Can Progressive Resistance Training Reverse Cachexia in Patients with Rheumatoid Arthritis? Results of a Pilot Study

SAMUELE M. MARCORA, ANDREW B. LEMMEY, and PETER J. MADDISON

ABSTRACT. ***Objective***. A Phase II trial was performed as a preliminary test of the efficacy and safety of progressive resistance training (PRT) as adjunct treatment for rheumatoid cachexia.

Methods. Ten mildly disabled patients with well-controlled rheumatoid arthritis (RA) trained, on average, 2.5 times per week for 12 weeks. Ten age and sex matched RA patients with similar disease characteristics were non-randomly assigned to a control group. Body composition, physical function, and disease activity were assessed pre and post intervention period.

Results. Between group comparisons at followup by ANCOVA using baseline scores as covariate showed significant increases in fat-free mass (+1253 g, p = 0.004), total body protein (+1063 g, p = 0.044), and arm (+280 g, p = 0.005) and leg (+839 g, p = 0.001) lean mass (a proxy measure of total body skeletal muscle mass) in response to PRT with no exacerbation of disease activity. There was also a trend for loss of fat mass in the trunk (–752 g, p = 0.084) and a significant reduction in percent body fat (–1.1%, p = 0.047). Changes in body composition were associated with improvements in various measures of physical function.

Conclusion. Intense PRT with adequate volume seems to be an effective and safe intervention for stimulating muscle growth in patients with RA. Pending confirmation of these results in a larger randomized controlled trial that includes patients with more active and severe disease, a similar PRT program should be included in the management of RA as adjunct treatment for cachexia. (J Rheumatol 2005;32:1031–9)

Key Indexing Terms:

RHEUMATOID ARTHRITIS | CACHEXIA | EXERCISE
MALNUTRITION | SKELETAL MUSCLE | DISABILITY

Rheumatoid arthritis (RA), like many other chronic systemic diseases, is complicated by cachexia, a syndrome characterized by cytokine-driven alterations in protein and energy metabolism and consequent accelerated loss of skeletal muscle[1]. Cachexia affects more than 50% of RA patients but only a minority appears wasted[2], as energy intake is normal in this population and the decrease in muscle mass is masked by a concomitant increase in fat mass consequent to low levels of physical activity/total energy expenditure[3,4]. Cachexia contributes not only to muscle weakness, fatigue and disability, but also to increased risk of infection and premature death in RA[5]. Therefore, interventions aimed at preventing/reversing muscle wasting in RA patients may significantly improve the longterm outcome of this disease.

Several therapeutic strategies such as dietary supplementation, physical training, anabolic hormones, and anticytokine therapy have been proposed for cachexia[1]. Unfortunately, few studies have included RA patients or an accurate measure of body composition, the recommended endpoint in clinical trials for the treatment of cachexia[6]. Therefore, at present, it is not possible to make specific and evidence-based recommendations for management of muscle wasting in this population, apart from tight control of disease activity with the least possible use of high-dose corticosteroid therapy[7].

We present the results of a Phase II trial aimed at testing the utility of progressive resistance training (PRT) as adjunct treatment for cachexia in patients with RA. Several studies have clearly shown that this type of physical training is effective in improving muscle strength in RA patients without exacerbating disease activity[8]. However, Rall and colleagues[9] failed to demonstrate any increase in total body potassium (a proxy measure of skeletal muscle mass[10]) and fat-free mass (FFM) in response to 12 weeks of high inten-

From the School of Sport, Health and Exercise Sciences, University of Wales-Bangor, and Department of Rheumatology, Gwynedd Hospital, Bangor, Wales, UK.

Supported by a grant from the Wales Office of Research and Development for Health and Social Care.

S.M. Marcora, PhD, Lecturer in Exercise Physiology; A.B. Lemmey, PhD, Lecturer in Exercise Physiology, School of Sport, Health and Exercise Sciences; P.J. Maddison, MD, Professor of Joint and Muscle Disorders, School of Sport, Health and Exercise Sciences, Consultant Rheumatologist, Department of Rheumatology, Gwynedd Hospital.

Address reprint requests to Dr. S. Marcora, School of Sport, Health and Exercise Sciences, George Building, University of Wales-Bangor, Holyhead Road, Bangor, Gwynedd, LL57 2PX United Kingdom.

Accepted for publication January 27, 2005.

sity PRT in a small group of RA patients despite a normalization of total body protein breakdown[11]. Although it is possible that systemic inflammation reduces the ability of skeletal muscle cells to respond to anabolic stimuli[12], we believe that the low training volume (5 resistance exercises per training session repeated twice a week) prescribed by Rall and colleagues[9] was not adequate to induce muscle growth in their subjects. In this investigation there was also no control group to assess the normal variation of body composition without any PRT in RA patients, and changes in regional body composition were not reported. Therefore, we designed the present controlled study to investigate whether a PRT program prescribed for optimal stimulation of muscle hypertrophy[13] is feasible and tolerable in mildly disabled patients with well-controlled RA, and to provide preliminary evidence for its efficacy as adjunct treatment of cachexia in this population. The main outcome variable was a significant increase in both arm and leg (appendicular) lean mass assessed by dual-energy x-ray absorptiometry (DEXA), a proxy measure of total body skeletal muscle mass[14]. Secondary outcomes were changes in other body compartments, physical function and disease activity. A secondary aim of this study was to examine whether an increase in muscle mass is associated with improvement in physical function in this population.

MATERIALS AND METHODS

Study design and ethics. This was a 2-group, matched, parallel, controlled, pretest-posttest study conducted between July 2000 and August 2001. The study protocol was approved by the North Wales Health Authority Research Ethics Committee.

