Efficacy of progressive resistance training for patients with rheumatoid arthritis and recommendations regarding its prescription

Rheumatoid arthritis (RA) is characterized by adverse changes in body composition including reduced muscle mass, increased fat mass (particularly central fat mass) and attenuated bone mass. These perturbations contribute directly to conditions and comorbidities common in RA; namely, impaired physical function (diminished strength and aerobic capacity), disability and exacerbated cardiovascular disease and osteoporosis risk. In this article, the efficacy and safety of progressive resistance training (PRT) – also known as systematic weight training – in restoring body composition and helping to treat these consequent conditions is discussed. Furthermore, to enable clinicians and relevant health professionals to prescribe appropriate PRT programs, the principles of PRT program design have been outlined, with particular reference made to experiences with RA patients.

KEYWORDS: disability ▪ exercise ▪ obesity ▪ osteoporosis ▪ physical function ▪ prescription ▪ progressive resistance training ▪ rheumatoid arthritis ▪ rheumatoid cachexia

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Rheumatoid arthritis (RA) is a disease characterized by a high incidence of disability, cachexia, obesity, cardiovascular disease (CVD) and osteoporosis. To deal with RA generally, and these associated conditions specifically, the WHO [201] and various national health authorities (e.g., the American College of Rheumatology [ACR], European League Against Rheumatism [EULAR], American College of Sports Medicine [ACSM] and the American Heart Association [AHA]) [1–7,202] have advocated progressive resistance training (PRT; i.e., systematic weight training) as adjunct therapy. Additionally, two *Cochrane Reviews* have supported the inclusion of this form of physical training in the routine treatment of RA patients [8,9]. However, despite this weighty advocacy, regular PRT is rarely prescribed for, or undertaken by, RA patients.

In this article, the efficacy and safety of PRT as a treatment for RA will be discussed, with training recommendations and considerations outlined.

Disability, rheumatoid cachexia & osteoporosis in RA patients

Disability

Despite advances in pharmaceutical treatment, disability remains a feature of RA. In the recently published report of the British Society for Rheumatology Biologics Register, large samples of patients receiving anti-TNF treatment (n = 12,672) or standard DMARDs (n = 3522) had median (interquartile range) Health Assessment Questionnaire (HAQ) scores of 2.1 (1.8–2.5) and 1.6 (0.9–2.1), respectively [10]. These scores represent moderate-to-severe disability. As well as the enormous suffering and reduced quality of life (QoL) experienced on a personal level, this disability also has huge social and economic costs [11–13]. For example, work disability prevalence of 35% within 10 years of RA diagnosis is currently reported for both US and European populations [14,15].

Whilst the causes of disability in RA are multifactorial [16,17], Giles *et al.* have shown that it is strongly associated with adverse changes in body composition [18], with HAQ scores inversely related to appendicular lean mass (ALM; a surrogate measure of muscle mass) and directly related to total and appendicular fat masses (FMs). Subsequently, Stavropoulos-Kalinoglou *et al.* have also shown that obesity in RA patients is independently associated with disability [19]. Such links between body composition and physical function are not surprising and reflect those observed in the elderly population in general. In this population classification as either muscle-wasted (sarcopenic) or obese significantly exacerbates the risk of disability, with the coincidence of both conditions (sarcopenic obesity) observed to increase the likelihood of disability 12-fold in women and ninefold in men [20].

Rheumatoid cachexia

Unfortunately, both reduced muscle mass and elevated adiposity, termed 'rheumatoid cachexia' [21], are common in RA. Muscle

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wasting due to RA was first observed by Sir James Paget in 1873 [22] and has been consistently reported over the last 20 years [23], most prolifically and notably by Roubenoff and colleagues [21,24–31]. This group, using below the 50th percentile for arm muscle circumference of a reference population as the threshold of significant muscle loss, identified that 67% of their RA patients were rheumatoid cachectic [27]. Using a more stringent cutoff of the 10th percentile, Munro and Capell concluded that 50% of their British RA sample was cachectic [32]. In a series of studies, mostly featuring patients who volunteered for high-intensity exercise training [33–35], we have found that two-thirds of our stable RA patients presented as muscle wasted according to the whole-body dual-energy x-ray absorptiometry (DXA) definitions outlined by Baumgartner *et al.* (i.e., ALM [kg]/height^2 [m^2] more than two standard deviations below the mean of a young reference group) [36]. Interestingly, using the same methodology we found a similar incidence of rheumatoid cachexia in treatment-naive patients with recent-onset RA (<6 months since diagnosis), suggesting that the loss of lean body mass (LBM) occurs early in the disease [37]. The magnitude of this loss in LBM is reported by Roubenoff's group (using the potassium-40 method) to be 14–16% in RA patients with controlled disease [26,27,29], which coincides with the approximately 15% loss we observe in stable RA patients relative to age- and sex-matched healthy sedentary controls [Lemmey AB *et al.*, Unpublished Data]. Given this magnitude of muscle loss, it is not surprising that RA patients have reduced muscle strength, with values ranging from 30 to 80% of normal being reported [38–44]. Also consistent with expectations is the very strong relationship between muscle weakness and disability (as assessed by HAQ) in RA patients Stucki *et al.* revealed [45]. In this study, HAQ was significantly correlated with muscle strength index, disease activity, morning stiffness, pain and joint damage. However, when analyzing the effect of change in these predictors with change in HAQ, only muscle strength index and pain remained significantly associated, thus confirming the importance of the association of strength and, by extension, muscle mass with disability in RA.

The degree and prevalence of cachexia typically present in RA patients is alarming since it represents approximately a third of the maximal loss of body cell mass or LBM compatible with survival (40%) [30]. Additionally, as in other catabolic diseases, such muscle loss as well as causing weakness and disability is associated with impaired immune and pulmonary function, glucose intolerance, low aerobic capacity, loss of independence, depression, compromised QoL, osteoporosis and increased mortality [6,46–48].

Obesity

Muscle depletion associated with RA is generally undiagnosed (and consequently, untreated) as body composition is rarely assessed by clinicians and a concomitant increase in FM masks the decrease in muscle mass when bodyweight is measured. Thus, for a given BMI, Stavropoulos-Kalinoglou *et al.* found that RA patients had on average 4.3% more body fat (BF) than matched, healthy controls [49]. Alternatively, for a given body fat percentage, RA patients have a BMI almost 2 kg/m^2 lower than members of the general population (note: these authors have proposed that BMI cutoffs for defining 'overweight' and 'obesity' in RA patients should be reduced to 23 and 28 kg/m^2, respectively [49]). Support for this point is made by comparisons of BMI and percentage BF values reported for RA patients. The mean BMIs typically reported for RA patients (25.2–29.1 kg/m^2) [33,34,49–51] are in accord with that of the general UK population (27.1 kg/m^2) [52], suggesting that RA patients, like the rest of the population, are generally merely overweight. However, when body composition is assessed [19,33–35,37,49,53,54], RA patients are revealed to be significantly fatter than the general population, with a mean percentage BF of approximately 40% [19,33–35,37] and a prevalence of obesity (using the criteria of 38% BF or more for women and 27% BF or more for men [30]) of approximately 80% [19,33–35,37]. Using a stricter criterion, Elkan *et al.* found that 33% of women and more than 50% of men with RA had a FM index above the 90th percentile for the whole population [55]. As with muscle loss, this high prevalence of obesity is evident in recently diagnosed RA patients [37], again indicating that the body composition perturbations characteristic of rheumatoid cachexia occur early in the disease.

The accumulation of FM in RA has, in part, been attributed to the chronic inflammation that characterizes the disease and in particular increases in TNF-α and the activation of the nuclear factor (NF)-κB pathway, which in turn both contribute to reduced muscle mass [21,56]. Additionally, the sedentary lifestyle typical of RA patients [57], which diminishes energy expenditure [29], also contributes to accumulation of BF [49].

Disturbingly, as well as favoring accumulation of higher total fat, RA appears to preferentially predispose to central obesity [53,54,58,59].

In the general population, obesity, and in particular central obesity, is a well-established, independent risk factor for CVD and many of the classical CVD risk factors [60,61]. Similarly, in RA patients, central obesity is linked with hypertension, elevated fasting glucose levels, metabolic syndrome [58] and arterial thickening and stiffening [59]. As there is an increased risk of CVD in RA patients, with rates of both CVD events and mortality increased approximately 50% relative to non-RA controls [62,63], one would assume that loss of fat, particularly centrally, would be highly beneficial for the cardiovascular health of this population.

Treatments for rheumatoid cachexia

Clearly, interventions successful in reversing cachexia in RA patients (i.e., increasing muscle mass and decreasing FM, especially trunk FM) have the potential to improve physical function and thus decrease disability, prolong independence, improve QoL, reduce comorbidities and perhaps increase life expectancy. Such an intervention would also significantly reduce the huge economic impact of RA (half of which results from production losses caused by functional impairment [64]). Several anabolic agents, such as recombinant human growth hormone and androgens, have been proposed for increasing muscle mass in sarcopenic/cachectic states [65–69]. However, growth hormone therapy is expensive and may cause carpal tunnel syndrome and insulin resistance, whilst anabolic steroids are associated with side effects such as liver disorders, masculinization in women and prostate cancer and testicular atrophy in men [68–71]. Furthermore, when used alone, despite increasing lean mass, these drugs often fail to improve physical function [65,67,68,72]. Consistent with these findings are the findings of an unpublished randomized controlled trial conducted in our laboratory, in which nandrolone decanoate, an anabolic steroid, was administered (intramuscular injection, 100 mg/week) for 6 months to 20 male RA patients with stable disease [Elamanchi SR *et al.*, Manuscript in Preparation]. Whilst nandrolone decanoate treatment increased mean ALM by approximately 1.5 kg in these patients, objective measures of physical function showed no improvement.

As rheumatoid cachexia has been attributed to cytokine (principally TNF-α)-driven muscle catabolism by the Roubenoff group [27,29,73], it would be anticipated that treatment with anti-TNF drugs could restore a healthier body composition phenotype to RA patients. However, Marcora *et al.* found that treatment of recently diagnosed RA patients for 6 months with etanercept (an anti-TNF agent) had no effect on body composition relative to treatment with methotrexate ('standard' DMARD) [37]. This lack of effect of anti-TNFs on LBM in RA patients has subsequently been confirmed by Metsios *et al.* [74]. Of concern was their observation of increased trunk fat in this sample of established RA patients following 3 months on anti-TNFs [74]. These findings are further supported by a recent report, which observed increased FM in recent-onset RA patients treated with anti-TNFs for 21 months relative to DMARD-treated patients (mean ± standard deviation [SD]: $+3.4 \pm 1.4$ kg; $p < 0.05$) and no changes in LBM for either treatment [75].

