Rheumatology 2002;41:157–166

Exercise can reverse quadriceps sensorimotor dysfunction that is associated with rheumatoid arthritis without exacerbating disease activity

L. M. Bearne, D. L. Scott[1] and M. V. Hurley

Physiotherapy Division, School of Biomedical Sciences and [1]Rheumatology Department, Guy's, King's and St Thomas' School of Medicine, King's College London, London, UK

Abstract

Objectives. To compare quadriceps sensorimotor function, lower limb functional performance and disability in patients with rheumatoid arthritis (RA) and healthy subjects, and to investigate the efficacy and safety of a brief rehabilitation regime.

Methods. Quadriceps strength, voluntary activation, proprioceptive acuity and the aggregate time [aggregate functional performance time (AFPT)] taken to perform four common activities [aggregate functional performance time (AFPT)] were compared between 103 RA patients who had lower limb involvement and 25 healthy subjects. In addition, disability (Health Assessment Questionnaire), clinical disease activity and the plasma concentration of proinflammatory cytokines were measured in the RA patients. In a follow-on randomized controlled trial of rehabilitation, these variables were used as baseline data for 93 of the RA patients, who were randomized to a rehabilitation or a control group. Changes in the variables were analysed within and between groups.

Results. Compared with healthy subjects, RA patients had weaker quadriceps [mean difference 157 N; 95% confidence interval (CI) 125–189], poorer activation (8%, 95% CI 4.5–15) and proprioceptive acuity (0.8°, 95% CI 0.4–1.3) and took longer to perform the AFPT (34 s, CI 23.5–44.8). Rehabilitation increased quadriceps strength (mean increase 61 N, 95% CI 28–95) and voluntary activation (8%, 95% CI 3–12.4) and decreased the AFPT (12.3 s, 95% CI −2 to 27.7) and subjective disability (0.21 HAQ points, 95% CI 0–0.35) without exacerbating disease activity. All the improvements were maintained at the 6-month follow-up. There was no change during the control period.

Conclusions. Patients with RA that affected their lower limb had quadriceps sensorimotor deficits that were associated with lower limb disability. A clinically applicable rehabilitation regime increased quadriceps sensorimotor function and decreased lower limb disability without exacerbating pain or disease activity. For patients with well-controlled RA that causes lower limb involvement, the regime is effective and safe.

KEY WORDS: Rheumatoid arthritis, Sensorimotor dysfunction, Randomised controlled trial, Exercise therapy, Disability.

Muscle weakness is a common sign and symptom of rheumatoid arthritis (RA) and may contribute to impaired performance of the common activities of daily living (ADL) and disability [1–4]. Muscle weakness is usually considered to be a consequence of disuse atrophy because the patient's normal activities are impeded by the widespread joint pain, inflammation and damage that characterize RA [2, 5–8]. Another cause of muscle weakness is incomplete voluntary activation of muscles crossing painful, inflamed or damaged joints, which has been reported following traumatic injury [9–12] and osteoarthritis (OA) [13, 14] but has only been reported in one small study of RA [15]. In traumatically injured joints and OA, rehabilitation increases voluntary activation and hence muscle strength, but the effect of rehabilitation on voluntary activation in RA has never been reported.

Recently, there has been increased interest in the role of muscle sensory dysfunction, i.e. decreased proprioceptive acuity, in patients with OA [16–18] and RA [19]. In knee OA rehabilitation may improve these proprioceptive deficits [20], but the influence of rehabilitation on proprioceptive acuity in RA has not been reported.

Submitted 27 March 2000; revised version accepted 7 August 2001.

Correspondence to: M. Hurley, Rehabilitation Research Unit, King's Healthcare (Dulwich), East Dulwich Grove, Dulwich, London SE22 8PT, UK.

As muscle weakness is associated with disability, patients with RA are often referred for rehabilitation to improve muscle strength and functional ability and to maintain independence. Although exercise can increase muscle strength [1–4], few studies have investigated whether this results in an improvement in functional performance and decreases disability. Moreover, these research studies usually involve prolonged and labour-intensive rehabilitation regimes—often patients are required to attend three exercise classes a week for 12 weeks—making them expensive and clinically impracticable. Therefore, effective and cost-effective rehabilitation regimes which could be implemented clinically are needed.

As well as being effective, rehabilitation regimes must also be safe. Recently, it has been suggested that exercise of inflamed joints might cause damage by hypoxic reperfusion injury [21–24], whereby contraction of muscles acting across inflamed joints raises the intra-articular pressure above the perfusion pressure, precluding the blood supply to the synovium, which becomes hypoxic. When the muscles relax the synovium is reperfused, but this liberates free oxygen radicals that cause tissue damage and persistent synovitis by the liberation of proinflammatory cytokines, i.e. interleukin (IL) 1β, IL-6 and tumour necrosis factor α (TNF-α) [23]. The implication of this hypothesis is that exercise—even common physical activities [23]—may be inappropriate, dangerous and contraindicated for patients with inflammatory joint conditions. Therefore, it is imperative to establish whether exercise in RA is safe for the large number of patients who are referred for rehabilitation, in which exercise therapy is the major component. Furthermore, advice to refrain from physical activity would exacerbate muscle weakness and disability and increase the likelihood of complications induced by decreased mobility. Although most trials assessing the efficacy of rehabilitation suggest that exercise does not exacerbate disease activity or inflammation, very few studies have simultaneously assessed disease activity [1–3] or the concentration of proinflammatory cytokines [25, 26].

This study (i) compared the quadriceps sensorimotor function (weakness, voluntary activation and proprioceptive acuity) of healthy subjects and RA patients with lower limb involvement and examined the association between muscle dysfunction and lower limb functional performance and disability; (ii) investigated the efficacy of a short, clinically practicable exercise regime designed to improve quadriceps sensorimotor function, lower limb functional performance and disability; and (iii) evaluated whether the rehabilitation regime exacerbated disease activity by simultaneously measuring clinical disease activity and plasma concentration of proinflammatory cytokines (IL-1β, IL-6 and TNF-α).

