Multiple sclerosis and progressive resistance training: a systematic review

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Review

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Abstract

Recently progressive resistance training (PRT) has been recognised as an effective tool in the rehabilitation of persons with multiple sclerosis (MS). The objective of this study was to systematically review the literature of PRT studies for persons with MS. A comprehensive literature search (PubMed, SveMed+, Embase, Cochrane, PEDro, SPORTDiscus and Bibliotek.dk) was conducted. Identified papers were rated according to the PEDro-scale. Sixteen studies were included and scored between 3 and 8 of 11 total points on the PEDro-scale, showing a general lack of blinding. Strong evidence regarding the beneficial effect of PRT on muscle strength was observed. Regarding functional capacity, balance and self-reported measures (fatigue, quality of life and mood) evidence is less strong, but the tendency is overall positive. Indications of an effect on underlying mechanisms such as muscle morphological changes, neural adaptations and cytokines also exist, but the studies investigating these aspects are few and inconclusive. PRT has a positive effect on muscle strength for persons with MS. Heterogeneous results exist regarding the effect on functional capacity and self-reported measures probably because of differences in training protocols, samples sizes, type and severity of MS. The area of underlying mechanisms deserves more attention in future research.

Keywords

strength training, muscle strength, functional capacity, fatigue, quality of life, balance, neural disorder

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Introduction

Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system (CNS) where no exact aetiology has been established. MS is an autoimmune disorder that leads to the destruction of myelin, oligodendrocytes and axons.[1] Depending on the type of MS, individuals demonstrate neurological and functional decline ranging from very slow progression to rapid deterioration.

In general MS patients are characterised by reduced muscle strength during both dynamic[2,3] and static[2,4] muscle contractions. These strength impairments seem to primarily target the lower compared to the upper limbs.[4] The mechanisms underlying the observed strength deficit in MS patients are probably of both muscular and neural origin. Some studies,[5-7] but not all,[8-10] have indicated a loss of muscle mass in MS patients, which inevitably leads to relative reductions in muscle strength. Furthermore, the distribution of muscle fibre types differs between MS patients and healthy controls, but the findings are inconsistent.[5,7,10] Strength deficits may adhere to impairment of neural mechanisms seen in MS patients as, for example, indicated from reduced ability to fully activate motor units in the thigh and lower leg muscles (47–93%) during maximal voluntary contractions (MVCs) when compared with healthy controls (94–100%).[9,11,12] In addition, it has been shown that the rate of force development (RFD)[9,13] is reduced among MS patients, which is also an impairment of mainly neural origin.

At the functional level a relationship between gait speed and lower extremity muscle strength has been established in healthy elderly people[14] and in frail elderly women.[15] Correspondingly, a relationship has been observed in MS patients.[16,17] Both comfortable and maximal gait has been reported to be reduced in MS patients when compared with matched healthy subjects.[4,17,18] Other frequent functional impairments include poor balance,[19] spasticity[20] and

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Table 1. Detailed list of retrieved articles and applied search terms in seven different databases.

Database	Articles Retrieved	Search Terms (MeSH etc.)
Bibliotek.dk	2	("dissemineret sklerose" OR "sklerose") AND ("styrketræning" OR "træning")
SveMed+	2	"Multiple-Sclerosis" AND ("Resistance-Training" OR "Exercise-Therapy")
PubMed	170	"Multiple Sclerosis" AND ("Resistance Training" OR "Exercise Therapy") Free text: "multiple sclerosis resistance training"
Embase	269	"Multiple Sclerosis" AND ("Resistance Training" OR "Kinesiotherapy" OR "Exercise")
Cochrane	46	"Multiple Sclerosis" AND ("Resistance Training" OR "Exercise Therapy")
SPORTDiscus	6	"MULTIPLE sclerosis" AND "WEIGHT training"
PEDro	34	Abstract & Title: "Multiple Sclerosis". Therapy: "Strength Training"

fatigue.[21] Together, all of these (and other) impairments translate into a lower level of health-related quality of life (HRQoL) in MS patients.[22]

The extent to which the impairments seen in MS patients is the result of the disease process per se (i.e. demyelination and axonal degeneration in the CNS),[23] and/or is a consequence of the reduced physical activity level, is unclear.[5,24] Similarly, it is still unresolved to what extent the impairments can be reversed in MS patients.[9] Yet, it seems likely that at least inactivity-related impairments are reversible.[25,26]

Up until the 1990s, MS patients were advised against participation in exercise because it was believed to lead to worsening of symptoms or fatigue.[27] In recent years, this contention has been challenged and exercise has become a well-established part of many MS rehabilitation programmes.[26,28] Thus, several recent reviews[25,27–33] and meta-analyses[34,35] have touched upon the different aspects of exercise and MS. In 2008 a review from our group was published summarising results of both endurance, resistance and combined training.[26] Here it was concluded that resistance training of moderate intensity was well tolerated and had beneficial effects in MS patients, but the methodological quality of the few existing studies were generally low. Since then, several randomized controlled trials (RCT) have been published evaluating progressive resistance training (PRT) in MS patients. So far, however, no systematic review has been published focusing exclusively on PRT. Consequently, the purpose of this review is (1) to systematically review the literature on the effects of PRT in persons with MS and (2) to give advice on directions of future research within this field.