Osteoporosis

Another feature of RA is secondary osteoporosis. RA patients have greater incidence of osteoporosis and osteoporotic fractures than matched non-RA controls [76–82], with this increase attributed to the disease itself (systemic inflammation), treatment with high-dose oral glucocorticoids and sedentary lifestyle [80–83]. Low BMD in RA patients typically occurs at the hip, femoral neck and distal forearm, although apparently not the spine [44,80]. In addition, after high-dose steroid therapy, this diminished BMD in RA patients has been found to be most strongly associated with low strength (quadriceps and handgrip) and poor physical function [44,80,84].

Efficacy of PRT

The most, perhaps the only, effective, safe and economical intervention known to increase both muscle and bone mass and also improve physical performance in subjects of various ages is PRT [85].

Effects on function

The efficacy of PRT for improving strength in RA patients (Table 1) was first demonstrated by Machover and Sapecky in 1966 [86]. In this pioneering study, 11 male RA patients performed maximal isometric contractions of the quadriceps three times a day, 5 days a week for 7 weeks, for an average strength gain of 23%. Since then, significant improvements in strength in RA patients have been elicited by a variety of resistance-training regimes [33,35,87–104], the only exception identified being the home-based intervention of Komatireddy *et al.* [105].

Table 1. Summary of interventions and effects of resistance training programs.

Intervention group† (n)	Exercise type	Training frequency and duration	Maximum intensity‡ (%)	Volume (sets/reps)	Control	Strength	Function	Body composition	Disease activity	Ref.
17	RT + aerobic + balance	2/week, 6 weeks			RCT ROM, isom	↑	↑		↔↓	[89]
30	Hand RT	14/week, 12 weeks			RCT ROM, NC	↑	↑		↓	[90]
21	PRT	2–3/week, 6 months	70–80	3 sets of 6–12 reps	RCT NC	↑	↑	↑LM*	↓	[91,96]
25	PRT + aerobic + circuits	3/week, 12 weeks			RCT ROM, isom	↑	↑		↔	[94]
25	PRT	3/week, 12 weeks	'Low intensity'	2–3 sets of 12–15 reps	RCT NC	↔	↑		↓	[105]
17	Leg PRT	14 sessions, 6 weeks	70	4 sets of 5 reps	RCT NC	↑	↑			[95]
32	PRT	2/week, 24 months	50–70	2 sets of 8–12 reps	RCT ROM	↑	↑		↓	[97,98,100,101]
34	PRT + aerobic	5/week, 4 weeks			RCT ROM, isom	↑	↑		↓	[103]
150	RT + aerobic	2/week, 24 months		8–15 reps	RCT NC	↑	↑		↔	[104,138]
13	PRT	2/week, 24 weeks	80	3 sets of 8 reps	RCT ROM	↑	↑	↑LM, ↓FM	↔	[35]
11	Unilateral leg isometric RT	15/week, 7 weeks	100	3 reps	Contralateral leg	↑			↔	[86]
10	Leg RT + aerobic	5/week, 6 weeks				↑	↑	↑ fiber x-sect area	↔	[87]
23	Leg RT + aerobic	1/fortnight, 4–8 years			RA	↑	↑		↓	[88]
9	PRT; isom	3/week, 3 weeks for each leg	50	48 reps; 24 reps		↑	↑		↔	[92]
8	PRT	2/week, 12 weeks	80	3 sets of 8 reps	HC	↑	↑	↔	↔	[93]
23	PRT + aerobic	3/fortnight, 21 weeks	50–80	4–6 sets of 3–12 reps	HC	↑	↑		↔	[99]
23	PRT + aerobic	3/fortnight, 21 weeks	50–80	3–5 sets of 5–12 reps	HC	↑	↑	↑LM*, ↓FM*	↔	[102]
10	PRT	3/week, 12 weeks	80	3 sets of 8 reps	RA	↑	↑	↑LM, ↓FM	↔	[33]

†Exercise group or, if multiple exercise groups, the highest intensity exercise group.
‡Percentage of one-repetition maximum.
↑: Improved strength/function; ↔: No change; ↓: Decreased disease activity; ↑ fiber x-sect area: Increase in vastus lateralis fiber cross-sectional area; ↓FM: Decreased total/trunk fat mass; ↓FM: Decreased quadriceps subcutaneous fat; ↑LM: Increased total lean mass; ↑LM*: Increased quadriceps lean mass; Aerobic: Aerobic training such as cycling, walking or swimming; Balance: Balance training; HC: Healthy controls; isom: Isometric strength exercises; NC: Normal care; PRT: Progressive resistance training; RA: Nonrandomized rheumatoid arthritis patients; RCT: Randomized controlled trial; reps: Repetitions; ROM: Range of movement exercises; RT: Resistance training.*

Consistent with the increases in strength are reports of improved physical function assessed objectively (e.g., walk tests, stair climbing, bench stepping, balance/coordination, hand-grip strength, timed up-and-go test, vertical jump, 30-s arm curl test, chair test and aerobic capacity) [33,35,87–95,97,99,101–103,105] and subjectively (e.g., 100-point truth-value scale, study-generated questionnaire, self-reported fatigue, HAQ, McMaster Toronto Arthritis [MACTAR] Patient Preference Disability Questionnaire) [33,89,91,92,95,98,101,103,105] (Table 1). However, it is notable that improvements in physical function following resistance training are usually not observed when function is subjectively measured by the HAQ [35,94,97,99,100,102,104]. The general inability of HAQ scores to reflect objectively assessed improvements in physical function is probably due to the insensitivity of this instrument in detecting performance gains in mildly disabled patients (i.e., the type of patient that typically volunteers for exercise intervention studies). This lack of sensitivity is best illustrated by results of the Rheumatoid Arthritis Patients in Training (RAPIT) program, which showed improvements in subjects in the high-intensity exercise groups when physical function was assessed subjectively by the MACTAR Questionnaire, but not when measured by the HAQ [104]. The unsuitability of the HAQ for detecting improvements in function following short-term exercise therapy has been highlighted by van den Ende *et al.*, who instead advocate objective measures related to performing activities of daily living as measures of efficacy [106].

Although only 14 of the 22 studies highlighted were randomized controlled trials (RCTs) [35,89–91,94–98,100,101,103–105] and, of these, only ten applied the principle of progression to their training programs (i.e., increasing the stress placed on the body as adaptations to training are made, thus ensuring maintenance of relative training intensity) [35,91,94,96–98,100,101,104,105], as concluded by the two *Cochrane Reviews* conducted to date, the effectiveness of resistance training programs in improving strength and physical function in RA patients is clear [8,9]. In fact, with appropriate training, it is not unreasonable to expect that patients with established, controlled RA can achieve physical function levels at least as good as sedentary, healthy individuals of the same age and sex. In the RCT conducted by our group, patients with established RA (11 women, two men; age 55.6 ± 8.3 years; disease duration 74 ± 76 months) whose objectively measured physical function was impaired relative to population norms at baseline, were able to achieve or exceed these performance norms following 24 weeks of high-intensity PRT [35]. Restoration of normal levels of strength and function in RA patients following PRT was also seen in our earlier pilot study [33] and in the studies by Hakkinen *et al.*, which featured healthy age- and sex-matched control subjects [99,102]. In a point that will be pursued later, it is notable that the only RCT that did not report significant increases in strength in RA patients following resistance training utilized a very low training intensity [105].

Effects on rheumatoid cachexia (body composition)

The effects of PRT on body composition in RA are less well reported (Table 1). In 1976, Nordemar *et al.* described increases in cross-sectional area of type I and especially type II fibers following 6 weeks of cycling, walking and quadriceps strength training in ten RA patients [87]. Consistent with this, Hakkinen *et al.* observed increased quadricep muscle cross-sectional area in RA patients following 6 months of PRT [91]. However, when Rall *et al.* reported no changes in whole-body composition by DXA in eight RA subjects following 12 weeks of PRT (despite significant improvements in strength), the fear was that RA patients are resistant to the anabolic effects of exercise [93]. This concern has subsequently been refuted by methodologically more robust trials. Initially, we reported significant increases in (DXA-assessed) LBM, ALM and estimated total body protein and reductions in percentage BF, with a trend toward reduced trunk fat (-0.75 kg) following 12 weeks of high-intensity PRT [33]. Subsequently, these effects were confirmed by our RCT [35]; LBM, ALM (~1.2 kg) and total body protein were all significantly increased ($p = 0.002–0.006$) and total and especially trunk FM (-2.5 kg; i.e., 18%) were substantially reduced following 24 weeks of PRT. Hakkinen *et al.* similarly observed hypertrophy of the quadriceps femoris ($p < 0.001$) and decrements in quadricep subcutaneous fat thickness ($p < 0.001$) in female RA patients who had completed 21 weeks of combined PRT and aerobic training [102].

Whilst aerobic exercise training, by increasing daily energy expenditure, has been shown to be an effective adjunct to restricted energy intake for weight loss in young adults, its efficacy in middle-aged and elderly individuals is questioned. This is because sedentary individuals of this age are usually so deconditioned that they are unable to perform exercise of sufficient intensity and duration to substantially augment energy expenditure [107]. By contrast, in elderly men and women an elevation of approximately 15% in resting metabolic rate (RMR) has been observed as a consequence of increased LBM following 12 weeks of PRT [108]. An increase in RMR of this magnitude is very relevant as RMR typically accounts for 60–75% of daily energy expenditure.

In our PRT studies, the elicited increases in muscle mass were significantly associated with improvements in objectively assessed physical function (i.e., 30-s arm curl, 30-s sit-to-stand, 50-foot walk, hand-grip strength and knee extensor strength; tests taken from the Senior Fitness Test [109] and designed to reflect the ability to perform ADLs) [33,35]. Interestingly, the increased muscle mass and reduced FM in the PRT subjects in our RCT caused a reclassification of the body types of many of these patients [35]. Whereas at baseline, nine out of 13 were classified as cachectic, ten as obese and five as both (i.e., 'cachectic obese'), after 24 weeks of PRT the number of patients in these disability-high-risk classifications were reduced to four, seven and two, respectively [20]. Given the reported links between adverse body composition and physical disability in RA patients [18] and the general elderly population [20], the positive effects of PRT on function in RA patients are anticipated. To emphasize the crucial role played by training intensity, in our RCT range-of-movement (ROM) exercises (i.e., the form of exercise most commonly prescribed for RA patients) were performed by the control group [35]. Despite good compliance to the intervention, this low-intensity exercise failed to have any effects on body composition or objective measures of physical function.