Subject recruitment and eligibility. Ten patients willing and able to participate in a supervised PRT program (training group) were recruited from the Outpatient Rheumatology Clinics at Gwynedd Hospital. Ten age (within 5 years) and sex matched patients willing to take part in the study, but not able to train regularly under supervision because of logistic reasons (e.g., living too far away from the only training site provided) were selected to serve as controls (control group). In order to be included into the study, all volunteers had to: (a) fulfil the American Rheumatism Association 1987 revised criteria for the diagnosis of RA[15]; (b) be functional class I or II; (c) be age 18 years or over; (d) not be cognitively impaired; (e) have been receiving stable drug therapy during the previous 3 months; (f) be free of other cachectic diseases and any condition preventing safe participation in the study; (g) not be taking drugs or nutritional supplements known to increase muscle mass; (h) not be participating in another regular and intense physical training program; and (i) not be pregnant. Before commencing the study, all subjects gave their written informed consent to participate.

Outcome measures. Outcome measures were taken at baseline (pretest) and followup (posttest) by the same investigator (SM) in the Bone Densitometry Laboratory in the School of Sport, Health and Exercise Sciences, University of Wales-Bangor, at about the same time of day. Subjects presented fasted and were asked to void and remove all metallic objects. Subjects were instructed beforehand to avoid strenuous exercise in the 24 hours preceding testing and were questioned as to whether they had orthopedic metal and silicone implants. During testing subjects were allowed to wear only socks, shorts, underwear (no bra) and a t-shirt.

Body mass and composition. Body mass was measured to the nearest 0.1 kg using a calibrated balance scale (Seca, Hamburg, Germany). Total and regional (left and right arm, left and right leg, trunk, head) body composition was assessed by DEXA using a pencil-beam scanner (QDR1500, Hologic, Bedford, Massachusetts), which calculates the masses (g) of 3 different compartments: bone mineral content (BMC), fat mass and lean mass. The sum of total BMC and total lean mass corresponds to FFM. Percent body fat was calculated as (total fat mass/total body mass by DEXA) × 100. The procedures recommended by the manufacturer for whole-body examination (subject positioning, scanning and analysis with software version V5.72) were followed, and the quality control procedure was performed daily.

Immediately after the DEXA scan, intracellular (ICW) and extracellular (ECW) water volumes (l) were estimated using bioelectrical impedance spectroscopy (BIS) (Hydra 4200, Xitron Technologies, San Diego, CA, USA). Total body water (TBW) is the sum of ICW and ECW. Bioelectrical impedance measurements were taken on the left side of the body, with the use of disposable electrodes and in accordance with a standard wrist-to-ankle protocol[16]. At the time subjects were measured, they had been supine for about 20 min. The quality control procedure recommended by the manufacturer was performed before each measurement and the proximity of the DEXA scanner had no effect on the validity and reliability of BIS (unpublished observations). The coefficient of variation (CV) for repeated measurements for both DEXA (lean mass) and BIS is between 1 and 3%[17]. By combining these 2 body composition methods, we calculated FFM hydration (TBW/FFM) and estimated total body protein as total lean mass –(0.2302 × total BMC)–TBW according to the model proposed by Fuller, *et al*[18]. For each of these calculations, TBW volume was converted into mass by assuming a water density of 0.99336 kg/l at a normal body temperature of 37°C.

Physical function. After body composition assessment, subjects performed calisthenics for 5 min under the direction and supervision of one of the authors (SM). The following objective physical function tests were then performed. Maximal voluntary hand-grip strength was measured using a Grip-A dynamometer (Takei Kiki Kogyo, Tokyo, Japan). Subjects were asked to stand erect holding the dynamometer parallel to their side, dial facing away from the body and to squeeze the hand-grip without moving the arm. Maximal voluntary strength of the knee extensors and elbow flexors was measured using a CSD300 hand-held dynamometer (Chatillon-Ametek, Largo, FL, USA). For the measurement of knee extensor strength, subjects sat on a medical table with hips and knees flexed 90° and arms across the chest. The curved push attachment of the dynamometer was positioned over the tibia just proximal to the 2 malleoli, and subjects were instructed to attempt to straighten the leg. For the measurement of elbow flexor strength, subjects were lying on a medical table with shoulder neutral, elbow flexed 90°, and forearm neutral. The curved push attachment of the dynamometer was positioned just below the styloid process of the radius, and subjects were instructed to attempt to flex the arm. All these isometric measures of muscle strength followed the same protocol: after 2 submaximal warm-up and familiarization trials (50% and 75% of maximum effort), subjects were asked 3 times to exert force maximally for about 5 s. Between all 5 trials 1 min rest was observed. Peak force produced during each of the 3 maximal trials was recorded in newtons and the best score noted. Both the right and left side of the body were tested and the average of the 2 best scores used for statistical analysis. The force of the tester (male, body mass 100 kg, height 1.79 m) was sufficient to fix the hand-held dynamometer against the forces produced by all subjects. None of the subjects approached the upper limit of the dynamometers, and their accuracy was verified periodically over the course of the study by vertically loading the dynamometers with certified calibration weights. The repeatability of isometric muscle force measurements was good (coefficient of variation < 5%) and compares well with fixed dynamometers[19]. Finally, subjects performed the 30-s maximal sit-to-stand test (SST-30) developed by Jones, *et al* in older adults[20]. After a practice trial, subjects were asked to sit-to-stand from a fixed chair (seat height 43.2 cm) as many times as possible in 30 s while keeping their arms folded across the chest. The number of full and properly performed repetitions was recorded and used for statistical analy-

sis. As suggested by McNair, *et al*[21], subjects were verbally encouraged during all tests in order to attain maximum performance.

Self-reported physical function was assessed by the modified Health Assessment Questionnaire (HAQ) and the advanced activities of daily living (ADL) scale designed by Pincus, *et al*[22] to overcome the "floor effects" of the traditional HAQ questionnaires in which patients may report normal scores although they experience meaningful functional limitations. Both the modified HAQ and advanced ADL scores have good psychometric properties[22] and are reported on a scale of 1 (without any difficulty), 2 (with some difficulty), 3 (with much difficulty), and 4 (unable to do).

