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Resistance Training for Patients with Rheumatoid Arthritis: Effects on Disability, Rheumatoid Cachexia, and Osteoporosis; and Recommendations for Prescription

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1. Introduction

Rheumatoid arthritis (RA) is characterised by disability, cachexia, and obesity, and features exacerbated risk of both cardiovascular disease (CVD) and osteoporosis. To deal with RA generally and these associated conditions specifically, the World Health Organisation (WHO, 2008) and various national health authorities (e.g. American College of Rheumatology, ACR, 2002, 2006; European League Against Rheumatism, EULAR, Combe et al., 2007; American College of Sports Medicine, ACSM, 2010a, 2010b, 2010c, 2010d; American Heart Association, AHA, Williams et al., 2007) have advocated progressive resistance training (PRT; i.e. systematic weight training) as adjunct therapy. Additionally, two Cochrane Reviews (Hurkmans et al., 2009; van den Ende et al., 2000) have supported inclusion of this form of exercise in the routine management of RA patients. However, despite this weighty advocacy regular PRT is rarely prescribed for or undertaken by RA patients.

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

2. Disability, rheumatoid cachexia and osteoporosis in RA patients

2.1 Disability

Despite advances in the pharmaceutical treatment of RA, disability remains a feature of the disease. In a recent report from the British Society for Rheumatology Biologics Register (Lunt et al., 2010), the median (interquartile range) Health Assessment Questionnaire (HAQ) scores for large samples of patients receiving anti-tumor necrosis factor (anti-TNF) treatment (n=12,672) or standard disease modifying anti-rheumatic drugs (DMARD's; n=3,522) were 2.1 (1.8-2.5) and 1.6 (0.9-2.1), respectively; which are levels indicative of moderate to severe disability. Such widespread disability, as well as causing enormous suffering and reduction of Quality of Life (QoL) on a personal level, also has huge social and economic costs (Verstappen et al., 2004; Yelin, 1996). For example, within 10 years of RA diagnosis a prevalence of 35% for work disability is currently reported for both US and European populations (Allaire et al., 2008; Eberhardt et al., 2007).

Whilst the causes of disability in RA are multifactorial (Escalante & del Rincon, 1999, 2002), Giles et al. (2008) has shown that it is strongly associated with adverse changes in body composition, 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. Subsequently, Stavropoulos-Kalinoglou et al. (2009) have also shown that obesity is significantly and independently associated with disability in RA patients. Such links between body composition and physical function are not surprising as they reflect those observed in the general elderly population, whereby classification as either muscle-wasted (sarcopenic) or obese significantly exacerbates the likelihood of disability, whilst the co-incidence of both conditions (sarcopenic-obesity) increases disability risk 12-fold in women and 9-fold in men (Morley et al., 2001).

2.2 Rheumatoid cachexia

Unfortunately, both reduced muscle mass and elevated adiposity, termed "rheumatoid cachexia" (Roubenoff et al., 1992), are characteristic of RA. Muscle wasting due to RA was first observed by Sir James Paget in 1873 and has been consistently reported in recent decades (see Summers et al., 2008 for a review); most prolifically and notably by Ronenn Roubenoff's group (Rall & Roubenoff, 1996, 2004; Rall et al., 1996a, 2002; Roubenoff, 2000; Roubenoff et al., 1992, 1994, 2002; Walsmith & Roubenoff, 2002; Walsmith et al., 2004). Using a definition of significant muscle loss as being below the 50th percentile for arm muscle circumference of a reference population, Roubenoff et al. (1994) found that 67% of their RA patients were cachectic. Whilst Munro and Capell (1997), employing the more stringent cut-off of the 10th percentile, concluded that 50% of their British RA sample was muscle wasted. More recently, in a series of studies, mostly featuring patients who volunteered for high intensity exercise training (Marcora et al., 2005a, 2005b; Lemmey et al., 2009; Elamanchi et al. and Lemmey et al., manuscripts in preparation), we have identified that 2/3's of our stable RA patients are muscle wasted according to the whole-body dual-energy x-ray absorptiometry (DXA) definitions of Baumgartner et al. (1998; i.e. ALM (kg) / height^2 (m^2) more than two standard deviations below the mean of a young reference group). Interestingly, using the same methodology we found a similar incidence of rheumatoid cachexia in treatment-naïve, recent-onset RA patients (<6 months since diagnosis), suggesting that the loss of lean body mass (LBM) occurs early in the course of the disease (Marcora et al., 2006).

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 (Rall et al., 2002; Roubenoff et al., 1994, 2002); which agrees with the ≈15% loss we observe in stable RA patients relative to age- and sex-matched healthy sedentary controls (Lemmey et al., unpublished observations). Given this magnitude of muscle loss, it is not surprising that RA patients have substantially reduced muscle strength, with values ranging from 30-80% of normal being reported (Ekblom et al., 1974; Ekdahl & Broman, 1992; Ekdahl et al., 1989; Hakkinen et al., 1995; Madsen et al., 1998; Nordesjo et al., 1983). Also consistent with expectations is the very strong relationship Stucki et al. (1998) revealed between muscle weakness and disability in RA patients. In this study, HAQ was significantly correlated with muscle strength index (MSI), disease activity, morning stiffness, pain, and joint damage. However, when analysing the effect of change in these predictors with change in HAQ, only MSI and pain remained significantly associated. Thus confirming the importance of strength's, and by extension – muscle mass's, association with disability in RA.