Mechanisms of rheumatoid cachexia

As mentioned earlier, the precise mechanisms underlying rheumatoid cachexia have not been clarified. However, additional insight was provided by the RCT by Lemmey *et al.* [35]. In this study diminished muscle levels of IGF-I (mIGF-I) were identified in (mostly cachectic) RA patients. This finding is consistent with reports of reduced mIGF-I levels in other conditions characterized by muscle wasting: chronic renal failure [110,111], chronic obstructive pulmonary disease [112], chronic heart failure [113] and advanced aging [114]; and with the proposed role of mIGF-I in regulating both the maintenance of adult skeletal muscle and its hypertrophic response to loading [115]. Following 24 weeks of PRT, along with muscle hypertrophy, mIGF-I levels were observed to increase 50% in our RA patients. Again, this finding of coincident increases in mIGF-I levels and muscle mass in cachectic individuals following exercise training is consistent with responses in dialysis [111] and chronic obstructive pulmonary disease patients [112] and the frail elderly [114].

Effects on bone

The importance of weight-bearing and strengthening exercise in maximizing and maintaining BMD and reducing the risk of falling by increasing strength and improving balance is well accepted in the general population [7]. With specific regard to RA, a sedentary lifestyle confers a relative risk of 1.6 for low BMD in RA patients and even moderate physical activity by RA patients has been found to reduce the risk of osteopenia by 50% [116]. Additionally, de Jong *et al.* showed that RA patients participating in the 2-year, high-intensity RAPIT exercise program had reduced bone loss at the hip (median -1.1 vs -1.9% for nonexercising controls; $p = 0.026$), although not in the lumbar spine (median +0.9 vs +0.9% for controls; $p = 0.697$) [117]. Further analysis of these data revealed that the changes in BMD were significantly and independently associated with changes in strength and aerobic power and that exercise training had a benefit comparable to that of biphosphonate treatment. This led the investigators to conclude that intense weight-bearing exercise, including PRT, is essential for improving BMD in RA patients [117]. Similar conclusions were made by Hakkinen *et al.* following their RCT [97,98,101]. In this trial, 12 months of PRT by RA patients resulted in mean BMD gains of +1.10% at the femoral head and +0.19% at the lumbar spine in contrast to respective losses of -0.03 and -1.14% in the ROM controls [97]. Following a further 12 months of PRT, the mean differences between the groups increased with the changes in BMD at the femoral head and the lumbar spine now being +0.51 and +1.17%, respectively, for the training group and -0.70 and -0.91% for the controls [98]. These observed trends in BMD were noted again at a 3-year follow-up [101]. Whilst the differences between the groups were not statistically significant, except for at the femoral head at 24 months ($p = 0.024$), it was suggested by the authors that such an effect would be substantial and of clinical significance if training was prolonged and its impact on BMD given longer to accrue.

Treatments for osteopenia or osteoporosis are judged on their ability to increase BMD or, more likely, to minimize bone loss. Thus, although evidence in RA patients is limited, PRT appears to be as efficacious in this population as it is generally [118–120].

In RCTs conducted to evaluate the effect of PRT on BMD in the general population, the evidence is compelling that intensity (i.e., loading) is the key variable [121]. This is consistent with Wolff's law, which states that the magnitude of the stress or mechanical load applied to bone via muscles and tendons directly determines the osteogenic response of the bone [122]. The results of Kerr *et al.* serve to illustrate this [123]. In this investigation, postmenopausal women (aged 51–62 years) were randomized to either high-intensity 'strength' PRT (high load, low repetitions; i.e., three sets of eight repetitions) or low-intensity 'endurance' PRT (low load, high repetitions; i.e., three sets of 20 repetitions). After training three times a week for 12 months, the high-intensity group had increased femoral head and distal radial BMD significantly more than the low-intensity group, with the site-specific gains in BMD significantly correlated to the site-specific strength increases. In non-RA, post-surgery patients, strength training has also been shown to be effective in countering glucocorticoid-induced bone loss [124]. However, as for the general population, the greatest benefit of PRT in reducing osteoporotic fractures in RA patents is likely to be due to the lowered incidence of falling as a consequence of improvements in strength and balance [118,121,125,126]. With regards to the suitability of high-intensity PRT for individuals with low BMD, Vanderhoek *et al.* specifically chose osteopenic or osteoporotic elderly women (mean ± SD; age = 69.0 ± 1.3 years) for 32 weeks of PRT in which they performed three sets of eight repetitions at 75–80% of one repetition maximum (1-RM; i.e., the maximum load that can be correctly lifted for a given exercise) for each exercise [126]. As anticipated, this high-intensity PRT resulted in substantial improvements in strength and balance, changes which interestingly were correlated. More importantly, it also proved to be safe and well tolerated with no compression fractures or other training-related injuries reported.

Responsiveness of RA patients to PRT

In terms of the magnitude of effects of PRT on strength and body composition typically observed in RA patients, these are similar to those generally reported for healthy middle-aged or older subjects [127–130]. The study by Hakkinen *et al.* described previously provides a direct comparison of training response. They identified comparable strength increases and similar body composition changes (with regard to both absolute and relative increases in quadriceps femoris cross-section and reductions in quadriceps femoris subcutaneous fat thickness) in female RA patients and age-matched healthy women following completion of the same combined resistance and aerobic exercise training program [102]. This similarity in training response is consistent with recent reports that muscle quality is unaffected by RA [131,132]. In these reports, a range of skeletal muscle parameters (e.g., specific force, muscle architecture, coactivation of antagonist muscles and voluntary activation capacity) were observed to be the same for well-controlled RA patients as for their matched healthy counterparts. Consequently, it was concluded that even in cachectic patients there is no effect of RA on muscle quality (muscle force per size) [131]. This finding that rheumatoid muscle is normal both qualitatively and in its response to resistance training is important for health professionals involved in prescribing exercise for people with RA.

Safety of PRT for RA patients

For many years, intensive weight-bearing exercise was considered inappropriate for RA patients due to concern that the increased stress on joints would exacerbate disease activity, pain and joint damage [92–94] and consequently patients were warned against such activities [133]. Even today, many rheumatologists and their multidisciplinary teams retain these anachronistic beliefs and advise their patients to avoid strenuous physical pursuits, in order to protect their joints and conserve their energy (i.e., the strategy of 'pacing') [134,135]. However, there is no evidence to support this outlook. In fact the literature is astonishingly unanimous in its findings that exercise training, including resistance training (Table 1), irrespective of the intensity employed, is safe in RA patients. And although most studies report no changes in disease activity following resistance training, findings of improvements are not uncommon, such as reductions in: number of tender and swollen joints (Ritchie articular index) [89,91,94,96], self-reported joint count [105], morning stiffness [89], pain [93,95,105], erythrocyte sedimentation rate [91,96,97] and disease activity score (DAS; DAS28 and DAS4) [97,98,101]. Intensive exercise even appears to be safe in patients with active disease. Van den Ende *et al.* randomly allocated RA patients admitted for disease flares to either an intense exercise group (which included isokinetic and isometric strength training) or a control group (who only performed ROM and isometric exercises [103]). After 24 weeks of training (three times/week), an improvement in DAS was observed in both groups with a trend toward greater improvement for the intense exercise group.

Prolonged training studies also give no cause for concern. Hakkinen *et al.*, in an RCT comparing home-based strength training to conventional physiotherapy (ROM exercises) over 2 years, found that DAS28 improved significantly for both groups, with the benefit more pronounced for the strength-training group [98]. Similarly, de Jong *et al.* in their 2-year RCT (the RAPIT trial) also found decreases in disease activity (DAS4) in both the intense exercise (including strength training) group and the 'usual care' control group [104], albeit this time with no difference between the groups.

In a broader investigation of the immune responses to PRT in RA patients, Rall *et al.* found no effects on stimulated production of TNF-α, IL-1β, IL-2, IL-6 or prostaglandin E_2, nor on peripheral blood mononuclear cell subpopulations or delayed hypersensitivity skin response, following 12 weeks of high-intensity training [136].

Although reassuring effects on joint counts, systemic inflammation, pain and more generalized disease activity are widely provided by studies of strength training interventions in RA patients, relatively few investigations have assessed the effects of training on radiographic damage of joints. One that did was the RAPIT trial. Initially, reports from this program raised concerns by suggesting that high-intensity exercise accelerated joint damage progression in large joints that had extensive pre-existing damage [104,137]. Results from an 18-month follow-up study, however, have seen the authors retract this conclusion [138]. Instead, the investigators are now confident that long-term, intense weight-bearing exercise does not exacerbate damage to the large joints, even those already extensively damaged. The same verdict had already been made with regard to the small joints of the hands and feet [104]. These conclusions are in accord with the findings of others, none of whom found radiological evidence of increased progression of joint damage following training [88,91,98,100]. In the earliest of these studies, Nordemar *et al.* found that subjects who had performed 4–8 years of training, which included strengthening exercises for the legs, actually had reduced joint damage in the lower extremities relative to nonexercising disease-matched controls [88]. In the other studies, all by Hakkinen and colleagues [91,98,100], no acceleration in joint damage was detected by x-ray in patients performing long-term, regular, high-intensity PRT relative to those receiving standard care (with or without ROM exercises) – even when the investigation period was 5 years [100].

Fundamentals of PRT prescription for RA patients

"The key factor to successful resistance training at any level of fitness or age is appropriate program design" [139], and this requires that specific needs and goals are addressed. For RA patients generally, the needs on which a PRT program should be focused are: counteracting the effects of rheumatoid cachexia by restoring muscle mass and reducing adiposity (especially central stores); improving strength and thus helping to restore function; and lowering osteoporotic fracture risk by increasing bone mass and by improving strength and balance, reducing the likelihood of falling. In specifying these aims, the intention is not to ignore the numerous generic benefits of exercise training such as reduced CVD risk, improved insulin sensitivity, decreased risk of certain cancers and enhanced mood and mental health, but to concentrate on those aspects of RA-relevant health for which PRT is particularly appropriate. Additionally, individuals may also have specific goals and these should be accounted for when designing the training program. Since untrained individuals will readily respond physiologically to most protocols, it is unnecessary to devise complicated or sophisticated programs, such as one might do for elite athletes.

To maximize the health and performance benefits and to best ensure safety, it is important that suitably qualified professionals are involved in designing the PRT program and, for the initial weeks at least, in supervising training. The training recommendations about to be made are all consistent with guidelines provided by the ACR [1,202], EULAR [2], ACSM [3–5,7] and AHA [6] either for RA specifically or for the comorbid conditions common in RA and by the WHO [201] "for promoting and maintaining health" in the general population. As with most exercise programs, these guidelines are based on the FITT principle: frequency, intensity, time (or volume) and type (or modality) [140].

