

The Effect of Progressive Resistance Training on Fatigue in Multiple Sclerosis Patients: A Systematic Review

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Abstract

Background: Fatigue is a frequent symptom of multiple sclerosis, with negative effects extending from general functioning to the quality of life. Progressive resistance training (PRT) can be an effective tool in the rehabilitation of fatigue in people with multiple sclerosis (MS). PRT can improve the performance of physical activities such as walking and the health-related quality of life of people with MS.

Aim of Study: The aim of this systematic review was to examine the effectiveness of PRT for fatigue in MS patients.

Material and Methods: The current study was conducted on patients with MS aged ≥ 18 years. We searched the following electronic databases: The Cochrane library, PubMed, Scopus, Physiotherapy Evidence Database (PEDro) and the Web of Science and a manual search of bibliography from inception till June 2021. Randomized Control Trials (RCTs) were only included in this review and the others were excluded according to eligibility criteria. The intervention used was PRT. Quality assessment of all eligible studies was done using the PEDro scale.

Intervention: Five relevant randomized controlled trials included progressive resistance training and its effects on fatigue in patients with multiple sclerosis.

Results: Five articles with 186 patients met our inclusion criteria and were included in our meta-analysis for fatigue as the primary outcome.

Conclusions: Progressive resistance training appears to be effective and safe in the management of fatigue in MS patients and patients should continue on PRT to maintain its positive benefits. But more future studies are still needed to cover this issue.

Key Words: Multiple sclerosis – Progressive resistance training – Fatigue – Systematic review.

Introduction

MULTIPLE sclerosis (MS) is an autoimmune disease in which the interchange between inflamma-

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tion and neurodegeneration causes more or less resolved relapses, and a different degree of neurological disability. MS is a chronic progressive inflammatory demyelinating disease of the central nervous system (CNS) with a clinical varying course. It is the most common cause of progressive neurological disability in young adults, with a major physical, psychological and financial impact [1].

The number of people with MS across the globe has increased from 2.3 million in 2013 to 2.8 million in 2020. The prevalence rate of MS among Egyptian population in different centers about 59 per 100,000 [2].

Fatigue is a frequent symptom of multiple sclerosis with negative effects extending from general functioning to quality of life. It was reported that up to 92% of patients with MS complain of fatigue. Fatigue presents itself as a chronic symptom, but it may be found even in the early stages of the disease and even in persons with mild disability due to MS. It can even appear before other MS symptoms and expects disease progression [3].

Abbreviation:

PRT : Progressive resistance training.
CON : Control group.
BMCT : Balance and motor control training.
EDSS : Expanded Disability Status Scale.
RR : Relapse remitting.
SP : Secondary progressive.
PP : Primary progressive.
Reps : Repetitions in each set.
RM : Repetition maximum.
MFIS : The Modified Fatigue Impact Scale.
FSS : The Fatigue Severity Scale.
EX : Home-based resistance training.
TMW : Tolerated maximum workload.
MFI-20 : The Multidimensional Fatigue Inventory.

Fatigue is defined as a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with personal activities. Subjectively, fatigue may be described as exhaustion, a lack of energy, or awesome tiredness that is widespread and can occur at rest [4].

The etiology and pathophysiology of fatigue in MS patients are not well explained and seem to be complex. The fatigue in MS is probably related to the underlying pathologic alterations in MS, such as sequelae from central nervous system damage, demyelination, inflammation, and axonal injury. Fatigue in MS can also arise from associated conditions or the accumulation of disease problems such as sleep disorders, depression, disability status and iatrogenicity [5].

It is reported that both the cause and effects of MS fatigue are multidimensional and need multidisciplinary treatment for successful management. Clinical practice guidelines suggest multiple interventions for fatigue consisting of medical interventions such as pharmacologic treatments and rehabilitation (e.g., exercise and aerobics in medical centers, cooling therapy, aquatic therapy) [6].

In recent years, Exercise Therapy (ET) has become a well-proven and highly effective part of many MS rehabilitation programs. ET includes a wide range of exercise modalities. A recent systematic review proposed several modalities of exercise for people with MS, including endurance, resistance, and combined training [7].

It was found that resistance training of moderate intensity had beneficial effects on MS patients, but the methodological quality of the few existing studies was generally low [8].

However, an exercise modality seems to be particularly effective in MS patients, namely progressive resistance training (PRT). PRT is an exercise modality using external resistance (or body weight) to encourage a few intense muscular contractions in which special consideration is put into progressively increasing the force output of the muscle through incremental weight increases and application of a variation of exercises and types of equipment to target specific muscle groups [9].

Recently, several randomized controlled trials have been published assessing PRT in MS patients. These studies have reported that PRT can diminish fatigue, but heterogeneous results exist, probably due to differences in PRT protocols, sample sizes, outcome measures and type and the severity of MS [10].

Evidence-based practice has been described as the conscientious, clear and prudent use of existing best evidence in making decisions about the care of patients. A Systematic review is a "study of studies". All relevant research is assessed in an effort to determine the overall evidence for a specific intervention [11].

