 1965, Kamermann 1966, Monsees et al. 1985). On the basis of this hypothesis immobilization of joints by splints and even bed rest was earlier recommended for RA patients (Gault & Spyker 1969, Mills et al. 1971, Nicholas & Ziegler 1977, Smith & Polley 1978). However, the benefits of rest and immobilization were less than expected (Alexander et al. 1983). On the other hand, in RA patients the degree of joint destruction seems to be related to the extent of limitation of joint mobility (De Carvalho & Graudal 1980, Fuchs et al. 1988) and to the absence of loading of the cartilage (Palmoski et al. 1979 and 1980, Salter 1980). Thus, intermittent motion with moderate physiological loading seems to be essential in the maintenance of normal cartilage (Parkkinen et al. 1993).

Nevertheless, a general fear of a detrimental effect on joint structures is often discussed in relation to physical exercise (Kottke et al. 1984, Ike et al. 1989). However, the results of more recent experimental exercise research do not seem to support this fear (Hansen et al. 1993, Stenström 1994).

2.4 Bone mineral density and fractures

A unanimous consensus exists that hip and spine fractures are closely associated with serious osteoporosis (Naessen et al. 1988, Lee et al. 1993). The Scandinavian countries have the highest prevalence of osteoporotic fractures in Europe (Marshall et al. 1996). The average annual increase in the total numbers of hip fractures in Finland has been 7.7% during the two recent decades. Thus, the respective number of fractures were 2239 and 6071 in 1970 and 1991 (Parkkari et al. 1994). Up to 20% of patients die during the first year following hip fracture and only approximately 33% of survivors regain the level of function that they had before the fracture (Poor et al. 1994). The incidence of vertebral fractures is similar to that of hip fractures (Melton 1997). Only 4% of patients with a vertebral fracture become completely dependent, but persistent pain interfering with the activities of daily living imposes a negative emotional impact and is a very important determinant of a reduced quality of life (Gold 1996, Bostrom and Lane 1997).

2.4.1 Rheumatoid arthritis and bone mineral density

Accelerated bone loss leading to osteoporosis is regarded as a common clinical problem in RA (Sambrook et al. 1987, Kröger et al. 1994, Hansen et al. 1996). Bone loss may be juxta-articular due to local inflammatory activity around joints, or generalized at sites distant from inflamed joints (Joffe and Ebstein 1991, Star and Hochberg 1994). The relative risk for hip fracture in patients with

RA is increased by about 1.5-2.5-fold (Hooyman et al. 1984, Cooper and Wickham 1990).

The pathogenesis of axial osteopenia in patients with RA is poorly understood. Bone mass in an individual is determined by several interacting genetic, metabolic and environmental factors (Smith & Gillahan 1991, Laan et al. 1993 a, Brandi et al. 1994, Cortet et al. 1995). Moreover, several factors specifically related to RA may affect bone mineral density (BMD). Most often the severity of the inflammatory process, the duration of the disease and the degree of functional impairment have been suggested as potential risk factors (Eggelmeijer et al. 1993, Gough et al. 1994, Åman et al. 1998). Systemic corticosteroid treatments have also been associated with greater bone loss in RA patients (Luckert & Raisz 1990, Hall et al. 1993, Laan et al. 1993 b).

2.4.2 Bone mineral density and exercise

Immobilization, bed rest and weightlessness are well known causes of accelerated loss of BMD (Mazess & Whedon 1983, Rambaut & Goode 1985, Le Blanc et al. 1990). In the absence of weight-bearing activity, bone resorption is favoured over formation in the remodeling cycle (Frost 1988). Thus, mechanical stimulation through physical activity is an important determinant of bone mass, architecture, and structural strength in healthy persons (El Haj et al. 1990, Smith & Gilligan 1991, Nordström et al. 1995). Cross-sectional studies of physically active and sedentary healthy subjects have shown a positive correlation between physical activity level and bone mineral mass (Chow et al. 1986, Heinrich et al. 1990, Heinonen et al. 1993, Suominen 1993). However, in longitudinal human exercise studies the changes in BMD have been small, and local rather than generalized (Snow-Harter et al. 1992, Lohman et al. 1995, Heinonen et al. 1996).

The effects of exercise on BMD in patients with RA have been little studied. The few studies where physical exercise has even been mentioned are mostly cross-sectional and have focused on the measurement of physical activity via the indices of daily activities (HAQ, Steinbrocker score) and joint motion scores rather than through physical loading (Als et al. 1985, Gough et al. 1991, Laan et al. 1993 a). The only study regarding the effects of longitudinal exercise concerned two cases and involved walking and low impact aerobics for 25 min 3 times/week each (Allen et al. 1993). However, after seven months of training, the subjects dropped out of the study due to ankle tendinitis and ankle pain. The changes in the markers of bone formation (serum bone-specific alkaline phosphatase and osteocalcin) were conflicting. The increases in BMD (amount not shown) decreased near the pre-training level during the subsequent five-month detraining period in both subjects. The result is consistent with the data from postmenopausal women who discontinued exercise (Dalsky et al. 1988).

2.5 Muscle function in rheumatoid arthritis

2.5.1 Effects of rheumatoid arthritis on muscle function

The muscle weakness of RA patients has been well known for several decades (Cohen and Calcins 1958). In 1969 Tiselius compared isometric strength in 44 patients with RA to that of healthy subjects (trunk and hip muscles were not tested because these actions necessitated a standing position). The total muscle strength index in patients with RA was only 69% of the reference value (an average of the strength in 12 muscle groups). Ekblom et al. (1974) reported that in female arthritics respective isometric and dynamic muscle strength values were 33% and 52% lower than the reference values for healthy subjects.

Rheumatoid arthritis is a catabolic disease and heightened disease activity may cause a loss of body cell mass due to negative energy, protein and micronutrient balances (Roubenoff et al. 1994). The losses of muscle mass and muscular weakness have also been associated with inactivity and disuse of the musculoskeletal system (Brooke & Kaplan 1972, Edström & Nordemar 1974, Halla et al. 1984, Ekdahl & Broman 1992). Nerve function impairment (Moritz 1963, Haslock et al. 1970), changes in muscle metabolism (Nordemar et al. 1974) and degeneration of muscle fibers (Wegelius 1969, Wroblewski & Nordemar 1975) have been suspected as possible mechanisms for these findings. Oka et al. (1971) have also demonstrated decreased muscle blood flow in rheumatoid patients compared to normal subjects. The disease process seems to have preferential effect on fast twitch muscle fibres (Nordemar et al. 1976, Danneskiold-Samsoe & Grimby 1986).

De Andrade et al. (1965) studied the role of swollen joints as a cause of muscle weakness. They injected fluid into normal and arthritic knee joints until the subjects were no longer able to contract their quadriceps muscle. The authors suggested that joint receptors stimulated by increased joint pressure may induce an inhibition of the adjacent muscles. On the other hand, Tiselius (1969) found that aspiration of rheumatoid joints did not increase the strength of the quadriceps.

2.5.2 Effects of physical exercise on muscle strength in rheumatoid arthritis

Several studies using various types of physical exercise have demonstrated improvement in muscle strength and in the performance of the ADL in patients with RA (Ekblom et al. 1975, Daltroy et al. 1995, Rall et al. 1996 a). Dynamic therapeutic exercise in patients with RA has most often included walking, swimming, bicycling or a mixture of several aerobic exercises. On the other hand, high-intensity resistance strength training has been avoided due to concerns about exacerbation of joint inflammation, rupture of tendons, popliteal cysts or joint capsules (Lyndberg et al. 1994 a).

The available results concerning isometric strength training in RA have been controversial. Machover and Sapecky (1966) reported a significant increase in quadriceps muscle strength after only a seven-week exercise period, while

two other studies over prolonged periods reported no changes (Cuddigan 1973, Luckhurst et al. 1974). However, isometric contraction performed at one point in the joint range does not necessarily lead to strength increases in other parts of the range; hence the patient has to exercise at various joint angles (Lindh 1979), which may partly explain the conflicting results.

Thistle et al. (1967) was the first to report upon the effects of dynamic isokinetic strength training in the treatment of RA. They concluded that high velocity isokinetic exercises involving muscle contraction through a range of motion were important in the prevention of atrophy of fast-twitch fibres. Furthermore, such exercises were also less painful than isometric ones. Since, several papers have been published regarding the effects of dynamic training on changes in muscle strength in RA, but only a few of them have utilized resistance strength training (Lyndberg et al. 1994 a, Rall et al. 1996 a). Table 1 lists the published studies related to physical performance and muscle strength in patients with RA. None of them reportedly had detrimental effects on disease activity. On the contrary, one study concluded that the progression of the destructive changes was more rapid in the joints of the inactive control group than in those of the exercise group (Nordemar et al. 1981 b). In these studies the duration of the disease was several years while in most of them the training period was relatively short. Thus, further research was needed to clarify the long term effects of dynamic strength training on the neuromuscular function and BMD in early stages of IA in particular.