Frequency

The general recommendation for strength training is to train 2–3 days a week with at least 48-h rest between sessions [107,139,141]. Training on alternate days is important, particularly for untrained and/or elderly individuals, to allow adequate time for recovery and adaptation [142]. Whilst there are benefits in performing PRT more frequently (e.g., daily) for highly trained individuals, for the previously untrained there is insufficient training benefit to justify the reduction in recovery time and the additional time commitment [143–145]. For example, Demichele *et al.* found that training twice a week elicited 80–90% of the strength gains achieved by training more frequently [143]. In addition to facilitating recovery, limiting PRT sessions to two or three times per week should also enhance adherence to the training program, as time constraint (i.e., 'insufficient time') is a common reason for not commencing or dropping out of structured exercise programs [146].

Once the effects of PRT have been established (after 8–12 weeks of training), it appears that training benefits can be maintained by training once per week, perhaps even once fortnightly in healthy individuals [147,148]. Whether this frequency of maintenance training is also appropriate for RA patients is unknown.

Intensity

To maximize gains in strength and muscle hypertrophy, it is necessary to recruit the maximal number of motor units. Since the high-threshold motor units may not be activated by light-to-moderate loads, it is essential to use heavy loads to ensure activation of all motor units. Thus, maximal or near-maximal loads elicit the greatest increases in strength and muscle mass [149,150]. Additionally, bone also responds most favorably to heavy loading [122,123].

In resistance training, intensity is determined from the percentage of the 1-RM a load (weight) corresponds to. Whilst studies have shown improvements in strength and muscle mass in previously untrained subjects following training with loads of 50% 1-RM, multiple studies have shown that loads of 80% or more of 1-RM are optimal for increasing strength and inducing muscle hypertrophy [107,139,141,144,145]. For untrained subjects and clinical populations aiming to enhance strength and muscle mass, an intensity of 80% 1-RM is typically prescribed, with higher intensities generally the preserve of serious athletes. For 80% 1-RM, six to 12 repetitions or lifts are usually possible. If fewer than six repetitions can be achieved then the weight is too heavy and if more than 12 repetitions can be accomplished then the weight is too light. It should be noted that even when the relative intensity is fixed (e.g., 80% 1-RM), the maximum number of repetitions that can be performed varies for different exercises [151].

It is crucial to highlight that in untrained individuals, intensity at the commencement of PRT should start low and progress slowly to allow the musculoskeletal system time to adapt to the unaccustomed demands of training. For example, in our RCT [35], although the aim was for patients to eventually perform three sets of eight to 12 repetitions at 80% 1-RM, to reduce muscle soreness training commenced at much lower intensities. Thus, one set of 15 repetitions at 60% 1-RM was performed for each exercise in the first week, then two sets at the same intensity in the second week and three sets in the third week. Intensity was then increased to 12 repetitions per set at 70% 1-RM for weeks 4–6, before finally progressing to eight repetitions per set at 80% 1-RM for weeks 7–24 (to ensure maintenance of relative intensities, 1-RMs were reassessed every 4 weeks). By adhering to this protocol substantial training benefits were gained (e.g., mean improvement of 119% in training-specific strength), with no occurrence of training-related injuries or dropouts from the program.

Time (volume)

With PRT, training volume is generally defined as the product of: the number of exercises × the number of sets per exercise × the number of repetitions per set, performed in a training session. Thus, training volume can be manipulated by altering any of these variables. It needs to be stated that there is no 'magic number' for any of these variables; and if there was it would no doubt vary from individual to individual and vary again within an individual for each exercise performed. As intensity and volume are inversely related, increases in volume should be closely monitored to avoid risk of overtraining [141,151].

With regard to the number of exercises, to maximize muscle hypertrophy and to facilitate improvement in the performance of ADLs, resistance training should involve the whole body. Thus, six to ten exercises each involving large muscle groups are usually prescribed (e.g., leg press, chest press, leg extension, seated rowing, leg curl, triceps extensions, abdominal crunches/curls, standing calf raises and bicep curl) [33,35].

Numerous studies have tried to determine the optimal number of sets per exercise, with comparisons of all permutations from one to six sets made and no consensus achieved [152–155]. When enhanced health and general function is the object of training, for both healthy and clinical populations, two or three sets are usually prescribed [1–7,201,202]. For novice trainers, both two and three sets have been shown to be very effective in eliciting training effects, with controversy persisting as to whether performing three sets delivers substantially better returns than performing two sets [156,157]. Of recent interest is the efficacy of single-set programs. In a number of studies one set of eight to 12 repetitions performed to voluntary failure has produced training benefits in previously untrained subjects comparable to those of conventional multiple-set programs [144,145], although there is disagreement with this finding [158], particularly in trained individuals [155,159–161]. Even if single-set protocols are marginally less effective than multiple-set programs, the time efficiency of the former may result in better training compliance, as programs that require sessions lasting in excess of 1 h have been shown to have higher dropout rates [162,163]. Thus, if time constraints prevail and especially if the patient wants to additionally perform aerobic training, the use of single-set protocols should be considered as, provided the intensity is sufficient, these will certainly produce beneficial musculoskeletal, CV and endocrine responses [141].

Another variable that can be manipulated is the duration of the rest period between sets. Researchers have found that short rest periods (≤1 min) elicit greater muscle hypertrophy [155] whilst longer rest periods (2–5 min) produce superior strength gains [164–166]. These differing effects have been attributed to the extent of ATP–phosphocreatine (ATP–PC; phosphagen system) repletion [139]; hence, for maximal strength gains, complete restoration of ATP–PC is required to enable maximal lifts, whereas incomplete restoration results in metabolic, hormonal and CV responses that facilitate hypertrophy [155,167–169]. Not surprisingly, body builders favor programs that feature short rest periods, whilst strength and power athletes generally employ longer intervals. Whether these effects of rest-period duration also operate in middle-aged and elderly previously untrained exercisers is unclear. As such, and given that training benefit is unlikely to be significantly compromised but training time will be markedly reduced if short rest periods are preferred to long rest periods, allocation of 1–2-min rests between sets appears optimal.

Type (modality)

For safety, training on variable resistance machines with incremental weight stacks rather than free weights is recommended [1,170,171]. Other relevant considerations are that machines are easier and quicker to set up, whilst free weights allow more variety in the exercises utilized and are better able to simulate ADLs. As mentioned previously, an optimal PRT program will feature exercises that involve each of the major joints and muscle groups. Such whole-body programs, as well as being more effective in increasing overall strength and muscle hypertrophy, are also associated with significant improvements in aerobic capacity (VO_2 max) and endurance performance. For example, Vincent *et al.* noted that 6 months of whole-body PRT increased peak oxygen uptake by 22% and treadmill time to exhaustion by 26% in elderly (60–85 years) men and women [172]. Similarly, 10–12 weeks of high-intensity PRT has been found to improve time to exhaustion while cycling (47%), running (12%) and walking (38%) [173,174].

Exercises should be performed rhythmically, in a slow, controlled movement (~2 s to lift and approximately 4 s to lower the weight) and breathing should be continuous, to avoid a Valsalva's maneuver and the resultant rises in blood pressure (BP). When proper technique is observed, systolic BP during weight lifting is considerably lower than it is during aerobic exercise of comparable intensity and CV stress is minimal [171]. Of course, with RA patients attention to affected joints is essential and joint pain, instability, poor proprioception or reduced ROM may necessitate modification or substitution of prescribed exercises [3].

Progression

Gains in strength following commencement of PRT are usually rapid and substantial, with 10–15% increases in strength typically observed for each of the first 8 weeks of training in healthy, previously untrained individuals [107]. Initially these improvements are due to enhanced neural factors such as improved motor unit recruitment, firing rate and synchronization [175,176], with muscle hypertrophy contributing from approximately week 4 onwards [176–179]. In order to continue to achieve the maximal muscle fiber recruitment necessary for increases in strength and muscle hypertrophy to occur, progressively greater loads need to be lifted. This increase in resistance (in response to increases in strength) to maintain a constant relative intensity is termed 'progressive overload' and is a fundamental principle of all exercise training regimes.

Whilst marked responses to training are to be expected in untrained or deconditioned individuals, after an extended period of training the 'law of diminishing returns' applies, for example as an individual gets fitter and approaches his/her genetic ceiling it becomes harder to achieve further fitness gains. Consequently, when PRT is prolonged, a plateau in training response is to be expected. The usual way of dealing with this situation is to manipulate the training program variables (types of exercises, training intensity, number of sets and/or repetitions, rest period between sets), so that the body is subjected to and forced to adapt to unfamiliar training stimuli.

Exclusion criteria & further recommendations

As discussed previously, appropriately designed PRT is recommended, safe and well tolerated by males and females of all ages and most conditions, including RA [144]. In the recommendations made by the AHA regarding resistance training for patients with and without CVD [171], the contraindications to PRT are: unstable angina, uncontrolled hypertension (≥160/100 mmHg), recent and untreated episodes of congestive heart failure, uncontrolled dysrhythmias, severe stenotic or regurgitant valvular disease and hypertrophic cardiomyopathy. Additionally, for low-to-moderate risk cardiac patients wanting to participate in PRT programs, they suggest preliminary aerobic exercise training for 2–4 weeks [171]. Overall, however, they concluded that "resistance training exercise is strongly recommended for implementation in primary and secondary cardiovascular disease-prevention programs" and "…is particularly beneficial for improving the function of most cardiac, frail and elderly patients" [171]. In part, this is because increased strength attenuates the myocardial demands (i.e., heart rate and BP) when patients perform ADLs because the task now requires a lower percentage of functional capacity [180].

Caution must also be taken with prescription of PRT to severely osteoporotic patients, with high-intensity exercise to be avoided [7]. In the case of these patients, specialist advice with regard to exercise should be sought.

Despite the benign consequences of training during acute flares shown by van den Ende *et al.* [103], we discourage training during flares. Similarly, as healthy individuals should be advised, we also discourage training during illness (e.g., colds and influenza) and tell patients to only resume training when health is restored. Upon resumption of training, loads (i.e., the weight lifted) should be adjusted to account for the loss of strength due to detraining. Under these circumstances, pre-illness fitness levels are usually rapidly regained. To underline the safety of and tolerance to PRT for RA patients, in our high-intensity PRT intervention studies [33,35], mean compliance to training sessions (i.e., sessions attended as a percentage of those scheduled) was around 80%. Thus, even when advised to skip sessions when feeling unwell, patients still complete a proportion of training similar to that expected of healthy individuals.