A systematic review is a literature review focused on a single clear question which tries to detect, select and assess all high-quality research evidence related to that question. One then makes an assessment of the included studies, the production of findings and a valid conclusion that can be generalized. It can also direct needed research efforts. It has ordinary specific steps which are reproducible. The best available evidence of the benefits and harms of therapy is provided by systematic reviews of randomized controlled trials [12].

This review will systematically review the literature of PRT studies on fatigue for people with Multiple Sclerosis.

Material and Methods

This systematic review aims to provide evidence for the effectiveness of Progressive Resistance Training (PRT) on Fatigue in MS Patients.

Literature search strategies:

A comprehensive search of the following electronic databases was conducted from inception till June 2021: The Cochrane library, PubMed, Scopus, Physiotherapy Evidence Database (PEDro) and the Web of Science. Searching was done using the following key words: "Progressive Resistance Training" OR "Progressive Resistance Exercises" OR "Progressive Strength Training" OR "Graded Resistance Training" OR "Resistance Training" OR "Exercise Therapy" OR "Strength Training" OR "Weight Training" and "Multiple Sclerosis" OR "Disseminated Sclerosis" and "Fatigue" OR "Physical fatigue" OR "mental fatigue" OR "central fatigue" OR "chronic fatigue" OR "fatigability" OR "fatigue impact" or "muscle fatigue".

An electronic search was followed by a manual search of reference lists of identified trials. Studies were screened by two independent reviewers, first by title, then by abstract, and finally by reading the full text.

Inclusion criteria:

Types of studies:

Randomized Controlled Trials (RCTs) that examined the effect of the effect of PRT on fatigue were included.

Types of participants:

Adult patients (≥ 18 years) with a clinical confirmed diagnosis of MS according to applicable diagnostic criteria.

Types of interventions:

Progressive Resistance Training (PRT), which can be described as dynamic muscle contractions against external loads, with sufficient progression in load is introduced when subjects can perform the desired number of repetitions.

Control/Comparator:

Studies that compared progressive resistance training to control, placebo or any other conservative treatment for fatigue were included.

*Outcome measures:**Primary outcome:*

We assessed fatigue as the primary outcome at the end of the intervention period, and during follow-up as measured by:

- 1- Questionnaires that primarily assessed fatigue, such as: Fatigue Severity Scale [13], Modified Fatigue Impact Scale [14], Multidimensional Fatigue Index [15] and Visual Analogue Scale for fatigue [13].
- 2- Sub-scales of questionnaires that measure fatigue or subscales not primarily designed for the assessment of fatigue but used insuch, for example: Short Form-36 sub-scale (e.g., vitality sub-scale) [16] and MultipleSclerosis Quality of Life 54 (e.g., physical functioning sub-scale) [17]. We only used these sub-scales if it was specifically noted that these were included to assess fatigue.

Secondary outcomes:

Safety of PRT in MS people during the treatment and follow-up periods, such as the rate of relapses, the rate of reported falling and any other adverse events.

*Exclusion criteria:**The studies will be excluded when:*

- 1- The studies have designs other than randomized trials, as case report, case series, review articles or observational studies).
- 2- Populations other than MS.
- 3- Abstracts with no full text articles available.
- 4- Articles were not published in the English language.
- 5- Studies including supplementary intervention therapies in addition to or different from strength training.

Search methods for identification of studies:

- 1- Searching electronic data bases: The following sources will be searched from 2012 to 2021:
 - Cochrane Central Register of Controlled Trials (CENTRAL).
 - PubMed.
 - Physiotherapy Evidence Database (PEDro).
 - Scopus.
 - Web of Science.
- 2- *Hand searching.*
- 3- Searching other resources: To identify other relevant trial data:
 - Authors of published trials will be contacted when reported data were incomplete.
 - Reference lists of review articles and primary trials found will be Screened.
 - Authors of unpublished manuscripts to ask if they were willing to disclose their unpublished data.
 - Experts in the field will be contacted to identify further published or unpublished trials.

Data extraction:

For studies that fulfill inclusion criteria, the following data were extracted and documented in data extraction form by two review authors independently: Trial design, Participant characteristics (number, age, type of MS, Expanded Disability Status Scale (EDSS) score, gender, and disease duration), Inclusion and exclusion criteria, Brief description and type of the experimental intervention(s), Brief description of the control intervention, Outcomes and visits reported any disagreements was resolved by discussion, or if required by a third author [18].

Methodological quality assessment:

Two independent reviewers assessed the risk of bias and methodological quality for all included trials by using Physiotherapy evidence database (PEDro) scale (Appendix III). The PEDro scale consists of 11 items assessing eligibility criteria, randomization, blinding, allocation concealment and other aspects). Each item is rated as 0 (no) or 1 (yes). The first item (description of inclusion criteria) is excluded from the final PEDro score as it is related to the external validity of the trial and not to the internal validity and methodological quality of the trial. Hence, the PEDro scale score is ranging from 0 to 10 points. The studies are rated as follows: excellent (9-10), good (6-8), fair

(4-5), and poor (<4) and score differences were discussed with the third reviewer until agreement was achieved [19].