Methods

This review is based on a systematic literature search of different databases (PubMed, Embase, Cochrane library, SveMed+, bibliotek.dk, PEDro and SPORTDiscus) that was performed to identify articles regarding MS and PRT published before 30 March 2011. The search was performed using the MeSH terms 'resistance training' or 'exercise therapy' in combination with 'multiple sclerosis' (for exact search terms in the various databases, see Table 1). Also, a regular text search in PubMed with the terms 'multiple sclerosis resistance training' revealed two recent studies not yet categorised with MeSH terms that were included.

In total the literature search yielded 529 publications of which 140 were duplicates leaving 389 unique publications for screening based on their title and abstract. The screening revealed 50 publications relevant for extensive reading. Only peer-reviewed, longitudinal studies using training interventions that could be categorised as PRT (i.e. few dynamic muscle contractions against external loads) with sufficient progression (in accordance to the 2009 ACSM guidelines,[36] stating that a minor increase in load is introduced whenever subjects can perform the desired number of repetitions) were included. Consequently, 36 publications not fulfilling the criteria for relevant training intervention, progression or being either reviews, abstracts, non-English, cross-sectional or case studies were excluded (for details see Figure 1).

A total of 14 publications were originally included. The reference lists of those were checked for further relevant publications, however this resulted in no further relevant studies. During the review process two papers related to the current topic of interest were published. Of those, one was included while the literature list of the other revealed a study not found during the systematic literature review. Thus, a total of 16 papers were included in this review. The studies were then divided into (1) randomised controlled trial (RCT) studies and (2) non-controlled studies. Despite not all included studies being RCTs, all were evaluated using the original PEDro scale,[37] and were assigned 0–11 points. The purpose of the PEDro scale is to determine the external (criterion 1) and internal validity (criteria 2–9) of a study as well as to evaluate whether sufficient statistical information was presented to make the results interpretable (criteria 10 and 11). Two investigators (TK and UD) independently scored all included studies and afterwards consensus was made where scoring differed. If information needed for the PEDro scoring was either not available or unclear in an included paper, the corresponding author of the study was contacted (necessary in three of the studies). Results from evaluation with the PEDro scale are shown in Table 2 and detailed information regarding the included studies is presented in Table 3.

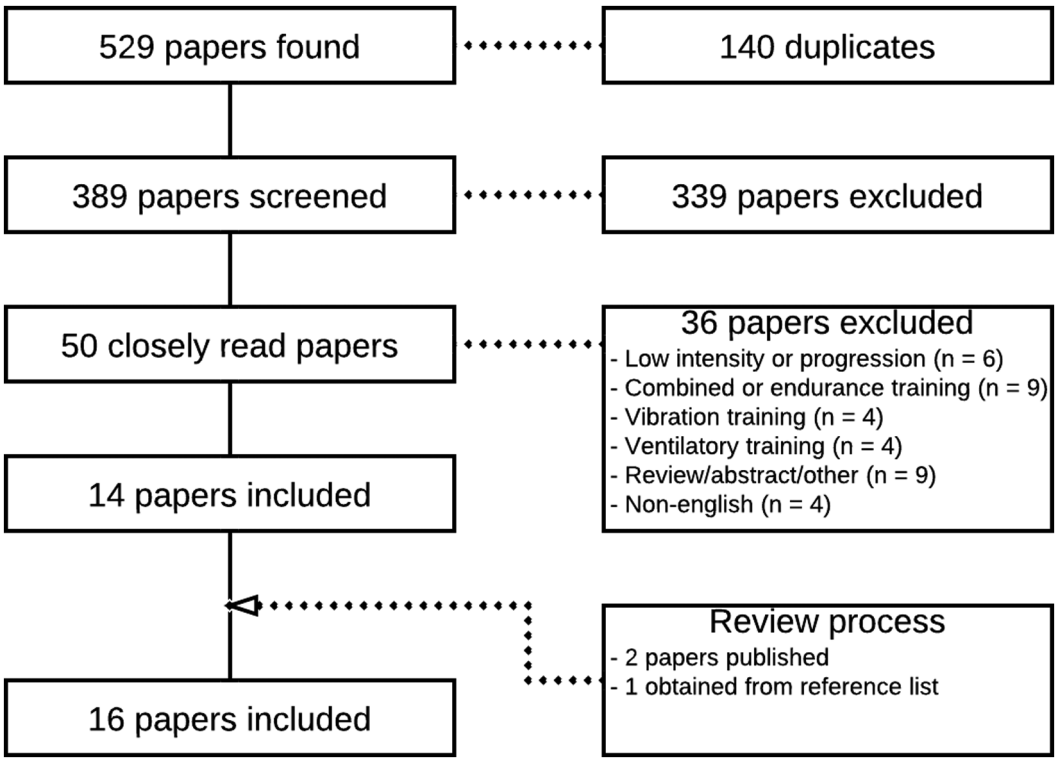

Figure 1. Flowchart illustrating the inclusion of literature.