2.6 Assessment of functional disability in rheumatoid arthritis

Disability represents the impact of a disease process or disorder on the ability of a patient to carry out activities within the range that is considered normal. Outcomes can be measured along the following continuum: pathology, impairment, disability and handicap (World Health Organization 1980, Fitzpatrick & Badley 1996). Although clear evidence exists on the relationship between inflammatory disease activity and the extent of joint damage with functional disability in RA, the long-term functional decline continues despite the achievement of clinical remission (Duthie et al. 1964, Mäkisara & Mäkisara 1982, Wolfe et al. 1991). Thus, it seems that other factors than the disease itself also influence the development of functional impairment in RA.

Recognition of the impact of this chronic disease on individuals has led to the development of RA-specific, patient self-administered instruments to assess functional capacity and quality of life. The questionnaires have also been shown to be of prognostic value in tracking the changes in health status over time (Mitchell et al. 1986, Pincus et al. 1987, Harwood et al. 1996). The most often used instruments among patients with arthritis are the Stanford Health Assessment Questionnaire, HAQ (Fries et al. 1980) and the Arthritis Impact Measurement Scale, AIMS (Meenan et al. 1980), the Lee Functional Index (Lee et al. 1973), the Toronto Activities of Daily Living Questionnaire (Helewa et al. 1982), the McMaster Health Index Questionnaire (Champers et al. 1982) and the

MACTAR Patient Preference Disability Questionnaire (Tugwell et al. 1987). However, of those only the HAQ and AIMS have received worldwide attention in rheumatology. The HAQ has repeatedly been shown to possess high reliability and validity and, slightly modified, has been translated into several languages (Fries et al. 1982, Pincus et al. 1983, Kirvan & Reeback 1986, Ekdahl et al. 1988).

2.7 Work disability

2.7.1 The impact of rheumatoid arthritis on working ability

The prevalence of permanent work disability among persons with RA has been reported to vary between 43 and 85% after 8-11 years from the onset of the disease (Mäkisara & Mäkisara 1982, Kaarela et al. 1987, Wolfe et al. 1994). Several disease-related risk factors, such as the duration of the disease, the patient's functional status and the extent of radiological joint damage, have invariably been associated with work disability in multivariate analysis (Yelin et al. 1980, Reisine et al. 1989, Allaire et al. 1996). Various work-related variables including type of job, job autonomy, salary, commuting difficulty, work commitment and the amount of support given by employer, co-workers and family members, have also been found to be influential (Yelin et al. 1987, Callahan et al. 1992, Reisine et al. 1995). Only two of the studies so far published concern patients with the disease in its early stages. Borg et al. (1991) found that younger age, lower disability and joint count scores as well as white-collar work were protective against early retirement. According to Eberhardt et al. (1993), on the other hand, a physically demanding job and a high initial HAQ score were the best predictors of work disability.

2.7.2 Measurement of occupational and leisure time physical activity

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. The amount of energy required to accomplish an activity can be measured in kilojoules or kilocalories per body weight or in metabolic unit values (MET). One MET represents the approximate rate of O₂ consumption of a seated individual at rest (Ainsworth et al. 1993, Montoye et al. 1996, Mälkiä 1996). Assessment of the quality and quantity of both occupational and leisure time physical activity is difficult. Some objective methods, for instance direct measurement of oxygen uptake and heart rate, and indirect measurements using mechanical devices such as step counters, movement sensors and accelerometers, are promising but are still at present impractical and costly in long-term follow-up studies (Grimby 1983, Caspersen et al. 1985, Linnarsson et al. 1989). In various studies with RA patients, the concept of physical loading of paid work has been assessed for example via classifications such as "blue-white collar", mental-physical work or level of

TABLE 1 Summary of studies on physical training in patients with rheumatoid arthritis.

Reference	n	Age (years)	Disease duration (years)	Training type	Training time (weeks)	Measurement of muscle strength	Training effect (%)	Disease activity recorded	Comments
Danneskiold-Samsoe et al. 1987	8	54	14	water exercise matched controls	8	isokinetic/knee (30°/s)	+14	joint activity	controls had baseline measurements only, no effect on disease activity
Ekdahl et al. 1990	67	53	11	strength, aerobic controls: mobility	6	isokinetic endurance/knee	+632 Nm** +84 Nm	ADL, pain, ESR, Ritchie	no increase in disease activity
van der Ende et al. 1996	25	51	12	high weight bearing	12	muscle strength index (knee)	+16.8**	ESR, HAQ, X-ray	no increase in disease activity
	25	48	8	low weight bearing			+7.7	Ritchie index	
	25	53	9	low stretching			+7.4	joint count	
	25	56	11	stretching, isometric			+7.4	morning stiffness	
Hansen et al. 1993	15	55	7	aerobic self training	104	isometric/knee	+23.7	ESR, HAQ, X-ray	no increase in disease activity
	15	52	7	70% pulse, bicycle			+36.5	joint count	
	15	51	7	self + group bicycle			+45.7	functional score	
	15	54	5	water exercise			+37.1	morning stiffness	
	15	51	8	no training			+35.6		
Harcokom et al. 1985	4	52	12	bicycle 15 min	12	isometric/knee	+1.8	joint count	reduce joint pain and fatigue
	3	48	11	bicycle 25 min			+17.0*	functional score	
	4	44	6	bicycle 35 min			+3.2		
	6	45	9	controls			+14.8		
Kirstein et al. 1991	20	37-70	-	tai-chi chuan matched controls	10	grip/50 m walk	+34**/-5 +10/-8	tender/swollen joints functional assessment	no changes in disease activity
Komatireddy et al. 1997	25	58	16	strength training	12	isokinetic/knee (60°/s)	+19.9	joint count, HAQ, functional outcome	safe exercise, increase functional capacity
	24	61	12	controls			-4.2		

Continues

TABLE 1 cont'd

Reference	n	Age (years)	Disease duration (years)	Training type	Training time (weeks)	Measurement of muscle strength	Training effect (%)	Disease activity recorded	Comments
Lyndberg et al. 1994 a	12 12	66 68	11 7	bicycle, step-climb -	12	Isokinetic/knee (30°/s)	-3 -40	tender/swollen joints, ESR, morning stiffness	no changes in disease activity
Lyndberg et al. 1994 b	9	60	12 (2-30)	isokinetic strength training 50% max for the right leg	3	isokinetic (30°/s) (60°/s) (90°/s) (120°/s)	+11/+6 +12*/+21* +30**/+24* +21**/+24*	joint count functional assessment	first result of right and then of left control knee, no increases in disease activity
Machover & Sapecky 1966	11	55	-	right leg/isometric left leg/control	7	isometric/knee	+23,3** +17.6	ESR	no changes in disease activity
Minor & Hewett 1995	20 22	50 55	8 10	water, dance, walk -	12	isokinetic/knee (60°/s)	+11,9* +9,7	grip strength, morning stiffness	grip strength correlates to overall outcome
Nordemar et al. 1976	10 -	54 -	12 -	water, strength no control group	30	isometric/knee	+12*	X-ray, joint index, ESR histological obs.	small increase in muscle fibre size, no controls
Nordemar et al. 1981 b	23 23	56 58	16 14	aerobic exercise	64	isometric/knee	+11.3 -8.8	ESR, joint count, X-ray sick-leave	less X-ray changes in exercise group
Noreau et al. 1995	19 10	49 49	8 11	aerobic dance -	12	isokinetic/knee (60°/s)	-0.1 +3.7	joint count, fatigue, pain, depression	disease activity was in favour of exercise group
Rall et al. 1996 a	8 8 8 8	42 26 70 69	15 no RA no RA no RA	strength 80% of RM strength 80% of RM strength 80% of RM water exercise	12	dynamic/knee	+53*** +52*** +36* +9	joint count, ESR, HAQ pain, depression	no change in number of swollen joint, decreased fatigue and pain
Stenström et al. 1996	27 27	54 55	15 7	strength/mobility relaxation	52	walking speed/ arm endurance	+11*/+34 +7/+46**	ESR, Ritchie, functional status	small clinical effects

* Statistically significant (p<0.05*, p<0.01**, p<0.001***)

precision (Reisine et al. 1989, Bornmann et al. 1996). The concept of physical exercise has also shown great variation in different studies and it has been expressed as the amount, type, intensity, duration or frequency of the types of exercise performed (Montoye et al.1996).

3 PURPOSE OF THE STUDY

The overall aim of this thesis was to examine the influence of intensive strength training on the neuromuscular system, on the progression of the disease and on bone mineral density in patients with recent onset inflammatory arthritis (IA). More specifically, the aims were to:

- 1) Compare the neuromuscular performance and bone mineral density of patients with recent onset IA to that of healthy age and sex-matched controls at the onset of the disease (I, V) and 3.5 years later (III).
- 2) Examine the effects of 6- and 12-month dynamic strength training on muscle strength, bone mineral density and disease activity in patients with IA (II,VI).
- 3) Examine to what extent the gains from 6-month strength training program in patients with IA could be maintained during a prolonged detraining period of 3 years (III).
- 4) Assess the impact of the physical loading of their occupational work and leisure time physical activity on the occupational outcome of the patients (IV).

4 MATERIAL AND METHODS

4.1 Subjects

A sample of 113 patients with rheumatoid arthritis and 38 healthy persons participated in the present studies. In the cross-sectional studies (I,V) and in the 42-month training-detraining study (III,IV) healthy subjects served as matched controls for the selected RA patients. Detailed informations on the study designs are given in the original papers.