Assessment of level of evidence:

The level of evidence of each article will be categorized using a modified Sackett approach which its levels of evidence are scored on a five-point ordinal scale, with each level indicating the strength of evidence. It includes PEDro ratings and added descriptions to each category to designate the appropriate level of evidence based on the type of research design [20].

Data analysis:

Extracted data from included trials will be illustrated in form of tables to document outcomes of each intervention comparison in an included review, as well as the number of studies and the number of participants, and (when available from the reviews) the mean difference (or standardized mean difference), 95% confidence intervals and I^2 statistic for heterogeneity [21].

In case of heterogeneity, descriptive analysis will be used. However, in case of homogeneity, the Meta-analysis will be used which is a quantitative statistical analysis of several separate but similar experiments or studies in order to test the pooled data for statistical significance.

For meta-analysis, we will use Review Manager (RevMan) [Computer program]. Version 5.4.1 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2021. To allow comparison of data from different scales, pooled statistics was calculated using Standardized Mean Differences (SMDs), which were computed using RevMan software. Means and Standard Deviations (SDs) for exercise therapy group and control group were used to compute SMDs. The forest plots were computed by means, SD, and sample size effect for PRT group versus control group for each study enters in meta-analysis. If appropriate, estimated effect size was calculated if the outcome variable was reported in ≥ 2 studies [22].

Testing for heterogeneity:

The following tests were used to test the heterogeneity of the estimates in the included studies in the meta-analysis:

- 1- Cochran Q Chi square test: A statistically significant test (p -value < 0.1) denoting the heterogeneity between the studies.
- 2- I-square (I^2) index which is interpreted as the following:

- $I^2 = 0\%$ to 40% : Insignificant heterogeneity.
- $I^2 = 30\%$ to 60% : Moderate heterogeneity.
- $I^2 = 50\%$ to 90% : Substantial heterogeneity
- $I^2 = 75\%$ to 100% : Considerable heterogeneity.

Results

The search of electronic databases and reference sections yielded 641 citations as illustrated in PRISMA flow chart (Fig. 1). No additional records were identified from the reference lists of the relevant articles. After the removal of duplicates by Mendeley computer software, the net studies became =575. Then, by screening by title and abstract, 13 articles were identified for assessment of eligibility for full review. Of those studies, five studies were met eligibility criteria and were subsequently included in this systematic review. The titles of these included studies are explained in (Table 1).

Study characteristics:

The data extracted from the four studies are summarized in (Table 2).

Study design:

The designs of all included studies were RCT.

Participants

The five eligible studies enrolled 186 patients with an age ranged between 18 and 62 years old. The sample size ranged between 26 and 76 in the included studies, with 2.0 to 6.5 scores on EDSS. Of these included studies, three studies; Gomez-Illan et al., (2020), Dodd et al., (2011), Dalgas et al., (2010); included MS patients with a RRMS course only, one study; Callesen et al., (2019); included MS patients with RRMS, SPMS, PPMS courses and one study; Cakt et al., (2010); included MS patients with RRMS, SPMS courses.

Regarding medication, 2 studies; Callesen et al., (2019), Cakt et al., (2010); stated that the participants should not receive any medication during the treatment period, while three studies; Gomez-Illan et al., (2020), Dodd et al., (2011), Dalgas et al., (2010); provided no information.

Intervention:

All included studies conducted by supervised PRT by weight machines. The training duration ranged between 8 and 12 weeks, with frequency ranging from 2 to 3 days per week, with two days per week being the most frequently applied.