The degree and prevalence of cachexia typically present in RA patients is alarming since it represents in excess of a third of the maximal loss of body cell mass or LBM that is compatible with survival (i.e. 40%; Walsmith & Roubenoff, 2002). Additionally, as in other catabolic diseases, muscle loss as well as causing weakness and disability is associated with osteoporosis, low aerobic capacity, impaired immune and pulmonary function, glucose intolerance, depression, loss of independence, compromised QoL, and increased mortality (see Kotler, 2000 for a review).

2.3 Obesity

Muscle depletion associated with RA, however, is generally undiagnosed (and consequently, untreated) as a concomitant increase in fat mass (FM) masks the decrease in muscle mass when bodyweight is measured. Thus, for a given body mass index (BMI), Stavropoulos-Kalinoglou et al. (2007) found that RA patients had on average 4.3% more body fat than matched, healthy controls. Alternatively, for a given body fat percentage (%BF), RA patients have a BMI almost $2kg/m^2$ lower than members of the general population. Consequently, these authors have proposed that the BMI cut-offs for defining "overweight" and "obesity" in RA patients should be reduced to $23kg/m^2$ and $28kg/m^2$, respectively (Stavropoulos-Kalinoglou et al., 2007). This recommendation is supported by comparisons of BMI and %BF values reported for RA patients. Mean BMI's usually reported for RA patients (25.2-29.1 kg/m^2) (Gordon et al., 2002; Marcora et al., 2005a, 2005b; Saravana & Gillot, 2004; Stavropoulos-Kalinoglou et al., 2007) are consistent with that of the entire adult UK population (27.1 kg/m^2) (Craig et al., 2009), suggesting that RA patients, like the overall population, are generally merely overweight. However, when body composition is assessed (Elkan et al., 2009; Lemmey et al., 2009; Marcora et al., 2005a, 2005b; Stavropoulos-Kalinoglou et al., 2007, 2009; Westhovens et al., 1997) RA patients are revealed to be significantly fatter than the overall population, with a mean %BF of around 40% and a prevalence of obesity (using the criteria of 38%BF or more for women, and 27%BF or more for men; Baumgartner et al., 1999) of approximately 80% (Lemmey et al., 2009; Marcora et al., 2005a, 2005b; Stavropoulos-Kalinoglou et al., 2009). Using a stricter criteria, Elkan et al. (2009a) found that 33% of female and >50% of male RA patients had a FM index above the 90th percentile for the whole population. As with muscle loss, this high prevalence of obesity is evident in recently diagnosed RA patients (Marcora et al., 2006), again indicating that the body composition perturbations characteristic of rheumatoid cachexia occur early in the disease.

Disturbingly, as well as favouring accumulation of higher total fat, RA appears to preferentially predispose to central obesity (Elkan et al., 2009b; Giles et al., 2010; Inaba et al., 2007; Westhovens et al., 1997). 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 (e.g. Mahabadi et al., 2009; Rosito et al., 2008). Similarly in RA patients, central obesity is linked with hypertension, elevated fasting glucose levels, and metabolic syndrome (Giles et al., 2010), and arterial thickening and stiffening (Inaba et al., 2007). 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 (Avina-Zubieta et al., 2008; Naranjo et al., 2008), one would assume that loss of fat, particularly trunk fat, would be highly beneficial for the CV health of this population.

2.4 Osteoporosis

Another feature of RA is secondary osteoporosis. RA patients have greater incidence of osteoporosis and osteoporotic fractures than matched non-RA controls (e.g. Frank & Gottwalt, 2009; Huusko et al., 2001; Sinigaglia et al., 2006); with this increase attributed to the disease itself (systemic inflammation), treatment with high dose oral glucocorticoids, and sedentary lifestyle (Cantley et al., 2009; Frank & Gottwalt, 2009; Huusko et al., 2001; Sinigaglia et al., 2006;). Interestingly, after high-dose steroid therapy, the reduced bone mineral density (BMD) in RA patients has been found to be most strongly associated with low strength (quadriceps and handgrip) and poor physical function (Huusko et al., 2001; Madsen et al., 1998, 2001).

2.5 Treatments for rheumatoid cachexia

Clearly, interventions capable of 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 (McIntosh, 1996)). Several anabolic agents, such as recombinant human GH and anabolic steroids, have been proposed for increasing muscle mass in sarcopenic/cachectic states (e.g. Bross et al., 1999; Johansen et al., 1999, 2006; Macdonald et al., 2007). However, GH therapy is expensive and may cause carpal tunnel syndrome and insulin resistance, whilst anabolic steroids are associated with side effects such as liver disorders, masculinisation in women, and prostate cancer and testicular atrophy in men (Bhasin, 2003; Johansen et al., 1999; Korkia & Stimson, 1997; Macdonald et al., 2007). Furthermore, when used alone, despite increasing lean mass, these drugs often fail to improve physical function (Bross et al., 1999; Johansen et al., 2006; Macdonald et al., 2007; Rodriguez-Arnao et al., 1999). Consistent with these findings, are the findings of an unpublished randomised controlled trial we conducted (Elamanchi et al., manuscript in preparation), in which nandrolone decanoate (ND), an anabolic steroid, was administered (i.m. injection, 100mg/wk) for 6 months to 20 male RA patients with stable disease Despite inducing substantial increases in mean ALM (≈1.5kg), administration of ND failed to improve any of the objective measures of physical function assessed.