4.1.1 Strength training - detraining study (I-IV)

Forty-three patients with recent onset IA and 20 healthy people volunteered for the strength training study (I-IV). The patients were randomly allotted either to the strength training group or the control group. They comprised 38 rheumatoid arthritis patients and 5 patients suffering from the polyarticular (rheumatoid arthritis-like) form of psoriatic arthropathy (PsA). The PsA patients (2 in the strength training and 3 in the control groups) were included in the study as the medical and physical treatments of both of these classes of patients are similar. The abbreviation IA in the text indicates that the PsA patients are included in the group. During the three-year detraining period, following the 6-month strength training, one person died and another was lost to follow-up from both the training and control groups. The numbers and demographic of subjects excluding the dropouts are presented in Table 2.

4.1.2 Bone mineral density study (V, VI)

Seventy patients with recent onset rheumatoid arthritis and 20 healthy women participated in the bone mineral density study (V,VI). The patients were allotted either to the 12-month strength training group or to the control group. Two patients from the training and three from the control group dropped out of the study after the baseline or 6-month measurements (two discontinued the

Table 2 Characteristics of the subjects (mean, SD) at baseline.

Strength training and detraining study (I-IV)	Training patients (n=21)	Control patients (n=18)	Healthy controls (n=18)
Age (years)	41(9)	46 (11)	41 (8)
Sex (female/male)	10/10	10/8	9/9
Height (cm)	172 (11)	169 (9)	172 (10)
Body mass (kg)	74 (15)	74 (9)	71 (14)
Duration of symptoms (months)	11 (10)	19 (25)	-
Cross-sectional strength and bone mineral density study (V)	RA women (n=20)	Healthy women (n=20)	
Age (years)	45 (10)	44 (10)	
Height (cm)	165 (5)	164 (6)	
Body mass (kg)	70 (8)	68 (8)	
Duration of symptoms (months)	11 (26)	-	
Longitudinal strength and bone mineral density study (VI)	Training group (n=32)	Control group (n=33)	
Age (years)	49 (10)	49 (11)	
Sex (female/male)	19/13	21/12	
Height (cm)	169 (8)	167 (9)	
Body mass (kg)	75 (14)	73 (11)	
Duration of symptoms (months)	13 (22)	8 (12)	

exercise, one fell ill with cancer, one drowned, and one was involved in an accident and suffered from neurological symptoms) (Table 2).

4.2 Measurements

All the measurements reported were always recorded according to the same measurement protocols and during the same time of the day.

4.2.1 Muscle strength

Before the measurements of neuromuscular performance all subjects carried out a general warm-up exercise with a bicycle ergometer. Thereafter, they performed a few contractions on the strength dynamometer in question with gradually added weights in order to become familiar with the testing procedure. In all the strength measurements the subjects received verbal encouragement to exert maximal force, and the highest value obtained from 3-4

trials was used in the final analysis. The dynamometers were calibrated by using standard weights suspended from the arms of the machines.

Maximal dynamic strength of the knee extensors was determined concentrically as the unilateral one repetition maximum (1 RM, kg) using a David 200 dynamometer (Häkkinen et al. 1987). The subject was measured in sitting position with the hips fixed on the dynamometer seat for a knee flexion angle of 110°. The ankle was supported just above the malleolus. The weights were gradually increased until the subject was unable to perform a full knee extension in order to record subject's 1RM.

Maximal isometric force and force-time curves of the knee extensors were measured using the same dynamometer. The knee angle was 100°. The subjects were asked to exert maximal bilateral force as rapidly as possible and to maintain that force for about 4-5 s. The force was recorded on magnetic tape and thereafter digitized and analyzed with a CODAS computer system (Datag Instruments Inc.) for the data measured at 0 and 6 months. In the force-time analysis the times taken to produce the same 5 different force levels were calculated. The isometric forces and isometric force-time curves at month 42 were analyzed using the Isopack program (Newtest Ltd, Oulu, Finland) and the force levels produced at five different time points were calculated. Thus, these results are presented by comparing the two patient groups to the healthy group on the three different testing occasions. The reproducibility of isometric maximal force measurements has reported to be high ($r = .98$, Viitasalo et al. 1980) and the coefficient of variation (CV%) between 2.9-8.1% (Sipilä et al. 1991).

Maximal isometric force of the trunk flexors and extensors was measured by an isometric analogous strain-gauge dynamometer (Digitest Ltd, Muurame, Finland) (Viitasalo et al. 1977, Rantanen et al. 1994). The subject was in a standing position. The hips were fixed at the level of the spina iliaca anterior superior. A 5-cm wide strap was tightened around the shoulders at the level of the clavicle for trunk flexion and at the level of the spina scapulae for trunk extension. The vertical and horizontal distances of the strap and dynamometer were recorded in the measurement diary.

Maximal isometric grip strength was measured by the Jamar Standard dynamometer (Mathiowetz & Candidate 1991). The arm was supported on a table and the elbow angle was 90°. The width of the grip was adjusted for each subject.

Muscle strength index: The sum of dynamic knee extension (right and left leg), isometric grip strength (right and left) and isometric trunk extension and flexion values were used as a muscle strength index in the analysis.

4.2.2 Muscle cross sectional area (CSA)

Muscle CSA of the knee extensor muscle group (quadriceps femoris) was measured and calculated by computerized tomography (CT) (Siemens Somatom DR). The CSA was evaluated from the midpoint between the great trochanter and lateral condylus of the femur. The measurement site was tattooed on the thigh to ensure that the measurements before and after the experimental period would take place in the same portion of the thigh. The reproducibility of the two different analyses of CSA was high ($r = .99$).

4.2.3 Bone mineral density (BMD)

BMD was measured at the Rheumatism Foundation Hospital by trained personnel using DXA bone densitometry (Lunar DPX, Lunar Radiation Corporation, Madison, WI) in duplicate measurements. The measurement sites included the lumbar vertebrae L2-L4 (BMD_{spine}) and the left proximal femur (BMD_{fem}). Quality assurance tests for densitometry were run daily. The precision of the method had previously been tested on adults and the coefficient of variation (CV%) calculated to be 1.0% for the spine and 1.8% for the femoral neck.

4.2.4 Radiographic methods

X-ray pictures of hands and feet were taken at the baseline and thereafter at 6 and 42 months in the strength training study. Radiographic changes in the wrists, subtalar, I-V MCP, II-V PIP, IP joints of thumbs, I-V MTP and IP joints of the first toe were estimated and scored (from 0 to 5) employing the method of Larsen et al. (1977) by a rheumatologist. The number of eroded joints was also counted on each occasion.

4.2.5 Disease activity and self-assessed functional capacity

Tenderness and joint swelling was recorded using the method introduced by Ritchie et al. (1968). The tenderness of a joint was graded from 0 to 3 (0 = not tender, 1 = tender, 2 = tender and winced, 3 = tender, winced and withdrew). The total clinical activity was determined by adding together the scores (tenderness and swelling) of each assessment. The Modified Disease Activity Score (DAS), including tender (28T) and swollen joints (28S), patient self-assessed general health (on a VAS) and erythrocyte sedimentation rate (ESR) were used to evaluate clinical disease activity (van der Heijde et al. 1990, Prevoo et al. 1995).

Patient self-reports by a modified version of the Stanford Health Assessment Questionnaire (HAQ) were used for the assessment of physical functional capacity (Fries 1982). Daily physical function was divided into eight categories, each of which consisted of two or three activities. The disability index ranged from 0 (able without difficulty) to 3 (not able) and had a maximum score of 24.

4.2.6 The assessment of physical activity at work and during leisure

Physical activity in daily life can be categorized into occupational, conditioning physical exercises, household tasks and other activities. In this study leisure time physical activity means planned exercise with the objective of improving or maintaining physical fitness and which may be related to specific aspects of health.

The intensity of physical activity at work was assessed on a 7-point scale accompanied by illustrations and descriptions of various types of work corresponding to each scale point. The scale ran from 1 (not at work) to 7 (very

heavy manual work). Each scale point was also evaluated using MET (metabolic equivalent unit) values from 1.5 MET to over 10 MET. One MET represents the approximate rate of O₂ consumption of a seated individual at rest = 3.5 ml × kg⁻¹ × min⁻¹. The results were expressed as intensity at work (MET) and energy expenditure at work per week (MET/week) (Mälkiä 1996).

Physical exercise during leisure was first graded into 3 levels: little physical exercise, physical exercise with hobbies or irregular physical exercise, regular physical exercise. The scale points were accompanied by illustrated descriptions. If irregular or regular exercise was reported, further questions were asked concerning its frequency, duration and intensity. The intensity of exercise was assessed on the basis of the criteria of getting out of breath and sweating. Each activity level was changed into a corresponding MET value. For example, a 3-MET activity requires three times the metabolic energy expenditure in comparison to sitting quietly (van der Sluijs 1972, Ainsworth 1993, Haskell 1993, Mälkiä et al. 1994). The reliability of the method has been demonstrated to be moderate or good, kappa coefficient > 0.50 (Mälkiä 1996).

4.2.7 Anthropometry

Conventional methods were used to measure body mass, body height and to calculate a body mass index (BMI). In papers I and II the fat percentage was estimated by measuring skin-fold thickness at 4 different sites according to Durnin and Rahaman (1967).