Conclusion

This article has described common consequences of RA that are currently regularly untreated (rheumatoid cachexia; i.e., diminished muscle mass and high FM, particularly central obesity) or are still prevalent despite pharmaceutical treatment (disability, CVD and osteoporotic fractures) and provided an overview of research into the efficacy and safety of progressive resistance training in treating these conditions. The evidence strongly suggests that PRT is an appropriate adjunct therapy for RA patients. In particular, its efficacy in positively affecting body composition and physical function is almost unique, particularly when accessibility and the apparent lack of negative side effects are considered. As such, rheumatologists and other health professionals overseeing the management of RA patients should be encouraging them to undertake PRT, ideally in conjunction with aerobic training. To better inform clinicians in their exercise training advice, the fundamental principles of PRT program design have been outlined, with particular reference made to experiences with the RA population.

Future perspective

The importance of including exercise training, particularly PRT, in the routine management of RA patients is apparent to those working in the field. However, wider acceptance of the prevalence of rheumatoid cachexia and its association with disability, CVD and osteoporosis in RA patients (as in the general population) needs to be achieved for the value of interventions such as PRT to be clinically appreciated. Also awaiting completion are large cost–effectiveness studies to justify national health authorities establishing programs that encourage and facilitate RA patients to undertake prescribed exercise training.

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Executive summary

Disability, rheumatoid cachexia & osteoporosis in rheumatoid arthritis patients

- The prevalence of significant muscle loss is approximately 67% and the incidence of obesity perhaps 80% in rheumatoid arthritis (RA) patients, despite advances in controlling disease activity.
- Reduced muscle mass and increased adiposity are major causes of disability in RA patients (and the general population).
- RA patients are predisposed to central obesity, which probably contributes toward their increased cardiovascular disease risk.
- Currently prescribed NSAIDs, DMARDs and biologics are ineffective in preventing or reversing rheumatoid cachexia.
- Anabolic hormone therapy is relatively expensive, has associated risks and on its own is usually ineffective in improving physical function.
- Muscle loss and attendant reductions in muscle strength contribute to the increased osteoporosis risk in RA.

Efficacy of progressive resistance training

- Progressive resistance training (PRT) has been shown to markedly improve physical function and reduce disability in RA patients and may lower the risk of cardiovascular disease; these benefits are largely due to its beneficial effects on body composition (increasing muscle mass and decreasing fat mass).
- PRT has been shown to reduce bone loss in RA.
- In osteoporotic patients, PRT has been shown to primarily attenuate the incidence of fractures by reducing falls; this effect has not been investigated in RA patients.
- PRT and exercise generally – even when conducted long term and at high intensity – does not exacerbate disease activity or joint damage in RA patients.

Fundamentals of PRT prescription for RA patients

- A high-intensity, whole-body PRT program is recommended such as six to eight exercises featuring one to two sets of eight to 12 repetitions at 80% of one repetition maximum, with 1–2-min rests between sets, to be performed 2–3 days per week.
- The PRT should commence at a low intensity and progress slowly to allow adaptation to the demands of training. Supervision is required initially.
- Training should feature ‘progressive overload’ so that high intensity is maintained and the training effects maximized.
- Ideally, PRT should be accompanied by aerobic exercise.
- Patients should avoid training during flares or when otherwise unwell.

Conclusion

- RA patients should be made aware of the potential benefits of PRT and encouraged to seek advice on devising and performing an appropriate training program.

Bibliography

Papers of special note have been highlighted as:
▪ of interest
▪▪ of considerable interest

1 American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines: Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum.* 46, 328–346 (2002).

2 Combe B, Landewe R, Lukes C *et al.*: EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann. Rheum. Dis.* 66, 34–45 (2007).

3 American College of Sports Medicine: Exercise prescription for other clinical populations: arthritis. In: *ACSM’s Guidelines for Exercise Testing and Prescription (8th Edition).* Lippincott, Williams & Wilkins, Baltimore, MA, USA, 225–228 (2010).

4 American College of Sports Medicine: Exercise prescription for other clinical populations: cardiac disease. In: *ACSM’s Guidelines for Exercise Testing and Prescription (8th Edition).* Lippincott, Williams & Wilkins, Baltimore, MA, USA, 212–213 (2010).

5 American College of Sports Medicine: Exercise prescription for other clinical populations. In: *ACSM’s Guidelines for Exercise Testing and Prescription (8th Edition).* Lippincott, Williams & Wilkins, Baltimore, MA, USA, 248–250 (2010).

6 Williams MA, Haskell WL, Ades PA *et al.*: American Heart Association Council on Nutrition, Physical Activity, and Metabolism. Resistance exercise in individuals with and without cardiovascular disease: 2007 update. A scientific statement from the American Heart Association Council on clinical cardiology and council on nutrition, physical activity, and metabolism. *Circulation* 116, 572–584 (2007).

7 American College of Sports Medicine: Exercise prescription for other clinical populations: osteoporosis. In: *ACSM’s Guidelines for Exercise Testing and Prescription (8th Edition).* Lippincott, Williams & Wilkins, Baltimore, MA, USA, 193–203 (2010).

8 Hurkmans E, van der Giesen FJ, Vliet Vlieland TPM, Schoones J, van den Ende ECHM: Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. *Cochrane Database Syst. Rev.* 4, CD006853 (2009).

9 van den Ende ECHM, Vliet Vlieland TPM, Munneke M, Hazes JMW: Dynamic exercise therapy for treating rheumatoid arthritis. *Cochrane Database Syst. Rev.* 2, CD000322 (2000).

10 Lunt M, Watson KD, Dixon WG, Symmons DPM, Hyrich KL: No evidence of association between anti-tumor necrosis factor treatment and mortality in patients with rheumatoid arthritis. Results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum.* 62(11), 3145–3153 (2010).

11 Mau W, Bommann M, Weber H, Weidemann HF, Hecker H, Raspe HH: Prediction of permanent work disability in a follow-up study of early rheumatoid arthritis: results of a tree structured analysis using RECPAM. *Br. J. Rheumatol.* 35, 652–659 (1996).

12 Verstappen SM, Bijlsma JW, Verkleij H *et al.*; on behalf of the Utrecht Rheumatoid Arthritis Cohort Study Group: Overview of work disability in rheumatoid arthritis patients as observed in cross-sectional and longitudinal surveys (review). *Arthritis Rheum.* 51, 488–497 (2004).

13 Yelin E: The costs of rheumatoid arthritis: absolute, incremental, and marginal estimates. *J. Rheumatol.* 44(Suppl.), 47–51 (1996).

14 Allaire S, Wolfe F, Niu J, Lavalley MP: Contemporary prevalence and incidence of work disability associated with rheumatoid arthritis in the US. *Arthritis Rheum.* 59(4), 474–480 (2008).

15 Eberhardt K, Larsson BM, Nived K, Lindqvist E: Work disability in rheumatoid arthritis: development over 15 years and evaluation of predictive factors over time. *J. Rheumatol.* 34, 481–487 (2007).

16 Escalante A, del Rincon I: How much disability in rheumatoid arthritis is explained by rheumatoid arthritis? *Arthritis Rheum.* 42(8), 1712–1721 (1999).

17 Escalante A, del Rincon I: The disablement process in rheumatoid arthritis. *Arthritis Rheum.* 47(3), 333–342 (2002).

18 Giles JT, Bartlett SJ, Andersen RE, Fontaine KR, Bathon JM: Association of body composition with disability in rheumatoid arthritis: impact of appendicular fat and lean tissue mass. *Arthritis Rheum.* 59(10), 1407–1415 (2008).

▪ **In a study investigating multiple causes of disability in rheumatoid arthritis (RA), the authors show the importance of rheumatoid cachexia (i.e., decreased muscle mass and increased fat mass) as a contributing factor.**

19 Stavropoulos-Kalinoglou A, Metsios G, Panoulas VF *et al.*: Underweight and obese states both associate with worse disease activity and physical function in patients with established rheumatoid arthritis. *Clin. Rheumatol.* 28, 439–444 (2009).

20 Morley JE, Baumgartner RN, Roubenoff R, Mayer J, Nair KS: From the Chicago meetings: sarcopenia. *J. Lab. Clin. Med.* 137, 231–243 (2001).

21 Roubenoff R, Roubenoff RA, Ward LM, Holland SM, Hellmann DB: Rheumatoid cachexia: depletion of lean body mass in rheumatoid arthritis. Possible association with tumor necrosis factor. *J. Rheumatol.* 19, 1505–1510 (1992).

22 Pajet J: Nervous mimicry of organic diseases. *Lancet* 2, 727–729 (1873).

23 Summers GD, Deighton CM, Rennie MJ, Booth AH: Rheumatoid cachexia: a clinical perspective. *Rheumatology (Oxford)* 47, 1124–1131 (2008).

24 Rall LC, Roubenoff R: Body composition, metabolism, and resistance exercise in patients with rheumatoid arthritis. *Arthritis Care Res.* 9, 151–156 (1996)

25 Rall LC, Roubenoff R: Rheumatoid cachexia: metabolic abnormalities, mechanisms and interventions. *Rheumatology (Oxford)* 43, 1219–1223 (2004).

26 Rall LC, Walsmith JM, Snydman L *et al.*: Cachexia in rheumatoid arthritis is not explained by decreased growth hormone secretion. *Arthritis Rheum.* 46, 2574–2577 (2002).

27 Roubenoff R, Roubenoff RA, Cannon JG *et al.*: Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. *J. Clin. Invest.* 93, 2379–2386 (1994).

28 Roubenoff R: Sarcopenic obesity: does muscle loss cause fat gain? Lessons from rheumatoid arthritis and osteoarthritis. *Ann. NY Acad. Sci.* 904, 553–557 (2000).

29 Roubenoff R, Walsmith J, Lundgren N, Snydman L, Dolnikowski G, Roberts S: Low physical activity reduces total energy expenditure in women with rheumatoid arthritis: implications for dietary intake recommendations. *Am. J. Clin. Nutr.* 76, 774–779 (2002).

30 Walsmith J, Roubenoff R: Cachexia in rheumatoid arthritis. *Int. J. Cardiol.* 85, 89–99 (2002).

31 Walsmith J, Abad L, Kehayias J, Roubenoff R: Tumor necrosis factor-α production is associated with less body cell mass in women with rheumatoid arthritis. *J. Rheumatol.* 31, 23–29 (2004).

32 Munro R, Capell H: Prevalence of low body mass in rheumatoid arthritis: association with the acute phase response. *Ann. Rheum. Dis.* 56, 326–329 (1997).