Methods

The trial profile is summarized in Fig. 1.

Comparison of motor function and disability in RA patients and healthy subjects

Patients. One hundred and eight patients (21 males) who had had definite RA [27] for 2 yr or more (mean duration 11 yr, range 2–40) that involved their lower limb were recruited. Patients were excluded if they (i) had an acute exacerbation of their disease (defined as more than six swollen joints, more than nine tender joints and an erythrocyte sedimentation rate >60 mm/h); (ii) suffered from unstable coexisting major medical problems (e.g. unstable hypertension, diabetes mellitus); (iii) been started on slow-acting drugs (e.g. gold injections) or systemic steroids within the previous 3 months; (iv) were using daily prednisolone >10 mg; or (v) were wheelchair-bound. During the baseline assessments, five patients experienced pain that interfered with the performance of the assessments and all their data were excluded (Fig. 1). The patient's normal drug regimen was recorded: 27 patients were on first-line agents, e.g. simple analgesia or non-steroidal anti-inflammatory agents; 68 patients were taking second-line agents, e.g. methotrexate or sulphasalazine; and 13 patients were on third-line agents, e.g. systemic steroids ($\leqslant 10$ mg prednisolone daily). Alterations in first-line agents were permitted during the study, but it was considered that change of second-line agents would confound the results; if this occurred, the patient's data were excluded.

Healthy subjects. Twenty-five age-related, healthy subjects (nine males) with no history of serious limb injuries and no unstable medical conditions were recruited from local elderly activity groups (e.g. bowls clubs) and were used as a comparative group.

Assessment of variables

A detailed description of the way in which the variables were assessed has been published [13]; a summary is given below.

Clinical examination. A full clinical examination of the knee joint was performed on all participants. This evaluated the range of movement, deformity, integrity and stability of the knee and the presence of effusion or synovitis.

Bilateral isometric quadriceps strength and voluntary activation. Quadriceps motor function was estimated using a strain gauge system attached to a specially constructed chair upon which the patient was seated with their hips and knee flexed to 90°. In this position the presence and degree of reduced activation were measured by superimposing percutaneous electrical stimulation on a voluntary isometric contraction [18, 28, 29]. Three maximum voluntary contractions (MVCs) were recorded and analysed off-line. The weakest leg was deemed the 'index leg'. If the strengths of both legs were comparable, the patient was asked to nominate which leg they considered most affected by the disease and this leg was designated the index leg. The muscle strength and voluntary activation recorded during the strongest MVC of the index leg was used in the data analysis.

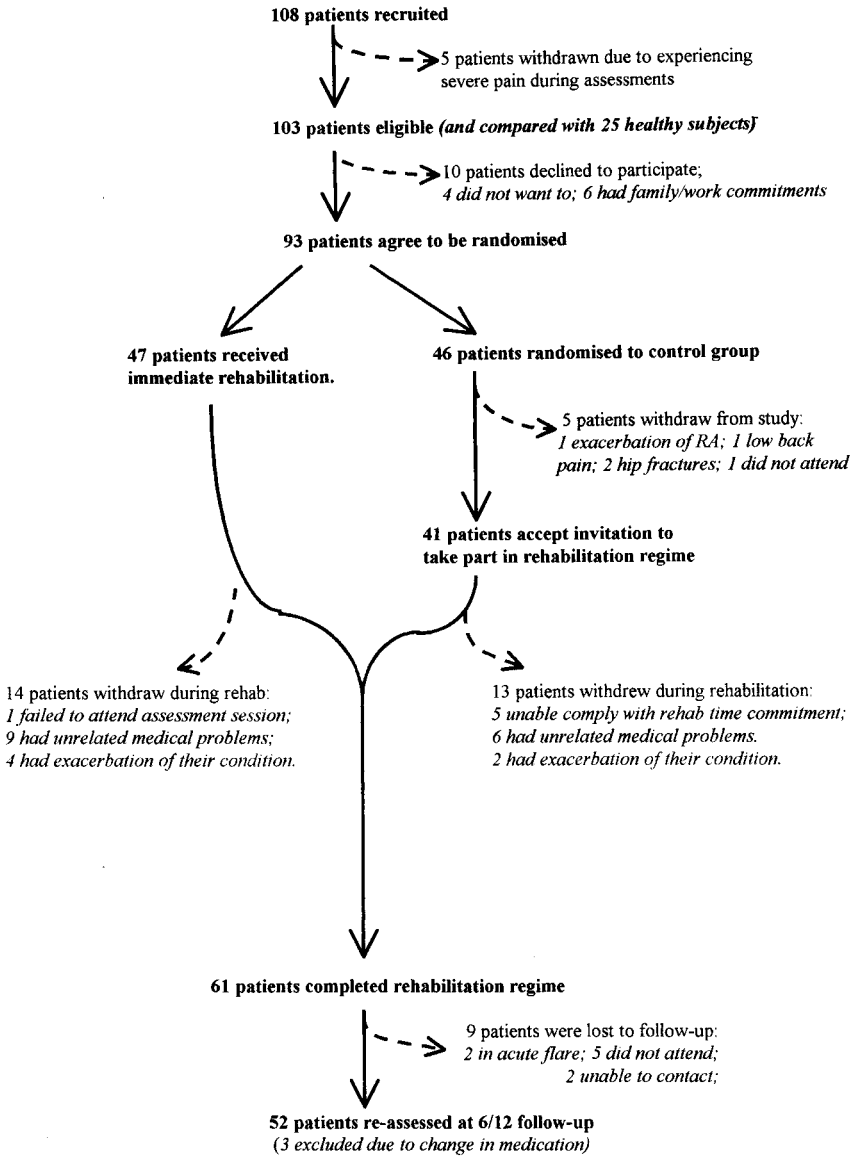

FIG. 1. Trial profile showing route taken by a patient entering the study. The numbers of patients who withdrew from the trial for different reasons are given.