Results

General study characteristics

Data from the PEDro scale showed that the existing studies scored between 3 and 8 of 11 total points (Table 2). With the exception of Dodd et al.,[38] no studies were awarded points in any of the criteria related to blinding because none had applied blinded assessors, therapists or participants (i.e. a control group doing sham exercise). A total of 289 MS patients have been included in the selected PRT studies with 188 enrolled in the intervention groups. Studies reporting the Expanded Disability Status Scale (EDSS, score going from 0–10, with 0 = no MS related impairments and 10 = death due to MS) scores shows that all studies have included patients scoring between 1 and 6.5 on the EDSS scale. Some of the studies[39–41] have only included MS patients with a relapsing–remitting disease course, whereas others have included several disease courses[42–44] or do not report on this patient characteristic.[45–47] Only the studies by Dalgas et al.[39,48] and Dodd et al.[38] provide detailed information concerning the screening and selection process for inclusion of patients. Regarding medication of the MS patients most of the studies do not provide any information[38,42–46,49–51] whereas the remaining studies report specific kinds of medication taken by the subjects.[39–41,48,52,53] The duration of the training interventions ranged from 3 to 26 weeks and the training frequency ranged from 2 to 5 days/week, with 2 days/week most commonly applied.[39,44,45,47,53] Intensity of training is in general reported in two different ways; expressed as a percentage of 1 repetition maximum (1RM is the heaviest load that can be lifted one time using proper technique), or as the resistance appropriate for a given number of repetitions, i.e. 10RM. Overall training intensity in the included studies ranged from 60% to 90% of 1RM[40,41,45–47,49,50,53] or 8–15RM[39,42,48,52] and the total number of exercise sessions ranged from 15 to 52. The PRT intervention solely aimed at the lower extremity in most studies[39,42,43,45,46] with only a few studies also including upper-body exercises.[44,47,51,53]Except for one study applying home-based training[43] all studies applied supervised PRT.

In summary, the included trials applied 3–26 weeks of primarily supervised PRT at intensities ranging from 60% to 90% of 1RM or 8–15RM and mainly targeting the lower extremities in persons with MS suffering from low to moderate impairments (EDSS 0-6.5).

Disease progression, tolerability, drop-out rates and adherence

MS disease progression is usually evaluated with the EDSS but the studies evaluating the effects of PRT on this score shows no effect.[39,46,53] None of the studies report on any adverse events or any serious symptom exacerbations. Also, high adherences (90–100%) and low drop-out rates (0–13%) from the PRT groups are consistently reported.

Table 2. Included papers rated according to the PEDro scale.

Trials		PEDro criteria											Score
		#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	
RCT	Broekmans et al.[42]	YES	YES	NO	YES	NO	NO	NO	YES	NO	YES	YES	6/11
	Dalgas et al.[39, 48, 52]	YES	YES	YES	YES	NO	NO	NO	NO	NO	YES	YES	6/11
	DeBolt et al.[43]	YES	YES	NO	YES	NO	NO	NO	YES	NO	YES	YES	6/11
	Dodd et al.[38]	YES	YES	YES	YES	NO	NO	YES	YES	NO	YES	YES	8/11
	Fimland et al.[46]	NO	YES	YES	YES	NO	NO	NO	YES	YES	YES	YES	7/11
	Sabapathy et al.[44]	NO	YES	NO	YES	NO	NO	NO	NO	NO	YES	YES	4/11
Non-controlled Trials	de Souza-Teixeira et al.[45]	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	YES	4/11
	Dodd et al.[49], Taylor et al.[47]	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	NO	3/11
	Filipi et al.[51]	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	NO	3/11
	Gutierrez et al.[40], White et al.[41, 50, 53]	YES	NO	NO	NO	NO	NO	NO	YES	YES	NO	NO	3/11

Publications from the same trial have been rated as one.
Criteria specification (for further specification of criteria, see Maher[37]:
Criteria #1: Specified elegibility criteria
Criteria #2: Randomized allocation
Criteria #3: Concealed allocation
Criteria #4: Similarity between groups at baseline
Criteria #5: Blinding of subjects
Criteria #6: Blinding of therapists
Criteria #7: Blinding of assessors
Criteria #8: Outcome measures obtained from at least 85% of initially allocated subjects
Criteria #9: All received treatment, or key outcome was analyzed by "intention to treat"
Criteria #10: Between-group statistical comparisons
Criteria #11: Both point and variability measures provided

In summary, the few short-term studies that have applied a clinical scale that evaluates disease progression do not indicate that PRT can influence disease progression.

Muscle strength

A consistent finding is improvement in muscle strength of the muscles trained during PRT. All included studies report significant increases in muscle strength. Most studies have focused on strength of the lower extremity and report relative increases in maximal voluntary contractions (MVC) ranging from ~7% to 21% for knee extensor,[39,40,42,45,53] knee flexor[39] and plantar flexor[46] muscles. MVC of lower extremity muscles at baseline and relative changes after PRT interventions are summarised in Table 4. Dynamic strength, measured as 1RM in different leg exercises, is reported to increase in the range of 20–50%.[38,39,42,47] Of the included studies only Taylor et al.[47] measured dynamic strength of the upper extremity, reporting a 14% increase in 1RM arm press. Dynamic strength has also been measured isokinetically. Broekmans et al.[42] observed no significant increase in peak torque of the knee extensors at 60°/s PRT. Dalgas et al.,[52] on the other hand, observed no significant increase in peak torque for the knee extensors at 90°/s while knee extensor peak torque at 180°/s and knee flexor torque at 90 and 180°/s significantly increased 10–22%. Two studies measured handgrip strength but found no changes;[39,44] however, the hand grip muscles were not specifically trained in these studies. Finally, DeBolt and McCubbin[43] reported a 37% increase in leg extensor power.