33 Marcora SM, Lemmey AB, Maddison PJ: Can progressive resistance training reverse cachexia in patients with rheumatoid arthritis? Results of a pilot study. *J. Rheumatol.* 32, 1031–1039 (2005).

▪▪ **Demonstrates that total lean mass increases in response to progressive resistance training (PRT), thus refuting the belief that RA patients are resistant to the anabolic effects of exercise. Also shows that RA disability is negatively associated with muscle mass.**

34 Marcora SM, Lemmey AB, Maddison PJ: Dietary treatment of rheumatoid cachexia with β-hydroxy-β-methylbutyrate, glutamine and arginine: a randomised controlled trial. *Clin. Nutr.* 24, 442–454 (2005).

35 Lemmey AB, Marcora SM, Chester K, Wilson S, Casanova F, Maddison PJ: Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomised controlled trial. *Arthritis Rheum.* 61, 1726–1734 (2009).

▪▪ **First randomized controlled trial (RCT) to show that muscle mass is increased in RA patients following exercise. In addition, provides evidence that muscle IGF-I levels are involved in muscle loss and hypertrophy in RA.**

36 Baumgartner RN, Koehler KM, Gallagher D *et al.*: Epidemiology of sarcopenia among the elderly in New Mexico. *Am. J. Epidemiol.* 147, 755–763 (1999).

37 Marcora SM, Chester KR, Mittal G, Lemmey AB, Maddison PJ: Randomised Phase 2 trial of anti-tumor necrosis factor therapy for cachexia in patients with early rheumatoid arthritis. *Am. J. Clin. Nutr.* 84, 1463–1472 (2006).

38 Tiselius P: Studies on joint temperature, joint stiffness and muscle weakness in rheumatoid arthritis: an experimental and clinical investigation. *Acta Rheumatol. Scand.* 14, 70–98 (1969).

39 Ekblom B, Lovgren O, Alderin M, Fridstrom M, Satterstrom G: Physical performance in patients with rheumatoid arthritis. *Scand. J. Rheumatol.* 3, 121–125 (1974).

40 Nordesjo LO, Nordgren B, Wigren A, Kolstad K: Isometric strength and endurance in patients with severe rheumatoid arthritis or osteoarthritis in knee joints. *Scand. J. Rheumatol.* 12, 152–156 (1983).

41 Ekdahl C, Andersson SI, Svensson B: Muscle function of the lower extremities in rheumatoid arthritis and osteoarthritis: a descriptive study of patients in a primary care district. *J. Clin. Epidemiol.* 42, 947–954 (1989).

42 Ekdahl C, Broman G: Muscle strength, endurance, and aerobic capacity in rheumatoid arthritis patients: a comparative study with healthy subjects. *Ann. Rheum. Dis.* 51, 35–40 (1992).

43 Hakkinen A, Hannonen P, Hakkinen K: Muscle strength in healthy people and in patients suffering from recent-onset inflammatory arthritis. *Br. J. Rheumatol.* 34, 355–360 (1995).

44 Madsen OR, Egsmose C, Hansen B, Sorensen OH: Soft tissue composition, quadriceps strength, bone quality and bone mass in rheumatoid arthritis. *Clin. Exp. Rheumatol.* 16, 27–32 (1998).

45 Stucki G, Bruhlmann S, Stucki S, Michel BA: Isometric muscle strength is an indicator of self-reported physical functional disability in patients with rheumatoid arthritis. *Br. J. Rheumatol.* 37, 643–648 (1998).

46 Kotler DP: Cachexia. *Ann. Intern. Med.* 133, 622–634 (2000).

47 Svenson KL, Pollare T, Lithell H, Hallgren R: Impaired glucose handling in active rheumatoid arthritis: relationship to peripheral insulin resistance. *Metabolism* 37, 125–130 (1988).

48 Sambrook PN, Spector TD, Seeman E *et al.*: Osteoporosis in rheumatoid arthritis. A monozygotic co-twin control study. *Arthritis Rheum.* 38, 806–809 (1995).

49 Stavropoulos-Kalinoglou A, Metsios G, Koutedakis Y *et al.*: Redefining overweight and obesity in rheumatoid arthritis patients. *Ann. Rheum. Dis.* 66, 1316–1321 (2007).

50 Gordon MM, Thomson EA, Madhok R, Capell HA: Can intervention modify adverse lifestyle variables in a rheumatoid population? Results of a pilot study. *Ann. Rheum. Dis.* 61, 66–69 (2002).

51 Saravana S, Gillott T: Ischaemic heart disease in rheumatoid arthritis patients. *Rheumatology (Oxford)* 43, 113–114 (2004).

52 Craig R, Mindell J, Hirani V: *Health Survey for England 2008 Volume 1. Physical Activity and Fitness*. The Health and Social Care Information Centre, London, UK (2009).

53 Westhovens R, Nijs J, Taelman V, Dequeker J: Body composition in rheumatoid arthritis. *Br. J. Rheumatol.* 36, 444–448 (1997).

54 Elkan AC, Engvall IL, Cederholm T, Hafstrom I: Rheumatoid cachexia, central obesity and malnutrition in patients with low-active rheumatoid arthritis: feasibility of anthropometry, Mini Nutritional Assessment and body composition techniques. *Eur. J. Nutr.* 48, 315–322 (2009).

55 Elkan AC, Hakansson N, Frostegard J, Cederholm T, Hafstrom I: Rheumatoid cachexia is associated with dyslipidemia and low levels of atheroprotective natural antibodies against phosphorylchlorine but not with dietary fat in patients with rheumatoid arthritis: a cross sectional study. *Arthritis Res. Ther.* 11, R37 (2009).

56 Stavropoulos-Kalinoglou A, Metsios G, Panoulas VF *et al.*: New resting energy expenditure prediction equations for patients with rheumatoid arthritis. *Rheumatology (Oxford)* 47, 500–506 (2008).

57 Sokka T, Hakkinen A, Kautiainen H *et al.*: Physical inactivity in patients with rheumatoid arthritis: data from twenty-one countries in a cross-sectional, international study. *Arthritis Rheum.* 59, 42–50 (2008).

58 Giles JT, Allison M, Blumenthal RS *et al.*: Abdominal adiposity in rheumatoid arthritis. Association with cardiometabolic risk factors and disease characteristics. *Arthritis Rheum.* 62, 3173–3182 (2010).

59 Inaba M, Tanaka K, Goto H *et al.*: Independent association of increased trunk fat with increased arterial stiffening in postmenopausal patients with rheumatoid arthritis. *J. Rheumatol.* 34, 290–295 (2007).

60 Rosito GA, Massaro JM, Hoffmann U *et al.*: Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. *Circulation* 117, 605–613 (2008).

61 Mahabadi AA, Massaro JM, Rosito GA *et al.*: Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham Heart Study. *Eur. Heart J.* 30, 850–856 (2009).

62 Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D: Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum.* 59, 1690–1697 (2008).

63 Naranjo A, Sokka T, Descalzo MA *et al.*: Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. *Arthritis Res. Ther.* 10, R30 (2008).

64 McIntosh E: The cost of rheumatoid arthritis. *Br. J. Rheumatol.* 35, 781–790 (1996).

65 Bross R, Javanbakht M, Bhasin S: Anabolic interventions for aging-associated sarcopenia. *J. Clin. Endocrinol. Metab.* 84, 3420–3430 (1999).

66 Welle S: Growth hormone and insulin-like growth factor-I as anabolic agents. *Curr. Opin. Clin. Nutr. Metabol. Care* 1, 257–262 (1998).

67 Johansen KL, Painter PL, Sakkas GK, Gordon P, Doyle J, Shubert T: Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: A randomized, controlled trial. *J. Am. Soc. Nephrol.* 17, 2307–2314 (2006).

68 Macdonald JH, Marcora SM, Jibani MM, Kumwenda MJ, Ahmed W, Lemmey AB: Nandrolone decanoate as anabolic therapy in chronic kidney disease: a randomised phase II dose finding study. *Nephron Clin. Prac.* 106, 125–135 (2007).

69 Johansen KL, Mulligan K, Schambelan M: Anabolic effects of nandrolone decanoate in patients receiving dialysis: a randomized controlled trial. *JAMA* 281, 1275–1281 (1999).

70 Bhasin S: Testosterone supplementation for aging-associated sarcopenia. *J. Gerontol. A Biol. Sci. Med. Sci.* 58, 1002–1008 (2003).

71 Korkia P, Stimson GV: Indications of prevalence, practice and effects of anabolic steroid use in Great Britain. *Int. J. Sports Med.* 18, 557–562 (1997).

72 Rodriguez-Arnao J, Jabbar A, Fulcher K, Besser GM, Ross RJ: Effects of growth hormone replacement on physical performance and body composition in GH deficient adults. *Clin. Endocrinol.* 51, 53–60 (1999).

73 Rall LC, Rosen CJ, Dolnikowski G *et al.*: Protein metabolism in rheumatoid arthritis and aging. Effects of muscle strength training and tumor necrosis factor α. *Arthritis Rheum.* 39, 1115–1124 (1996).

74 Metsios GS, Stavropoulos-Kalinoglou A, Douglas KM *et al.*: Blockade of tumor necrosis factor alpha in rheumatoid arthritis: effects on components of rheumatoid cachexia. *Rheumatology* 46, 1824–1827 (2007).

75 Engvall I-L, Trengstrand B, Brismar K, Hafstrom I: Infliximab therapy increases body fat mass in early rheumatoid arthritis independently of changes in disease activity and levels of leptin and adiponectin: a randomised study over 21 months. *Arthritis Res. Ther.* 12, R197 (2010).

76 Laan RF, Buijs WC, Verbeek AL *et al.*: Bone mineral density in patients with recent onset rheumatoid arthritis: influence of disease activity and functional capacity. *Ann. Rheum. Dis.* 52, 21–26 (1993).

77 Gough AK, Lilley J, Eyre S, Holder RL, Emery P: Generalised bone loss in patients with early rheumatoid arthritis. *Lancet* 344, 23–27 (1994).

78 Saario R, Sonninen P, Mottonen T, Viikari J, Toivanen A: Bone mineral density of the lumbar spine in patients with advanced rheumatoid arthritis: influence of functional capacity and corticosteroid use. *Scand. J. Rheumatol.* 28, 363–367 (1999).

79 Haugeberg G, Orstavik RE, Uhlig T, Falch JA, Halse JI, Kvien TK: Bone loss in patients with rheumatoid arthritis: results from a population-based cohort of 366 patients followed up for two years. *Arthritis Rheum.* 46, 1720–1728 (2002).

80 Huusko TM, Korpela M, Karppi P, Avikainen V, Kautiainen H, Sulkava R: Threefold increased risk of hip fractures with rheumatoid arthritis in Central Finland. *Ann. Rheum. Dis.* 60, 521–522 (2001).