Proprioception. Proprioceptive acuity was estimated from the acuity of reproduction of knee joint position sense (JPS). An electrogoniometer (Penny and Giles, Gwent, UK), attached to the lateral aspect of the knee, was used to measure the mean error of 10 actively reproduced knee joint angles, randomly selected between 90° flexion and full knee extension [13].

Objective functional performance. The time taken to perform four common ADL (walking 50 feet on level ground, rising from a chair and walking 50 feet, and ascending and descending a flight of stairs) were recorded and aggregated to produce an assessment of functional performance, called the aggregate functional performance time (AFPT) [13].

Disability. Patient-reported disability and handicap were assessed using the Health Assessment Questionnaire (HAQ) [30]; higher HAQ scores indicate greater disability. The healthy subjects completed the Lequesne index for knee OA in order to evaluate whether this joint condition, which is common in this age group, was causing lower limb disability [31].

Clinical disease activity. Disease activity was assessed using the outcomes advised at the Conference on Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT); these are listed in Table 2 [32].

Biochemical markers. Venous blood samples were obtained from the patients only and spun on a centrifuge, and the plasma was extracted, frozen and stored at $-70°C$. The samples were assayed to estimate the concentrations of TNF-α, IL-1β and IL-6 (Biosource Europe, Nivelles, Belgium) by the Clinical Biochemistry Department, King's Healthcare Trust.

Randomized controlled trial of the efficacy and safety of rehabilitation for patients with RA

Patients. All 103 patients assessed were invited to participate in a prospective, randomized, controlled trial of rehabilitation; six patients declined to participate because of work/family commitments and four did not wish to participate (Fig. 1). The 93 patients who agreed to participate were randomized by selection of a sealed, opaque envelope that contained their treatment allocation, to begin rehabilitation immediately, or to a control group (Fig. 1).

Assessments. The data from the cross-sectional comparison (i.e. quadriceps strength, activation, knee JPS, AFPT) and HAQ score, disease activity and plasma concentrations of TNF-α, IL-1β and IL-6 were used as the baseline data for the patients who undertook the rehabilitation regime. All the variables were reassessed at the end of the control period or the rehabilitation regime. In addition, to investigate whether exercising caused an immediate increase in the circulating concentrations of proinflammatory cytokines, additional blood samples were taken from 15 patients selected at random, immediately before and after the second and tenth exercise sessions. All the blood samples were stored and assayed as described above.

Control period. Patients randomized to the control group ($n = 46$) continued their normal activities and were recalled after 8 weeks, when the baseline variables were reassessed. All the patients in the control group were invited to undertake the rehabilitation regime; 41 patients agreed (Fig. 1), and these are called the 'delayed rehabilitation patients'. Data from the post-control assessment of the delayed rehabilitation patients were used as the pre-rehabilitation baseline data and changes during rehabilitation were compared with these data.

Rehabilitation. Data from the 47 patients randomized to begin rehabilitation immediately and the 41 delayed rehabilitation patients were pooled for within-group analysis ($n = 88$ rehabilitated patients) (Fig. 1).

The rehabilitation regime consisted of 10 exercise sessions (two a week for 5 weeks) and comprised relatively simple, progressive, individually prescribed exercises designed to increase quadriceps strength, address each patient's disabilities and improve balance and coordination, using inexpensive and unsophisticated equipment. Each exercise session consisted of warm-up exercises (e.g. 5 min cycling on a static bicycle, stretching/range of movement), 24 isometric MVCs (performed in four sets of six contractions, each set separated by 1 min of rest to minimize fatigue) at 90° knee flexion to increase quadriceps strength, three individually prescribed functional exercises (e.g. sit-to-stand, step-ups, etc.) and three balance exercises (e.g. wobble-board). The functional and balance exercises were each performed for 1–5 min and the number of repetitions was recorded. The patient was encouraged to work as hard as they could, improvements in MVC and exercise performance were fed back to the patient, and the exercises were made more challenging by increasing the number of repetitions, increasing the Theraband resistance, stepping on/off higher blocks etc. and improving the quality of performance of an exercise to improve muscle control. If a patient reported pain during a training session, the exercise intensity was reduced. Each exercise session lasted approximately 30–45 min. To standardize the delivery of the rehabilitation regime and ensure patient adherence, the patients were treated individually and all the exercise sessions for all the patients were supervised by the same physiotherapist in an out-patient department.

Ethics approval

Approval was obtained from King's Healthcare, Guys and St Thomas's NHS Trust Local Ethics Committees. Each patient received verbal and written information about the study and then gave their informed consent.

Data analysis

The distributions of all variables were assessed using a rootogram; continuous variables that were normally distributed (i.e. anthropometric data, muscle strength and AFPT) were analysed using parametric statistical tests (e.g. Student's *t*-test, paired or unpaired) [33, 34]; ordinal variables (i.e. HAQ, clinical disease activity) or continuous variables with a skewed distribution (e.g. voluntary activation) were analysed using non-parametric tests (e.g. Wilcoxon's signed rank test). The strength of association between muscle function, functional ability, clinical disease activity and biochemical markers was assessed using Pearson's correlation for continuous and normally distributed variables and Spearman's rank correlation for ordinal or skewed variables.

In the randomized controlled trial of exercise therapy, the primary outcome variable was chosen *a priori* to be change in quadriceps strength.

To establish between-group changes, data from patients initially randomized to the control group ($n = 46$) and the rehabilitation group ($n = 47$) were compared. Within-group change for the rehabilitated patients (the pooled data of the immediate and delayed rehabilitation patients; $n = 88$) was established by comparing the pre- and post-rehabilitation data. To assess sustained benefits, prerehabilitation data were compared with data collected 6 months after the end of rehabilitation.

Data were analysed using an intention-to-treat analysis, i.e. patient data were analysed in the groups they were allocated to, whether or not they completed the intervention. No data were excluded because the patient did not complete the study.

Data are presented as between- or within-group mean differences with the 95% confidence interval (CI) unless stated. The level of statistical significance was set at $P < 0.05$. To aid the interpretation of clinical relevance, effect sizes (ES) were calculated to determine a standard measure of change within groups. The ES was calculated by taking the difference between the mean of the variable before (M1) and after (M2) intervention and

dividing by the preintervention standard deviation (S1): ES = (M1−M2)/S1 [35].