4.3 Training programs

4.3.1 Strength training study

The effects of progressive dynamic strength training on the neuromuscular system were investigated in study II. The strength training program for 21 experimental patients was individually designed with respect to the present capacity of each subject. Special rubber bands (Thera band®) were used as a resistance. Each training session included 9 different exercises for the upper and lower extremities and for the trunk together with corresponding stretching exercises. The training loading was progressively increased throughout the training period. During the first two months strength training was carried out twice a week with loads of 40% of the repetition maximum (RM). The subjects performed each exercise in two sets, 15-30 repetitions per set. From the 3rd month and onwards they trained 2 to 3 times a week with heavier loads of 50-60% of RM performing 10-15 reps. From the 5th month and onwards the loads were 70-80% of RM, and each exercise was performed in 3 sets, 6-12 repetitions per set. The experimental subjects also continued to take part in recreational physical activities such as walking, biking, swimming and skiing about 2 times a week as they used to do before the experiment. After the six-month training period, the patients returned to their habitual physical activities, which did not include strength training for the next three years (study III).

The subjects in the patient control and healthy control groups were instructed to continue their habitual physical activities, such as walking, biking, swimming, skiing, 3-4 times a week. None of them were involved in strength training. All patients were instructed to fill out a training diary during the 6-month strength training period.

4.3.2 Bone mineral density study

In the bone mineral density study (study VI) the subjects were allotted to two different exercise groups. The exercise program in the training group consisted of various strengthening, stretching and aerobic exercises. The subjects were asked to carry out resistance training twice a week with moderate loads of 50-70% of 1RM for 2 sets, 8-12 repetitions per set, using exercises for upper and lower limbs, abdominal and back muscles. Half of the sets were instructed to perform with as high action speed as possible. They were also encouraged to undertake recreational physical activities (walking, cycling, skiing and swimming) 2-3 times a week for 30-45 minutes at a time.

The patients in the control group were instructed to perform range of motion and stretching exercises twice a week without any resistance to maintain their joint mobility. These patients were free to continue their habitual physical activities without strength training of any kind. All the subjects filled in training diaries during the entire follow-up year. The subjects in the healthy group were chosen from normally physically active people, but none of them was involved in strength training of any kind.

4.4 Statistical methods

The results are described as means with standard deviations (SD) or standard errors (SE), means with 95% confidence intervals or range, and as median values (Md) with interquartile ranges (IQR; 25-75%). Correlation coefficients were calculated by the Pearson method for continuous variables and the Spearman method for discrete variables. At the baseline the differences between the study groups were assessed using analysis of variance (ANOVA). The training effects were statistically analyzed using a multivariate analysis of variance (MANOVA). The level of significance was set at $p < 0.05$. In study V the differences were localized by the non-parametric Wilcoxon's test and Bonferroni adjustments were performed to correct significance levels for the multiple test. In the bone mineral density study changes in BMD and muscular strength at the end of the training program are expressed as percentages of the baseline values. To estimate the BMD, disease activity and muscle strength differences between the groups, analysis of covariance (ANCOVA) was used. The baseline values were used as covariates in the analyses.

4.5 Study approval

The study was conducted according to the Helsinki Declaration and the Ethics Committee of the Central Finland Health Care approved the study designs.

5 RESULTS

5.1 Descriptive data

In the 6-month training study the patients were actively treated with various disease-modifying antirheumatic drugs (DMARDS's); for 81.3% and 94.4% ($p=0.034$) of the total follow-up time in the training and control groups, respectively. The respective mean numbers of DMARDS's used were 1.9 and 2.7 (ns). Five training and nine control patients used a small dose of peroral prednisolone periodically and six and three patients from the respective groups achieved remission (III,IV). Twenty eight percent of the patients (six subjects from each groups) prematurely retired from work due to arthritis during the 3.5 year follow-up period (IV). At the 42-month check-up visit, the mean ages of those 12 patients who had prematurely retired and of the 27 still gainfully employed were 53(7) and 44(10) years, respectively ($p=0.003$). Furthermore, two patients from the training group and one from the control group started a rehabilitation course for a new, physically less demanding occupation.

During the 12-month trial 10 patients in the training and 20 in the control group had to change their initial DMARD due to inefficacy and/or adverse events. The respective numbers of prednisolone users in the training and control groups were 3 and 12 (VI). At the onset of RA 54 out of the 65 patients were gainfully employed, but after 12 months only 57% of the initially working subjects continued in their earlier occupation while the others were on prolonged sick leave.

In the strength training study the average number of weekly strength training sessions were 2 times a week during the first two months and 2.4 times a week during the last four months. In the bone mineral density study the attendance rate of the subjects in the strength training group was on average 1.6 times a week for the first six months and 1.4 times a week for the second six months. More detailed information about exercise compliance is given in the original papers.

5.2 Muscle strength in healthy subjects and in patients at the baseline

At the baseline both patients groups had lower muscle strength values in the tested muscle groups compared to those of the healthy subjects (I,V) (figure 1 A, 1 B). The maximal concentric 1 RM (figure 1A) and isometric strength of the knee extensors (figure 2) were significantly lower in patients with RA (V) compared to healthy subjects (46%; $p < 0.001$ and 31%; $p < 0.001$, respectively). In study I, a difference of 20% ($p = 0.003$) in the 1 RM between the patients and healthy subjects was recorded. At the baseline the healthy subjects were able to produce higher force levels during the rapid early phases of 50, 100, 150, 200, 250 and 300 ms of the isometric knee extension action compared to the RA subjects (figure 2). These differences in the shapes of the force-time curve were statistically significant at all force levels ($p < 0.001$ in study V and $p = 0.041-0.004$ in study I).

At the baseline the patient groups also demonstrated lower isometric grip strength values in comparison to the healthy subjects (differences of 29% in study I and of 31% in study V; $p < 0.001$) (figure 1A, 1 B). In study V, the healthy subjects had higher isometric trunk flexion strength (14%; $p < 0.001$) compared to the RA subjects, while in study I the difference was only 3% (ns.). The corresponding differences in trunk extension strength were 6% (V) and 8% (I), but these minor differences between the groups were not statistically significant. On the other hand, the differences of 29%; $p < 0.001$ (V) and 17%; $p = 0.026$ (I) in the muscle strength indices between the patient and healthy groups were significant.

5.3 Changes in muscle strength during strength training

The six-month strength training (I) led to a significant increase of 44% ($p < 0.001$) in the 1 RM of the knee extensors in the training group, while a change of only 9% (ns.) was recorded in the control group (figure 3). The increase in the 1 RM was accompanied by an enlargement of 5.5% ($p = 0.004$) in the CSA of the quadriceps femoris muscle in the training group, while in the control group the CSA remained unaltered (-0.1%, ns.). The respective increases in the 1 RM during the 12-month training study (VI) were 30% ($p < 0.001$) and 10% (ns.) for the training and control groups. No significant changes took place in the maximal isometric forces or in the shape of the isometric force time curves of the knee extensors during the 6-month strength training period (I). However, during the 12-month training study significant increases ($p = 0.045-0.001$) took place in both groups in the earlier portions of the force-time curve, but at post-training the forces during 300-500ms were significantly ($p = 0.028-0.014$) higher in the training group compared to the values recorded for the controls.

Both training studies led to significant increases in the strength values of the trunk extension muscles; 10% ($p = 0.032$) in study I and 22% ($p < 0.001$) in

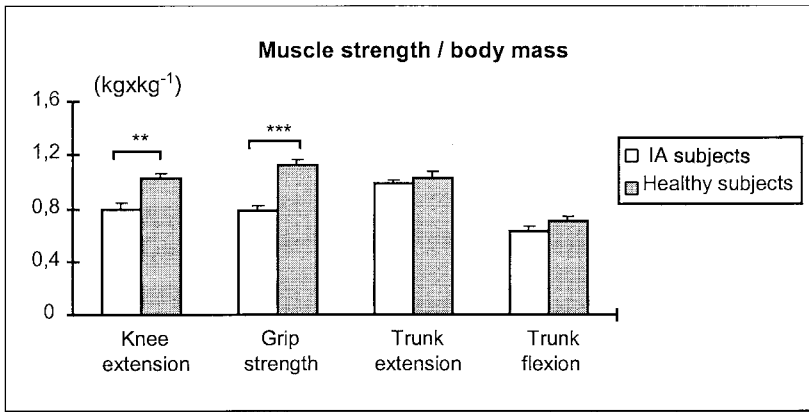


FIGURE 1A Maximal muscle strength per body mass (mean, SE) in healthy subjects and in patients with inflammatory arthritis (IA) at the baseline.

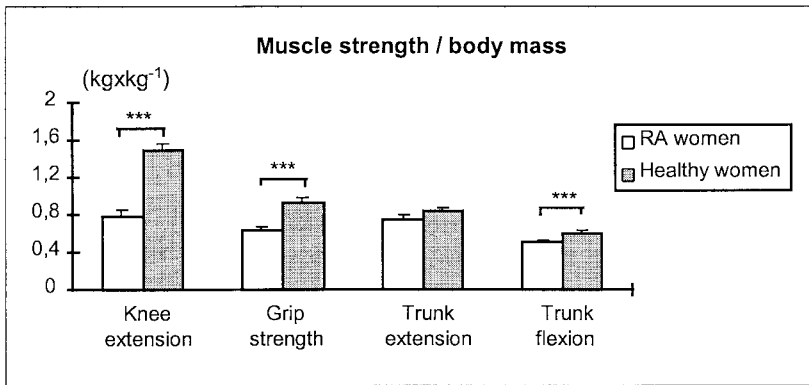


FIGURE 1B Maximal muscle strength per body mass (mean, SE) in healthy women and in women with rheumatoid arthritis (RA) at the baseline.