81 Franck H, Gottwalt J: Peripheral bone density in patients with rheumatoid arthritis. *Clin. Rheumatol.* 28, 1141–1145 (2009).

82 Sinigaglia L, Varenna M, Girasole G, Bianchi G: Epidemiology of osteoporosis in rheumatic diseases. *Rheum. Dis. Clin. North Am.* 32, 631–658 (2006).

83 Cantley MD, Smith MD, Haynes DR: Pathogenic bone loss in rheumatoid arthritis: mechanisms and therapeutic approaches. *Int. J. Clin. Rheumatol.* 4(5), 561–582 (2009).

84 Madsen OR, Sorensen OH, Egsmose C: Bone quality and bone mass as assessed by quantitative ultrasound and dual energy x ray absorptiometry in women with rheumatoid arthritis: relationships with quadriceps strength. *Ann. Rheum. Dis.* 61, 325–329 (2001).

85 Kraemer WJ, Fleck SJ, Evans WJ: Strength and power training: physiological mechanisms of adaptation. *Exerc. Sport Sci. Rev.* 24, 363–397 (1996).

86 Machover S, Sapecky AJ: Effect of isometric exercise on the quadriceps muscle in patients with rheumatoid arthritis. *Arch. Phys. Med. Rehab.* 47, 737–741 (1966).

87 Nordemar R, Edstrom L, Ekblom B: Changes in muscle fibre size and physical performance in patients with rheumatoid arthritis after short-term physical training. *Scand. J. Rheumatol.* 5, 70–76 (1976).

88 Nordemar R, Ekblom B, Zachrisson L, Lundqvist K: Physical training in rheumatoid arthritis: a controlled long-term study. I. *Scand. J. Rheumatol.* 10, 17–23 (1981).

89 Ekdahl C, Andersson SI, Moritz U, Svensson B: Dynamic versus static training in patients with rheumatoid arthritis. *Scand. J. Rheumatol.* 19, 17–26 (1990).

90 Hoenig H, Groff G, Pratt K, Goldberg E, Franck W: A randomised controlled trial of home exercise on the rheumatoid hand. *J. Rheumatol.* 20, 785–789 (1993).

91 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.* 23, 237–242 (1994).

92 Lyngberg KK, Ramsing BU, Nawrocki A, Harreby M, Dannskiold-Samsoe B: Safe and effective isokinetic knee extensor training in rheumatoid arthritis. *Arthritis Rheum.* 37, 623–628 (1994).

93 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.* 39, 415–426 (1996).

94 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.* 55, 798–805 (1996).

▪▪ **RCT which demonstrates the superiority of high- versus low-intensity exercise for improving aerobic capacity, strength and joint mobility in RA patients.**

95 McMeeken J, Stillman B, Story I, Kent P: The effects of knee extensor training and flexor muscle training on the timed-up-and-go test in individuals with rheumatoid arthritis. *Physiother. Res. Int.* 4, 55–67 (1999).

96 Hakkinen A, Malkia E, Hakkinen K, Jappinen I, Laitinen L, Hannonen P: Effects of detraining subsequent to strength training on neuromuscular function in patients with inflammatory arthritis. *Br. J. Rheumatol.* 36, 1075–1081 (1997).

97 Hakkinen A, Sokka T, Kotaniemi A *et al.*: Dynamic strength training in patients with early rheumatoid arthritis increases muscle strength but not bone mineral density. *J. Rheumatol.* 26, 1257–1263 (1999).

98 Hakkinen A, Sokka T, Kotaniemi A, Hannonen P: A randomized two-year study of the effects of dynamic strength training on muscle strength, disease activity, functional capacity, and bone mineral density in early rheumatoid arthritis. *Arthritis Rheum.* 44, 515–522 (2001).

▪▪ **RCT featuring long-term (2 years) PRT training combined with aerobic activities, which demonstrates the efficacy and safety, even when prolonged, of this form of training.**

99 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.* 49, 789–797 (2003).

100 Hakkinen A, Sokka T, Hannonen P: A home-based two-year strength training period in early rheumatoid arthritis led to good long-term compliance: a five-year follow-up. *Arthritis Rheum.* 51, 56–62 (2004).

101 Hakkinen A, Sokka T, Kautiainen H, Kotaniemi A, Hannonen P: Sustained maintenance of exercise induced muscle strength gains and normal bone mineral density in patients with early rheumatoid arthritis: a 5 year follow up. *Ann. Rheum. Dis.* 63, 910–916 (2004).

102 Hakkinen A, Pakarinen A, Hannonen P *et al.*: Effects of prolonged combined strength and endurance training on physical fitness, body composition and serum hormones in women with rheumatoid arthritis and in healthy controls. *Clin. Exp. Rheumatol.* 23, 505–512 (2005).

▪▪ **Study showing the equivalence of training benefits on body composition, strength and aerobic capacity for RA patients and matched healthy controls following completion of 21 weeks of combined PRT and aerobic exercise.**

103 van den Ende CHM, Breedveld FC, le Cessie S, Dijkmans BAC, de Mug AW, Hazes JMW: Effect of intensive exercise on patients with active rheumatoid arthritis: a randomised clinical trial. *Ann. Rheum. Dis.* 59, 615–621 (2000).

104 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.* 48, 2415–2424 (2003).

▪▪ **Long-term (2 year), large-scale (n = 300) RCT (Rheumatoid Arthritis Patients in Training [RAPIT] trial) which demonstrates that high-intensity exercise, including strength training, is more effective than usual care in improving physical function in RA patients.**

105 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.* 24, 1531–1539 (1997).

106 van den Ende CHM, Breedveld FC, Dijkmans BAC, Hazes JMW: The limited value of the Health Assessment Questionnaire as an outcome measure in short term exercise trials. *J. Rheumatol.* 24, 1972–1977 (1997).

107 Evans WJ: Exercise training guidelines for the elderly. *Med. Sci. Sports Exerc.* 31, 12–17 (1999).

108 Campbell WW, Crim MC, Young VR, Evans WJ: Increased energy requirements and body composition changes with resistance training in older adults. *Am. J. Clin. Nutr.* 60, 167–175 (1994).

109 Rikli RE, Jones CJ: *Senior Fitness Test Manual.* Human Kinetics, Champaign, IL, USA (2001).

110 MacDonald JH, Phanish MK, Marcora SM *et al.*: Muscle insulin-like growth factor status, body composition, and functional capacity in hemodialysis patients. *J. Renal Nutr.* 14, 248–252 (2004).

111 MacDonald JH, Phanish MK, Marcora SM, Jibani M, Holly JMP, Lemmey AB: Intradialytic exercise as anabolic therapy in haemodialysis patients – a pilot study. *Clin. Physiol. Funct. Imaging* 25, 113–118 (2005).

112 Vogiatzis I, Stratakos G, Simoes DC *et al.*: Effects of rehabilitative exercise on peripheral muscle TNF-α, IL-6, IGF-I and MyoD expression in patients with COPD. *Thorax* 62, 950–956 (2007).

113 Hambrecht R, Schulze PC, Gielen S *et al.*: Effects of exercise training on insulin-like growth factor-I expression in the skeletal muscle of non-cachectic patients with chronic heart failure. *Eur. J. Cardiovasc. Prev. Rehabil.* 12, 401–406 (2005).

114 Fiatarone Singh MA, Ding W, Manfredi TJ *et al.*: Insulin-like growth factor I in skeletal muscle after weight-lifting exercise in frail elders. *Am. J. Physiol.* 277, 135–143 (1999).

115 Adams GR: Invited Review: Autocrine/paracrine IGF-I and skeletal muscle adaptation. *J. Appl. Physiol.* 93, 1159–1167 (2002).

116 Tourinho TF, Capp E, Brenol JC, Stein A: Physical activity prevents bone loss in premenopausal women in rheumatoid arthritis: a cohort study. *Rheumatol. Int.* 28, 1001–1007 (2008).

117 de Jong Z, Munneke M, Lems WF *et al.*: Slowing of bone loss in patients with rheumatoid arthritis by long-term high-intensity exercise. *Arthritis Rheum.* 50, 1066–1076 (2004).

118 Nelson ME, Fiatarone MA, Morganti CM, Trice I, Greenberg RA, Evans WJ: Effects of high-intensity strength training on multiple risk factors for osteoporotic fractures. A randomised controlled trial. *JAMA* 272, 1909–1914 (1994).

119 Dornemann TM, McMurray RG, Renner JB, Anderson JJB: Effects of high-intensity resistance exercise on bone mineral density and muscle strength on 40–50-year-old women. *J. Sports Med. Phys. Fitness* 37, 246–251 (1997).

120 Rhodes EC, Martin AD, Taunton JE, Donnelly M, Warren J, Elliot J: Effects of one year of resistance training on the relation between muscular strength and bone density in elderly women. *Br. J. Sports Med.* 34, 18–22 (2000).

121 Layne JE, Nelson ME: Resistance training for the prevention of osteoporosis. In: *Resistance Training and Health Rehabilitation.* Graves JE, Franklin BA (Eds). Human Kinetics, Champaign, IL, USA, 385–404 (2001).

122 Chamay A, Tschantz P: Mechanical influences in bone remodelling. Experimental research on Wolff's law. *J. Biochem.* 5, 173–180 (1972).

123 Kerr D, Morton A, Dick I, Prince R: Exercise effects on bone mass in postmenopausal women are site-specific and load-dependant. *J. Bone Miner. Res.* 11, 218–225 (1996).

124 Braith RW, Mills RM, Welsh MA, Keller JW, Pollock ML: Resistance exercise training restores bone mineral density in heart transplant recipients. *J. Am. Coll. Cardiol.* 28, 1471–1477 (1996).

125 Rutherford OM: Is there a role for exercise in the prevention of osteoporotic fractures? *Br. J. Sports Med.* 33, 378–386 (1999).

126 Vanderhoek KJ, Coupland DC, Parkhouse WS: Effects of 32 weeks of resistance training on strength and balance in older osteopenic/osteoporotic women. *Clin. Exerc. Physiol.* 2(2), 77–83 (2000).

127 Pedersen BK, Saltin B: Evidence for prescribing exercise as therapy in chronic disease. *Scand. J. Med. Sci. Sports* 16, 3–63 (2006).

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

129 Morse CI, Thom JM, Mian OS, Birch KM, Narici MV: Gastrocnemius specific force is increased in elderly males following a 12-month physical training programme. *Eur. J. Appl. Physiol.* 100, 563–570 (2007).