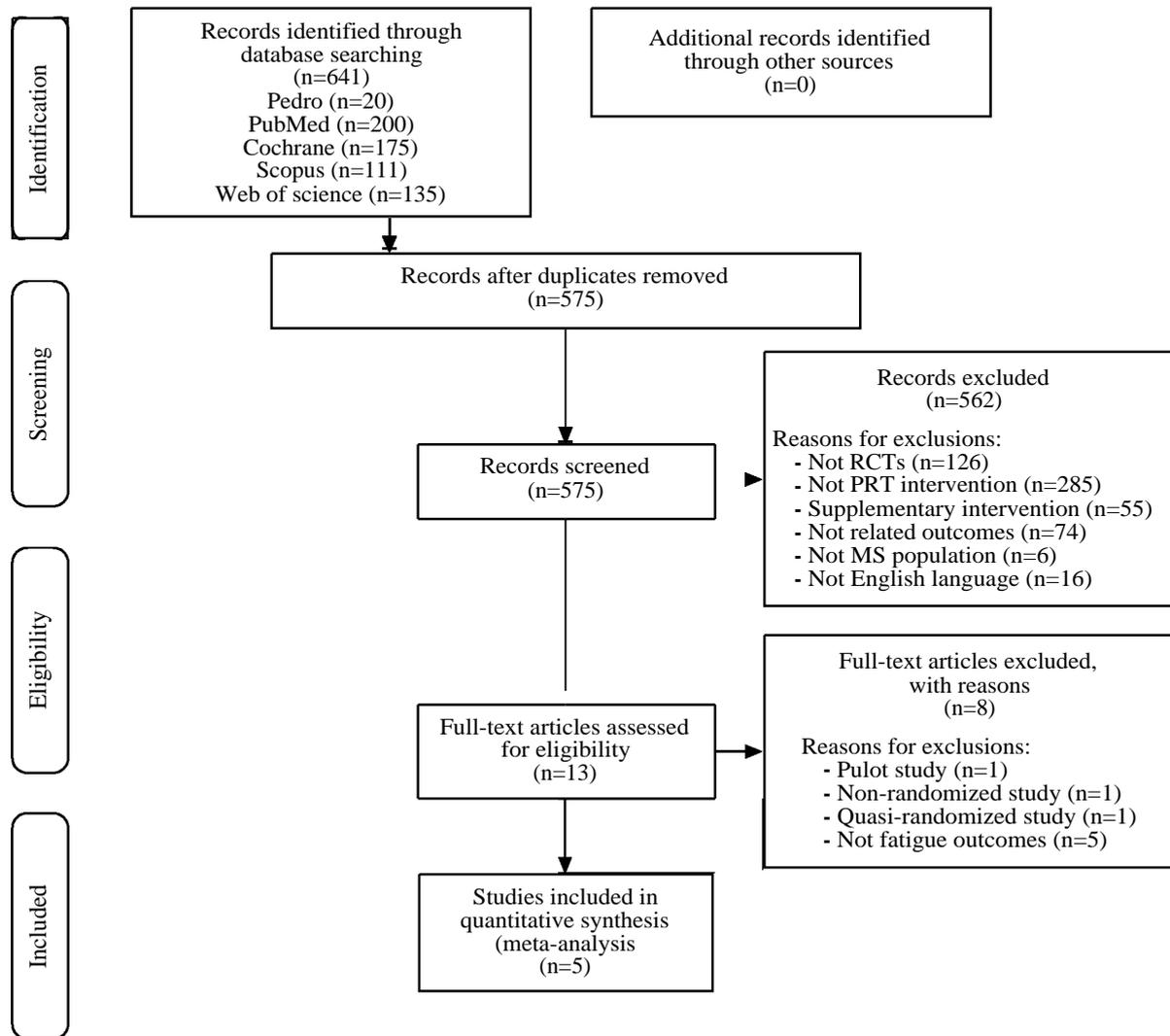


Fig. (1): Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of study refinement and selection procedure (PRISMA), 2009.

Table (1): The titles of included studies.

Study	Title
Gomez-Illan et al., (2020) [23]	- Effects of maximal strength training on perceived-fatigue and functional mobility in persons with relapsing-remitting multiple sclerosis
Callesen et al., (2019) [24]	- How do resistance training and balance and motor control training affect gait performance and fatigue impact in people with multiple sclerosis? A randomized controlled multi-center study.
Doddet et al., (2011) [25]	- Progressive resistance training did not improve walking but can improve muscle performance, quality of life and fatigue in adults with multiple sclerosis: A randomized controlled trial.
Caktet et al., (2010) [26]	- Cycling Progressive Resistance Training for People with Multiple Sclerosis: A Randomized Controlled Study.
Dalgaset et al., (2010) [27]	- Fatigue, mood and quality of life improve in MS patients after progressive resistance training.

Two different approaches were used to express the training intensity; reported as a ratio of 1 RM (repetition maximum) that could be defined as the maximum load lifted for one time), or as the load

can be lifted for a specific times of repetitions, i.e., 15 RM. In the included studies, the exercises intensity ranged from 40% to 90% of 1RM [Gomez-Illan et al., (2020); Cakt et al., (2010)] or 8 to 15

RM [Callesen et al., (2019); Dodd et al., (2011); Dalgas et al., (2010)] and the overall number of intervention sessions ranged between 16 and 24.

In all the included studies, the PRT intervention included only lower extremity exercises, except in Gomez-Illan et al., (2020), where the PRT intervention included both lower and upper extremity exercises. Control group continued their usual care and physical activity and did not receive any inter-

vention in all included studies except in Dodd et al., (2011) whereas patients received additional social Program.

In conclusion, the included studies conducted supervised progressive resistance training for 8 to 12 weeks with 40% to 90% of 1RM or 8 to 15RM training intensity and were mostly aimed the lower extremity in fatigued MS people with 2.0-6.5 EDSS score.

Table (2): Data extraction sheet.

