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Effects of Physical Exercise on Functional and Respiratory Capacity, Quality of Life, and Fatigue Perception in Myasthenia Gravis Patients: A Systematic Review

Victoire Aupetitallot[a] & Alberto Bermejo Franco[b,*]

[a]Bichat Claude Bernard Hospital, 46 Rue Henri Huchard, P.C.: 75018, Paris, France;
[b]Universidad Europea de Madrid, C/Tajo, s/n, P.C.: 28670 Villaviciosa de Odón, Madrid, Spain

*Address all correspondence to: Alberto Bermejo Franco, Universidad Europea de Madrid, C/Tajo, s/n, P.C.: 28670 Villaviciosa de Odón, Madrid, Spain; Tel.: +34912115535; Fax: +34911413585, E-mail: alberto.bermejo@universidadeuropea.es

ABSTRACT: We aim to assess the effectiveness of physical exercise on functionality, fatigue perception, respiratory capacity, and quality of life in patients who are diagnosed with myasthenia gravis (MG). Study materials and methods follow Preferred Reporting Items for Systematic Reviews and Meta-Analyses declaration criteria. The evaluation was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement for observational and cross-sectional studies and the Consolidated Standards of Reporting Trials checklist for clinical trials. Searches were conducted on Physiotherapy Evidence, Cochrane, and PubMed databases. Our initial search yielded 312 articles. Of these, 146 were duplicated and 157 excluded, because they did not meet inclusion criteria. Thus, a total of nine articles were eligible for our review, including prospective cohorts of randomized controlled trials that assessed physical exercise effectiveness in patients with MG. Results and conclusions found that physiotherapy protocols that are based on therapeutic exercise produce positive and immediate impacts on functional capacity of MG patients. Physical exercise may help to improve MG patients' quality of life. However, the literature suggests that a need exists for more studies to obtain conclusive results regarding exercise leading to improved quality of life for MG patients.

KEY WORDS: myasthenia gravis, therapeutic exercise, physiotherapy

I. INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder of neuromuscular transmission that is characterized by easy fatiguability and muscle weakness. MG is considered to be the most common primary disorder of neuromuscular junction/transmission.[1–3] The disease can affect certain muscle groups (i.e., in eyes, limbs, or diaphragm) or produce generalized effects on multiple muscle groups.[4,5] MS results from high and uncontrolled production of anti-acetylcholine receptor (AchR) antibodies that attack AchRs, blocking neuromuscular transmission and thus preventing muscles from flowing and contracting normally.[5,6]

This illness is a rare disorder, whose annual incidence is eight to ten cases/1 million individuals. Its prevalence is 150 to 250 cases/1 million and affects patients of any age.[7] However, a significant increase has been observed among females aged between 20 and 40 years and males between 50 and 60 years of age.

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Incidence tends to decrease after age 70.[6,8] A stressful situation or context, coexistence of other diseases, fatigue, or medications such as anesthetics are factors that can aggravate MG symptoms.[9] Furthermore, patients with MG family history or those affected by thymus gland tumors/thyomas are more likely to develop MG.[10,11]

An accurate diagnosis requires a complete anamnesis to guide the physical and neurological examination.[5,12] Osserman classification for MG is most frequently used to establish illness level based on location and degree of muscle weakness.[13,14] An examination should not show muscle mass loss or altered sensation and reflexes.[15] After anamnesis and examination, various tests can be conducted to confirm the diagnosis.[16] In MG management, different therapeutic multidisciplinary alternatives can improve symptoms, slow disease evolution, or improve quality of life, but no curative treatment exists.[4,6,9,17,18]

The treatment approach must specifically focus on the patient's clinical situation, level of functional participation, and basic activities.[19,20] Drugs such as corticosteroids or atropine and its derivatives are used to attenuate symptoms,[16] thymectomy can improve MG-related symptoms in selected patients,[8,9,16,19] and physiotherapeutic treatment can improve management of the clinical situation to reduce MG impact on quality of life.[17–26]