Disease activity. Disease activity was assessed using the RA Disease Activity Index (RADAI)[23]. With the exception of fatigue, this patient questionnaire quantifies the most apparent signs and symptoms of RA: (a) global disease activity over the past 6 months, (b) current disease activity in terms of swollen and tender joints, (c) arthritis pain, (d) duration of morning stiffness, and (e) amount of pain in several joint areas. These 5 items are then combined to provide a single index of disease activity on a 0 to 10 scale where higher scores indicate more active disease. The RADAI compares well with physician assessment of disease activity and is sensitive to changes over time, i.e. flare-ups[24]. Fatigue over the past week was measured with a numerical rating scale ranging from 0 (fatigue is no problem) to 10 (fatigue is a major problem). Additionally, the erythrocyte sedimentation rate (ESR) was assessed by the Westergren method in the Public Health Laboratory of Gwynedd Hospital to provide an objective measure of disease activity.

Other measures. At baseline the following measures were also taken. Height was measured to the nearest 0.5 cm using a wall-mounted stadiometer (Body Care, Warwickshire, UK). Body mass index (BMI) was calculated as body mass(kg)/height(m)^2. Typical dietary intake was estimated using a semiquantitative food frequency questionnaire[25]. Habitual physical activity both at work and during leisure time was ranked from mainly sedentary (score = 1) to heavy and regular (score = 4) using the questionnaire proposed by Saltin, *et al*[26]. The degree of muscle atrophy was calculated as the percentage of actual total body skeletal muscle mass estimated from appendicular lean mass, age, and sex[14] compared to normal total body skeletal muscle mass estimated from body mass, height, age, sex, and ethnicity[27]. Other baseline information (e.g., disease duration, current therapy, etc.) was collected by a structured interview and review of medical records. At followup, all subjects were questioned as to whether changes in habitual physical activity, diet, medications, and other aspects of their lifestyle had occurred during the study.

Intervention. After baseline assessment and an introductory week (Week 0) for familiarization with exercise equipment and technique, subjects in the training group underwent 12 weeks of PRT that consisted of 8 resistance exercises per session (Leg Press, Chest Press, Leg Extension, Seated Row, Leg Curl, Triceps Pushdown, Standing Calf Raise, Biceps Curl). Each resistance exercise had the following characteristics: (a) dynamic muscle action at moderate repetition velocity (1–2 s concentric, 1–2 s eccentric); (b) 3 sets of 8 repetitions with a load corresponding to 80% of one repetition maximum; (c) 1- to 2-min rest periods between sets and exercises. Subjects were required to train 3 times a week with at least 48 h between training sessions (Monday, Wednesday and Friday, or Tuesday, Thursday and Saturday). One repetition maximum was assessed at the end of Week 0 and every 2 weeks thereafter to enable adjustment of the exercise load in proportion to changes in specific muscle strength. Each training session lasted about 75 min including warmup (5 min low intensity aerobic exercise plus one set of 15 repetitions with half the load before each exercise) and cool-down (10 min of core stability and static stretching exercises) phases. The occurrence of adverse events was also recorded. Subjects in the training group exercised in small groups on Powersport resistance exercise machines (Bridgend, United Kingdom) at Maes Glas Sports Centre under supervision of one of the authors (SM). A record of each session was kept, and training load calculated as the total weight lifted.

After baseline assessment, subjects in the control group continued their usual care (medications and joint mobility exercises) with no additional PRT. All subjects were instructed to maintain their habitual physical activity and dietary habits throughout the study. Followup assessment of all subjects was conducted on the Monday or Tuesday of Week 13.

Statistical analysis. The null hypothesis of no difference between groups in all baseline measures was examined using multiple paired t tests for continuous variables and Fisher's exact probability tests for categorical variables. Multiple one-way analyses of covariance (ANCOVA) were employed to test the null hypothesis of no difference between groups (independent variable) on each outcome measure with the posttest score as the dependent variable and the pretest score as the covariate. However, because the assumption of homogeneity of regression slopes was violated for ESR, one way analysis of variance (ANOVA) on change (posttest minus pretest score) was used in this instance. For these analyses, the between-subject effect size for group was calculated as eta squared. Thresholds for small, moderate, large, and very large effects were set at 0.01, 0.08, 0.26 and 0.50, respectively. We used a one-way repeated measure ANOVA to test the null hypothesis of no change in the average weekly training load within the training group. Pearson's correlation coefficient was used to express and test the significance of the relationships between measures of interest (body mass by scale with body mass by DEXA; changes in arm and leg lean mass with changes in muscle strength and disability) after pooling the data of both groups. Significance was set at 0.05 (2-tailed) for all analyses with a p level > 0.05 and < 0.10 being considered a trend. Data were analyzed using the Statistical Package for the Social Sciences Version 11.

RESULTS

Subject characteristics. All subjects (6 women and 4 men in each group) completed the study. Their baseline characteristics are shown in Tables 1, 2, and 3. In terms of age, sex distribution, disease characteristics, and therapy, our subjects are representative of functional class I and II patients[22,23]. Despite a BMI in the overweight category, adequate protein-energy intake and normal levels of physical activity, all but one of the patients presented with muscle atrophy. Actual total body skeletal muscle mass was, on average, 79% (range 62-118%) of normal muscle mass in the training group and 74% (range 64-83%) in the control group ($p = 0.293$). A minority of patients were taking low doses of vitamin and mineral complexes, calcium, cod liver oil, and glucosamine, with no significant differences between groups (all $p \geq 0.474$). Two women in the training group and one woman in the control group had regular menstruations ($p = 0.999$). All other female subjects were postmenopausal. None of these women in the training group was on hormone replacement therapy, while 2 in the control group were ($p = 0.444$). With the exception of sleep duration, there were no significant differences between groups at baseline in any of the measured characteristics. We did not include sleep duration as an additional covariate as it was not significantly correlated with any of the outcome measures (data not shown), and both groups reported having sufficient sleep. No subject had silicone implants, but one subject in the training group had bilateral hip replacement. Because the influence of orthopedic metal on DEXA measures of body composition is reproducible and relatively small when computerized, high-density detection analysis is employed[28,29], we decid-

Table 1. Demographic, anthropometric, lifestyle, and disease characteristics of patients with RA participating in the study. Data are presented as means ± SD or frequency. Differences between groups were tested by paired t tests or Fisher's exact probability tests as appropriate.