As rheumatoid cachexia has been attributed to cytokine (principally TNF-α) driven muscle catabolism by Roubenoff group (Rall & Roubenoff, 2004; Rall et al., 1996a; Roubenoff et al., 1994, 2002), it was anticipated that treatment with anti-TNF drugs could restore a healthier body composition to RA patients. However, Marcora et al. (2006) found that treatment of recently diagnosed RA patients for 6 months with etanercept (anti-TNF agent) had no effect on body composition relative to treatment with methotrexate ("standard DMARD"). This lack of effect of anti-TNF's on LBM in RA patients has subsequently been confirmed by Metsios et al. (2007). Of concern was their additional observation of increased trunk fat in established RA patients following 3 months on anti-TNF's. These findings are further supported by a recent report (Engvall et al., 2010), which observed increased FM in recent-onset RA patients treated with anti-TNF's for 21 months relative to DMARD treated patients (mean±sd; +3.4±1.4kg, $p<0.05$), and no changes in LBM for either treatment.

3. Efficacy of progressive resistance training

The most, perhaps the only, effective, safe and economical intervention known to increase both muscle and bone mass and also improve strength and physical function in subjects of various ages is progressive resistance training (PRT) (see Kraemer et al., 1996 for a review).

3.1 Effects on function

The efficacy of resistance training for improving strength in RA patients (Table 1) was first demonstrated by Machover and Sopecky in 1966. In this pioneering study, 11 male RA patients performed maximal isometric contractions of the quadriceps 3 times a day, 5 days/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 (Table 1). The only exception identified being the home-based intervention of Komatireddy et al. (1997).

Consistent with the increases in strength are reports of improvements in physical function assessed objectively (e.g. walk tests, stair climbing, bench stepping, balance/coordination, hand-grip strength, timed up and go, vertical jump, 30-sec arm curl test, chair test, aerobic capacity; Ekdahl et al., 1990; Hakkinen et al., 1994, 1999, 2003, 2004a, 2005; Hoenig et al., 1993; Komatireddy et al., 1997; Lemmey et al., 2009; Lyngberg et al., 1994; Marcora et al., 2005a; McMeeken et al., 1999; Nordemar et al., 1976, 1981; Rall et al., 1996b; van den Ende et al., 1996, 2000) and subjectively (e.g. 100-point truth-value scale, study generated questionnaire, self reported fatigue, HAQ, McMaster Toronto Arthritis (MACTAR) Patient Preference Disability Questionnaire; Ekdahl et al., 1990; Hakkinen et al., 1994, 2001, 2004a; Komatireddy et al., 1997; Lyngberg et al., 1994; Marcora et al., 2005a; McMeeken et al., 1999; van den Ende et al., 2000) (Table 1). Although it is notable that improvements in physical function are usually not observed when it is subjectively assessed by the HAQ (de Jong et al., 2003; Hakkinen et al., 1999, 2003, 2004b, 2005; Lemmey et al., 2009; van den Ende et al., 1996). 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 likely to feature in exercise intervention studies. This lack of sensitivity is evident in findings from the Rheumatoid Arthritis Patients in Training (RAPIT) program (de Jong et al., 2003) which showed improvements in patients' self-reported physical function following high intensity exercise training when assessment was by the MACTAR Questionnaire, but not when the HAQ was used. The unsuitability of the HAQ for detecting improvements in function following exercise therapy has been highlighted by van den Ende et al. (1997), who advocate objective measures related to performing activities of daily living (ADL's) as measures of efficacy.

As concluded by the 2 Cochrane Reviews conducted to date (Hurkmans et al., 2009; van den Ende et al., 2000), the efficacy of resistance training programs in improving strength and physical function in RA patients is clear. In fact, with appropriate training it is not unreasonable to expect that patients with established, controlled RA can achieve levels of physical function at least as good as sedentary, healthy individuals of the same age and sex. In the RCT conducted by our group (Lemmey et al., 2009), patients with established RA (11

Study (author/year/ref)	Intervention group † (n)	Exercise type	Training frequency & duration	Intensity % max ‡	Volume (sets/reps)	Control Ψ	Strength
Ekdahl et al., 1990	17	RT + aerobic + balance	2/wk, 6 wks	_	_	**RCT** ROM, isom	↑
Hoenig et al., 1993	30	Hand RT	14/wk, 12 wks	_	_	**RCT** ROM, NC	↑
Hakkinen et al., 1994, 1997	21	PRT	2-3/wk, 6 mths	70-80	3 sets of 6-12 reps	**RCT** NC	↑
van den Ende et al., 1996	25	PRT + aerobic + circuits	3/wk, 12 wks	_	_	**RCT** ROM, isom	↑
Komatireddy et al., 1997	25	PRT	3/wk, 12 wks	"low intensity"	2-3 sets of 12-15 reps	**RCT** NC	↔
McMeeken et al., 1999	17	Leg PRT	14 sessions over 6 wks	70	4 sets of 5 reps	**RCT** NC	↑
Hakkinen et al., 1999, 2001, 2004[a,b]	32	PRT	2/wk, 24 mths	50-70	2 sets of 8-12 reps	**RCT** ROM	↑
van den Ende et al., 2000	34	PRT + aerobic	5/wk, 4 wks	_	_	**RCT** ROM, isom	↑
de Jong et al., 2003, 2009	150	RT + aerobic	2/wk, 24 mths	_	8-15 reps	**RCT** NC	↑
Lemmey et al., 2009	13	PRT	2/wk, 24 wks	80	3 sets of 8 reps	**RCT** ROM	↑
Machover & Sapecky, 1966	11	Unilateral leg isometric RT	15/wk, 7 wks	100	3 reps	contralateral leg	↑
Nordemar et al., 1976	10	Leg RT + aerobic	5/wk, 6 wks	_	_	none	↑
Nordemar et al., 1981	23	Leg RT + aerobic	1/fortnight, 4-8 yrs	_	_	RA	↑
Lyngberg et al., 1994	9	PRT; isom	3/wk, 3 wks for each leg	50	48 reps; 24 reps	none	↑
Rall et al., 1996b	8	PRT	2/wk, 12 wks	80	3 sets of 8 reps	HC	↑
Hakkinen et al., 2003	23	PRT + aerobic	3/fortnight, 21 wks	50-80	4-6 sets of 3-12 reps	HC	↑
Hakkinen et al., 2005	23	PRT + aerobic	3/fortnight, 21 wks	50-80	3-5 sets of 5-12 reps	HC	↑
Marcora et al.,	10	PRT	3/wk, 12 wks	80	3 sets of 8 reps	RA	↑