Study	Gomez-Illan et al., (2020)	Callesen et al., (2019)	Dodd et al., (2011)	Cakt et al., (20 10)	Dalgas et al., (20 10)
Design	RCT	RCT	RCT	RCT	RCT
Sample size	n=26 PRT: 13 Con: 13	n=71 PRT: 23 BMCT: 28 Con: 20	n=76 PRT: 39 Con: 37	n=45 PRT = 15 EX= 15 Con= 15	n=38 PRT: 19 Con: 19
	Age=(43.73±10.12) years	Age ≥ 18 years	Age ≥ 18 years	Age = (25: 62) years	Age ≥ 18 years
Subjects Disease Scale	EDSS=2.58±1.19	EDSS: 2.0-6.5	Ambulation Index score: 2-4	EDSS ≤ 6.0	EDSS: 3.0-5.5
MS course	Type: RR	Type: RR/ SP/ PP	Type: RR	Type: RR - SP	Type: RR
PRT Intervention regime	Upper and lower body resistance exercises 2-5 set/4-14 reps at 50-90% 1 RM	Lower extremity exercises 3-4 sets / 8-10 reps at 8- 15 RM	Lower extremity resistance exercises 2 sets / 10-12 reps at 10-12 RM	Cycling progressive resistance training on static bicycle 15 sets of reps /session at 40% TMW	Lower extremity resistance exercises 3-4 sets / 8-12 reps at 8-15 RM
Intervention Duration & frequency	8 weeks 3 sessions/week 1 hour/sessions	10 weeks 2 sessions/week 1-hour/sessions	10 weeks 2 sessions/ week 1hour/sessions	8 weeks 2 sessions /week 1hour/sessions	12 weeks 2 sessions / week
Control intervention	Usual care and level of physical activity	Habitual lifestyle	Usual activity + social Program	Usual normal living	Usual daily activity
Outcomes	Perceived fatigue	Fatigue	Fatigue	Fatigue	Fatigue
Outcomes measures	FSS	MFIS	MFIS	FSS	FSS, (MFI-20)
Results	Significant improvement of FSS	Significant improvement of MFIS	Significant improvement of MFIS	Significant improvement of FSS	Significant improvement of both FSS and (MFI-20)

Outcome Measured:

Primary outcome:

All the included studies assessed the effects of PRT on fatigue perception in MS patients. Three included studies assessed fatigue perception by the Fatigue severity scale (FSS) [Gomez-Illan et al., (2020); Cakt et al., (2010); Dalgas et al., (2010)], while two included studies assessed fatigue perception by the MFIS (Modified Fatigue Impact

Scale) [Callesen et al., (2019); Dodd et al., (2011)]. Also, Dalgas et al., (20 10) used the MFI-20 (Multidimensional Fatigue Inventory) to assess fatigue perception.

Secondary outcomes:

According to the safety of PRT intervention in MS people, Dodd et al., (2011) assessed the rate of relapses. Also, all included studies [Gomez-

Illan et al., (2020), Cakt et al., (2010), Dalgas et al., (2010), Dodd et al., (2011) and Callesen et al., (2019)] assessed the adverse events or injuries that happened during the training period and during the follow-up evaluation as muscle soreness, low back pain and exacerbation of symptoms. In addition, Cakt et al., (2010) assessed fear of falling (FOF) by using the Falls Efficacy scale (FES).

Follow-up:

The evaluation's timing was at the end of the treatment period as well as follow-up evaluation; after 10-week [Gomez-Illan et al., (2020), Callesen et al., (2019)], after 12 weeks [Dalgas et al., (2010)] or after 22 weeks (Dodd et al., 2011).

Methodological quality assessment:

All included studies were rated according to the PEDro scale. The two included studies were of a good quality scored (Table 3). Judgements about each risk of bias item for each included study

using the Cochrane 'Risk of bias'stool is illustrated in (Fig. 2).

Level of evidence of the included studies:

According to the modified sackett scale, the two included study were ranked on level one (RCT, PEDro score ≥ 6) as presents in (Table 3).

Effects of interventions of included studies:

Fatigue result:

As illustrated in (Fig. 3), the heterogeneity was significant in the pooled result among the included studies (n=5 studies, n=186 participants, Chi square value=20.10; $I^2=80\%$ and $p<0.0005$). The pooled analysis showed that the diamond shape is toward the left side, which means that a statistically significant overall effect was between the PRT group and the control group in fatigue outcome which was in favor of study group (SMD=-0.85, 95%CI=-1.58 to -0.11; $p=0.02$).

Table (3): PEDro scores and level of evidence for included studies.

(PEDro) criteria	Dalgas et al., (2010)	Cakt et al., (2010)	Dodd et al., (2011)	Callesen et al., (2019)	GomezIllan et al., (2020)
Eligibility criteria	Yes	Yes	Yes	Yes	Yes
Random allocation	Yes	Yes	Yes	No	Yes
Concealed allocation	Yes	Yes	Yes	Yes	No
Baseline characteristics Comparable	Yes	Yes	Yes	Yes	Yes
Subjects blinded	No	No	No	No	No
Therapists blinded	No	No	No	No	No
Assessors blinded	No	No	Yes	Yes	No
Outcomes for 85% of initial participants	No	No	Yes	No	Yes
Intention-to-treat analysis	Yes	No	Yes	Yes	Yes
Between-group statistical Comparison	Yes	Yes	Yes	Yes	Yes
Point and variability Measures	Yes	Yes	Yes	Yes	Yes
Total score	6	5	8	6	6
Level of evidence	Level 1	Level 2	Level 1	Level 1	Level 1