Variable	Training Group, n = 10	Control Group, n = 10	p
Age, yrs	53 ± 13	54 ± 10	0.791
Height, m	1.67 ± 0.08	1.64 ± 0.08	0.213
BMI, kg/m^2	27.9 ± 4.6	29.1 ± 2.2	0.529
Energy intake, kcal/day	1908 ± 430	1981 ± 469	0.720
Protein intake, g/day	78.2 ± 23.4	81.8 ± 24.1	0.739
Activity at work, 1–4	1.6 ± 0.7	1.8 ± 0.6	0.443
Leisure-time activity, 1–4	2.1 ± 0.6	2.3 ± 0.5	0.443
Current smokers	2	4	0.628
Cigarettes per day	8.0 ± 9.9	6.0 ± 6.2	0.768
Alcohol measures per week	5.8 ± 4.6	4.6 ± 8.6	0.645
Sleep duration, h	8.2 ± 1.0	6.3 ± 1.2	0.002
RF positive	6	8	0.628
Disease duration, yrs	8.9 ± 5.7	7.3 ± 5.3	0.565
Methotrexate[a]	5	5	0.999
Other DMARD	6	9	0.628
NSAID	6	5	0.999
Corticosteroids	2	3	0.999
Dose, mg/day	6.2 ± 1.8	8.3 ± 5.8	0.668

BMI: body mass index; RF: rheumatoid factor; DMARD: disease modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drugs. [a] All subjects treated with methotrexate were also receiving folate supplementation.

ed to include this subject in the analysis. All subjects were Caucasian and sedentary.

Compliance and adverse events. Compliance to PRT was, on average, 85% (range 67–94%). This corresponds to a mean training frequency of 2.5 sessions per week (range 2.0–2.8 sessions per week). The progressive nature of the proposed resistance training program was confirmed by a significant increase in the weekly average training session load throughout the intervention period (Figure 1). There were no flare-ups of disease activity, training-related injuries, or any other adverse event during the study in either group. All subjects declared that habitual physical activity, diet, medications, and other aspects of their lifestyle remained unchanged during the study. The tolerability and patient perceived benefits of PRT were such that 9 out of 10 RA patients in the training group continued training without supervision after completion of the study. The remaining subject in the training group commenced regular swimming instead.

Effects on body mass and composition. Body mass and composition at baseline and followup, and the results of ANCOVA are shown in Table 2. PRT did not have a significant effect on body mass. The change in body mass measured by scale was highly correlated to the change in body mass measured by DEXA (r = 0.985, p = 0.001), thus confirming the internal validity of our DEXA in assessing changes in body composition[30].

PRT had a large and significant effect on total lean mass (+1242 g) and FFM (+1253 g). This increase in FFM mostly reflects a significant and moderate increase in estimated total body protein (+1063 g) as PRT did not have a significant effect on TBW and total BMC. The significant increase in lean mass was concentrated in the arms (+280 g) and legs (+839 g), suggesting a very large effect on total body skeletal muscle mass, the primary outcome measure of this clinical trial. PRT did not significantly affect total fat mass, but there was a trend for a moderate loss of fat mass in the trunk (–752 g) and a significant albeit moderate reduction in percent body fat (–1.1%). None of the other regional measures of body composition was significantly affected by PRT (data not shown). The hydration of the FFM was within normal limits (~0.73) at both baseline and followup, and was not affected by PRT (data not shown).

Effect on physical function. Objective and subjective measures of physical function at baseline and followup, and the results of ANCOVA are shown in Table 3. Progressive resistance training caused a moderate increase in hand-grip strength (+53 N), a large increase in elbow flexor strength (+54 N), and a very large increase in SST-30 performance (+3.6 repetitions). All these effects were statistically significant. The moderate increase in knee extensor strength (+39 N) approached statistical significance. Although PRT did not affect modified HAQ scores, at followup the training group reported, on average, less difficulty in advanced ADL compared to the control group when adjusting for baseline scores. This effect (–0.25) was very large, statistically significant and clinically relevant[31].

Effect on disease activity. Self-reported and laboratory

Table 2. Effects of 12 weeks of progressive resistance training on body mass and composition in patients with RA. Pretest and posttest scores are presented as means ± SD. Adjusted scores (posttest scores adjusted for pretest scores) are presented as means ± SEM. Differences between groups at baseline were tested by paired t tests. Differences between groups in the adjusted scores were tested by ANCOVA.