† = exercise group or, if multiple exercise groups, the highest intensity exercise group. PRT = progressive re
training, isom = isometric strength exercises, aerobic = aerobic training e.g. cycling, walking, swimming etc, ba
repetition maximum. **Ψ RCT** = randomised controlled trial, ROM = range of movement exercises, NC = no
rheumatoid arthritis patients, HC = healthy controls. ↑ = improved strength/function, ↔ = no change. ↑LM =
decreased total/trunk fat mass, ↑LM* = increased quadriceps LM, ↓FM* = decreased quadriceps subcutaneous
in vastus lateralis fibre cross-sectional area. ↓ = decreased disease activity. _ = not assessed +/or reported.

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

women, 2 men; age 55.6±8.3 years; disease duration 74±76 months) whose objectively measured physical function at baseline was poor relative to population norms, were able to achieve or exceed these performance norms following 24 weeks of high-intensity PRT. Restoration of normal levels of strength and function in RA patients following PRT has also been observed in the studies of Hakkinen et al. (2003, 2005) which featured healthy, age- and sex-matched control subjects, and in our uncontrolled pilot study (Marcora et al., 2005). In a point that will be pursued later, it should be noted that the only investigation that did not report significant increases in strength in RA patients following resistance training utilised a very low training intensity (Komatireddy et al., 1997).

3.2 Effects on rheumatoid cachexia (body composition)

The effects of resistance training on body composition in RA are less well reported (Table 1). In 1976, Nordemar et al. observed increased cross-sectional area of type I and especially type II fibres in 10 RA patients following 6 weeks of cycling, walking and quadriceps strength training. Similarly, Hakkinen et al. (1994) observed increases in quadriceps muscle cross-sectional area in RA patients following 6 months PRT. However, when Rall et al. (1996b) reported no changes in whole-body composition (DXA assessed) in 8 RA subjects following 12 weeks PRT (despite significant improvements in strength), the conclusion was that RA patients are resistant to the anabolic effects of exercise. This concern has subsequently been refuted by methodologically more robust trials. Initially, we (Marcora et al., 2005a) reported significant increases in (DXA assessed) LBM, ALM and estimated total body protein (TBP), and reductions in %BF, with a trend toward reduced trunk fat (-0.75kg) following 12 weeks of high-intensity PRT. Subsequently, these effects were confirmed by our RCT (Lemmey et al., 2009); LBM, ALM (≈1.2kg), and TBP were all significantly increased (p's=0.002-0.006) and total and especially trunk FM (-2.5kg, i.e. 18%) were substantially reduced following 24 weeks of PRT. Additionally, Hakkinen et al. (2005) have reported quadriceps femoris hypertrophy (p<0.001) and reduced quadriceps subcutaneous fat thickness (p<0.001) in female RA patients following 21 weeks of combined PRT and aerobic training.

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 questionable. This is because sedentary individuals of this aged are usually so deconditioned that they are unable to perform exercise of sufficient intensity and duration to significantly elevate daily energy expenditure (Evans, 1999). In contrast, in elderly men and women an elevation of approximately 15% in resting metabolic rate (RMR) has been observed following 12 weeks PRT as a consequence of increased LBM (Campbell et al., 1994). An increase in RMR of this magnitude is very relevant as RMR typically accounts for 60-75% of 24 hr energy expenditure.

In our PRT studies (Lemmey et al., 2009; Marcora et al., 2005a), the elicited increases in muscle mass were significantly associated with improvements in objectively assessed physical function (i.e. 30 sec arm curl, 30 sec sit-to-stand, 50' walk, hand-grip strength, and knee extensor strength; tests taken from the Senior Fitness Test (Rikli & Jones, 2001), and designed to reflect the ability to perform ADL's). Interestingly, the increased muscle mass and reduced fat mass in the PRT subjects in our RCT (Lemmey et al., 2009) caused a reclassification of the body types of many of these patients. Wherein, whereas at baseline, 9 (out of 13) were classified as cachectic, 10 as obese, and 5 as both (i.e. "cachectic-obese"),

after 24 weeks of PRT the number of patients in these high disability risk categories (Morley et al., 2001) were reduced to 4, 7 and 2, respectively. Given the reported links between adverse body composition and physical disability in RA patients (Giles et al., 2008) and the general elderly population (Morley et al., 2001), the positive effects of PRT on function in RA patients are anticipated. To emphasise the crucial role played by training intensity, in our RCT study (Lemmey et al., 2009) range-of-movement (ROM) exercises (i.e. the form of exercise most commonly prescribed for RA patients) were performed by the control group. Despite good compliance to the intervention, this low intensity exercise failed to have any effect on the various measures of body composition or objective physical function.