Physical exercise for healthy people is highly recommended; its benefits are well established. In patients with MG, physical exercise can improve different aspects that are related to subject functionality and autonomy such as coordination, muscle strength, and fatigue levels to maintain or promote independence. In addition, exercise may influence respiratory capacity with inspiratory and expiratory muscle involvement, helping avoid possible complications.[17–26] However, little evidence is available regarding exercise intervention programs, duration intensity, rest time, prescribed medication, time of day for physical effort, or other variables to help optimize treatment results in MG patients.[18,20] Conforming to this, an evident need exists to review effectiveness of physiotherapy programs based on well-established therapeutic exercise programs to improve funcional and respiratory capacity, quality of life, and fatigue perception for those suffering from MG.

II. MATERIALS AND METHODS

We conducted searches using the Physiotherapy Evidence database (PEDro) as well as Cochrane and PubMed databases. Selected articles were published between January 2005 and December 2020 using the following medical subject heading terms and key words: ("myasthenia gravis" AND "physical therapy" AND "physiotherapy treatment") AND ("therapeutic exercise" OR "physical exercise" OR "endurance therapy" OR "quality of life" OR "breathing training"). The most recent search took place March 10, 2021. Randomized controlled trials (RCTs) and prospective cohort studies that were published in English, Spanish, or French were used as filters. Selected studies included those with patients who were medically stable and diagnosed with MG after 18 years

of age, whose intervention included physiotherapy treatment based on therapeutic exercise. Studies that included patients with cardiac pathology or other neuromuscular pathology were not considered.

The identified articles were independently analyzed by two authors to check whether article title, abstract, and content met inclusion/exclusion criteria that are described above. In addition, the same authors independently assessed article quality for this review using the PEDro scale (in duplicate when articles did not have a score) and Agència d'Avaluació de Tecnologia Mèdica de la Generalitat de Catalunya (AATM) classification. Then, final selected articles were read in their entirety and summarized. To interpret results, we took into account different Cochrane bias criteria: selection, performance, detection, attrition, and selective outcome description.[27]

This systematic review followed criteria outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses declaration. We studied independent and dependent variables. Independent variables included physiotherapy treatments for MG patients based on aerobic therapeutic exercises, strength therapeutic exercises, balance and proprioception exercises, and inspiratory and expiratory therapeutic exercises. Dependent variables were functionality (qualitative ordinal variable), fatigue (qualitative ordinal variable), respiratory capacity (quantitative continuous variable), and quality of life (qualitative ordinal variable).

III. RESULTS

To analyze effectiveness of therapeutic exercises in MG, we selected nine articles that included two RCTs and seven prospective cohort studies. Study selection followed procedures that are described above and can be seen in the flow chart in Fig. 1. We carried out methodological quality assessment of the present systematic review using quality-rating scales. The corresponding results highlight average methodological quality of the selected articles. We show main results of the PEDro scale (scored from 1 to 10 for lowest to highest methodological quality) and the AATM classification,[28] with evidence determined from I to IX according to most to least evidence, in Table 1. Each selected article's characteristics (design, sample, duration, and study objective) are summarized in Table 2.

Results reveal that physiotherapists prescribe a variety of therapeutic exercises to maintain normal muscle function and avoid respiratory complications that contribute most to cause of death in MG patients. Table 3 summarizes type of physiotherapy intervention, evaluation measures, results, and limitations of each study.

Despite the results that were obtained in the nine articles, evidence levels are largely compromised by study bias risk. Main bias risks were related to sample size and study design. In eight of the selected articles, only two were randomized[21,22] and three included a control group.[21,22,30] In addition, sample size in each article was small, decreasing the ability to generalize results from the different studies. Table 4 lists results using the Cochrane scale for risk of bias in the clinical trials selected.[28]