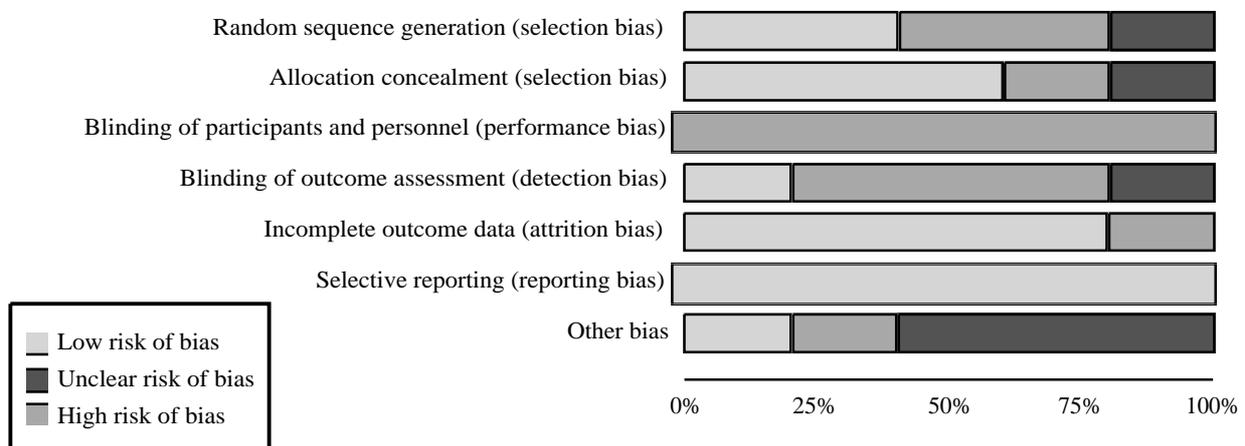


Fig. (2): Risk of bias graph: Review authors' judgements about each risk of bias item presented as percentages across all included studies.

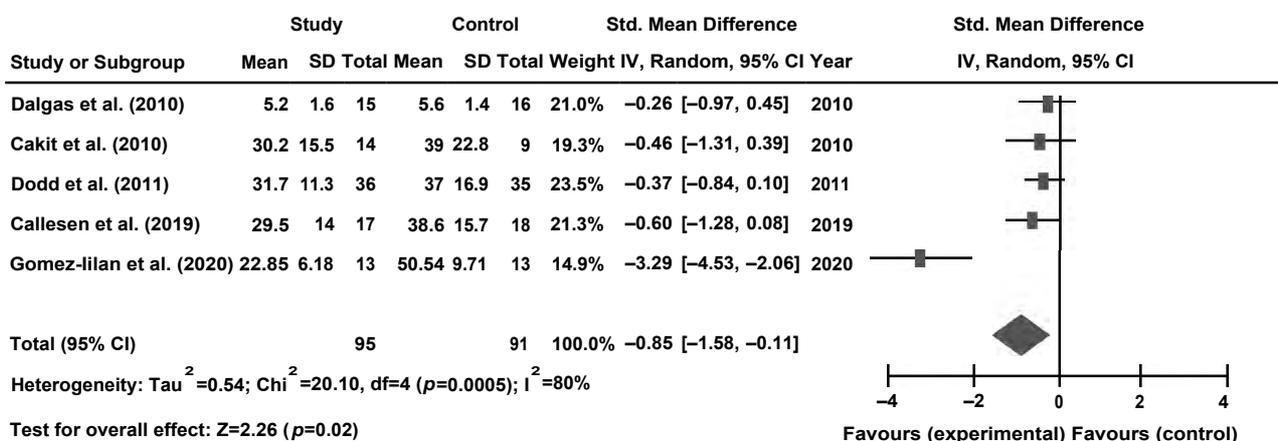


Fig. (3): Forest plot of Overall analysis of fatigue.

Safety results:

According to (FOF) fear of falling, Cakt et al., (2010) reported a significant improvement in the Falls Efficacy scale (FES) score after eight weeks of twice weekly progressive resistance training, in comparison to the control group ($p < 0.01$).

Regarding the adverse events or injuries that happened during and after PRT period, Gomez-Illan et al., (2020) reported no adverse events or injuries that occurred during the intervention period and the follow-up evaluation. While Dalgas et al., (2010) stated that one subject had lower back pain after the PRT sessions and dropped out. Also, Cakt et al., (2010) reported no adverse events or incidents occurred, except that one participant had an acute exacerbation and dropped out.

In addition, Dodd et al., (2011) found that the participants in the progressive resistance training group showed decreases in muscle spasm and muscle stiffness symptoms compared to the control group. However, temporary muscle soreness was reported by many participants during the early weeks of training (25 out of 36) and disappeared within a few days. Also, Dodd et al., (2011) reported no relapses happened during or after the training period.

Finally, Callesen et al., (2019) reported that two participants in the PRT group suffered from adverse events; one had a worsening of fatigue after intervention sessions and dropped out; the other had recurrent low back pain during the training period but completed the training.

Discussion

The objective of this current systematic review was to assess the effect of PRT on fatigue treatment in multiple sclerosis people and to investigate the

strength of qualitative evidence that supports PRT's effectiveness in treating fatigue in MS people and to determine the possible adverse events of PRT.

Rehabilitation of fatigue in MS patients is still a challenge, without a clear decision on the best treatment procedure. Presenting systematic reviews produces a dominant second level of evidence for different neurological rehabilitation approaches.