In summary, there is strong evidence that PRT interventions successfully increase lower extremity muscle strength in MS patients, however the evidence for upper-body strength adaptations is modest. The results indicate that strength improvements only occur in the muscle groups specifically targeted during training.

Muscle morphological and neural adaptations

Only few studies have evaluated muscle morphological and neural adaptations after PRT in MS patients. Two non-controlled training studies of similar duration (8 weeks) have evaluated the effects of PRT on knee extensor[45,53] and knee flexor[53] cross-sectional area (CSA) measured by MRI. In a non-controlled study, White et al.[53]

Table 3. Schematic overview of included studies.

Trials		Sample Size Dropouts Adherence %	Subjects Disease Scale MS disease course	Duration & frequency	Training regime	Outcome
RCT	Broekmans et al.[42]	RT: 11, RT+es: 11, Con: 14 Total dropout: 3/36 = 8% RT dropout: 1/22 = 5% Adherence: 99%	EDSS: 2.0-6.5 Type: RR, SP, PP	20 weeks 5 sessions / 2 weeks	3 leg exercises (unilateral) 1-2sets x 10-15reps at 60% 1RM / 10-15RM	Strength ↑ FC → RT+es = RT
	Dalgas et al.[39, 48, 52]	RT: 19, Con: 19 Total dropout: 7/38 = 18% RT dropout: 5/38 = 13% Adherence: 99%	EDSS: 3.0-5.5 Type: RR	12 weeks 2 sessions / week	5 leg exercises 3-4sets x 8-12reps at 8-15RM	Strength ↑ FC ↑ CSA ↑ QoL ↑ Fatigue ↓ (improved) Mood↑ (improved)
	DeBolt et al.[43]	RT: 20 Con: 17 Total dropout: 1/37 = 3% RT dropout: 1/20 = 5% Adherence: 95%	EDSS: 1.0-6.5 Type: RR, CP, PP	8 weeks 3 sessions / week	BodyWeight + Vest 2-3sets x 8-12reps	Balance → Leg Power ↑ FC →
	Dodd et al.[38]	RT: 39 Con: 37 Total dropout: 5/76 = 7% RT dropout: 3/39 = 8% Adherence: 92%	Ambulation Index score: 2-4 Type: RR	10 weeks 2 sessions / week	5 leg exercises 2sets x 10-12reps at 10-12RM	FC → Strength ↑ Fatigue ↓ (improved) QoL-physical ↑
	Fimland et al.[46]	RT: 7, Con: 7 Total dropout: 0/14 = 0% RT dropout: 0/14 = 0% Adherence: 100%	EDSS: 2.0-6.5 Type: Not reported	3 weeks 5 sessions / week	2 leg exercises 4sets x 4reps at 85-90% 1RM	EMG ↑ Strength ↑ Voluntary motor output ↑
	Sabapathy et al.[44]	RT: 15, END: 6 Total dropout: 5/21 = 24% RT dropout: 1/21 = 5% Adherence: ~90%	DSS: 1-3 Type: RR, SP, PP	8 weeks crossover 2 sessions / week	8 exercises (3 leg) 2-3sets x 6-10reps	Mood → Fatigue ↓ (improved) QoL → FC ↑ Balance ↑ MSISphysical ↑ MSISpsychological →
Non-controlled trials	de Souza-Teixeira et al.[45] (8-week control period)	RT: 13 RT dropout: 0/13 = 0% Adherence: 100%	EDSS: 1-6 Type: Not reported	8 weeks 2 sessions / week	1 leg exercise 3sets x 10-15reps at 40-70% MVC	Strength ↑ FC ↑ CSA ↑
	Dodd et al.[49], Taylor et al.[47]	RT: 9 RT dropout: 1/9 =11% Adherence: 94%	DSS: 0-2 Type: Not reported	10 weeks 2 sessions / week	6 exercises (3 leg) 2sets x 10-12reps at 60-80% 1RM	Strength ↑ FC → MSISphysical ↑ MSISpsychological → Interviews: Physical, psycological and social benefits

(Continued)

Table 3. (Continued)

Trials		Sample Size Dropouts Adherence %	Subjects Disease Scale MS disease course	Duration & frequency	Training regime	Outcome
	Filipi et al.[51]	RT: 33 RT dropout: 0 Adherence: 100%	EDSS: 1.0-6.5 Type: RR, SP, PP	26 months 2 sessions / week	3 phases consisting of: 9-10 exercises (2 leg) 2-3 sets x 10reps at 10RM	MSFC ↑ Fatigue ↓ (improved) MFES ↑ (improved) Gait-characteristics ↑
	Gutierrez et al.[40]	RT[40]: 8	EDSS[40]: 2.5-5.5	8 weeks	5 exercises (3 leg)	Strength[40,53] ↑
	White et al.[41, 50, 53]	RT[53]: 8 RT[41]: 10 RT[50]: 12 RT dropout: 0/8-12 = 0% Adherence[40, 50, 53]: 100% Adherence[41]: Not reported	Type[40]: RR EDSS-sr[53]: 1.0-5.0 Type[53]: Not reported EDSS[41]: 2.5-5.5 Type[41]: RR EDSS-sr[50]: 4.00±1.37 Type[50]: Not reported	2 sessions / week	1 set x 5reps at 40% 1RM 1 set x 10-15reps at 60-70% 1RM	Gait-characteristics[40] ↑ SR-EDSS[40,53] →(↑) Fatigue[40,53] ↓ (improved) Activation ratio[53] → CSA[53] → FC[53] →↑ Pro-inflammatory cytokines[41]↓ Anti-inflammatory cytokines[41] ↓ CAD-risk factors[50] ↓