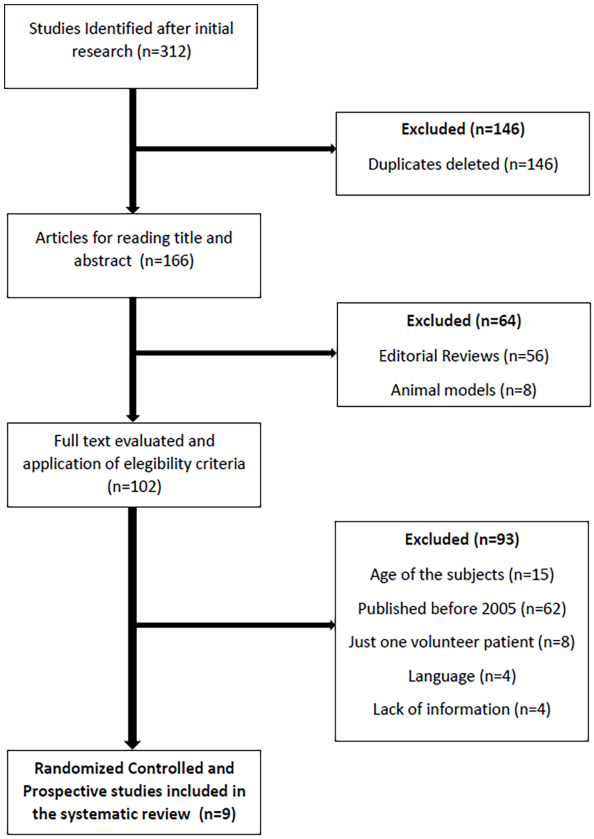

FIG. 1: Systematic review flow chart

IV. DISCUSSION

The results of this review show that physiotherapy in the forms of aerobic exercise, breathing training, and balance training is effective for maintaining muscle strength, decreasing MG symptoms, and useful in preventing respiratory complications. However, we observed discrepancies among study authors in terms of physiotherapy treatment.

MG, a neuromuscular disorder, negatively impacts patient functional capacity and often affects daily life. Rahbek et al.[21] and Westerberg et al.[24] analyzed functional capacity with different therapeutic exercise protocols in isolation or in combination (balance, aerobic, resistance) on MG patients. In general, both studies show that applying these exercises (aerobic, balance, and resistance) helps improve functional capacity. However, Westerberg et al.[24] found no improvement with use of balance exercises in isolation. Similarly, both groups did not observe improvement in functional capacity with aerobic exercises only. Functional capacity can be limited by muscle weakness and associated fatigue, negatively impacting daily life activities, and possibly by patient motivation and

TABLE 1: Methodological quality of selected studies

Ref.	Study type	Year published	PEDro scale	AATM scale[29]	Physiotherapeutic intervention
Farrugia et al.[17]	Prospective cohort	2018	Not evaluable	IV	Therapeutic aerobic exercises and stretching with psychological support
Rahbek et al.[21]	RCT	2017	5/10	III	Aerobic and resistance therapeutic exercises
de Freitas Fregonezi et al.[22]	RCT	2005	6/10	III	Basic inspiratory and respiratory exercise intervals (pursed lips; diaphragmatic)
Westerberg et al.[23]	PrProspective cohort	2018	Not evaluable	IV	Aerobic, resistance, and balance exercises
Westerberg et al.[24]	PrProspective cohort	2017	Not evaluable	IV	Aerobic, resistance, and equilibrium exercises in two long-term phases
Rassler et al.[25]	Prospective cohort	2011	Not evaluable	IV	Hyperpnea normocapnea exercises for long-term respiratory muscle resistance
Rassler et al.[26]	Prospective cohort	2007	5/10	IV	Hyperpnea normocapnea exercises for respiratory muscle resistance
Elsais et al.[29]	PrProspective cohort	2010	Not evaluable	IV	Aerobic exercise with bicycle; respiratory with spirometer
Freitag et al.[30]	PrProspective cohort	2018	5/10	IV	Normocapnic hyperpnea exercises for long-term RMET

AATM, Agència d'Avaluació de Tecnologia Mèdica de la Generalitat de Catalunya; PEDro [scale], Physiotherapy Evidence database; RCT, randomized clinical trial; RMET, respiratory muscle endurance training.