Statistical analysis was performed using Minitab version 12 (State College, PA, USA).

Results

Quadriceps motor function and disability of patients with RA and healthy subjects

The quadriceps of the patients with RA was weaker than that of the 25 healthy subjects (mean difference 157 N, 95% CI 125–189; $P < 0.0001$; Table 1) and could not be fully activated during an MVC (mean difference 8%, 95% CI 4.5–15; $P < 0.0001$; Table 1). Voluntary activation was directly related to quadriceps strength ($r_s = 0.55$; $P < 0.001$). In addition, the objective functional performance (AFPT) of the patients was slower than that of the healthy subjects (mean difference 34 s, 95% CI 23.5–44.8; $P < 0.0001$; Table 1) and was inversely related to their quadriceps strength ($r_s = -0.6$; $P < 0.0001$).

Knee JPS was less accurate in patients with RA than in the healthy subjects ($P < 0.005$; Table 1).

The HAQ score of 1.58 indicated the patients were moderately disabled (Table 1); it was inversely related to quadriceps strength ($r_s = -0.52$; $P < 0.001$) and directly related to the AFPT ($r_s = 0.65$; $P < 0.001$). The healthy subjects had a median Lequesne index of 1 (interquartile range 0–4; Table 1), indicating that they had very little, if any, lower limb pain or disability [31].

Randomized controlled trial of rehabilitation for patients with RA

Between-group changes. Prior to rehabilitation, there were no differences between the control group and the rehabilitation group for any of the baseline variables (Table 2). Following rehabilitation, the quadriceps muscles of the rehabilitated patients were stronger (mean 67 N, 95% CI 19–116; $P < 0.01$) and better activated (5%, 95% CI 0–10; $P < 0.05$) than those of the control group. There were no significant between-group differences for the other variables (Table 2).

Within-group changes. There were no differences in the response to rehabilitation of patients who undertook the rehabilitation regime immediately and those whose rehabilitation was delayed (results not shown); these data were pooled for analysis. Following the rehabilitation regime, the quadriceps strength of the patient's index leg increased by a mean of 61 N (95% CI 28–95; ES 0.66; $P < 0.0005$; Table 3) and their voluntary activation increased by 8% (95% CI 3–12.4; $P < 0.0005$; Table 3). The acuity of knee JPS was unchanged, and although the patients' function and disability improved [the AFPT decreased by 12.3 s (95% CI −2 to 27.7 s; ES 0.23) and their HAQ score decreased by 0.21 points (CI −0.13 to 0.5)], these improvements did not attain statistical significance (Table 3). Although all the measures of clinical disease activity tended to decrease after rehabilitation, only the reduction in morning stiffness reached statistical significance ($P < 0.01$; Table 3). There was no increase in plasma concentrations of the proinflammatory cytokines (TNF-α, IL-1β and IL-6) following a single exercise session (Fig. 2a) or after completion of the rehabilitation regime (Fig. 2b and Table 3).

Twenty-seven patients (approximately 33%) who undertook the rehabilitation regime (immediately or delayed) withdrew before the end of the intervention (Fig. 1). Analysis of the baseline variables showed no differences between patients who completed rehabilitation ($n = 61$) and those who withdrew ($n = 27$).

Six-month follow-up

To assess whether there was a lasting benefit from rehabilitation, 52 of 61 (approximately 85%) patients attended for the 6-month follow-up; three of these patients had to be excluded because of changes in second-line agents during this period (Fig. 1), but analysis of the data carried out with and without these patients yielded similar results (not shown). In the patients reassessed at the 6-month follow-up, the improvements attained during rehabilitation had been maintained. There were further improvements in the AFPT (mean decrease from baseline 18.6 s; 95% CI 3.5–33.6; $P < 0.02$), HAQ score (0.44, 95% CI 0.0–0.63; $P < 0.05$), knee JPS (0.4°, CI 0.1–1.2; $P < 0.05$) and some measures of clinical disease activity (Table 3).

TABLE 1. Differences in anthropometric data, quadriceps sensorimotor function and objective functional performance of the healthy subjects and patients with RA [mean (95% CI) unless stated otherwise]

	Healthy subjects ($n = 25$)	RA patients ($n = 103$)
Anthropometric data		
Age (yr)	65.5 (50–82)	59.5 (30–82)
Height (m)	1.64 (1.52–1.82)	1.62 (1.25–1.83)
Body mass (kg)	74 (50–122)	71 (31–183)
Quadriceps motor function		
MVC (N)	352 (326–378)	195 (174–214)**
Activation[a] (%): median	93 (90–97)	85 (64–94)**
Quadriceps sensory function		
Knee joint position sense (°)	2.3 (1.9–2.7)	3.1 (2.8–3.4)**
Objective functional performance		
AFPT (s)	35.6 (32.7–38.6)	69.7 (59.3–80.0)**
Subjective disability		
HAQ score[a]	–	1.58 (1–2)
Lequesne index[a]	1 (0–4)	–
Knee X-ray score		
Index leg[a]	–	2.00
Non-index leg[a]	–	1.67

*$P < 0.05$; **$P < 0.001$; significant difference between healthy subjects and RA patients.

[a]Median (interquartile range).