Variable	Training Group, n = 10	Control Group, n = 10	p	η^2
Body mass, kg				
Pre	78.2 ± 14.6	79.0 ± 11.3	0.868	
Post	78.6 ± 13.0	78.8 ± 11.9		
Adjusted	79.0 ± 0.7	78.5 ± 0.7	0.586	0.018
Arm lean mass, kg				
Pre	4.26 ± 1.51	4.24 ± 1.77	0.901	
Post	4.52 ± 1.59	4.22 ± 1.72		
Adjusted	4.51 ± 0.06	4.23 ± 0.06	0.005	0.386
Leg lean mass, kg				
Pre	13.3 ± 3.2	12.9 ± 3.4	0.477	
Post	14.1 ± 3.1	12.9 ± 3.3		
Adjusted	13.9 ± 0.1	13.1 ± 0.1	0.001	0.757
Total lean mass, kg				
Pre	44.5 ± 9.4	43.8 ± 10.2	0.577	
Post	45.4 ± 8.9	43.5 ± 10.1		
Adjusted	45.0 ± 0.3	43.8 ± 0.3	0.005	0.381
Total BMC, kg				
Pre	2.58 ± 0.40	2.47 ± 0.52	0.382	
Post	2.59 ± 0.42	2.48 ± 0.53		
Adjusted	2.54 ± 0.01	2.53 ± 0.01	0.726	0.007
FFM, kg				
Pre	47.1 ± 9.7	46.3 ± 10.7	0.540	
Post	47.9 ± 9.2	45.9 ± 10.5		
Adjusted	47.6 ± 0.3	46.3 ± 0.3	0.004	0.389
Trunk fat mass, kg				
Pre	14.7 ± 6.5	16.9 ± 4.4	0.493	
Post	14.0 ± 5.9	16.8 ± 4.7		
Adjusted	15.0 ± 0.3	15.8 ± 0.3	0.084	0.165
Total fat mass, kg				
Pre	30.1 ± 9.9	31.6 ± 6.1	0.712	
Post	29.5 ± 9.6	31.7 ± 6.4		
Adjusted	30.2 ± 0.5	30.9 ± 0.5	0.345	0.053
Percent body fat				
Pre	38.6 ± 9.9	40.9 ± 7.8	0.453	
Post	37.7 ± 10.1	41.1 ± 7.6		
Adjusted	38.9 ± 0.4	40.0 ± 0.4	0.047	0.213
ECW, l				
Pre	15.5 ± 2.2	15.7 ± 2.9	0.761	
Post	15.5 ± 1.9	15.7 ± 2.8		
Adjusted	15.6 ± 0.1	15.6 ± 0.1	0.889	0.001
ICW, l				
Pre	18.6 ± 3.3	19.3 ± 4.5	0.477	
Post	18.8 ± 3.5	19.0 ± 4.8		
Adjusted	19.1 ± 0.3	18.7 ± 0.3	0.320	0.058
TBW, l				
Pre	34.1 ± 5.1	35.0 ± 7.2	0.561	
Post	34.3 ± 5.2	34.7 ± 7.5		
Adjusted	34.8 ± 0.3	34.2 ± 0.3	0.256	0.075
Total body protein, kg				
Pre	9.79 ± 5.29	8.27 ± 3.61	0.196	
Post	10.42 ± 4.53	8.18 ± 3.12		
Adjusted	9.78 ± 0.31	8.81 ± 0.31	0.044	0.217

BMC: bone mineral content; FFM: fat-free mass; ECW: extracellular water; ICW: intracellular water; TBW: total body water.

Table 3. Effects of 12 weeks of progressive resistance training on physical function and disease activity in patients with RA. Pretest and posttest scores are presented as means ± SD. Adjusted scores (posttest scores adjusted for pretest scores) are presented as means ± SEM. Differences between groups at baseline were tested by paired t tests. Differences between groups in the adjusted scores were tested by ANCOVA. The difference between groups in ESR change score (posttest score–pretest score) was tested by ANOVA.

Variable	Training Group, n = 10	Control Group, n = 10	p	η^2
Hand-grip strength, N				
Pre	187 ± 108	223 ± 133	0.415	
Post	224 ± 115	204 ± 135		
Adjusted	241 ± 17	187 ± 17	0.045	0.215
Elbow flexor strength, N				
Pre	171 ± 43	196 ± 87	0.295	
Post	222 ± 63	194 ± 97		
Adjusted	235 ± 14	181 ± 14	0.016	0.298
Knee extensor strength, N				
Pre	297 ± 85	312 ± 154	0.753	
Post	347 ± 46	319 ± 147		
Adjusted	352 ± 15	313 ± 15	0.073	0.177
SST-30, repetitions				
Pre	11.3 ± 2.8	12.2 ± 3.2	0.450	
Post	15.7 ± 3.3	12.8 ± 2.7		
Adjusted	16.1 ± 0.6	12.4 ± 0.6	0.001	0.519
Modified HAQ, 1–4				
Pre	1.3 ± 0.3	1.5 ± 0.6	0.320	
Post	1.3 ± 0.2	1.3 ± 0.4		
Adjusted	1.2 ± 0.1	1.2 ± 0.1	0.900	0.001
Advanced ADL, 1–4				
Pre	2.1 ± 0.4	2.4 ± 0.6	0.085	
Post	1.8 ± 0.3	2.3 ± 0.6		
Adjusted	1.9 ± 0.1	2.2 ± 0.1	0.008	0.351
RADAI, 0–10				
Pre	2.5 ± 1.1	2.8 ± 1.7	0.721	
Post	2.0 ± 1.4	2.3 ± 1.5		
Adjusted	2.1 ± 0.3	2.2 ± 0.3	0.893	0.001
Fatigue, 0–10				
Pre	4.4 ± 1.8	4.9 ± 3.2	0.601	
Post	3.1 ± 2.1	4.4 ± 3.3		
Adjusted	3.2 ± 0.8	4.3 ± 0.8	0.363	0.049
ESR, mm/h				
Pre	18.8 ± 16.6	22.5 ± 17.6	0.644	
Post	16.7 ± 8.9	20.9 ± 18.1		
Change	–2.1 ± 11.0	–1.6 ± 7.0	0.905	0.001

SST-30: 30-s maximal sit-to-stand test; HAQ: Health Assessment Questionnaire; ADL: activities of daily living; RADAI: Rheumatoid Arthritis Disease Activity Index; ESR: erythrocyte sedimentation rate.

measures of disease activity at baseline and followup, and the results of ANCOVA are shown in Table 3. Despite its high intensity and volume, the proposed PRT program did not significantly affect RADAI, fatigue, or ESR.