TABLE 2: Study characteristics

Ref.	Study design	MG patient severity and sample size (*n*)	The study purpose	Duration	Intervention	Evaluation measures
Farrugia et al.[17]	Prospective cohort	MG (9)	Analyze combination of physical and psychological therapy to reduce fatique symptoms in stabilized but symptomatic MG; quantify fatigue with different scores to determine most relevant	10 wk	Simple exercises (aerobic, resistance, stretching, breathing, relaxation when resting) combined with psychological intervention; patients filled in daily throughout intervention	MFIS, VAFS, and FSS at beginning of study, during the program, and 3 mo later
Rahbek et al.[21]	RCT	Generalized MG (15)	Effect of muscular strength, aerobic resistance, and functional capacity for 8 wk of AT and PRT	8 wk maximum	Six progressive resistance exercises: Five sessions every 2 wk (20 sessions total) focused on whole body; three series of 12 repetitions of each exercise or three series of eight repetitions, thereby increasing resistance	QMG, isokinetic dynamometry (strength, fatigue), nerve transmission, functional capacity test (6-min walk test, 30-s sitting test, "box and block test," and stair climbing), MG QoL15, depression, and MFIS

TABLE 2: (*continued*)

de Freitas Fregonezi et al.[22]	RCT	MG (27)	Effect of basic interval training with IMT combined with respiratory training (BR) in patients with generalized MG; partial home program	8 wk	Patients divided into two random groups. Control group: respiratory retraining with diaphragmatic breathing exercises and pursed lips; experimental group: 10 min of diaphragmatic breaths, 5 min rest, 10 min breaths with pursed lips; three times/wk for 8 wk	FVC, FEV_1, FEV_1/FVC, and MVV measured with spirometer; helium dilution technique for lung volume, inspiratory capacity, total pulmonary, and residual; diffusion lung capacity with single-breath method and respiratory force with pressure gauge; thoracic mobility with standard method (flat tape) health and quality of life by questionnaire
Westerberg et al.[23]	Prospective cohort	MG (11)	Benefit of treatment with physical exercises (aerobic and resistance) in muscular response, functional capacity, and fatigue in MG patients	12 wk	Balance, endurance, and aerobic exercises; 5-min warming up in cycloergometer of seven 2-min intervals at different load, with 5-min cooling at end; followed by one phase of two balance exercises and six stretches; 90 min twice/wk	Isometric dynamometry, QMG, PEF, nerve stimulation conduction and repetition before and after intervention, neuromuscular ultrasound before and after, functional capacity tests (time up, walk test, 30-s chair stand, and hand pressure), blood test, height and weight, and MG QoL15

TABLE 2: (*continued*)

Ref.	Study design	MG patient severity and sample size (*n*)	The study purpose	Duration	Intervention	Evaluation measures
Westerberg et al.[24]	Prospective cohort	Moderate MG (10)	Effectiveness of exercise program, based on exercise recommendations, on muscle fatigue; effectiveness of aerobic and resistance muscular exercise on neuromuscular state in MG patients	12 wk	Balance exercises, muscular endurance, and aerobic exercises; 5-min warming up in cycloergometer of seven 3-min intervals: two at high load and one at minimum load, with 5-min cooling at end; 75 min twice/wk	MGC score, repetitive nerve stimulation, muscular strength, capacity-based measures, serum level of interleukin-6, potential for compound action, muscle enzymes; evaluations before and after intervention
Rassler et al.[25]	Prospective cohort	Moderate to severe MG (10)	Establish appropriate and maintained training; test effects on moderate to severe MG patients	4–6 wk	Normocapnea hyperpnea exercise protocol of five 30-min sessions/wk for up to 20 sessions; frequency reduction phase for five sessions every 2 wk	Besinger score and lung function and respiratory resistance before and after first month and after 4 mo
Rassler et al.[26]	Prospective cohort	Moderate to severe MG (10)	Establish appropriate and maintained training; test effects on moderate to severe MG patients	4–6 wk	30-min hyperpnea normocapnea during 20 sessions with five sessions/wk and 2-d rest; ventilation per minute of 50%–60% MVV, with tidal volume 50%–60% of vital capacity and 25–35 breaths/min respiratory rate; 3–5 mo deconditioning	MG score, lung function, and respiratory resistance before and after intervention