Discussion

Compared with healthy subjects, patients with stable RA that involved their lower limb and moderate levels of pain had substantial quadriceps weakness, reduced voluntary activation and proprioceptive deficits, which

TABLE 2. Physiological and biochemical variables and disability of patients randomized to the control ($n = 46$) and rehabilitation groups ($n = 47$), and between-group differences before and after the control period or rehabilitation [mean (95% CI) unless stated otherwise]

	Baseline		After control or rehabilitation treatment	
	Control	Rehabilitation	Control	Rehabilitation
Quadriceps motor function (index leg)				
Strength (N)	190 (156–224)	179 (155–205)	189 (156–220)	256 (220–293)**
Activation[a] (%)	85 (62–94)	76 (64–92)	85 (67–92)	90 (83–95)*
Quadriceps sensory function (index leg)				
JPS (°)	3.1 (2.6–3.5)	3.3 (2.8–3.9)	2.9 (2.5–3.4)	3.3 (2.6–4.0)
Objective functional performance				
AFPT (s)	67.2 (51.1–83.4)	78.1 (60.9–95.3)	66.2 (50.8–81.5)	58.5 (48.0–69.0)
Subjective disability				
HAQ score[a]	1.62 (1.21–2.15)	1.50 (1.00–2.25)	1.62 (1.00–2.25)	1.12 (0.50–2.25)
Clinical disease activity				
Morning stiffness[a] (min)	20 (5–60)	20 (5–60)	30 (5–60)	5 (1–60)
Pain[a] (mm)	31 (21–51)	33 (17–50)	32 (21–55)	29 (14–54)
Patient assessment[a] (mm)	36 (21–60)	41 (16–65)	39 (21–60)	34 (22–55)
Assessor assessment[a] (mm)	24 (14–36)	22 (10–37)	29 (15–37)	23 (8–37)
Swollen joint count[a]	3 (1–6)	4 (0–7)	2 (1–6)	3 (−4–8)
Tender joint count[a]	7 (3–11)	8 (4–11)	7 (4–10)	7 (1–8)
Plasma concentration of cytokines				
IL-1β (pg/ml)	8.7 (5.3–12.0)	15.2 (5.6–24.6)	11 (6.8–15.1)	10.2 (5.5–15.0)
Interleukin-6 (pg/ml)	33.3 (20.2–46.4)	35.6 (7.4–63.8)	42.7 (22.3–63.0)	13.8 (7–20.6)
TNF-α (pg/ml)	22.4 (16.2–28.6)	21.7 (18.1–25.3)	26.0 (16.4–35.6)	21.8 (17.5–26.0)

*$P < 0.05$; **$P < 0.01$; significantly different from control group.
[a]Median (interquartile range).

TABLE 3. Within-group changes in physiological and biochemical variables and disability of all the patients ($n = 88$) who undertook rehabilitation, i.e. the pooled data of the 47 patients who were randomized to receive rehabilitation immediately and the 41 patients who undertook rehabilitation after the control period [mean (95% CI) unless stated otherwise]

	Rehabilitation period: index leg		
	Baseline ($n = 88$)	Post-rehabilitation ($n = 61$)	6-month follow-up ($n = 52$)
Quadriceps motor function			
Strength (N)	184 (164–204)	245 (218–273)**	239 (213–266)**
Voluntary activation (%)	83 (66–92)	91 (84–96)**	91 (87–96)**
Quadriceps sensory function			
Knee joint position sense (°)	3.1 (2.8–3.5)	3.0 (2.5–3.5)	2.5 (2.1–2.8)*
Objective functional performance			
AFPT (s)	72.7 (61.2–81.2)	60.4 (50.9–69.9)	54.1 (44.2–64.0)*
Subjective disability			
HAQ[a]	1.56 (1–2.25)	1.35 (0.75–2.0)	1.125 (0.69–1.88)*
Variables of clinical disease activity			
Morning stiffness[a] (min)	25 (5–60)	5 (4–45)*	10 (0.5–30)*
Pain[a] (mm)	33 (19–53)	27 (10–52)	24 (10–45) ($P = 0.06$)
Patient assessment[a] (mm)	39 (17–60)	32 (13–53)	33 (14.5–54)
Assessor assessment[a] (mm)	27 (12–37)	21 (7–35)	12 (5–30)*
Swollen joint count[a]	2 (1–6)	2 (0–7)	1 (0–5)
Tender joint count[a]	7 (4–10)	6 (2–10)	4 (1–6.5)*
Plasma concentration of cytokines			
IL-1β (pg/ml)	8.71 (6.01–11.42)	6.04 (4.61–7.46)	8.94 (4.15–13.73)
IL-6 (pg/ml)	41.42 (24.64–58.2)	35.75 (17.9–53.56)	52.5 (5.6–110.6)
TNF-α (pg/ml)	23.84 (18.82–28.87)	24.58 (16.9–32.27)	19.36 (15.44–23.29)

**$P < 0.0005$, *$P < 0.05$; significantly improved after rehabilitation.
[a]Median (interquartile range).

were associated with impaired performance of common ADL and disability. For this population of patients, a brief rehabilitation regime that consisted of strengthening and functional exercises improved motor deficits and lower limb functional performance without exacerbating disease activity or increasing the concentrations of proinflammatory cytokines.

In RA, quadriceps weakness is usually considered to be due to muscle atrophy resulting from disuse, because pain and disability curtail the patient's activities.