↑ indicates increase, → indicates no change, ↓ indicates decrease, (↑) tendency to increase.

Abbreviations:

RCT = Randomized Controlled Trials, RT = Resistance Training, RT+es = Resistance training combined with electrical stimulation, Con = Control group, END = Endurance group, EDSS = Expanded Disability Status Scale, DSS = Disease Steps Scale, RR = Relapsing Remitting, SP = Secondary Progressive, PP = Primary Progressive, CP = Chronic Progressive, RM = Repetition Maximum, FC = Functional Capacity (generalized valuation from various functional tests), CSA = Cross-Sectional Area, QoL = Quality of Life, EMG = Electromyography, MSIS = Multiple Sclerosis Impact Scale (physical and physiological aspects), MSFC = Multiple Sclerosis Functional Composite, MFES = Modified Fall Efficacy Scale, SR-EDSS = Self-Reported EDSS, CAD = Coronary Artery Disease

Table 4. Summary of baseline means and relative changes of lower extremity muscle strength and walking performance.

Trials		Duration, choice of leg and disease scale	Lower Extremity MVC			Short Walk Test / TUG			Long Walk Test		
			Group	Baseline	Change#	Group	Baseline	Change#	Group	Baseline	Change#
RCT	Broekmans et al.[42]*	20 weeks, 50 sessions Mean of both legs EDSS 2.0-6.5	Knee Extension			T25FWT			2MWT		
			RT	128Nm	+8 %	RT	6.2s	NS	RT	167m	NS
			RT+es	117Nm	NS	RT+es	5.4s		RT+es	178m	
			Control	98Nm	NS	Control	5.8s		Control	166m	
			Knee Flexion			TUG					
			RT	56Nm	NS	RT	8.2s	NS			
			RT+es	59Nm	NS	RT+es	7.1s				
			Control	50Nm	-11%	Control	7.7s				
	Dalgas et al.[39, 48, 52]	12 weeks, 24 sessions Best functioning leg (self-reported) EDSS 3.0-5.5	Knee Extension[39]			10MWT			6MWT		
			RT	175Nm	+16%	RT	7.7s	-12%	RT	438m	+15%
			Control	169Nm	NS	Control	7.3s	NS	Control	441m	NS
			Knee Flexion								
			RT	73Nm	+21%						
			Control	67Nm	NS						
	DeBolt et al.[43]	8 weeks, 24 sessions EDSS 1.0-6.5	NA			TUG			NA		
						RT	11.3s	NS			
						Control	11.1s				
	Dodd et al. [38]	10 weeks, 20 sessions Ambulation Index 2-4	NA			MWS			2MWT		
						RT	1.38m/s	NS	RT	120m	NS
						Control	1.28m/s		Control	112m	
	Fimland et al.[46]	3 weeks, 15 sessions Right leg EDSS 2.0-6.5	Plantar flexion			NA			NA		
			RT	88Nm	+20%						
			Control	88Nm	NS						
	Sabapathy et al.[44]	8 weeks, 16 sessions DSS 1-3	NA			TUG			6MWT		
						RT	7.5s	-9%	RT	447m	+9%
						ET	7.2s	-7%	ET	484m	+4%

(Continued)

Table 4. (Continued)

Trials		Duration, choice of leg and disease scale	Lower Extremity MVC			Short Walk Test / TUG			Long Walk Test		
			Group	Baseline	Change#	Group	Baseline	Change#	Group	Baseline	Change#
Non-controlled Trials	de Souza-Teixeira et al.[45]	8 weeks, 16 sessions Bilateral EDSS 1-6	Knee Extension RT	267Nm	+14%	TUG RT	8.4s	-8%	NA		
	Dodd et al.[49]	10 weeks, 20 sessions	NA			MWS			2MWT		
	Taylor et al.[47]	DSS 0-2				RT	2.09 m/s	+6%	RT	148m	NS
	Filipi et al. [51]	26 weeks, 52 sessions EDSS 1.0-6.5	NA			T25FWT RT	6.9s	NS	NA		
	Gutierrez et al.[40], White et al.[41, 50, 53]	8 weeks, 16 sessions Self-reported more-affected leg[40] EDSS 2.5-5.5	Knee Extension[40] RT Knee Flexion RT Plantar Flexion RT Dorsi Flexion RT	75Nm 39Nm 60Nm 29Nm	+7% NS +55% NS	T25FWT[53] RT	6.1s	NS	NA		

*Measured at two different joint angles. The highest mean is presented.