130 Nichols JF, Omizo DK, Peterson KK, Nelson KP: Efficacy of heavy-resistance training for active women over sixty: muscular strength, body composition, and program adherence. *J. Am. Geriatr. Soc.* 41, 205–210 (1993).

131 Matschke V, Murphy P, Lemmey AB, Maddison PJ, Thom JM: Muscle quality, architecture, and activation in cachectic patients with rheumatoid arthritis. *J. Rheumatol.* 37, 282–284 (2010).

132 Matschke V, Murphy P, Lemmey AB, Maddison PJ, Thom JM: Skeletal muscle properties in rheumatoid arthritis patients. *Med. Sci. Sports Exerc.* 42, 2149–2155 (2010).

133 Sutej PG, Hadler NM: Current principles of rehabilitation for patients with rheumatoid arthritis. *Clin. Orthop.* 265, 116–124 (1991).

134 Metsios GS, Stavropoulos-Kalinoglou A, Veldhuijzen van Zanten JJCS *et al.*: Rheumatoid arthritis, cardiovascular disease and physical exercise: a systematic review. *Rheumatology* 47(3), 239–248 (2007).

135 Munneke M, de Jong Z, Zwinderman AH *et al.*: High intensity exercise or conventional exercise for patients with rheumatoid arthritis? Outcome expectations of patients, rheumatologists, and physiotherapists. *Ann. Rheum. Dis.* 63, 804–808 (2004).

136 Rall LC, Roubenoff R, Cannon JG, Abad LW, Dinarello CA, Meydani SN: Effects of progressive resistance training on immune response in aging and chronic inflammation. *Med. Sci. Sports Exerc.* 28, 1356–1365 (1996).

137 Munneke M, de Jong Z, Zwinderman AH *et al.*: Effect of a high-intensity weight-bearing exercise program on radiologic damage progression of the large joints in subgroups of patients with rheumatoid arthritis. *Arthritis Rheum.* 53, 410–417 (2005).

138 de Jong Z, Munneke M, Kroon HM *et al.*: Long-term follow-up of a high-intensity exercise program in patients with rheumatoid arthritis. *Clin. Rheumatol.* 28, 663–671 (2009).

▪ **Follow-up report from the RAPIT trial which retracts the earlier conclusion that prolonged, high-intensity exercise training may accelerate radiological damage to large joints with extensive pre-existing damage, thus supporting claims that this form of exercise is safe in RA patients. Also shows high compliance to continued training after termination of the original 2-year RAPIT trial.**

139 Kraemer WJ, Ratamess NA: Fundamentals of resistance training: progression and exercise prescription. *Med. Sci. Sports Exerc.* 36, 674–688 (2004).

140 American College of Sports Medicine: General principles of exercise prescription. In: *ACSM's Guidelines for Exercise Testing and Prescription (8th Edition)*. Lippincott, Williams & Wilkins, Baltimore, MA, USA, 152–182 (2010).

141 Hass CJ, Feigenbaum MS, Franklin BA: Prescription of resistance training for healthy populations. *Sports Med.* 31, 953–964 (2001).

142 Hakkinen K: Neuromuscular fatigue and recovery in women at different ages during heavy resistance loading. *Electromyogr. Clin. Neurophysiol.* 35, 403–413 (1995).

143 Demichele PD, Pollock ML, Graves JE *et al.*: Effect of training frequency on the development of isometric torso rotation strength. *Arch. Phys. Med. Rehabil.* 27, 64–69 (1997).

144 American College of Sports Medicine position stand: the recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness and flexibility in healthy adults. *Med. Sci. Sports Exerc.* 30, 975–991 (1998).

145 Feigenbaum MS, Pollock ML: Strength training: rationale for current guidelines for adult fitness programs. *Phys. Sportsmed.* 25, 44–64 (1997).

146 Dishman RK: *Exercise Adherence: Its Impact on Public Health (2nd Edition)*. Human Kinetics, Champaign, IL, USA (1994).

147 Moorehouse C: Development and maintenance of isometric strength of subjects with diverse initial strengths. *Res. Q.* 38, 449–456 (1966).

148 Graves JE, Pollock ML, Foster D *et al.*: Effect of training frequency and specificity on isometric lumbar extension strength. *Spine* 15, 504–509 (1990).

149 Fleck SJ, Kraemer WJ: *Designing Resistance Training Programs (2nd Edition)*. Human Kinetics, Champaign, IL, USA (1997).

150 Sale DG: Influence of exercise and training on motor unit activation. In: *Exercise and Sports Sciences Reviews.* Pandolf KB (Ed.). MacMillan, NY, USA, 95–152 (1987).

151 Hoeger WW, Barette SL, Hale DF, Hopkins DR: Relationship between repetitions and selected percentages of one repetition maximum. *J. Appl. Sports Sci. Res.* 1, 11–13 (1987).

152 Berger RA: Optimum repetitions for the development of strength. *Res. Q.* 33, 334–338 (1962).

153 Campos GER, Lubcke TJ, Wendeln HK: Muscular adaptations in response to three different training regimens: specificity of repetition training zones. *Eur. J. Appl. Physiol.* 88, 50–60 (2002).

154 Housh DJ, Housh TJ, Johnson GO, Chu WK: Hypertrophic response to unilateral concentric isokinetic resistance training. *J. Appl. Physiol.* 73, 65–70 (1992).

155 Kraemer WJ: A series of studies – the physiological basis for strength training in American Football: fact over philosophy. *J. Strength Cond. Res.* 11, 131–142 (1997).

156 Ostrowski KJ, Wilson GJ, Weatherby R, Murphy PW, Lyttle AD: The effect of weight training volume on hormonal output and muscular size and function. *J. Strength Cond. Res.* 11, 148–154 (1997).

157 Berger RA: Comparison of the effect of various weight training loads on strength. *Res. Q.* 36, 141–146 (1963).

158 Paulsen G, Myklestad D, Raastad T: The influence of volume of exercise on early adaptations to strength training. *J. Strength Cond. Res.* 17, 113–118 (2003).

159 Kraemer WJ, Ratamess N, Fry AC *et al.*: Influence of training volume and periodization on physiological and performance adaptations in college women tennis players. *Am. J. Sports Med.* 28, 626–633 (2000).

160 Rhea MR, Alvar BA, Ball SD, Burkett LN: Three sets of weight training superior to 1 set with equal intensity for eliciting strength. *J. Strength Cond. Res.* 16, 525–529 (2002).

161 Schlumberger A, Stec J, Schmidtblecher D: Single- vs. multiple-set strength training in women. *J. Strength Cond. Res.* 15, 284–289 (2001).

162 Pollock ML: Prescribing exercise for fitness and adherence. In: *Exercise Adherence: Its Impact on Public Health.* Dishman RK (Ed.), Human Kinetics, Champaign, IL, USA, 259–282 (1988).

163 Hass CJ, Garzarella L, De Hoyos *et al.*: Single versus multiple sets and long-term recreational weightlifters. *Med. Sci. Sports Exerc.* 32, 235–242 (2000).

164 Pincivero DM, Lephart SM, Karunakara RG: Effects of rest interval on isokinetic strength and functional performance after short term high intensity training. *Br. J. Sports Med.* 31, 229–234 (1997).

165 Robinson JM, Stone MH, Johnson RL, Penland CM, Warren BJ, Lewis RD: Effects of different weight training exercise/rest intervals on strength, power, and high intensity exercise endurance. *J. Strength Cond. Res.* 9, 216–221 (1995).

166 American College of Sports Medicine: Position stand: progression models in resistance training for healthy adults. *Med. Sci. Sports Exerc.* 34, 364–380 (2002).

167 Kraemer WJ, Noble BJ, Clark MJ, Culver BW: Physiologic responses to heavy-resistance exercise with very short rest periods. *Int. J. Sports Med.* 8, 247–252 (1987).

168 Kraemer WJ, Marchitelli L, Gordon SE *et al.*: Hormonal and growth factor responses to heavy resistance exercise protocols. *J. Appl. Physiol.* 69, 1442–1450 (1990).

169 Kraemer WJ, Gordon SE, Fleck SJ *et al.*: Endogenous anabolic hormonal and growth factor responses to heavy resistance exercise in males and females. *Int. J. Sports Med.* 12, 228–235 (1991).

170 Foran B: Advantages and disadvantages of isokinetic, variable resistance and free weights. *Natl Strength Cond. Assoc. J.* 7, 24–25 (1985).

171 Pollock ML, Franklin BA, Balady GJ *et al.*: Resistance exercise in individuals with and without cardiovascular disease. Benefits, rationale, safety, and progression. An advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association. *Circulation* 101, 828–833 (2000).

172 Vincent KR, Vincent HK, Braith R *et al.*: Effects of 6 months of resistance exercise on lipid peroxidation in older adults. *Med. Sci. Sports Exerc.* 32, S105 (2000).

173 Hickson RC, Rosenkoetter MA, Brown MM: Strength training effects on aerobic power and short-term endurance. *Med. Sci. Sports Exerc.* 12, 336–339 (1980).

174 Ades PA, Ballor DL, Ashikaga T, Utton JL, Nair KS: Weight training improves walking endurance in healthy elderly persons. *Ann. Intern. Med*. 124, 568–572 (1996).

175 Rutherford GM, Jones DA: The role of learning and coordination in strength training. *Eur. J. Appl. Physiol.* 55, 100–105 (1986).

176 Sale DG: Neural adaptations to strength training. In: *Strength and Power in Sports (2nd Edition)*. Komi PV (Ed.). Blackwell Science, Malden, MA, USA, 281–314 (2003).

177 Kraemer WJ, Patton JF, Gordon SE *et al.*: Compatibility of high-intensity strength and endurance training on hormonal and skeletal muscle adaptations. *J. Appl. Physiol.* 78, 976–989 (1995).

178 Phillips SM: Short-term training: when do repeated bouts of resistance exercise become training? *Can. J. Appl. Physiol.* 25, 185–193 (2000).

179 Staron RS, Karapondo DL, Kraemer WJ *et al.*: Skeletal muscle adaptations during early phase of heavy-resistance training in men and women. *J. Appl. Physiol.* 76, 1247–1255 (1994).

180 McCartney N, McKelvie RS, Martin J, Sale DG, MacDougall JD: Weight-training-induced attenuation of the circulatory response of older males to weight lifting. *J. Appl. Physiol.* 74, 1056–1060 (1993).

Websites

201 WHO: Recommended Amount of Physical Exercise (2008) www.who.int/dietphysicalactivity/factsheet_recommendations/en/index.html

202 ACR: Exercise and Arthritis (2006) www.rheumatology.org/public/factsheets/diseases_and _conditions/exercise.asp