Association between changes in appendicular lean mass and changes in physical function. There was a moderate and significant correlation between change in arm lean mass and change in handgrip strength (r = 0.444, p = 0.050), and change in elbow flexor strength (r = 0.511, p = 0.021) but not with change in advanced ADL score (r = –0.204, p = 0.388). On the other hand, change in leg lean mass correlated moderately and significantly with change in advance ADL score (r = –0.496, p = 0.026). There was also a strong and significant association between change in leg lean mass and change in SST-30 performance (r = 0.746, p = 0.001).

DISCUSSION

This is the first study to demonstrate that high intensity PRT with adequate volume is an effective adjunct treatment of cachexia in RA patients. In fact, we found a significant increase in both arm and leg lean mass, the primary outcome measures in this clinical trial, which suggests generalized muscle growth in response to our PRT program. This is in contrast with Rall and colleagues[9] who could not demonstrate any significant increase in total body potassium, another proxy measure of skeletal muscle mass[10], in their

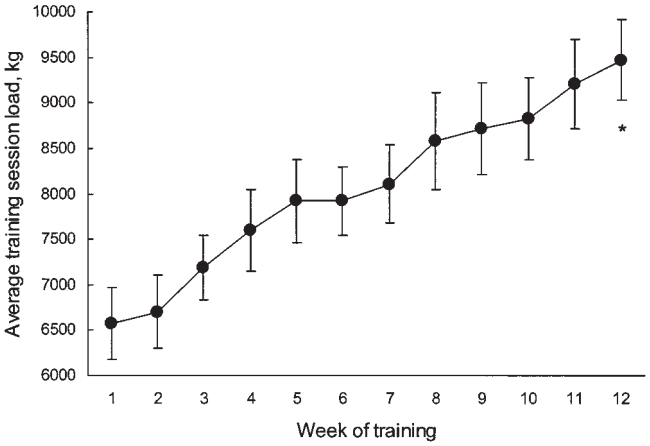

Figure 1. Weekly increase in average training session load (total weight lifted) in 10 RA patients participating in 12 weeks of progressive resistance training. Data are presented as means ± SEM. *Main within-subject effect of time by ANOVA, p = 0.002.

subjects after 12 weeks of high intensity PRT. As patient characteristics were similar, and as the programs were identical with respect to relative exercise intensity, number of sets and repetitions per exercise, muscle action and repetition velocity, rest periods, training duration, and exercise adherence, we believe that the combination of a higher number of resistance exercises per training session and higher training frequency, and the consequently higher total weekly training volume (576 vs 240 weight lifts per week), accounts for the superior anabolic effects of our PRT program compared to the one prescribed by Rall, *et al*[9].

Contrary to Rall, *et al*[9], we also found a significant increase in FFM, which was secondary to a significant accretion of estimated total body protein. As changes in body composition reflect the "area under the curve" of the organism's metabolic state[32], this finding suggests that PRT is able to overturn the negative nitrogen balance characteristic of RA[7]. This is not surprising as a similar resistance exercise protocol stimulated net mixed muscle protein synthesis in healthy humans[33]. Overall, the results of our study suggest that PRT can reverse whole-body protein catabolism and stimulates skeletal muscle hypertrophy in RA patients and serve to reject the hypothesis of resistance to anabolic stimuli in this population. In fact, the 5–6% increase in FFM measured in our study is comparable to the one measured in healthy subjects undergoing a similar PRT program[34]. This observation, together with the recent findings of Häkkinen, *et al*[35], suggests that RA patients can adapt normally to physical training provided proper exercise mode, intensity, duration, frequency, and progression are prescribed and adhered to.

The positive anabolic effects of our PRT program were accompanied by significant increases in 3 out of 4 objective measures of physical function, and the increase in knee extensor strength approached statistical significance. The smaller overall increase in muscle strength found in our study (+22%) compared to that observed by Rall, *et al*[9] (+57%) can be explained by the fact that our static measures of muscle strength were chosen to minimize training specificity whereas Rall, *et al*[9] used the same dynamic resistance exercises for both testing and training[36]. An improvement in sit-to-stand performance in response to PRT in RA patients has also been reported by other authors[37,38]. We also measured a significant reduction in self-reported difficulties in advanced ADL in response to PRT. This finding is particularly important because the change in this HAQ score was larger than that considered clinically relevant[31]. Previous studies on the effects of physical training in RA patients, despite proving efficacy in improving aerobic capacity, muscle strength, and joint mobility, have not convincingly demonstrated a positive effect on subjective measures of physical function[39]. Van den Ende, *et al*[39] suggested this discrepancy might be explained by the low sensitivity of questionnaires commonly used in RA to measure difficulty in ADL, particularly in patients with mild disability, i.e., those usually recruited for physical training studies. Our results support this conclusion as we measured a substantial decrease in disability when using the advanced ADL scale (designed by Pincus and colleagues to reduce the floor effects of other HAQ questionnaires when administered to RA patients with mild disability[22]), but not when using the modified HAQ. Interestingly, changes in physical function were generally associated with changes in appendicular lean mass. However, most correlations, albeit significant, were only moderate, and relative improvements in physical function exceeded the relative increases in arm and leg lean mass. This is a well-known phenomenon, and studies in healthy subjects and RA patients[40] suggest that increased muscle strength over the first few weeks of PRT is mainly due to neural rather than muscular adaptations. Nevertheless, this finding gives some empirical support to the assumption that therapies targeting muscle atrophy would improve clinically relevant outcomes such as functional status in RA patients.

In addition to the significant anabolic and functional responses, we measured a moderate loss of fat mass in the trunk after only 12 weeks of high intensity PRT. Although this effect was only a trend, its size and potential impact on outcome in RA patients are of great clinical interest. RA predisposes to central obesity even in patients not taking corticosteroids[3], and its combination with insulin resistance, blood lipid abnormalities, hypertension and systemic inflammation (the so-called metabolic syndrome) greatly increases the probability of developing cardiovascular disease[41], a common co-morbidity in patients with RA[42]. Therefore, PRT might reduce mortality not only by augmenting the body protein mass disposable to the liver and other vital organs in situations of acute stress[43], but also by reducing cardiovascular risk in RA patients.