Although, There are many systematic reviews that had evaluated the effect of exercise training on fatigue as in Moss-Morris et al., 2021; Abeer et al., 2020; Jørgensen et al., 2017; Heine et al., 2015; Pilutti et al., 2013 [25-29] but Kjølhed et al., 2012 [8] was the only systematic review focusing exclusively on using PRT alone for fatigue management in MS patients.

According to Kjølhed et al., 2012, there is a weak evidence of using PRT for fatigue management in MS patients but there was an overall positive tendency in most but not all studies [8].

In this review, the intensive electronic databases of PubMed, Web of Science, Scopus, the Cochrane library, and PEDro provided 575 studies that were screened by the titles and abstracts and 562 were excluded because they did not fulfil our inclusion and exclusion criteria. From these trials, interventions in 285 trials could not be considered PRT intervention, 126 trials were not of a randomized controlled design (pilot studies, case reports, systematic reviews and non-randomized studies). The fatigue outcome was not in 74 trials, 6 trials presented with no MS population, 16 trials presented with not English language, 55 trials presented with supplementary intervention combined with PRT intervention; and were therefore not included.

After that, 13 full-text studies were evaluated for eligibility. Eight trials were excluded from

these studies (one pilot study, one non-randomized trials, one quasi-randomized trial and five trials with no related outcomes trials). Finally, five studies were included in this systematic review and also in our meta-analysis. To obtain the highest level of evidence, this review included randomized control trails only.

The primary outcome searched in the included studies was fatigue evaluated by questionnaires which mainly measured fatigue, such as: FSS (the Fatigue Severity Scale), MFIS (the Modified Fatigue Impact Scale) and MFI-20 (the Multidimensional Fatigue Inventory), while the secondary outcomes searched in the included studies were the rate of relapses, the fear of falling (FOF) and the adverse events or injuries that happened during the training and the follow-up period. The scan of all studies were checked up by the two independent reviewers. Any differences were solved by the third author.

This review used (PEDro) scale scores to assess the quality of included studies, the quality of four studies was good Gomez-Illan et al., (2020), Callesen et al., (2019) and Dalgas et al., (2010), Dodd et al., (2011)) and fair for the other study (Cakt et al., (2010)). PEDro scores showed an overall lack of blinding of participants, assessors and therapists. Additionally, Cochrane assessment, by using several methodological domains (adequate sequence generation, adequate concealment of allocation, adequate outcomes data, adequate reporting and blinding of assessors, participants and therapists) was used for assessing the bias risk in the included studies.

The evidence level was assessed by the modified sackett scale. The level of evidence of all included studies was level one (RCT, PEDro score ≥ 6) Gomez-Illan et al., (2020), Callesen et al., (2019); Dodd et al., (2011); Dalgas et al., (2010), except one study was of level two evidence (RCTs, PEDro score < 6) Cakt et al., (2010).

This review used meta-analysis to analyze the overall effect of PRT exercises on fatigue in MS patients. Overall, our meta-analysis indicated that PRT had been associated with a statistically significant reduction in fatigue in MS people ($p=0.02$), in a comparison to the control group.

In comparison to the control group, both Callesen et al., (2020) and Dodd et al., (2011) reported a significant reduction in MFIS scores after ten weeks of PRT targeting lower limbs only ($p<0.01$, $p<0.05$, respectively).

Also, Gomez-Illan et al., (2020) stated that there was a significant improvement in FSS scores after 8 weeks of PRT intervention that included both upper and lower extremity exercises ($p<0.01$) as compared to a control group. These findings agreed with those of Dalgas et al., (2010) that found a significant reduction in FSS and MFI-20 scores after twelve weeks of PRT targeting only the lower limbs ($p<0.05$) versus the control group.

In addition, Cakt et al., (2010) reported that the FSS and FES scores improved significantly after 8 weeks of twice weekly cycling PRT ($p<0.05$, $p<0.01$ respectively) versus the control group.

From previous studies, the following underlying mechanisms have been suggested for fatigue reduction after PRT, Cardiovascular changes as improved aerobic capacity, small vessel conditions, blood flow, nutrient delivery, angiogenesis and vascular regeneration; Immunologic changes as upregulation of anti-inflammatory cytokines leading to inflammation reduction; CNS changes as decreased neurodegeneration, improved synaptic plasticity and neurogenesis; Neuroendocrine changes as normalizing the immunologic profile (HPA function), restoration of corticosteroid receptor function and Neurotrophic changes as improvement in brain-derived neurotrophic factor (BDNF) levels, neuronal function and structure in the brain areas.

Also, Cakt et al., (2010), Dodd et al., (2011) and Dalgas et al., (2010) suggested that the improvement in fatigue might be due to the improvement in leg muscles strength, leg functions as well as muscle endurance after PRT, and the stronger muscles could work more effectively for a longer time without having to rest or being tired.

In addition, both Dodd et al., (2011) and Gomez-Illan et al., (2020) reported that the improvement in fatigue after PRT was associated with positive impacts on the daily activities and the life quality of MS people.

From the included studies, we can say that PRT is a generally safe and tolerable kind of exercises for multiple sclerosis people as no negative impacts or injuries were informed in most of the included studies, except for muscle soreness that was reported during the early weeks of training and improved later with training.