TABLE 2: (*continued*)

Elsais et al.[29]	Prospective cohort	Moderate MG (10)	Evaluate exercise capacity and lung function in stable MG patients	One 1-hr session	Dynamic spirometry evaluated lung function; cardiopulmonary exercise test evaluated ventilation and gas exchange; single 8–12 min session with cycloergometer	Functional ventilatory capacity, expiratory ventilatory capacity in 1 s; ratio of both; MVV
Freitag et al.[30]	Prospective cohort	Mild to moderate MG (23)	Effect of a long-term respiratory endurance training in mild to moderate MG patients	1 yr and 5 wk	Long-term respiratory endurance training based on normocapnic hyperpnea with 1 wk pretraining, 4 wk intensive training (five 30-min training sessions for 1 wk); 12 mo maintenance training (five 30-min training sessions for 2 wk)	QMG; lung function and respiratory endurance before and after interventions

AE, Aerobic exercise; BR, respiratory training; FEV, forced expiratory volume; FSS, fatigue severity scale; FVC, functional ventilatory capacity; IMT, inspiratory muscle training; MFIS, fatigue impact scale; MG, myasthenia gravis; MGC, MG component; MVV, maximum voluntary ventilation; PEF, maximum expiratory flow; PRT, progressive resistance training; QMG, quantitative MG; QOL, quality of life; VAFS, visual analog fatigue scale.

TABLE 3: Study results

Ref.	Results	Limitations
Farrugia et al.[17]	Improved MFIS during study and significant ($p < 0.001$) improvement in VAFS at study end; physical and psychological improvements but not in MG severity at 3 mo after study; results not maintained, but 50% of patients reported changes in daily life	Limited sample; different degrees of MG; lack of psychological information and motivation
Rahbek et al.[21]	12 patients completed intervention with mean adherence of 95% ± 8%. Both groups reported side effects, cured bulbar symptoms ($n = 2$), and increased fatigue, but no QMG score change. Patients following protocol increased 10% isometric knee extension force, 23% maximum shoulder abduction force, and improved functional capacity	Nonrepresentative sample of general MG population; significant daily symptom variations in MG
de Freitas Fregonezi et al.[22]	Experimental group: improved respiratory pattern and breathing-involved muscle resistance; MIP increased 27%, MEP by 18%, and MVV by 8%; upper thoracic mobility expansion improved 44% and muscle contraction by 43%; lower thoracic mobility expansion improved 44% and muscle contraction by 41%	Sample reduced. Relative accuracy of thoracic mobility, but study demonstrated that intersubject variability in chest mobility clearly improved with protocol
Westerberg et al.[23]	Improved functional capacity ($p = 0.0039$) and muscle resistance in lower limbs (increased isometric muscle strength [$p = 0.014$] and muscle thickness by ultrasound [$p = 0.0098$]); no muscle changes in upper limbs. Improved quality of life when carrying out activities; no significant changes in fatigue	Limited sample; complicated to have a placebo control group for exercise setting not blinded by evaluator
Westerberg et al.[24]	Exercises tolerated by patients; MGC unchanged; patients reported increased ability to perform physical activity and increased aerobic capacity; ratio of muscle to fat mass increased.	No control group; reduced sample; MG disease fluctuation studied every day at the same time to avoid bias

TABLE 3: (*continued*)

Rassler et al.[25]	Improved Besinger score ($p = 0.007$) and respiratory resistance ($p < 0.001$); achievable and significant program with long-term benefits for MG patients	No control group; small sample; technique not applicable to all MG patients; dependent on patient motivation
Rassler et al.[26]	Respiratory resistance significantly increased ($p < 0.0001$) as did total ventilation volume ($p = 0.004$); 25% of increase lost 3–5 mo after exercises stopped. There was a 75% gain which resulted from improved neuromuscular coordination instead of muscle training. No change in MG score and lung function. Patients assessed effects of physical and respiratory training as positive.	Small sample; selection of participants by neurologist who knew patients beforehand; no control group
Elsais et al.[29]	Concluded that MG patients have obstructive respiratory patterns that predominate if medically treated with pyridostigmine (acetylcholinesterase inhibitor)	Protocol not well explained; sample reduced
Freitag et al.[30]	MG score improved from 0.67 ± 0.09 to 0.41 ± 0.1. Some improvements after intervention in respiratory endurance as time until exhaustion; breathing patterns at rest measured with prolonged aspiration; number of squats increased by 412%, 122%, and 160%; no significative changes in control group	Patients in training and control groups not randomly allocated; dependence on patient motivation; time consuming; interrupted training due to health state of patients; interventions not adapted to all MG patients; no demonstration of mitochondrial and enzymatic changes in respiratory tissue