Importantly, we have also demonstrated that our PRT program, despite its much higher total weekly training volume, is feasible, well tolerated, and does not exacerbate disease activity in mildly disabled patients with well-controlled RA as previously feared by Rall, *et al*[9], who did not train their subjects with more resistance exercises per session and more frequently to avoid potentially excessive articular stress[44]. This adds to many other studies on PRT in RA patients, which found no deleterious effects on pain and other measures of disease activity[8].

Our study has several limitations. Because of limited resources, we could provide supervised PRT sessions only at one site and this presented a serious problem for recruitment of volunteers in our rural area. Therefore, treatment was not randomly allocated, and RA patients willing and able to travel regularly to the training site were conveniently assigned to the training group. A group of RA patients with similar disease characteristics and matched for age and sex served as controls. Although many other characteristics that might have had an effect on the outcome of the study (e.g., baseline body composition and functional status, dietary intake, and habitual physical activity) did not differ between groups, non-random allocation to treatment cannot control for unrecognized potential confounding factors. For example, subjects more likely to participate in sports and leisure-time physical activities might have different genetic characteristics compared to sedentary subjects[45]. Nevertheless, spontaneous changes in body composition such as those measured in the subjects who underwent the prescribed PRT program have not been reported in the literature and seem highly unlikely as aging people and people with chronic diseases characteristically lose total body protein and muscle mass[46]. Other possible threats to the internal validity of our study are the low power for detection of a significant change in trunk fat mass and knee extensor strength, the assessor being aware of subjects' allocation, and the absence of "placebo" treatment such as flexibility exercises. However, objective measures of total body composition by DEXA cannot be influenced by the assessor and are unlikely to be significantly affected by placebo[47]. In terms of external validity, our study is limited by the exclusion of severely disabled patients and patients with active RA and, therefore, our findings cannot be readily generalized to these subgroups of patients. Also, the recent results of de Jong, *et al*[48] suggest that the safety of physical training programs should be considered not only in terms of disease activity but also by assessing radiological progression over a much longer period of time, particularly in RA patients with considerable damage to the large joints. It is important to note, however, that PRT is a low impact activity and has been successfully used to treat knee osteoarthritis[49].

Despite these limitations, this is the first study to demonstrate that high intensity PRT with adequate volume can reverse cachexia in RA patients. Pending confirmation of our results in a larger randomized, double-blind, placebo-controlled Phase III trial, a similar PRT program should be included in the clinical management of this debilitating disease. Future studies should also investigate the mechanisms behind PRT-induced increases in skeletal muscle mass and physical function in RA patients, its longterm effects (e.g., on joint damage and mortality), and the efficacy of PRT combined with other interventions such as dietary supplementation and anabolic hormones.

ACKNOWLEDGMENT

The authors thank all staff at the Department of Rheumatology, Gwynedd Hospital, and Maes Glas Sports Centre for their assistance in conducting this study, and the subjects for their commitment.

REFERENCES

1. Kotler DP. Cachexia. Ann Intern Med 2000;133:622-34.
2. Munro R, Capell H. Prevalence of low body mass in rheumatoid arthritis: association with the acute phase response. Ann Rheum Dis 1997;56:326-9.
3. Westhovens R, Nijs J, Taelman V, Dequeker J. Body composition in rheumatoid arthritis. Br J Rheumatol 1997;36:444-8.
4. Roubenoff R, Walsmith J, Lundgren N, Snydman L, Dolnikowski GJ, Roberts S. Low physical activity reduces total energy expenditure in women with rheumatoid arthritis: implications for dietary intake recommendations. Am J Clin Nutr 2002;76:774-9.
5. Rall LC, Roubenoff R. Rheumatoid cachexia: metabolic abnormalities, mechanisms and interventions. Rheumatology Oxford 2004;43:1219-23.
6. Bone HG. Summary remarks. J Nutr 1999;129 Suppl:317S-318S.
7. Roubenoff R, Roubenoff RA, Ward LM, Stevens MB. Catabolic effects of high-dose corticosteroids persist despite therapeutic benefit in rheumatoid arthritis. Am J Clin Nutr 1990;52:1113-7.
8. Hakkinen A. Effectiveness and safety of strength training in rheumatoid arthritis. Curr Opin Rheumatol 2004;16:132-7.
9. Rall LC, Meydani SN, Kehayias JJ, Dawson-Hughes B, Roubenoff R. The effect of progressive resistance training in rheumatoid arthritis. Increased strength without changes in energy balance or body composition. Arthritis Rheum 1996;39:415-26.
10. Wang Z, Zhu S, Wang J, Pierson RN, Jr., Heymsfield SB. Whole-body skeletal muscle mass: development and validation of total-body potassium prediction models. Am J Clin Nutr 2003;77:76-82.
11. Rall LC, Rosen CJ, Dolnikowski G, et al. Protein metabolism in rheumatoid arthritis and aging. Effects of muscle strength training and tumor necrosis factor alpha. Arthritis Rheum 1996;39:1115-24.
12. Frost RA, Lang CH, Gelato MC. Transient exposure of human myoblasts to tumor necrosis factor-alpha inhibits serum and insulin-like growth factor-I stimulated protein synthesis. Endocrinology 1997;138:4153-9.
13. Kraemer WJ, Adams K, Cafarelli E, et al. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sports Exerc 2002;34:364-80.
14. Kim J, Wang Z, Heymsfield SB, Baumgartner RN, Gallagher D. Total-body skeletal muscle mass: estimation by a new dual-energy X-ray absorptiometry method. Am J Clin Nutr 2002;76:378-83.
15. 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.
16. Van Loan MD, Withers P, Matthie J, Mayclin PL. Use of bioimpedance spectroscopy to determine extracellular fluid, intracellular fluid, total body water, and fat-free mass. Basic Life