Change calculated as percentage difference in means; 1-post/pre (unless mean percentage change explicitly stated in paper)

Abbreviations: 10MWT = 10 Meters Walking Test, 2MWT = 2 Minute Walking Test, 6MWT = 6 Minute Walking Test, DSS = Disease Steps Scale, EDSS = Expanded Disability Status Scale, ET = Endurance Training group, MVC = Maximal Voluntary Contraction, MWS = Maximal Walking Speed, NA = Not Available, NS = Non-Significant, RT = Resistance Training group, RT+es = Resistance Training with electrical stimulation, T25FWT = Timed 25 Foot Walk Test, TUG = Timed Up and Go

found non-significant changes of 0.7% and 9.6% in knee extensor and knee flexor CSA, respectively. A non-controlled study[45] reported an increase of 3.6% in knee extensor CSA. Dalgas et al.[52] obtained biopsies from m. vastus lateralis before and after 12 weeks of PRT and reported significant increases in the mean CSA of all muscle fibres (7.9%) and of the type II muscle fibres in particular (14.0%) in comparison with a control group. No change in the distribution of fast and slow fibre types occurred. Applying the method of superimposing electrically induced twitches to maximal isometric contractions, enables one to assess voluntary neural activation of skeletal muscles. Using this method White et al. did not observe any change in m. quadriceps activation[53] after 8 weeks of PRT. Fimland et al.,[46] on the other hand, reported that soleus EMG activity (an indicator of neural drive) and the voluntary motor output increased by 40% and 55%, respectively, compared with the control group, after 3 weeks (15 sessions) of PRT. This led the authors to conclude, that PRT is effective in augmenting the magnitude of efferent motor output of spinal motor neurons.

These preliminary findings suggest that PRT may induce both muscle hypertrophy and neural adaptations.

Functional capacity

The results regarding the effects of PRT on functional capacity in MS patients are less consistent. Accordingly, the effects on walking performance (distance) in 2 or 6 minutes walking tests (2MWT / 6MWT) are mixed. Two studies both measuring distance walked during a 6MWT reported increases in distance in the range of 6–15%,39,44 whereas three studies, measuring distance walked during a 2MWT, reported no increases.[38,42,47] Several studies have measured maximal walking velocities by applying either the timed 25 foot walk test (T25FW) or the 10 m walk test (10MWT). Three studies reported no change in T25FW.[42,51,53] While one study reported a 12% improvement in the 10MWT,[39] another observed no improvement in maximal walking speed.[38] Several studies have performed the 'Timed Up and Go test' (TUG). Two studies observed no change in TUG,[42,43] with one of the studies showing a tendency ($p = 0.09$) to a 13% improvement.[43] Two other studies observed improvements in TUG of 8% and 9%, respectively.[44,45] The baseline values and relative changes in the above-mentioned walking tests has been summarised in Table 4. Other measurements to evaluate functional capacity include a stair climb test (SCT), chair stand test (CST) and also kinematic gait analysis. With regard to SCT no changes were observed by Taylor et al.,[47] however Dalgas et al.[39] reported improvements in both SCT and CST of 12% and 28%, respectively. Gutierrez et al.[40] and Filipi et al.[51] measured kinematic gait parameters and observed various alterations suggesting improved gait. The aforementioned functional tests consisting of more strength demanding tasks than pure walking in general shows better improvements than the short and long walking test.

In summary, PRT may improve some strength demanding functional tasks, but improvements in timed or distance based walking tests are generally lacking.

Balance

Four studies evaluated the effects of PRT on balance.[42-44,51] Broekmans et al.[42] reported a significant increase in balance (measured as functional reach) in the PRT group as compared with the control group. Sabapathy et al.[44] found an effect in the functional reach test for the PRT group. Finally, DeBolt and McCubbin[43] did not find any change in a balance test (body sway) performed on a force platform in a study evaluating home-based PRT although the PRT group decreased the anterior-posterior sway by 10.3% and the control group increased by 6.4% ($p = 0.1$). Filipi et al.[51] applied a questionnaire used to assess fear of falling (Modified Fall Efficacy Scale) and observed improvements.

In summary preliminary findings suggest that PRT might improve balance in MS patients.

Self-reported fatigue, mood and quality of life

Three RCT studies[38,44,48] have evaluated the effects of PRT on self-reported fatigue, mood and quality of life. Dalgas et al.[48] compared scoring on the Fatigue Severity Scale (FSS) in a PRT group with a control group and found significant improvements. Also, improvements in mood score (Major Depression Inventory) and in the physical component score of the Short Form 36 (SF-36) questionnaire were reported after PRT. Sabapathy et al.[44] found effect in the Modified Fatigue Impact Scale (MFIS), but not in the mood score (Becks Depression Inventory) or quality of life (SF-36). When Sabapathy et al. evaluated mood score (Becks Depression Inventory) and quality of life (SF-36) neither between-group nor within-group effects were found. Dodd et al.[38] also utilised MFIS to quantify fatigue and found an overall significant difference between groups. However, Dodd et al. only observed a significant difference between the groups in the physical component of the MFIS scale. Dodd et al. also applied the WHO Quality of Life-BREF questionnaire to assess quality of life. An effect was observed in the physical health component, but not in the overall score. The MFIS findings were confirmed in a non-controlled study White et al.,[53] who also reported a positive effect on the MFIS after 8 weeks of PRT. Also the non-controlled study by Filipi et al.[51] reported a significant improvement in the physical component of the MFIS. Finally, Dodd et al.,[49] using a qualitative approach, reported reduced fatigue in seven out of nine patients after 10 weeks of PRT.