MEP, maximum expiratory pressure; MFIS, fatigue impact scale; MG, myasthenia gravis; MGC, myasthenia gravis component; MIP, maximum inspiratory pressure; MVV, maximum voluntary ventilation; VAFS, visual analog fatigue scale.

TABLE 4: Study bias risks

Ref.	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinded participants and personnel (performance bias)	Blinded outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Farrugia et al.[17]	High	High	High	Not evaluable	Not evaluable	Not evaluable
Rahbek et al.[21]	Unclear	High	High	Unclear	Low	Low
de Freitas Fregonezi et al.[22]	Low	Unclear	Unclear	Low	Low	Low
Westerberg et al.[23]	High	High	High	Unclear	Not evaluable	Not evaluable
Westerberg et al.[24]	High	High	High	Unclear	Not evaluable	Not evaluable
Rassler et al.[25]	High	High	High	Not evaluable	Not evaluable	Not evaluable
Rassler et al.[26]	High	High	High	Not evaluable	Not evaluable	Not evaluable
Elsais et al.[29]	High	High	High	Not evaluable	Not evaluable	Not evaluable
Freitag et al.[30]	High	Unclear	High	Not evaluable	Not evaluable	Low

treatment involvement.[21,23,24] Study results regarding physical therapy through physical exercises with psychological support did not find significant changes in reduced fatigue and muscle weakness. The authors proposed carrying out longer studies, with greater methodological quality, to observe statistically significant results.[17,21,23,24]

On the other hand, MG involvement in the respiratory system can vitally impact patients. In this regard, studies such as Elsais et al.[29] show that patients with MG treated with pyridostigmine (acetylcholinesterase inhibitor) present a slight obstructive respiratory pattern on spirometry. Studies carried out by Rassler et al.[25,26] and Freitag et al.[30] with normocapnic hyperpnea exercise protocols and by de Freitas Fregonezi et al.[22] with two other exercise protocols for respiratory muscles combined with a home protocol aimed to increase inspiratory muscle strength[22] and resistance.[25,26,30] Results of both studies[22,25,26,30] showed positive results in relation to dyspnea and muscle strength and endurance, associated with decreased MG symptoms using the Besinger score.[25,30] Results are in concordance with Corrado et al.,[7] who found respiratory training to be a very effective approach in managing fatigable weakness and respiratory failure in MG patients.

To conclude, reviewed articles show that physiotherapy positively influences MG patients. Similar reviews also reveal beneficial changes in functional muscle status as a result of aerobic and high resistance strength training in MG patients with mild disease actively exercise safely.[31–33] Physiotherapy protocols based on therapeutic exercise through aerobics, resistance, balance, and stretching exercises have a highly positive and immediate impact on MG patient functional capacity. But, the fatigue that is perceived by MG patients does not change significantly with therapeutic exercises, and this could compromise results. Physiotherapy treatment is considered to be effective for managing respiratory complications in patients with MG and in improving respiratory capacity. In addition, results from published studies show that therapeutic exercises allow patients with physical disabilities to optimize performance of specific activities, which might help them to improve their quality of life. However, given the current inconclusive and limited literature, further studies regarding therapeutic exercise effectiveness in management of physical therapy in MG patients are needed to obtain conclusive results. It is recommended that new studies with high levels of scientific evidence and methodological rigour take place to confirm results found in the studies reviewed here and to establish concrete conclusions on the influence of physiotherapy based on therapeutic exercise in patients with MG.

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