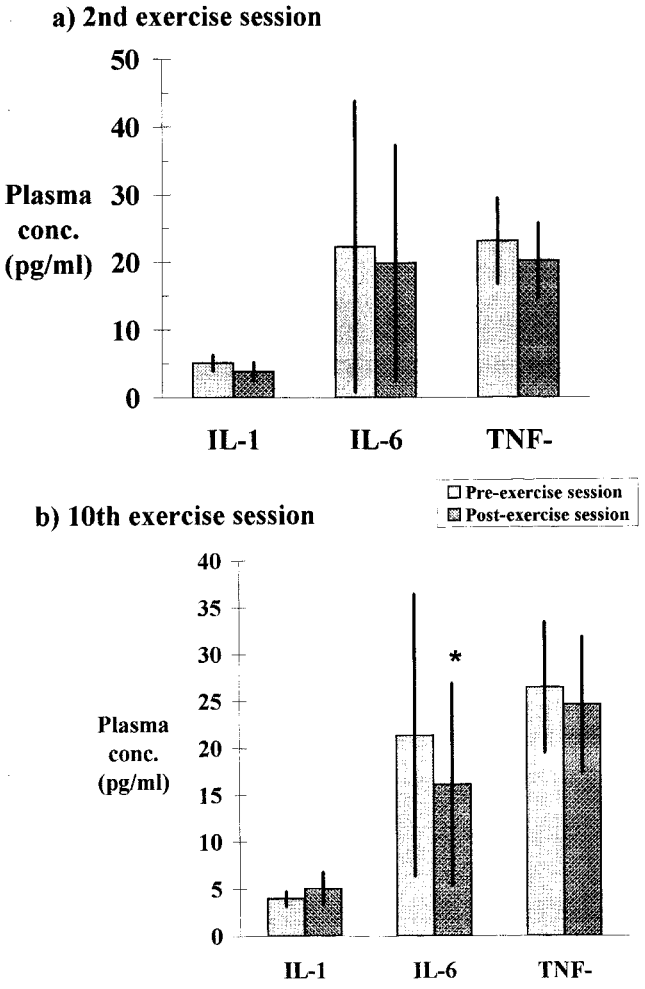

FIG. 2. Plasma concentrations of IL-1β, IL-6 and TNF-α before and after the second and tenth exercise sessions. Mean and 95% CI. *Lower than before exercise ($P < 0.05$).

However, as in other rheumatic conditions, patients with RA could not fully activate their quadriceps during an MVC, which contributed to quadriceps weakness [13]. The stimulus for incomplete voluntary activation is unknown, but it has been proposed that abnormal afferent information from articular mechanoreceptors, occurring as a result of joint damage, effusion, pain and/or psychological factors, decreases quadriceps α-motor neurone excitability via neurophysiological pathways in the spinal cord and supraspinal centres [36, 37], and that this impairs voluntary activation, which is manifested as quadriceps weakness [10, 11, 18, 38, 39].

The lower limb rehabilitation regime increased quadriceps strength (the *a priori* primary outcome variable) by amounts comparable with those seen in other studies [1, 4, 40–43]. Part of this increase was due to improved voluntary activation because of decreased pain, better activation of the neurophysiological pathways of motor control, improved coordination and motivation. The important difference between this rehabilitation regime and previous efficacious research regimes is that the current regime was much shorter and involved simple exercises and unsophisticated, inexpensive equipment. The current regime is therefore as effective, but its brevity and simplicity make it clinically more applicable than previous research regimes. It may not substantially benefit RA patients who do not have lower limb involvement.

Quadriceps weakness is clinically important because it is associated with impaired functional performance and disability [7]. As in OA [18, 44], in patients with RA with lower limb involvement we found that quadriceps weakness is associated with objective and subjective disability, and interventions that increase quadriceps strength would therefore be expected to decrease disability. By combining strength and functional exercises and adapting these to address each patient's individual deficits, as in routine clinical practice, the rehabilitation regime improved the patient's performance of common ADL and subjective disability. Although the improvements in function and disability were too small to attain statistical significance immediately after rehabilitation, these improvements may be clinically important as they are more relevant to the patient's needs than change in physiological variables, such as strength. Moreover, the change in the HAQ score was greater than the change considered to be clinically significant (0.17 HAQ points) [45], shifted the patients' categorization from moderately to mildly disabled [46] and compares favourably with changes in disability effected during drug trials. It is likely that the sample size (calculated to detect changes in quadriceps strength) was too small to detect statistically significant changes in the secondary outcome measures of disability (HAQ and AFPT).

However, another problem may be that there is no disease-specific measure of lower limb disability for RA patients and our rehabilitation regime was specifically designed to improve lower limb function, not overall disability. Although the HAQ is widely used to assess disability in RA, it measures global disability with a bias towards upper limb disability and is insensitive to change in lower limb disability. Therefore, by using the HAQ we are unlikely to detect small but possibly clinically meaningful changes in lower limb disability. This makes the HAQ inappropriate for the evaluation of rehabilitation regimes that concentrate on improving lower limb function [47] and highlights the need for disease-specific assessment of lower limb disability. Further studies with sample sizes sufficient to detect clinically meaningful changes in objective and subjective lower limb disability can assess whether regimes such as the one described improve lower limb function.

An interesting aspect of the findings was the continued improvement in proprioceptive acuity, functional performance and disability during the follow-up period (Table 2). This has also been noted by other research groups [48, 49], but its significance and causes are unknown. The patients may have participated in a new, beneficial activity during this period, but none

of the patients reported doing so when asked. Alternatively, patients with chronic disabling disease who undergo rehabilitation may require time to appreciate subtle improvements they have achieved, with a consequent time lag in subjective improvement in patient-reported disability [48, 49].

The improvements in proprioceptive acuity, although small, were comparable to the changes reported in an earlier study [20], in which we suggested that even small improvements in proprioceptive acuity may reduce harmful impact forces during gait, resulting in better timing of placement of the foot. It is interesting to speculate that the delayed improvements in proprioceptive acuity and patient-reported functional ability may not be coincidental. It may be that greater awareness and better control of limb position enable the patient to function better; conversely, it could be suggested that restoration of function may lead to better proprioception. Although these findings are of interest and contribute to a field of increasing research interest, these hypotheses are very speculative and require verification in well-designed studies.

Before they are implemented, management regimes must be shown to be safe as well as effective. Therefore, exercise must not exacerbate disease activity, cause persistent synovitis or joint damage, as has been suggested [21–23]. Our results support the findings from many studies that exercise does not exacerbate any of the measures used to assess clinical disease activity [1, 3, 42, 50–53], and only six patients (7%) withdrew from our study because of an exacerbation of joint inflammation and pain (usually involving upper limb joints). More importantly, this is the first and largest trial of rehabilitation that has simultaneously measured plasma concentrations of proinflammatory cytokines to evaluate whether rehabilitation exacerbates RA. We found no increase in the plasma concentrations of TNF-α, IL-1β and IL-6 before or after an exercise session or the whole rehabilitation regime, which refutes the argument that patients with RA should refrain from exercise: patients with well-controlled RA can exercise without exacerbating disease activity.