In summary, the existing studies evaluating the effects of PRT on self-reported fatigue shows improvements, whereas findings regarding mood and quality of life diverge.

Cytokines and health risk

In a non-controlled study by White et al.,[41] significant decreases were found in the resting blood levels of the pro-inflammatory cytokines interferon gamma (IFNγ) and C-reactive protein (CRP) and anti-inflammatory cytokines interleukin 4 (IL-4) and IL-10. In another non-controlled study, White et al.[50] observed a decrease in the overall number of elevated coronary artery disease (CAD) risk factors following 8 weeks of PRT.

In summary the results from these studies suggest that PRT might positively modulate resting blood levels of cytokines and reduce CAD risk factors. However, it needs to be emphasised that these studies were non-controlled and need further support from future RCT studies.

Discussion

A systematic literature search revealed 16 publications regarding PRT interventions for MS patients. MS patients with an EDSS below 6.5 tolerated PRT without any adverse effects and showed excellent adherence to the training programs in all studies. A consistent finding following PRT is increased isometric and dynamic strength of the trained muscles. Attempting to relate the increases in muscle strength to muscle morphological parameters, two non-controlled[45,53] studies performing MRI scans of the trained muscles have shown (at least tendencies to) small increases in whole muscle CSA. At the cellular level increased muscle fibre CSA has been reported.[52] Neurological improvements related to increased muscle strength have also been reported[46] but not in all studies.[53] However, the fact that White et al.[53] observed no change in m. quadriceps activation ratio might be due to a ceiling effect. The activation ratio before training was at 95%, leaving little room for improvement. The consistent strength improvements do, however, only in few cases translate to improvements of functional capacity and balance. Regarding self-reported fatigue, mood and quality of life significant improvements are reported in most, but not all studies. A mechanism for improvements in fatigue is provided in a recent review by Andreasen et al.[54]

Testing muscle strength

The results from the various strength tests applied in the existing literature illustrate the specificity of adaptation to PRT. Isometric MVCs obtained from 'gold standard' dynamometry showed increases in the range of 7–21%, whereas dynamic strength (1RM), tested similarly to the way exercises had been conducted, showed changes in the range of 20-50%. This discrepancy in strength adaptation is commonly observed, and is believed to reflect learning that is task specific.[55] The point concerning task-specific strength adaptations is, furthermore, exemplified by Dalgas et al.[39] observing no change in handgrip strength after 12 weeks of PRT for the lower extremities. Furthermore, specificity of adaptations might also explain why Sabapathy et al.[44] observed no improvement in strength when only measuring handgrip strength after upper-body PRT. Altogether this demonstrates the importance of choosing an appropriate and relevant method to measure changes in maximal strength. All studies employed PRT for the lower extremity, and only four studies[44,47,51,53] also included exercises for the upper extremity. This may be explained by the larger strength deficit in the lower extremity than in the upper extremity when compared with matched healthy controls.[4] A last important point to consider when testing lower extremity muscle strength is what leg to test. As can be seen in Table 4, no consensus exists regarding testing of muscle strength in terms of choosing least or most affected leg or both.

Muscle strength and walking performance

As established in the introduction, people with MS suffer from reduced muscle strength[2,4] and walking performance[17] compared with healthy individuals. Several studies has shown correlations between lower extremity strength and walking performance,[14,15,17] and increased walking performance has been observed to accompany increased muscle strength in frail elderly people.[56]

Table 4 summarises the mean and relative changes for lower extremity muscle strength (MVC measurements) and walking performance for the included studies. Consistent increases are observed with regard to muscle strength, however, in several occasions the translation into improved walking performance does not take place. Several factors account as possible explanations for this discrepancy. First, the relatively small population sizes and the concomitant risk of type II errors can be a possible explanation. The RCT by Dodd et al.[38] was powered specifically to investigate the effect of PRT on walking performance (resulting in the largest population size of the included studies), but failed to detect any effect. A second explanation could be a possible ceiling effect with regard to walking performance, i.e. the included subjects do not suffer from sufficiently reduced walking performance in order to improve significantly. If so, this would be expected to be reflected by baseline differences in EDSS or walking performance between studies. However, Table 4 does not reveal any major differences between EDSS or baseline walking performance between the trials that can explain the discrepancy in improvements in walking performance. A third explanation could be differences in training intensity, frequency and/or