Sci 1993;60:67-70.
17. Ellis KJ. Human body composition: in vivo methods. Physiol Rev 2000;80:649-80.
18. Fuller NJ, Wells JC, Elia M. Evaluation of a model for total body protein mass based on dual-energy X-ray absorptiometry: comparison with a reference four-component model. Br J Nutr 2001;86:45-52.
19. Brinkmann JR. Comparison of a hand-held and fixed dynamometer in measuring strength of patients with neuromuscular disease. J Orthop Sports Phys Ther 1994;19:100-4.
20. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport 1999;70:113-9.
21. McNair PJ, Depledge J, Brettkelly M, Stanley SN. Verbal encouragement: effects on maximum effort voluntary muscle action. Br J Sports Med 1996;30:243-5.
22. Pincus T, Swearingen C, Wolfe F. Toward a multidimensional Health Assessment Questionnaire (MDHAQ): assessment of advanced activities of daily living and psychological status in the patient-friendly health assessment questionnaire format. Arthritis Rheum 1999;42:2220-30.
23. Stucki G, Liang MH, Stucki S, Bruhlmann P, Michel BA. A self-administered rheumatoid arthritis disease activity index (RADAI) for epidemiologic research. Psychometric properties and correlation with parameters of disease activity. Arthritis Rheum 1995;38:795-8.
24. Fransen J, Hauselmann H, Michel BA, Caravatti M, Stucki G. Responsiveness of the self-assessed rheumatoid arthritis disease activity index to a flare of disease activity. Arthritis Rheum 2001;44:53-60.
25. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51-65.
26. Saltin B, Grimby G. Physiological analysis of middle-aged and old former athletes. Comparison with still active athletes of the same ages. Circulation 1968;38:1104-15.
27. Lee RC, Wang Z, Heo M, Ross R, Janssen I, Heymsfield SB. Total-body skeletal muscle mass: development and cross-validation of anthropometric prediction models. Am J Clin Nutr 2000;72:796-803.
28. Giangregorio LM, Webber CE. Effects of metal implants on whole-body dual-energy x-ray absorptiometry measurements of bone mineral content and body composition. Can Assoc Radiol J 2003;54:305-9; quiz 270-1.
29. Madsen OR, Egsmose C, Lorentzen JS, Lauridsen UB, Sorensen OH. Influence of orthopaedic metal and high-density detection on body composition as assessed by dual-energy X-ray absorptiometry. Clin Physiol 1999;19:238-45.
30. Lohman TG, Harris M, Teixeira PJ, Weiss L. Assessing body composition and changes in body composition. Another look at dual-energy X-ray absorptiometry. Ann N Y Acad Sci 2000;904:45-54.
31. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol 2003;30:167-78.
32. Roubenoff R. Inflammatory and hormonal mediators of cachexia. J Nutr 1997;127 Suppl:1014S-1016S.
33. Phillips SM, Tipton KD, Aarsland A, Wolf SE, Wolfe RR. Mixed muscle protein synthesis and breakdown after resistance exercise in humans. Am J Physiol 1997;273 Pt 1:E99-107.
34. Campbell WW, Crim MC, Young VR, Evans WJ. Increased energy requirements and changes in body composition with resistance training in older adults. Am J Clin Nutr 1994;60:167-75.
35. Hakkinen A, Hannonen P, Nyman K, Lyyski T, Hakkinen K. Effects of concurrent strength and endurance training in women with early or longstanding rheumatoid arthritis: comparison with healthy subjects. Arthritis Rheum 2003;49:789-97.
36. Morrissey MC, Harman EA, Johnson MJ. Resistance training modes: specificity and effectiveness. Med Sci Sports Exerc 1995;27:648-60.
37. Komatireddy GR, Leitch RW, Cella K, Browning G, Minor M. Efficacy of low load resistive muscle training in patients with rheumatoid arthritis functional class II and III. J Rheumatol 1997;24:1531-9.
38. McMeeken J, Stillman B, Story I, Kent P, Smith J. The effects of knee extensor and flexor muscle training on the timed-up-and-go test in individuals with rheumatoid arthritis. Physiother Res Int 1999;4:55-67.
39. Van Den Ende CH, Vliet Vlieland TP, Munneke M, Hazes JM. Dynamic exercise therapy for rheumatoid arthritis. Cochrane Database Syst Rev 2000(2):CD000322.
40. Bearne LM, Scott DL, Hurley MV. Exercise can reverse quadriceps sensorimotor dysfunction that is associated with rheumatoid arthritis without exacerbating disease activity. Rheumatology Oxford 2002;41:157-66.
41. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 2003;107:391-7.
42. Watson DJ, Rhodes T, Guess HA. All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis in the UK General Practice Research Database. J Rheumatol 2003;30:1196-202.
43. Rosenblatt S, Clowes GH, Jr., George BC, Hirsch E, Lindberg B. Exchange of amino acids by muscle and liver in sepsis. Arch Surg 1983;118:167-75.
44. Jawed S, Gaffney K, Blake DR. Intra-articular pressure profile of the knee joint in a spectrum of inflammatory arthropathies. Ann Rheum Dis 1997;56:686-9.
45. Maia JA, Thomis M, Beunen G. Genetic factors in physical activity levels: a twin study. Am J Prev Med 2002;23 Suppl:87-91.
46. Hansen RD, Raja C, Allen BJ. Total body protein in chronic diseases and in aging. Ann N Y Acad Sci 2000;904:345-52.
47. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. J Intern Med 2004;256:91-100.
48. de Jong Z, Munneke M, Zwinderman AH, et al. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. Arthritis Rheum 2003;48:2415-24.
49. Ettinger WH, Jr, Burns R, Messier SP, Applegate W, et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The Fitness Arthritis and Seniors Trial (FAST). JAMA 1997;277:25-31.