3.3 Impact on mechanisms of rheumatoid cachexia

As mentioned earlier, the precise mechanisms underlying rheumatoid cachexia have not been clarified. However, an additional insight was provided by Lemmey et al's RCT (2009). In this study diminished muscle levels of insulin-like growth factor-I (mIGF-I) were identified in our RA patients. This finding is consistent with reports of reduced mIGF-I levels in other conditions characterised by muscle wasting: chronic heart failure (CHF) (Hambrecht et al., 2005), chronic obstructive pulmonary disease (COPD) (Vogiatzis et al., 2007), chronic renal failure (Macdonald et al., 2004, 2005), and advanced aging (Fiatarone Singh et al., 1999); and with the proposed role of mIGF-I in regulating the maintenance of adult skeletal muscle (Adams, 2002). Following 24 weeks 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 COPD (Vogiatzis et al., 2007) and dialysis (Macdonald et al., 2005) patients, and the frail elderly (Fiatarone Singh et al., 1999); and the pivotal role put forward for mIGF-I in muscle's hypertrophic response to loading (Adams, 2002).

3.4 Responsiveness of RA patients to PRT

The magnitude of effects of PRT on strength and body composition observed in RA patients are similar to those reported for healthy middle-aged or older individuals (e.g. Frontera et al., 1991; Morse et al., 2007; Nichols et al., 1993; Pedersen & Saltin, 2006). The study by Hakkinen et al. (2005) described previously provides a direct comparison of training responses. This investigation featured female RA patients and age-matched healthy women who completed the same 21 week combined resistance and aerobic exercise training program, and noted remarkably similar improvements in strength and body composition (with regard to both absolute and relative increases in quadriceps femoris cross-section and reductions in quadriceps femoris subcutaneous fat thickness) following training. This similarity in training response is consistent with recent reports that muscle quality (muscle force per size) is not compromised in RA patients (Matschke et al., 2010a, 2010b). In these studies, a range of skeletal muscle parameters (e.g. specific force, muscle architecture, co-activation of antagonist muscles, voluntary activation capacity) were observed to be the same for well controlled RA patients, including those classified as cachectic, as for matched healthy subjects. 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.

3.5 Effects on bone

The benefit of weight-bearing and strengthening exercise in maximising and maintaining BMD, and reducing the risk of falling by improving strength and balance is well accepted in the general population (ACSM, 2010a). With specific reference to RA, a sedentary lifestyle confers a relative risk of 1.6 for low BMD in RA patients, and even moderate physical activity has been shown to reduce this risk by 50% (Tourinho et al., 2008). Additionally, de Jong et al. (2004) showed that bone loss at the hip was reduced in RA patients participating in the 2 year, high-intensity RAPIT exercise program (median -1.1% vs -1.9% for non-exercising controls, p<0.05). Further analysis revealed that these changes in BMD were significantly and independently associated with changes in strength and aerobic power, and that the high-intensity training had a benefit comparable to that of biphosphonate treatment. This finding led the investigators to conclude that intense weight-bearing exercise, including PRT, is essential for improving BMD in RA patients. Similar conclusions were made by Hakkinen et al. following their RCT (1999, 2001, 2004a). In this trial, twelve months 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 losses of -0.03% and -1.14%, respectively, in the ROM controls (Hakkinen et al., 1999). Following a further 12 months PRT, the mean differences between the groups increased with the changes in BMD at the femoral head and the lumbar spine now +0.51% and +1.17% for the training group and -0.70% and -0.91%, respectively, for the controls (Hakkinen et al., 2001). These observed trends in BMD were noted again at a 3 year follow-up (Hakkinen et al., 2004a). Whilst the differences between the groups were not statistically significant, except for the femoral head at 24 months, it was suggested by the authors that such an effect would be substantial and of clinical significance if PRT 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 failing that, to minimise bone loss. Thus, although the evidence from RA patients is limited, PRT appears to be as efficacious in this population as it is generally (e.g. Dornemann et al., 1997; Nelson et al., 1994; Rhodes et al., 2000).

In RCT's 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 (see Layne and Nelson, 2001 for a review). 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 (Chamay & Tschantz, 1972). The results of Kerr et al. (1996) serve to illustrate this. In this study, post-menopausal women (aged 51-62 years) were randomised to either high-intensity (HI) "strength" PRT (high load, low repetitions i.e. 3 sets of 8 repetitions) or low-intensity (LI) "endurance" PRT (low load, high repetitions i.e. 3 sets of 20 repetitions). After training 3x's/week for 12 months, the HI group had increased femoral head and distal radial BMD significantly more than the LI group; with the site-specific gains in BMD significantly correlated to the site-specific strength increases. In patients recovering from surgery, strength training has also been shown to be effective in countering glucocorticoid-induced bone loss (Braith et al., 1996). However, as for the general population, the greatest benefit of PRT in reducing osteoporotic fractures in RA patents is likely to be a consequence of lowering the incidence of falling due to improved strength and balance (Layne and Nelson, 2001; Nelson et al., 1994; Vanderhoek et al., 2000). With regards to the suitability of high-intensity PRT for individuals with low BMD; Vanderhoek et al. (2000) specifically chose osteopenic or osteoporotic elderly women (mean±sd; age = 69.0±1.3

years) for 32 weeks of HI PRT in which they performed 3 sets of 8 repetitions at 75-80% of 1-repetition maximum (1-RM, i.e. the maximum load that can be correctly lifted for a given exercise) for each exercise. As anticipated, this high intensity PRT resulted in substantial, and correlated, improvements in strength and balance. More importantly, it also proved to be well tolerated and safe with no compression fractures or other training related injuries observed.