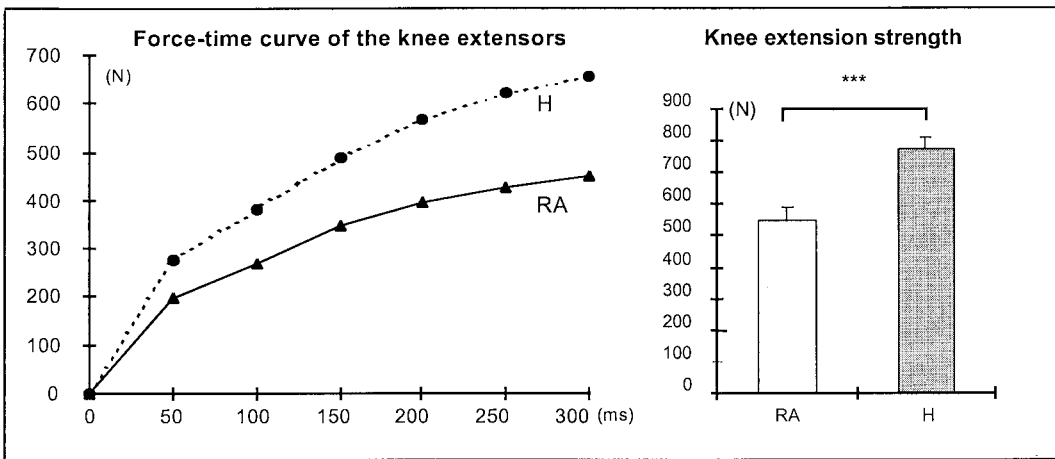


FIGURE 2 Force-time curves and maximal strength (mean, SE) of isometric knee extension in rheumatoid arthritis (RA) and healthy (H) women at the baseline.

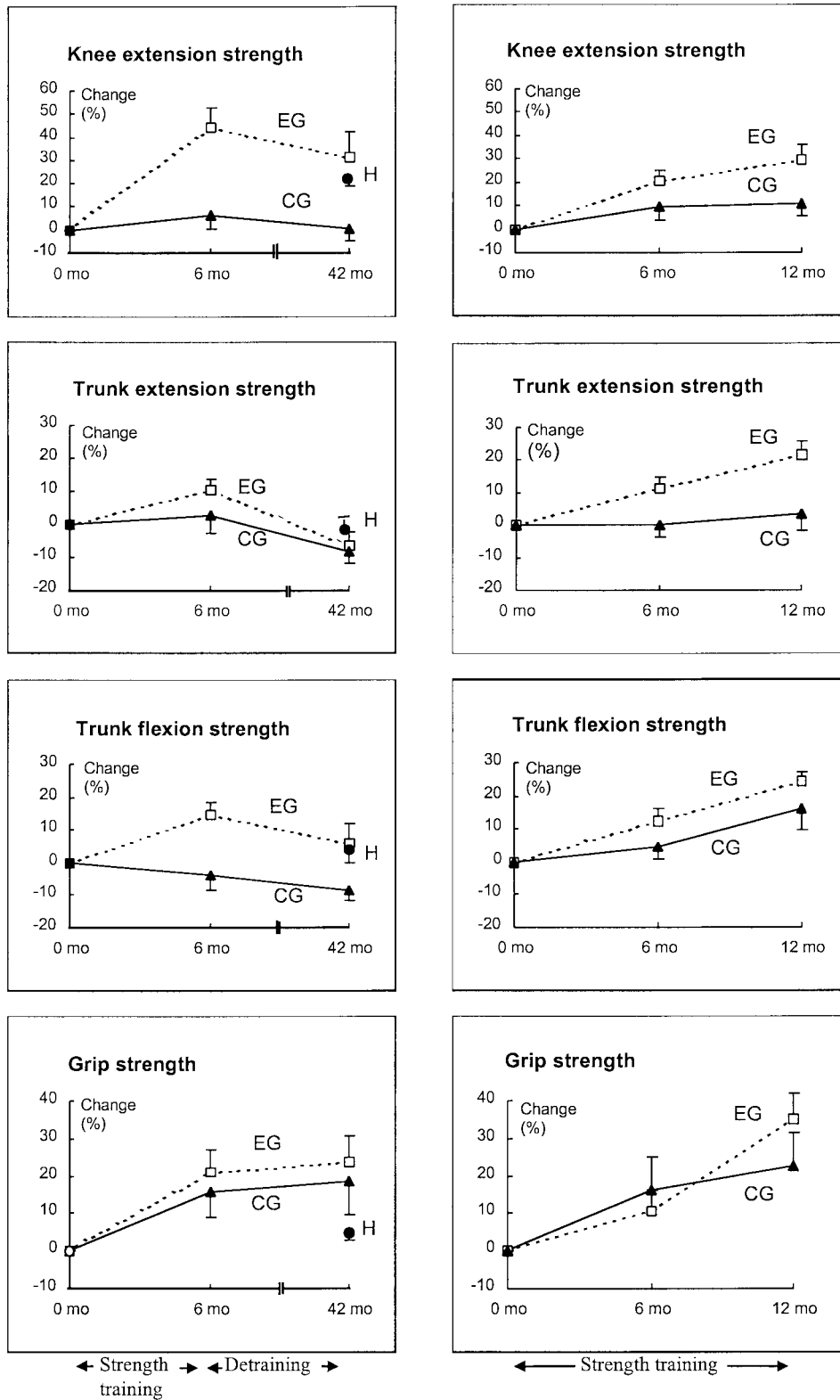


FIGURE 3 Percentage changes (mean, SD) in maximal muscle strength of different muscle groups in experimental (EG) and control (CG) patient groups and healthy group (H) during the experimental periods.

study VI (figure 3). The respective changes in trunk flexion strength were 14% ($p=0.032$) and 24% ($p<0.001$). In the 6-month training study the changes in strength of the trunk muscles of the controls were not significant. In the 12-month study the corresponding strength changes in the control group were 3% (ns.) in trunk extension and 16% ($p=0.017$) in trunk flexion. The grip strength of the experimental groups increased by 22% ($p=0.000$) in the 6-month study and by 35% ($p=0.001$) in the 12-month study. The respective changes were 16% ($p=0.023$) and 22% ($p=0.010$) for the control groups. In both training studies the muscle strength increases were significantly ($p=0.050-0.005$) in favour of the training groups, with the exception of grip strength.

5.4 Detraining and muscle strength

During the prolonged detraining period of three years after the 6-month training period, the 1 RM of the training group decreased by 9% ($p=0.033$) while still remaining 32% ($p<0.001$) above the baseline value (III) (figure 3). The control patients demonstrated a slight decrease of 3%. At the post-tests the 1 RM of the training group was still 22% higher than that of the controls ($p=0.033$). Throughout the 3.5 year follow-up period the healthy controls showed an increase of 20% ($p<0.001$) in their 1 RM. At the post-test, the differences of 19% ($p=0.007$) between the healthy controls and the trained patients and of 37% ($p<0.001$) between the healthy controls and the control patients were statistically significant. The mean (SD) dynamic knee extension strength values at post-test were 76 (30) kg in the training group, 59 (23) kg in control patient group and 92 (36) kg in healthy controls.

The detraining led to significant decreases of 15% ($p=0.001$) and 10% ($p=0.007$) in trunk extension and flexion strength in the trained patients. Thus, the strength values of the trunk extensors were 6% below and those of the trunk flexors 2% above the baseline level. The controls showed respective decreases of 8% ($p=0.032$) and 8% ($p=0.021$) in the trunk extension and flexion strength for the whole follow-up period, while the corresponding values of the healthy controls remained unchanged. The post-training differences between the three groups for the trunk muscles were significantly ($p=0.046-0.021$) in favour of the healthy subjects.

Both patient groups preserved their elevated grip strength throughout the detraining period of 3 years. However, at the post-test the intergroup difference of 22% ($p<0.001$) between the healthy subjects and all patients (26%; $p<0.001$) remained significant. The mean (SD) grip strength values at post-test were 68 (22) kg in the training patients, 63 (28) kg in control patients and 84 (22) kg in healthy controls. The muscle strength index of 299 (91) kg of the healthy controls was significantly higher than that of 252 (76) kg ($p=0.040$) of the trained patients and 223 (77) kg ($p=0.005$) of the control patients. There were no significant intergroup differences between the two patient groups at the post-test.