When interpreting the results of this rehabilitation study, some aspects of its design require consideration. Most importantly, although the biochemical assays were performed by an independent researcher blind to the intervention, the rehabilitation study was 'open', i.e. the same researcher performed the assessments and supervised the exercise sessions and the patients were aware that they were undertaking rehabilitation. This will probably exaggerate the size of the treatment response, though it is unlikely to negate the improvements.

The rehabilitation trial used a partial cross-over design to maximize recruitment and give all the participants the opportunity to undertake the rehabilitation regime. This helped ease the increasing ethical problem of withholding exercise from patients with arthritis. Although unusual, this research design is appropriate for use in chronic conditions and has been used recently in rheumatological conditions [20, 54, 55]. We do not believe this study design influenced the results adversely, because (i) we found no evidence that delaying rehabilitation affected the patients' response to training, (ii) improvements in subjective and objective disability make it unlikely that an attention placebo affected the results, (iii) there was no difference in the number of patients who withdrew from either arm of the study, and (iv) although cross-over trials can have treatment carry-over effects necessitating a 'wash-out period', treatment cross-over effects were averted because the control period involved no change in the patients' management.

Finally, while strenuous attempts were made to contact and re-call all patients who underwent rehabilitation, follow-up was incomplete (85%). The patients who were followed up were not selected in any way and we have no reason to believe they are unrepresentative of those lost to follow-up. This makes it unlikely that the limited follow-up may account for the delayed improvements in AFPT, HAQ and/or proprioceptive acuity, but this cannot be refuted completely.

This study is one of the largest investigations of changes in quadriceps sensorimotor function in patients with RA. We demonstrated that patients with RA had quadriceps sensorimotor dysfunction which was associated with impaired performance of common lower limb activities of daily living and with disability. In addition, following a relatively short, clinically applicable rehabilitation regime, lower limb motor function improved and, most importantly, functional performance improved and patient-reported disability decreased. Neither clinical disease activity nor the concentrations of plasma proinflammatory cytokines (TNF-α, IL-1β, IL-6) increased after exercise. This safe, efficacious and clinically practicable regime could be used to improve the management of RA patients with lower limb involvement.

Acknowledgements

This study was funded by the NHS Research and Development Physical and Complex Disabilities Programme. We would like to thank the staff of the Rheumatology Departments of King's Healthcare, Guy's and St Thomas' NHS Trusts for access to their patients during the study. We would also like to thank the anonymous reviewers for their constructive comments. We are also extremely grateful to the patients who gave up a great deal of their time and agreed to participate in this study.

References

1. Ekblom B, Lovgren O, Alderin M *et al.* Effect of short term physical training on patients with rheumatoid arthritis. Scand J Rheumatol 1975;4:80–6.
2. Ekdahl C, Andersson SI, Svensson, B. Muscle function of the lower extremities in rheumatoid arthritis and osteoarthritis. J Clin Epidemiol 1989;42:947–54.