3.6 Safety of PRT for RA patients

For many years, intensive weight-bearing exercise was considered inappropriate for RA patients due to concern that this unaccustomed stress on the joints would exacerbate inflammation, pain, and joint damage (e.g. Sutej & Hadler, 1991). Even today, many rheumatologists and their multidisciplinary teams retain these anachronistic beliefs and advise patients to avoid strenuous physical pursuits in order to protect their joints and conserve their energy (i.e. the strategy of "pacing") (for further discussion on this see Metsios et al., 2007; Munneke et al., 2004). This is despite the unanimity of research findings that exercise training, including resistance training (Table 1), irrespective of the intensity employed, is safe in RA patients. In fact, although most studies report no changes in disease activity following resistance training, findings of improvements are not uncommon; e.g. reductions in: erythrocyte sedimentation rate (ESR; Hakkinen et al., 1994, 1997, 1999), morning stiffness (Ekdahl et al., 1990), number of tender and swollen joints (Ritchie articular index; Ekdahl et al., 1990; Hakkinen et al., 1994, 1997; van den Ende et al., 1996), self-reported joint count (Komatireddy et al., 1997), pain (Komatireddy et al., 1997; McMeeken et al., 1999; Rall et al., 1996b), and Disease Activity Score (DAS28, DAS4; Hakkinen et al., 1999, 2001, 2004a). High-intensity exercise even appears to be safe in patients with active disease; van den Ende et al. (2000) randomly allocated RA patients admitted to hospital for RA flares to perform either HI exercise (isokinetic and isometric strength training) or LI exercise (ROM and isometric exercises). After 24 weeks of training (3x's/week), improvements in DAS were observed for both groups with a trend toward greater improvement in the HI patients.

Adherence to PRT over prolonged periods also provides no cause for concern. Hakkinen et al. (2001) in an RCT comparing 2 years of strength training to conventional physiotherapy (ROM exercises), found that although DAS28 improved significantly for both groups, the strength training group enjoyed greater benefit. Similarly, de Jong et al. (2003) in their 2 year RCT (the RAPIT trial) also identified reductions in disease activity (DAS4) in their HI exercise (including strength training) group; albeit, this time with no difference between the exercise and control ("usual care") groups.

In a broader investigation of immune responses to PRT in RA patients, Rall et al. (1996c) detected no effects of 12 weeks HI training on peripheral blood mononuclear (PBMC) subpopulations, or stimulated proliferation of TNF-α, interleukin (IL)-1β, IL-2, IL-6, or prostaglandin E$_2$, or delayed type hypersensitivity skin response.

Although reassuring effects on joint counts, systemic inflammation, pain, and more generalised disease activity are provided by studies of strength training interventions in RA patients, relatively few studies have assessed the effects of training on radiographic joint damage. An exception to this was the RAPIT trial. Initially, reports from this investigation (de Jong et al., 2003; Munneke et al., 2005) raised concerns by suggesting that high intensity

exercise exacerbated joint damage progression in large joints with extensive pre-existing damage. Results from an 18 month follow-up study (de Jong et al., 2009), however, have seen the investigators retract this conclusion. Instead, they are now confident that long-term, intense weight-bearing exercise does not cause further damage to large joints, even those already extensively damaged. This revised interpretation thus accords with the verdict they had previously made with regard to the small joints of the hands and feet (de Jong et al., 2003). This general conclusion of training not increasing radiological progression of joint damage agrees with the findings of others (Hakkinen et al., 1994, 2001, 2004b; Nordemar et al., 1981). In the earliest of these studies, Nordemar et al. (1981) found that RA patients who had performed 4-8 years of resistance exercises for the legs had reduced joint damage in these limbs relative to non-exercising disease-matched controls. Whilst in the other studies, all by Hakkinen's group (1994, 2001, 2004b), no acceleration in joint damage was detected by x-ray in RA patients performing long-term (up to 5 years; Hakkinen et al., 2004b), regular, HI PRT relative to patients receiving standard care.

4. 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" (Kraemer & Ratamess, 2004); and this requires that specific needs and goals are addressed. For RA patients generally, the needs a PRT program should address are: counteracting rheumatoid cachexia by restoring muscle mass and reducing adiposity (especially central stores); augmenting strength and thus improving physical function and the ability to perform ADL's; and lowering osteoporotic fracture risk by stabilizing or increasing bone mass and reducing the likelihood of falling by enhancing strength and balance. 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 specific cancers, enhanced mood and mental health etc., but to concentrate on those aspects of RA-specific health for which PRT is particularly appropriate. Additionally, individuals may also have personal goals and these should be taken into account when designing the training program. Since untrained individuals readily respond physiologically to most protocols, it is unnecessary to devise complicated or advanced programs.

To maximise the health and performance benefits, and to best ensure safety, it is important that appropriately qualified professionals are involved in designing the PRT program and, for the initial weeks at least, in supervising training. The following training recommendations are all consistent with guidelines provided by the ACR (2022, 2006), EULAR (Combe et al., 2007), ACSM (1998, 2010a-e) and AHA (Williams et al., 2007) either for RA specifically or for the co-morbid conditions common in RA, and by the WHO (2008) "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) (ACSM, 2010e).

4.1 Frequency
It is generally recommended that strength training is performed 2-3 days a week with at least 48 hours rest between sessions (Evans, 1999; Hass et al., 2001; Kraemer & Ratamess, 2004). Training on alternate days allows adequate time for recovery and adaptation, and this

is particularly important for untrained and/or elderly individuals (Hakkinen, 1995). Whilst there are benefits for highly trained individuals in training more frequently (e.g. daily), for the previously untrained there is insufficient additional training gain to justify the reduction in the recovery period and the additional time commitment (ACSM, 1998; Demichele et al., 1997). For example, Demichele et al. (1997) found that training twice a week elicited 80-90% of the strength gain achieved when training more frequently. In addition to facilitating recovery, limiting PRT sessions to 2-3 times per week should also enhance adherence to the training program, as "insufficient time" is a common reason for not commencing or dropping out of exercise programs (Dishman, 1994).