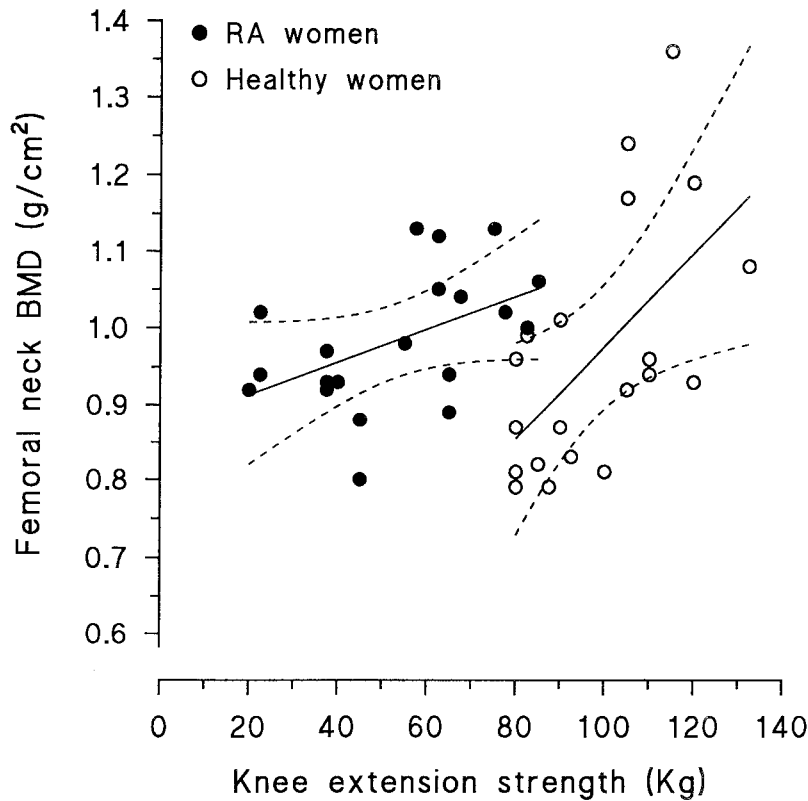


FIGURE 5 The relationship between femoral neck BMD and knee extension strength in healthy women and in women with rheumatoid arthritis at the baseline.

However, when a comparison was made between all the patients with ($n=15$) and without ($n=50$) glucocorticoids, there was a significant ($p=0.023$) bone loss at BMD_{fem} among those who were treated with glucocorticoids (the respective BMD_{fem} changes were -1.37% and $+1.19\%$). The corresponding intergroup differences of -0.37% and -1.09% at BMD_{spine} did not reach statistical significance.

5.6 Changes in disease activity, patients self-assessed functional capacity and joint radiology

In the 6-month strength training study, the groups did not differ with regard to ESR, HB, HAQ and Ritchie indices or the number of eroded joints (NEJ) at the baseline (Table 1, paper IV). During the 6-month training period ESR decreased significantly by 39%, HAQ by 53% and RI by 47% in the training group, while in the control group only the decrease in RI (-18%) was significant. During the

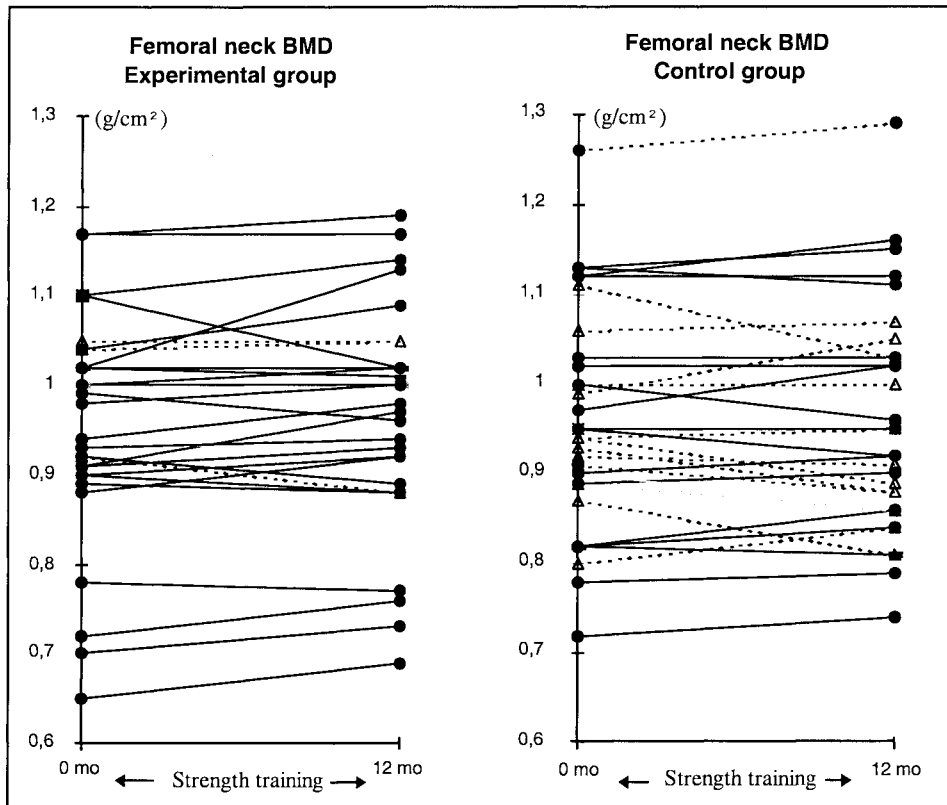


FIGURE 6 Individual values in femoral neck BMD (g/cm^2) in the experimental and control patient groups at the baseline and after the 12-month follow-up. Solid line = subjects with no periodical glucocorticoid treatment, broken line = subjects with periodical glucocorticoid treatment.

detraining period the disease activity parameters and HAQ deteriorated slightly from the 6-month check-up visit in both patient groups but remained higher than the initial values. They all were in favor of the training group, but the difference between the groups did not reach statistical significance.

In study VI, the baseline Ritchie ($p=0.021$) and DAS 28 indices ($p=0.046$) were lower in the training than in the control group (Table 2, paper VI). The parameters improved significantly during the follow-up period in both groups. However, the significant difference between the groups remained in favour of the training group in ESR ($p=0.015$) and in DAS 28 index ($p=0.019$) at month 12.

At the baseline, NEJ was slightly higher in the training group than in the controls (ns.) (Table 1, paper IV). During the 6-month strength training period NEJ increased slightly (ns.) in both patient groups, but at the post-test both in the trained subjects ($p=0.019$) and in the controls ($p=0.005$) NEJ was significantly higher than at the baseline. At the end of the 3.5 year follow-up period the respective number of non-erosive subjects had decreased from six to five in the trained and from four to two in the control subjects.

Median Larsen's index was slightly higher among the controls but the difference between the groups was not significant by the end of the study (Table 1, paper II). On the other hand, the Larsen's index values for the training and control subjects who continued in paid work (Md;IQR 2;0-13 and 6;1-17) were significantly lower ($p=0.045$ and $p=0.008$) than those of prematurely retired training and control subjects (10;6-53 and 17;11-40, respectively).

5.7 Physical loading at work and during leisure

The calculated MET values mirroring the energy expenditure and intensity of work at the baseline were significantly higher in both patient groups compared to the healthy subjects (Table 2, paper V). During the last 12 months of the follow-up both energy expenditure and intensity of work were significantly lower in those trained and control subjects who were able to continue in their paid work compared with those who were obliged to retire during the study.

The calculated energy expenditures of all three groups were significantly higher during paid work than those during leisure time activities both in the year before the study and in the follow-up period ($p<0.001$) (Table 3, paper IV). The intensity and energy expenditure of the trained patients increased significantly ($p=0.008$ and $p<0.001$) above the values of the control patients during the strength training period, but returned to the pre-training levels after the supervised training period. After the strength training period, the intensity, energy expenditure and exercise time per week did not differ between the three groups.

6 DISCUSSION

The findings of the present cross-sectional studies indicated that the patients with recent onset inflammatory arthritis had significantly lower muscle strength but no differences in BMD very early during the disease process compared to the healthy subjects. The dynamic strength training interventions, on the other hand, led to considerable increases in muscle strength characteristics without exacerbating the disease. However, the increases in muscle strength performance were to a great extent lost during the detraining period, which did not include strength training. Furthermore, the strength training for 12 months did not induce any significant change in the BMD of the femoral neck and lumbar spine. The study also indicated that work, rather than disease-related factors are of central importance for the subsequent work disability and premature professional retirement of patients.

6.1 Strength training and detraining

The lower muscle strength and explosive force observed at the onset of the disease were well in line with the results of earlier studies of RA and healthy subjects (Ekblom et al. 1974, Danneskiold-Samsøe and Grimby 1986, Ekdahl and Broman 1992). The present resistance training for 6 months led to increases from 11 to 44% in both dynamic and isometric strength of the muscle groups examined. The corresponding increases in the 12-month study were 22-35%. Progressive strength training for 6 months increased dynamic knee extension strength by 44%. The increase in strength during the present progressive resistance exercise occurred at a rate much greater than could be accounted by morphological changes within the muscles. It is likely that the increases in maximal strength during the first weeks and/or months of training are largely attributable to the motor learning and increased motor unit activation of the previously untrained muscles and/or decreased coactivation of the antagonists

enhancing the net force production of the agonists (Hellebrandt and Houtz 1956, Moritani and DeVries 1979, Häkkinen and Komi 1983, Häkkinen et al. 1998). Because the training period was sufficiently long, further progress could partly also be explained by training-induced muscle hypertrophy, as indicated by the enlargement of 5.5% in the CSA of quadriceps femoris muscle demonstrated in paper II and in earlier studies in healthy subjects (Häkkinen et al. 1981, Edström & Grimby 1986). The active drug treatment policy certainly partly contributed to the observed improvements in disease activity. Further, the decrease in joint inflammation probably facilitated muscle performance.