3. Minor M, Hewett J, Webel R *et al*. Efficacy of physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. Arthritis Rheum 1989; 32:1396–405.
4. van den Ende CHM, Hazes JMW, le Cessie S *et al*. Comparison of high and low intensity training in well controlled rheumatoid arthritis. Results of a randomised clinical trial. Ann Rheum Dis 1996;55:798–805.
5. Nordesjo L-O, Nordgren B, Wigren A *et al*. Isometric strength and endurance in patients with severe rheumatoid arthritis or osteoarthritis in the knee joint. Scand J Rheumatol 1983;12:152–6.
6. Herbison GJ, Ditunno JF, Jaweed MM. Muscle atrophy in rheumatoid arthritis. J Rheumatol 1987;14(Suppl. 15): 78–81.
7. Stucki G, Bruhlmann P, Stucki S *et al*. Isometric muscle strength is an indicator of self reported physical functional disability in patients with rheumatoid arthritis. Br J Rheumatol 1998;37:643–8.
8. Ekdahl C, Broman G. Muscle strength, endurance and aerobic capacity in rheumatoid arthritis: a comparative study with healthy subjects. Ann Rheum Dis 1992; 51:35–40.
9. Blockey NJ. An observation concerning the flexor muscles during the recovery of function after dislocation of the elbow. J Bone Joint Surg 1954;36A:833–40.
10. Stokes M, Young, A. The contribution of reflex inhibition to arthrogenous muscle weakness. Clin Sci 1984;67:7–14.
11. Shakespeare DT, Stokes M, Sherman KP *et al*. Reflex inhibition in the quadriceps after meniscectomy: lack of association with pain. Clin Physiol 1985;5:137–44.
12. Hurley MV, Jones DW, Newham DJ. Arthrogenic quadriceps inhibition and rehabilitation of patients with extensive, traumatic knee injuries. Clin Sci 1994;86:305–10.
13. Hurley MV, Scott, DL, Rees J, Newham DJ. Sensorimotor changes and functional performance in patients with knee OA. Ann Rheum Dis 1997;56:641–8.
14. Hurley MV, Newham, DJ. The influence of arthrogenous muscle inhibition on quadriceps rehabilitation of patients with early, unilateral osteoarthritic knees. Br J Rheumatol 1993;32:127–31.
15. Hurley MV, O'Flanagan SJ, Newham DJ. Isokinetic and isometric muscle strength and inhibition after elbow arthroplasty. J Orthop Rheumatol 1991;4:83–95.
16. Pai Y-C, Rymer WZ, Chang RW *et al*. Effect of age and osteoarthritis on knee proprioception. Arthritis Rheumatol 1997;40:2260–5.
17. Sharma L, Pai Y-C. Impaired proprioception and osteoarthritis. Curr Opin Rheumatol 1997;9:253–8.
18. Hurley M, Scott DL, Rees J *et al*. Sensorimotor changes and functional performance in patients with knee osteoarthritis. Ann Rheum Dis 1997;56:641–8.
19. Ferrell W, Crighton A, Sturrock R. Position sense at the proximal interphalangeal joint is distorted in patients with rheumatoid arthritis of finger joints. Exp Physiol 1992;77:678–80.
20. Hurley MV, Scott DL. Improvements in quadriceps sensorimotor function and disability of patients with knee osteoarthritis following a clinically practicable exercise regime. Br J Rheumatol 1998;37:1181–7.
21. Blake DR, Merry P, Unsworth J *et al*. Hypoxic–reperfusion injury in the inflamed human joint. Lancet 1989;i:289–93.
22. Bodamyali T, Stevens CR, Billingham MEJ *et al*. Influence of hypoxia in inflammatory synovitis. Ann Rheum Dis 1998;57:703–10.
23. Merry P, Kidd BL, Mapp PI *et al*. Mechanisms of persistent synovitis. Scand J Rheumatol 1988; 76 (Suppl.):85–93.
24. Merry P, Williams R, Cox N *et al*. Comparative intra-articular pressure dynamics in joints with acute traumatic and chronic inflammatory effusions: potential implications for hypoxic–reperfusion injury. Ann Rheum Dis 1991; 50:917–20.
25. Rall LC, Meydani SN, Kehayias JJ *et al*. The effect of progressive resistance training in rheumatoid arthritis. Arthritis Rheum 1996;39:415–26.
26. Baslund B, Lynberg K, Andersen V. Effect of 8 wk bicycle training on the immunological system of patients with RA. J Appl Physiol 1993;75:1691–5.
27. Arnett FC, Edworthy SM, Bloch DA *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
28. McComas AJ, Kereshi S. A method for detecting functional weakness. J Neurol Neurosurg Psychiatry 1983;46:280–2.
29. Rutherford OM, Jones DA, Newham DJ. Clinical and experimental application of the twitch superimposition technique for the study of human muscle. J Neurol Neurosurg Psychiatry 1986;49:1288–91.
30. Kirwan JR, Reeback JS. Stanford Health Assessment Questionnaire modified to assess disability in British patients with rheumatoid arthritis. Br J Rheumatol 1986;25:206–9.
31. Lequesne MG. The algofunctional indices for hip and knee osteoarthritis. J Rheumatol 1997;24:779–81.
32. Tugwell P, Boers MJ. OMERACT conference on outcome measures in rheumatoid arthritis clinical trials: an introduction. J Rheumatol 1993;20:528–9.
33. Altman DG. Practical statistics for clinical research. London: Chapman & Hall, 1991.
34. Pocock SJ. Clinical trials: A practical approach. Chichester: John Wiley & Sons, 1984.
35. Kazis L, Anderson J, Meenan R. Effect sizes for interpreting changes in health status. Med Care 1989;27:S178–89.
36. Baldissera F, Hultborn H, Illert M. Integration in spinal neurone systems. In: Brooks V, ed. Handbook of physiology, Vol. II, Section 1. Bethesda, MD: American Physiological Society, 1981:509–97.
37. McCrea DA. Can sense be made of spinal interneuron circuits? Behav Brain Sci 1992;15:633–43.
38. De Andrade JR, Grant C, Dixon ASJ. Joint distension and reflex muscle inhibition in the knee. J Bone Joint Surg 1965;47A:313–22.
39. Spencer JD, Hayes KC, Alexander IJ. Knee joint effusion and quadriceps inhibition in man. Arch Phys Med Rehab 1984;65:171–7.
40. Danneskiold-Samsoe B, Lyngberg K, Risum T *et al*. The effects of water exercise therapy given to patients with rheumatoid arthritis. Scand J Rehab Med 1987;19:31–5.
41. Ekdahl C, Andersson SI, Moritz U *et al*. Dynamic versus static training in patients with rheumatoid arthritis. Scand J Rheumatol 1990;19:17–26.
42. Lyngberg K, Ramsing B, Nawrocki A *et al*. Safe and effective isokinetic knee extension training in rheumatoid arthritis. Arthritis Rheum 1994;5:623–8.
43. Komatireddy GR, Leitch RW, Cella K *et al*. Efficacy of low load resistive training in patients with rheumatoid arthritis functional class II and III. J Rheumatol 1996; 24:1531–9.

44. McAlindon TE, Cooper C, Kirwan JR *et al*. Determinants of disability in osteoarthritis of the knee. Ann Rheum Dis 1993;52:258–62.
45. Redelmeier DA, Lorig K. Assessing the clinical importance of symptomatic improvement. Arch Intern Med 1993;153:1337–42.
46. Guillemin F, Briancon N, Pourel J. Validity and discrimination of the HAQ functional index in early RA. Dis Rehab 1992;14:71–7.
47. van den Ende CHM, Breedveld FC, Hazes JMW. The relationship between physical impairment and functional ability as measured by the Health Assessment Questionnaire (HAQ). Br J Rheumatol 1997; 36:225–32.
48. Stenstrom CH. Therapeutic exercise in rheumatoid arthritis. Arthritis Care Res 1994;7:190–7.
49. Keefe FJ, Caldwell DS, Williams DA *et al*. Pain coping skills training in the management of osteoarthritic knee pain. II. Follow-up results. Behav Ther 1990; 21:435–47.
50. Hakkinen A, Hakkinen K, Hannonen P. Effects of strength training on neuromuscular function and disease activity in patients with recent onset inflammatory arthritis. Scand J Rheumatol 1994;23:237–42.
51. Ekdahl C. Postural control, muscle function and psychological factors in rheumatoid arthritis. Scand J Rheumatol 1992;21:297–301.
52. Rall LC, Roubenoff R, Cannon JG, Abad LW, Dinarello A, Meydani SN. Effects of progressive resistance training on immune response in aging and chronic inflammation. Med Sci Sport Exerc 1996;28:1356–65.
53. Noreau L, Moffet H, Drolet M *et al*. Dance-based exercise programme in rheumatoid arthritis. Am J Phys Med Rehab 1997;76:109–13.
54. Helewa A, Goldsmith C, Lee P *et al*. Effects of occupational therapy home services on patients with rheumatoid arthritis. Lancet 1991;337:1453–6.
55. Berman BM, Singh BB, Lao L *et al*. A randomized trial of acupuncture as an adjunctive therapy in osteoarthritis of the knee. Rheumatology 1999;38:346–54.