In healthy individuals it appears that once the training effects of PRT have been established (after 8-12 weeks training), that training once per week, perhaps even once fortnightly is sufficient to maintain these benefits (Graves et al., 1990). A similar maintenance training frequency seems to be appropriate for RA patients, as in the RAPIT study (de Jong et al., 2009), strength gains following 2 years of twice weekly HI training (including strength training) were maintained by patients who continued exercising once/week for the subsequent 18 months, but completely lost by those who stopped exercising. .

4.2 Intensity

To maximise improvements in strength and muscle hypertrophy, it is necessary to recruit the maximal number of motor unit; and 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 gains in strength and muscle mass (Fleck & Kraemer, 1997). Additionally, as mentioned previously bone also responds most favourably to heavy loading (e.g. Chamay & Tschantz, 1972; Kerr et al., 1996).

In resistance training, intensity is determined by the percentage of the 1-RM a load (weight) corresponds to. Although improvements in strength and muscle mass in previously untrained subjects have been demonstrated following training with loads of 50% 1-RM, multiple studies have shown that loads of ≥ 80% 1-RM are optimal for increasing strength and inducing muscle hypertrophy (e.g. ACSM, 1998; Evans, 1999; Hass et al., 2001; Kraemer & Ratamess, 2004). For untrained subjects and clinical populations aiming to enhance strength and muscle mass, an intensity of 80% 1-RM is generally prescribed, with higher intensities usually the preserve of competition athletes. For 80% 1-RM, 6-12 repetitions or lifts are usually possible. If less than 6 repetitions can be performed then the weight is too heavy, and if more than 12 repetitions can be achieved 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 both between individuals and for a given individual performing different exercises (Hoeger et al., 1987).

It is absolutely crucial that for untrained individuals, intensity at the commencement of PRT, should start low and progress slowly to allow the musculo-skeletal system sufficient time to adapt to the (unaccustomed) demands of training. For example, in our RCT (Lemmey et al., 2009), although the aim was for patients to eventually perform 3 sets of 8-12 repetitions at 80% 1-RM, (primarily to reduce muscle soreness) training was initially performed at much lower intensities. Thus, one set of 15 repetitions at 60% 1-RM was performed for each exercise in the first week, increasing to 2 sets at the same intensity in the second week and 3 sets at the same intensity in the third week. Intensity then increased to 70% 1-RM (12

repetitions per set) for weeks 4-6. Before finally progressing to 8 repetitions per set at 80% 1-RM for weeks 7-24 (note: to ensure maintenance of relative intensities, 1-RM's were reassessed every 4 weeks). By adhering to this protocol substantial training benefits were gained (e.g. increased LM and improvements of 119% in training specific strength), with no occurrences of training related injuries or dropouts from the program.

4.3 Time (volume)

With PRT, training volume is defined as the product of: number of exercises x number of sets per exercise x number of repetitions per set. 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.

With regard to the number of exercises; to maximise muscle hypertrophy and to facilitate improvement in the performance of ADL's, resistance training should involve the whole-body. Thus, 6-10 exercises each involving large muscle groups are usually prescribed (e.g. 1) leg press; 2) chest press; 3) leg extension; 4) seated rowing; 5) leg curl; 6) triceps extensions; 7) abdominal crunches/curls; 8) standing calf raises; 9) bicep curl (Lemmey et al., 2009; Marcora et al., 2005a).

Numerous studies have tried to determine the optimal number of sets per exercise, with comparisons of all permutations from one to 6 sets made, but no single number has consistently emerged as the best (e.g. Campos et al., 2002; Kraemer, 1997). When enhanced health and general function is the principle aim of training, for both healthy and clinical populations, 2 or 3 sets are usually prescribed (e.g. ACR, 2002, 2006; ACSM, 2010a-d; Combe et al., 2007; WHO, 2008, Williams et al., 2007). And for novice trainers, both 2 and 3 sets are very effective in eliciting training effects, with controversy persisting as to whether performing 3 sets delivers substantially better returns than performing 2 sets (Ostrowski et al., 1997). Of recent interest is the efficacy of single-set programs. In a number of studies one set of 8-12 repetitions performed to voluntary failure has, in previously untrained subjects, produced training gains comparable to those of conventional multiple set programs (ACSM, 1998); although there is disagreement with this finding (Paulsen et al., 2003), particularly in trained individuals (Kraemer, 1997). Even if single-set protocols are marginally less effective than multi-set programs, the time efficiency of the former may result in better training compliance, as programs that require in excess of 1 hour per session have higher dropout rates (Pollock, 1988). Thus, if time constraint is an important consideration, 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 responses (Hass et al., 2001).

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 more pronounced muscle hypertrophy (Kraemer, 1997) whilst longer rest periods (2-5 min) produce greater strength gains (ACSM, 2002). These differing effects have been attributed to the extent of ATP-PC (phosphagen system) repletion (Kraemer & Ratamess, 2004); 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 (Kraemer, 1997; Kraemer et al., 1987, 1991). Not surprisingly, body builders

favour programs which feature short rest periods, whilst strength and power athletes generally employ longer rest intervals. Whether these differential 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 rest between sets appears optimal.