In the 6-month study the training frequency was 2-2.4 times a week and the loading was increased progressively every second month. During the first six months in the 12-month study the patients exercised 1.6 times a week with moderate loads of 50-70% and improved their dynamic knee extension strength by 20%. During months 7-12 they trained 1.4 times a week and their knee extension strength improved by a further 10%. In line with earlier findings in healthy subjects the major muscle strength development took place during the first months of training (Häkkinen et al. 1998). The strength training done in two weekly sessions at a progressively increasing intensity at 2-month intervals led to greater increases in strength in shorter period of time and thus seemed to be a more effective training modality than the training used in the 12-month study.

In both training studies the control patient subjects were also able to increase their muscle strength. This improvement may be due to an increase in the intensity of their physical activities compared to the time before the diagnosis. The contributory role of medication, and the motor learning in the repeated strength measurements has been discussed earlier (Moritani and DeVries 1979, Rutherford and Jones 1986). However, the increases in the control groups were significantly inferior to those recorded in the training groups, thus demonstrating the advantage of the applied dynamic strength training regimen.

Fast muscle fibers are reported to be more vulnerable to disuse than the slow fibers in RA patients (Edström & Nordemar 1974, Nordemar et al. 1976). In the present 6-month training study the subjects were free to choose their movement velocity in the various strength exercises. No significant changes took place in the shape of the force-time curves in either patient group. However, in the 12-month study a half of the training sessions were instructed to be performed at high movement velocities, leading to considerable increases in explosive strength of the knee extensors. The observed increases in explosive strength indicate that some training-induced increases may have taken place in the rapid neural activation of the motor units. Although not proved, it is suggested that the present strength training may also induce some selective hypertrophy of fast twitch muscle fibers (MacDougall et al. 1980, Frontera et al. 1988, Häkkinen et al. 1985). Thus, a training program should also include exercises performed at high movement velocities to achieve improvement in explosive strength capacity and minimize the disuse-induced atrophy of type II fibers (Edström and Nordemar 1974, Hsieh et al. 1987).

The patients who participated in the intensive 6-month strength training program were not able to maintain their strength level after the termination of training. Nevertheless, some positive effects were still left 3 years later (III). The increase of 44% in the dynamic knee extension strength of the exercise group restored the strength level to that of healthy subjects (I). The increase was much greater than the corresponding loss of 9% during the detraining. On the other hand, the strength of the back muscles decreased, even to below the pre-training level during the prolonged detraining period of 3 years. The finding indicates the importance of strength training for these patients, since poor trunk muscle strength increases the risk of low back disorders (Biering-Sorensen 1984, Holmström et al. 1992) and osteoporosis of the spine even in the early stages of the disease (Gough et al. 1994, Celiker et al. 1995). The subjects who improved their muscle strength most during the strength training period suffered from more remarkable losses after the cessation of training (III). In this study it was not possible to estimate the rate of strength loss, because the measurements were performed only once at the end of the detraining period. However, it has been shown earlier both in healthy subjects and in patients with RA that both functional and structural properties deteriorate most dramatically and the rate of loss in muscle strength is most rapid during the first weeks of detraining and/or inactivity (Thorstensson 1977, Häkkinen and Komi 1983, Narici et al. 1989). In a study with RA patients the increases of 17% in knee extension and flexion strength had disappeared 12 weeks after the termination of training (van den Ende et al. 1996).

The detected inverse association of disease activity (by DAS) and muscle strength (V) suggests that catabolic mediators of inflammation may also impair muscle function (Roubenoff et al. 1994, Moulton 1996). Rall et al. (1996 b) studied the effects of a 12-week resistance strength training (80% of 1RM) on immune parameters in RA patients with disease duration of 15 years. The data demonstrated that exercise did not lead to the significant alterations in immune response taking place after an acute bout of exercise. Furthermore, the RA patients demonstrated similar improvements in muscle strength compared with healthy subjects. In previous studies concerning RA patients with longer disease duration, limited joint mobility, pain and reflex inhibition have also been related to decreased muscle strength (Jayson & Dixon 1970 b, Wessel & Quinney 1984, Fuchs et al. 1988). However, in the cross-sectional study (V), strength loss was most notable particularly in knee extension strength, although the subjects did not have either limited mobility or tender or swollen knee joints during the measurements. This finding supports the assumption that disuse of the muscles explains a major part of the differences in muscle strength between patients and healthy subjects at the time of diagnosis, although disease-related causes may become more important during the later phases of an active disease.

6.2 Bone mineral density

Although bone remodeling aberrations in RA have not been thoroughly defined, decreased physical activity, clinical disease activity and glucocorticoid treatment are probably the most important contributory factors (Als et al. 1985, Laan et al. 1993 b). The present cross-sectional study of patients with a mean duration of symptoms of 10.9 months and no glucocorticoid treatment showed that the BMD of the women with newly diagnosed RA was compatible to that of healthy women (V). Furthermore, BMD_{fem} correlated positively with all the muscle strength measurements and the correlations were statistically significant with respect to knee extension strength and the muscle strength index in both the patient and healthy groups. Part of the correlations detected between muscle strength and BMD_{fem} could be explained by the higher body weight and age of the subjects. The correlations between BMD_{fem} and body weight ($r = 0.36$; $p=0.004$) and between BMD_{fem} and age ($r = -0.32$; $p=0.008$) reached statistical significance in the multiple regression analysis. This result is in accordance with two previous studies (Pocock et al. 1989, Snow-Harter et al. 1990). On the other hand, the present study was unable to demonstrate a significant correlation between BMD_{spine} and muscle strength values consistent with the data published by Snow-Harter et al. (1990). However, some earlier studies of healthy subjects have reported a significant relationship between the strength of the trunk extensors and BMD_{spine} (Sinaki et al. 1986, Bevier et al. 1989, Kyllönen et al. 1991, Eickhoff et al. 1993, Forwood and Burr 1993). Unfortunately, it is difficult to compare the results of existing studies on BMD_{spine} and trunk muscle strength because of variations in the age distribution of the subjects as well as the methodology of muscle testing. Further, in an elderly population the reliability of spinal DXA measurement decreases due to the increase of degenerative changes in the spine.

Gough et al. (1994) showed that RA patients with a disease duration of less than 6 months had significantly higher BMD than those with a longer disease duration. On the other hand, in that study all patients showed a reduction in BMD during the first 12 months of the follow-up and those with a clinically active disease lost BMD significantly more rapidly compared to patients with an inactive disease. In the present study (V) the comparable BMDs in RA and healthy women most probably depended on the short disease duration preceding the BMD measurements, since most of the patients were active RA. It is known that in a healthy adult person, the duration of the activation and resorption phase of the bone remodelling cycle is about four months and that mineralization is completed in another three to four months (Jee 1988, Frost 1989). Thus, the possible delay in the change in BMD may be related to the duration of the bone remodelling cycle, especially as the skeletal sites measured in the present study were distant from the inflammation. On the other hand, the observed negative association between the BMDs and disease activity as assessed by the DAS 28 index indicates that patients with a clinically active RA

are at an increased risk for osteoporosis. Further, the results suggest the view that the DAS 28 index may be utilized as a prognostic measure for future decreased BMD in early RA patients (Gough et al. 1994, Laan et al. 1993 a).

Physical exercise increases peak bone mass in childhood and in adolescence and it can be utilized as an adjunct in the prevention or treatment of osteoporosis (Haapasalo et al. 1994, Berard et al. 1997). Despite the substantial training effects on muscular strength (VI) the 12-month training did not lead to an indisputable change in BMD. However, the increase of +1,1% (ns.) in BMD_{fem} of the training group is close to those of the other strength training studies with healthy subjects (Gleeson et al. 1990, Pruitt et al. 1992, Kohrt et al. 1995). Snow-Harter et al. (1992) reported an increase of 1.2% in BMD_{spine} but not in BMD_{fem} after 8 months of weight training. In another study, despite of great increase in muscle strength a decrease of 3.96% was found in BMD_{spine} in 36-year-old females after 9 months of weight training (Rockwell et al. 1990). The present training consisted of strengthening exercises performed mostly in supine, sitting or standing positions using an elastic band as a resistance. Previous studies on biking, swimming or rowing (Orwoll et al. 1989, Wolman et al. 1991, Taaffe et al. 1995) suggest that these typical nonweight-bearing exercises do not generate such ground reaction forces on the skeleton required to increase BMD. It seems that the "smooth" movements generally recommended for RA patients (for example by The Arthritis Foundation of Atlanta) and applied in the present study are insufficient to increase BMD (Boulware and Byrd 1993, Shephard and Shek 1997).