One disadvantage of PRT, as observed by the majority of the included studies, was that the benefits of the training began to decline once the training had ended. So, MS patients are advised to keep training to maintain the advantages of PRT. Only one study

revealed that the PRT's positive influences were maintained at the follow-up assessment, 12 weeks later after ending the training period (Dalgas et al., 2010). This could be because this exercise group included relapsing-remitting multiple sclerosis people only with a lower degree of impairment than in the other included studies (EDSS 3-5.5) and the exercise group was advised to resume training independently after finishing the intervention period (Dalgas et al., 2010).

One weak point of this review is the inadequate number of included studies and we think this is due to the fact that our systematic review was limited to RCTs that evaluated the effect of PRT exercises only for MS related fatigue and not combined with other interventions.

On the other hand, we discovered many trials such as Mayo et al., 2020; Kezele et al., 2020; Tarakci et al., 2013; Mikul'áková et al., 2018; Rietberg et al., 2014 [30-34] that evaluated the effects of PRT combined with other exercises for fatigue in MS patients rather than PRT alone. Furthermore, we discovered many trials as Kjølhedede et al., 2015, Medina-Perez et al., 2014; de Oliveira et al., 2018; Akbar et al., 2020; Kjølhedede et al., 2016 [35-39] that assessed the PRT effects on outcomes other than fatigue, such as cytokine responses, muscle strength and walking performance. Finally, we found many trials that assessed the effects of resistance exercises but not progressive mood on fatigue in multiple sclerosis people, as in Kierkegaard et al., 2016; Karpatkin et al., 2016; Aydin et al., 2014; Razazian et al., 2020 [40-43].

Based on this available literature, it can be said that progressive resistance training could be considered to be a feasible and beneficial option for fatigue treatment in multiple sclerosis people and its benefits can persist after a supervised training is completed as soon as patients continue training independently, but more future research is still required on this topic.

Conclusion:

According to the results of this study, According to the results of this review, progressive resistance training appears to be effective and safe in the management of fatigue in MS people and patients should continue on PRT to maintain its positive benefits. However, more future research is still needed to cover this issue.

Recommendations:

1- Well-designed, randomized controlled trials on the effectiveness of PRT alone not combined with other exercises on fatigue in MS patients are needed.

- 2- Long-term follow-up studies with a larger population of subjects must be performed to determine the effect of PRT on fatigue in MS patients.
- 3- Further RCTs on the effectiveness of PRT in people with progressive multiple sclerosis who have a severe level of impairment are also required, as most available studies include patients with relapsing remitting MS only.

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تأثير تمارين المقاومة التدريجية على الاجهاد فى مرضى التصلب المتعدد : مراجعة منهجية

الاجهاد هو عرض متكرر فى مرضى التصلب المتعدد وله الكثير من الآثار السلبية عليهم فقد يؤثر على أنشطة الحياة اليومية ونوعية الحياة الخاصة بهم. تمارين المقاومة التدريجية من الممكن أن تكون أداة فعالة فى تقليل الاجهاد لدى الأشخاص المصابين بالتصلب المتعدد. كما يمكن أن تحسن أداء الأنشطة البدنية مثل المشى وجودة الحياة الصحية للأشخاص المصابين بمرض التصلب المتعدد.

تهدف هذه المراجعة المنهجية إلى عمل مسح للدراسات السابقة وتقييم قوة ونوعية الأدلة المتعلقة بفعالية استخدام تمارين المقاومة التدريجية على الاجهاد فى مرضى التصلب المتعدد. وقد تم استخدام قواعد البيانات الالكترونية التالية من ٢٠١٢ إلى ٢٠٢١: scholar, PEDro, PubMed, Cochrane library, google بجانب إجراء البحث اليدوى عن مراجع هذه المقالات وكما تم تضمين تجارب التحكم العشوائية فقط فى هذه المراجعة وتم استبعاد الآخرين وفقاً لمعايير الاشتمال المختارة وتم إجراء تقييم الجودة لجميع الدراسات المؤهلة باستخدام مقياس PEDro.

كشفت النتائج أن خمس دراسات مع ١٨٦ مريضاً تفى بمعايير الاشتمال. وكانت معظم الدراسات ذات جودة جيدة وفقاً لمقياس PEDro وتم تحليلهم جميعاً تحليلاً إحصائياً. وقد أظهرت النتائج فروق ذات دلالة إحصائية بين مجموعة تمارين المقاومة التدريجية ومجموعة التحكم فى الاجهاد مع التأثير الكلى ($SD=-0.85, 95\%CI=-1.58 \text{ to } -0.11; p=0.02$).

الخلاصة: أثبتت النتائج أن تمارين المقاومة التدريجية قد يكون لها تأثيراً إيجابياً فى علاج الاجهاد فى مرضى التصلب المتعدد ويجب على المرضى الاستمرار فى أداة التمارين للحفاظ على آثاره الإيجابية. ولكن ما زال هناك حاجة إلى مزيد من التجارب السريرية عالية الجودة لتأكيد هذه النتيجة ولسد العجز فى هذا الموضوع.