4.4 Type (modality)

For safety, training on resistance machines with incremental weight stacks rather than using free weights is recommended (ACR, 2002; Pollock et al., 2000). Machines are also easier and quicker to set up. On the other hand, free weights allow more variety in the exercises performed and are better able to simulate ADL's. As mentioned previously, an optimal PRT program will feature exercises that collectively involve all the major joints and muscle groups. Such whole-body programs, as well as being more effective in increasing overall strength and muscle hypertrophy, also produce significant improvements in aerobic capacity (VO_2max) and endurance performance. For example, Vincent et al. (2000) noted that 6 months whole-body PRT increased peak VO_2 by 22% and treadmill time to exhaustion by 26% in elderly (60-85 years) men and women. Similarly, 10-12 weeks of HI PRT has been shown to improve time to exhaustion while cycling (47%), running (12%) and walking (38%) (Ades et al., 1996; Hickson et al., 1980).

Exercises should be performed rhythmically, in a slow, controlled movement (≈2 secs to lift and ≈4 secs to lower the weight) and, to avoid a Valsalva's manoeuvre and the resultant rises in blood pressure (BP), breathing should be continuous. When proper technique is observed, systolic BP during weight lifting is considerably lower than it is during aerobic exercise of similar intensity, and CV stress is minimal (Pollock et al., 2000). Naturally, 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 (ACSM, 2010c).

4.5 Progression

Gains in strength are usually rapid and substantial following commencement of PRT, with 10-15% increases in strength typically observed each week for the first 8 weeks of training in healthy, previously untrained individuals (Evans, 1999). Initially these improvements are due to enhanced neural factors i.e. improved motor unit recruitment, firing rate and synchronisation (Sale, 2003), with muscle hypertrophy contributing from about week 4 onwards (Sale, 2003). In order to maintain the maximal muscle fibre recruitment necessary for optimal increases in strength and muscle hypertrophy to occur, progressively higher loads need to be lifted. This increase in resistance (in accordance with 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 expected in untrained or deconditioned individuals, after an extended period of training the "law of diminishing returns" applies i.e. as an individual's fitness improves and he/she approaches their genetic ceiling it becomes harder to achieve further fitness gains. Consequently, when PRT is prolonged, plateaus in training response should be anticipated. 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 challenged by an unfamiliar training stimulus.

4.6 Exclusion criteria and further recommendations

As discussed previously, appropriately designed PRT is safe, and well tolerated by males and females of all ages and most conditions, including RA (ACSM, 1998). In the recommendations made by the AHA regarding resistance training for patients with and without CVD (Pollock et al., 2000), the contraindications to PRT are: unstable angina, uncontrolled hypertension (≥160/100 mm Hg), 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 (Pollock et al., 2000). 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"(Pollock et al., 2000). In part, this is because increased strength reduces the myocardial demands (i.e. heart rate and BP) when patients perform ADL's because the task requires a lower percentage of functional capacity (McCartney et al., 1993).

Caution must be taken when prescribing PRT to severely osteoporotic patients, with high-intensity exercise to be avoided (ACSM, 2010a). In the case of these patients, specialist advice with regard to exercise should be sought.

Despite the apparently beneficial consequences of training during acute flares shown by Van den Ende et al. (2000), we discourage training during flares. Similarly, as healthy individuals should be advised, we also discourage training during illness (e.g. colds, influenza etc), and tell patients to only resume training when health is restored. Upon resumption of training, loads should be adjusted to account for loss of strength due to detraining. Under these circumstances, pre-illness strength levels are usually rapidly regained. To underline the safety of and tolerance to PRT for RA patients, in our high intensity PRT intervention studies (Lemmey et al., 2009; Marcora et al., 2005a), mean compliance to training sessions (i.e. sessions attended as a % of those scheduled) was around 80%. Thus, even when advised to avoid training when unwell, patients training compliance was similar to that expected of healthy individuals.

5. Conclusion

This chapter has described important consequences of RA which are usually untreated (i.e. diminished muscle mass and high fat mass, particularly central obesity; rheumatoid cachexia) or are still prevalent despite enhanced pharmaceutical treatment (disability, CVD, osteoporotic fractures), and then reviewed the research into the efficacy and safety of PRT in treating these conditions. The evidence indicates 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 lack of negative side effects are considered. As such, rheumatologists and allied 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

advice, the fundamental principles of PRT program design have been outlined, with particular reference made to experiences with the RA population.

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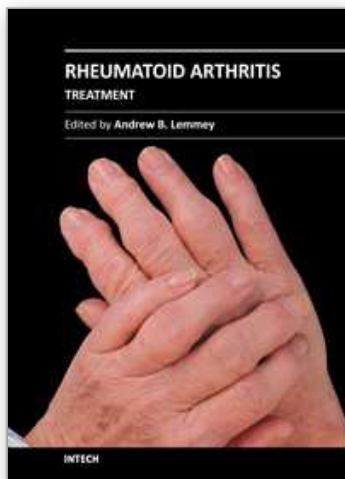
Rheumatoid Arthritis - Treatment

Edited by Dr. Andrew Lemmey

The purpose of this book is to provide up-to-date, interesting, and thought-provoking perspectives on various aspects of research into current and potential treatments for rheumatoid arthritis (RA). This book features 17 chapters, with contributions from numerous countries (e.g. UK, USA, Canada, Japan, Sweden, Turkey, Bosnia and Herzegovina, Slovakia), including chapters from internationally recognized leaders in rheumatology research. It is anticipated that Rheumatoid Arthritis - Treatment will provide both a useful reference and source of potential areas of investigation for research scientists working in the field of RA and other inflammatory arthropathies.

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