Three EG and 12 CG subjects used prednisolone periodically during the follow-up. The improvement in muscle strength in these cases did not, however, differ from the rest of the patients. On the other hand, the change in the BMD_{fem} during the follow up of all glucocorticoid-treated subjects (n=15) differed significantly from that of the other patients ($p=0.023$) (VI). Although glucocorticoids have a well-documented deleterious effect on bone turnover (Verstraeten and Dequeker 1986, Compston et al. 1988), their effect in RA has been more controversial (Hall et al. 1993, Peel et al. 1995, Hansen et al. 1996, Lems et al. 1996, Lems et al. 1998). Cortet et al. (1997) found that the BMD_{spine} decreased by 11.5% and BMD_{fem} by 10.4% in steroid-treated patients versus nonsteroid-treated patients with a mean disease duration of 13 years, while other authors suggest that low-dose steroid therapy is not harmful to the skeleton (Sambrook et al. 1986, Sambrook et al. 1987). In the present study prednisolone was started to control the symptoms of early RA patients with a highly active disease. Since in active RA bone resorption is increased more than bone formation (Eggelmeijer 1993, Hansen 1996), it is impossible to determine whether it was inflammatory disease activity or the low dose of prednisolone that led to the decrease in BMD in our 15 subjects. On the other hand, glucocorticoid-induced control of joint inflammation may even counteract the decrease in BMD by improving the patient's capacity for physical activity. Moreover, the individual changes of BMD values in the nonsteroid-treated patients also behaved individually. Altogether, more exclusive and extended

randomised physical exercise trials are needed to draw definitive conclusions about the effects of exercise on BMD in RA.

6.3 Disease activity, patients self-assessed functional capacity and radiological progression

During the dynamic strength training for 6 and 12 months the disease activity parameters and patient self-assessed functional capacity (HAQ) improved significantly. Moreover, positive changes in some of these variables (ESR, HAQ and Ritchie's indices) were in favor of the training subjects compared to those recorded for the controls. The result is in accordance with all the studies so far published regarding physical exercise interventions (Table 1). Previous studies have consisted of patients with advanced RA, while the present subjects were involved in these studies at the diagnosis and commencement of the treatment. This may have contributed substantially to the observed significant improvements in disease activity and functional capacity parameters. However, the findings concerning the exercise interventions support unanimously the assumption that patients with IA can safely use individually tailored dynamic strength training to increase/maintain their muscle strength without exacerbating the disease.

Several studies have shown that the progression of joint damage is more rapid during the first few years of RA (Brook & Corbett 1977, Pincus et al. 1998). Only a minor increase was observed in the number of eroded joints during the present 6-month training period (II), but the extent of joint damage increased significantly in both patient groups throughout the total follow-up of 3.5 years (IV). A limited amount of information has so far been published regarding the relationship between physical activity and the development of joint destruction in RA. Nordemar et al. (1981 a, 1981 b) reported that training for a period of 4-8 years could inhibit the joint progression visible in X-rays, but they examined only the asymptomatic joints in the lower extremities. Hansen et al. (1993), found a significant progression in joint erosions over two years in both aerobically trained and control groups, while another study reported that aerobic exercise twice a week or more for 4 years did not have any negative effects on the rate of radiological progression (Stenström et al. 1994). In an inflamed rheumatoid joint the normally subatmospheric or weakly atmospheric resting and exercise related intra-articular pressure exceeds the capillary pressure, resulting in collapse of the capillaries and hypoxia (Gaffrey et al. 1995, Mapp et al. 1995). Hypoxia is said to be a major drive to cytokine release, which creates an environment for joint damage (Edmonds et al. 1995). Although the long term effects of dynamic exercise is still unclear, the available data do not support the view that dynamic exercise is likely to exacerbate the arthritis. Consequently, there is no reason to fear that exercise will lead to progressive radiological damage. Moreover, the present (II, VI) and several earlier studies

have even reported a decrease in the number of tender and swollen joints in training patients (van den Ende 1996, Stenström et al. 1996). Thus, dynamic strength training with rather short muscle contractions, which may raise the intra-articular pressure of the trained joints for short periods appears to be safe for IA patients.

6.4 Work disability and inflammatory arthritis

An interesting finding that emerged from study IV was that the physical loading of the work in calculated MET values, in comparison to the other patients, was significantly higher in those who were obliged to retire during the 3.5 year study period. The retired subjects were also significantly older than those continuing in paid work. Furthermore, all seven patients who remained non-erosive were able to continue in their jobs. On the other hand, subjects with physically heavier work developed more structural damages in their peripheral small joints. In the present 3.5 year study (IV), 31% of the patients retired. In study VI, 43% could not continue their earlier occupation but received work disability payments at month 12.

Previous studies have shown that more than 50% of patients with rheumatoid arthritis become work-disabled within 10 years of the disease (Mäkisara & Mäkisara 1982, Borg et al. 1991) and the fastest decline is seen within the three first years (Kaarela et al. 1987, Mau et al. 1996). Two reports with early RA subjects have also studied the prognostic factors of premature retirement. In a 2-year follow-up Borg et al. (1991) observed that younger age, lower disability scores and joint counts as well as "white-collar" occupations were protective against early retirement. On the other hand, a physically demanding job and high initial HAQ score were found to be the best predictors for work disability in a Swedish report by Eberhardt et al (1993). In the present study HAQ did not prove to be a predictor of IA work disability.

As expected all existing studies are unanimous in concluding that age is one of the best predictors of premature work disability (Allander 1970, Mäkisara & Mäkisara 1982, Wolfe et al. 1994, Mau et al. 1996). The present study in turn also confirmed that older IA patients, especially those in physically demanding jobs have the highest predisposition to retire prematurely. Therefore, vocational rehabilitation should be applied in an early stage of the disease as it may facilitate the ability of patients to remain in their jobs.

CONCLUSIONS

The main findings and conclusions of the thesis can be summarized as follows:

1. The patients with early inflammatory arthritis had lower maximal muscle strength in the upper and lower extremities and lowered explosive strength levels of the knee extensors compared to those of the healthy persons. However, no significant difference was observed in bone mineral density at the femoral neck and lumbar spine between the study groups at the diagnosis of the disease.
2. Both exercise intervention studies showed that dynamic strength training in early arthritis resulted in significant improvements in dynamic and isometric muscle strength without exacerbating the disease. A minor but non-significant increase in BMD_{fem} was found, while BMD_{spine} remained unchanged. High clinical disease activity and concomitant glucocorticoid treatment most probably play important roles as modulators of BMD in RA patients.
3. The increases in muscle strength obtained by strength training were lost to a great extent during the prolonged detraining period. Therefore, to be effective, continuous strength training should be included in physical exercise as a part of multifaceted patient management.
4. Occupational physical loading appeared to be important in the progression of joint destruction, work disability and the premature retirement from work of the patients. Thus, the ability of early occupational rehabilitation to reduce premature retirement should be tested.

8 YHTEENVETO

Tutkimuksen tarkoituksena oli selvittää dynaamisen voimaharjoittelun vaikutuksia tulehduksellista reumasairautta sairastavien hermolihasjärjestelmään, luuntiheyteen, taudin aktiivisuuteen sekä työkykyyn. Kaikkiaan 113 potilasta ja 38 tervettä verrokkaa osallistui kahteen poikkileikkaus- ja kahteen satunnaistettuun seurantatutkimukseen. Harjoittelujaksojen pituudet olivat 6 ja 12 kk ja sisälsivät dynaamista voimaharjoittelua sekä venyttelyjä. Dynaaminen ja isometrinen polven ojennusvoima sekä voimantuottonopeus (David 200), isometrinen vartalon ojennus- ja koukistusvoima sekä puristusvoima (Digitest) mitattiin dynamometreilla. Reisilihaksen poikkipinta-ala määritettiin tietokone-tomografialla (Siemens Somaton DR) sekä reisiluun kaulan ja lannerangan (L2-L4) luuntiheys (BMD) kaksiennergisellä röntgenabsorbtiolla (DXA). Sairauden aktiivisuutta seurattiin laskon ja Ritchien sekä DAS 28-indeksien avulla, nivelten radiologista syöpymistä erosoituneiden nivelten lukumäärällä ja Larsenin indeksillä sekä subjektiivista toimintakykyä HAQ-indeksillä. Ansiotyön sekä vapaa-ajan fyysisen kuormittavuuden määrää selvitettiin MET-kyselylomakkeella. Poikkileikkaustutkimuksissa vasta diagnosoitujen potilaiden lihasvoima- ja voimantuottonopeusarvot olivat tilastollisesti merkitsevästi matalammat kuin terveillä verrokeilla lähes kaikissa mitatuissa lihasryhmissä, mutta BMD ei eronnut ryhmien välillä. Voimaharjoitteluun osallistuneiden potilaiden lihasvoimien kasvu oli merkitsevästi suurempi kuin kontrolliryhmien, mutta BMD-arvoihin 12 kk:n harjoittelu ei vaikuttanut. Taudin tulehduksellinen aktiivisuus aleni harjoitteluryhmän potilailla verrokkeja enemmän. Kolmen vuoden voimaharjoittelutauon aikana oli suuri osa 6 kk:n intensiivisen harjoittelun voimanlisäyksestä menetetty. Työn kuormittavuus, taudin aktiivisuus ja ikä osoittautuivat merkitseviksi tekijöiksi potilaiden ennenaikaisessa sairauseläkkeelle jäämisessä. Tulokset viittaavat siihen, että tulehduksellista reumasairautta sairastavat voivat turvallisesti käyttää voimaharjoittelua osana fyysistä kuntoutusta ja näin estää hermolihasjärjestelmän suorituskyvyn ennen aikaista heikkenemistä.

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