length of training periods between studies. However, the RCT by Broekmans et al.[42] and the non-controlled trial by Filipi et al.[51] applied the longest training interventions but did not observe improved walking performance. On the other hand, the study by Dalgas et al.[39,48,52] which show improvements in walking speed is the study applying the most comprehensive training intervention when considering the combination of duration of intervention, intensity per repetition and volume per session (for the lower extremity). A final explanation may be differences in the sensitivity (responsiveness) of the applied walking tests. To our knowledge no single study has evaluated the responsiveness of different walking tests in MS patients. However, the T25FW, for instance, appears to have limited sensitivity to change in the middle range of the EDSS (mean ± SD of 5.6 ± 1.1)[57] as well as reduced sensitivity to change in the lower range of the scale (EDSS <4.0)[58] probably indicating a floor effect in mildly affected persons with MS. A longer walking test like the 2MWT or 6MWT is not limited by a floor effect and may, therefore, be more sensitive to change when evaluating the effects of PRT on walking performance in MS patients. Regarding test–retest Paltamaa et al.[59] reported excellent intraclass correlation coefficients (>0.9) for both short and long walking test. Also, Paltamaa et al.[60] reported a minimal detectable change of 92 m in the 6MWT and 0.26 m/s in maximal walking speed (obtained from the 10MWT). Consequently, some of the significant improvements in walking performance may not be of clinical importance. To allow more direct comparisons in future studies consensus on walking outcome measures should be reached. A recent study has provided a proposal for such a consensus.[61] Some trials also applied functional tasks such as chair and stair case test. Performance in these test seem to improve as a result of PRT, perhaps because of a larger direct contribution from muscle strength and less dependence on coordination.

Methodological quality of the included studies

All included studies were rated according to the PEDro scale.[37] Scores ranged from 3 to 8 of 11 total points, and revealed a general lack of blinding of both assessors and participants. Of the 16 publications, only 8 employed RCTs. The non-controlled trials scored between 3 and 4 on the PEDro scale which were lower than the RCT studies. In order to improve the methodological quality of future studies, these finding suggest that a RCT design with blinding of assessors, therapists (if possible) and subjects (by applying 'sham exercise') is important to consider. Another way of improving the methodological quality, which is not reflected by the PEDro scale, is detailed information regarding the screening and inclusion process for patients. This could be presented as flow diagrams as suggested in the CONSORT statement 2010. The size of the intervention groups varies, ranging from 7 to 39 MS patients. The few studies[39,43,47] that utilised initial power calculations to determine population size have primarily focused on muscle strength as the primary outcome. These studies have intervention groups of 19[39] and 20[43] subjects, respectively. Since muscle strength shows the most consistent and in general the largest relative improvements of the included outcome measures, it seems likely that the statistical power of the other outcome measures is lower. Acknowledging this, Dodd et al.[38] used walking performance to determine population size and found groups of 35 participants required to detect changes.

Future directions

Substantial evidence now exists that PRT is efficient in improving muscle strength *per se,* whereas less convincing evidence exist that PRT is efficient in producing improvements in balance, functional capacity, mood and quality of life. Future studies should, therefore, as their primary purpose, target these areas and be powered accordingly. In such studies, we also suggest that only participants with well-defined deficits in the area of interest are included (i.e. only clinically fatigued patients are included in studies evaluating the effect of PRT on fatigue).

It also remains to be investigated how PRT is optimally applied to MS patients with different disease courses and how the mechanisms underlying disease progression is influenced by PRT. The investigation of both aspects seems closely related to challenges in stratification of different patient profiles. Only few studies have stratified patients according to disease course, gender and/or type of medication, which may blur the effect of PRT for MS patients. Also, no studies have evaluated PRT in the more severely disabled patients having an EDSS score above 6.5. Regarding outcome measures and PRT interventions, future studies might benefit from improved consensus on applied methods and by development of more functional PRT exercises that are investigated in long-term studies that ideally also includes a follow-up period. Accordingly, a long-lasting PRT intervention including a large sample size would better allow evaluation of a possible influence of PRT on disease progression evaluated with clinical scales (EDSS, MFSC, etc.) and/or MRI. However, this is obviously a difficult study to complete. Another warranted approach would be to look at the underlying mechanisms potentially implicated in disease progression, such as cytokines. While the pioneering study on this aspect[41] certainly deserves merit, it is also inherent of limitations relating to gender, specific medication and/or disease course. In relation to the gender aspect, animal studies imply that females display a more profound pro-inflammatory profile compared with males, but at the same time oestrogen is believed to perform an anti-inflammatory function.[62] In relation to medication, different medical compounds may exert variable effects on different immune system components. Also, it

can be speculated that some disease courses may be more strongly causally related to immune system mechanisms than others.[63] Accordingly, to explore such research questions, future studies should seek to improve (a) stratification of gender and within profiles of female MS patients (e.g. pre- versus post-menopausal women, timing of sampling/testing with reference to female menstrual cycle and/or with/without intake of oral contraceptives), (b) stratification of patients receiving prescribed immunosuppressant medication versus non-immunosuppressant medication and/or (c) stratification of patients by disease course. While certainly challenging, such strategies could serve to provide important information on how to optimally individualise PRT.

Conclusion

Persons with MS having an EDSS below 6.5 can both tolerate and benefit from PRT. It is consistently reported that PRT improves lower extremity muscle strength, however the transfer to improved walking performance is questionable. Another consistent finding is improvement in fatigue. Furthermore, PRT may improve mood and quality of life but heterogeneous results exist probably due to differences in PRT protocols, sample sizes, outcome measures and type and severity of MS. Indications of beneficial muscle morphological changes and neural adaptations (enhanced neural drive) has been observed, however these areas deserves further attention in future research.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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