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Review

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Exercise and myasthenia gravis

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Abstract

Myasthenia gravis (MG) is an autoimmune disease primarily affecting the neuromuscular junction. Its main clinical manifestations are fluctuating muscle weakness and easy fatigability, which are currently believed to be caused by disease-specific autoantibodies. Pharmacological therapy is the first-line treatment for MG, and treatment regimens including glucocorticoids, immunosuppressants, and pyridostigmine are considered to significantly improve patients' clinical manifestations, enabling patients to achieve the treatment goal of minimal manifestation status (MMS). Supportive therapy is also considered equally important in clinical practice. Traditionally, it was thought that exercise might exacerbate symptoms in MG patients; however, with a deeper understanding of MG and the publication of relevant research findings, it is now believed that moderate exercise can benefit stable MG patients.

Keywords: Myasthenia gravis, neuroimmunological diseases, treatment, exercise

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease in which antibodies bind to the postsynaptic membrane of skeletal muscle cells. These antibodies impair acetylcholine receptor (AChR) function and induce changes in cell membrane morphology[1]. Most autoimmune antibodies target the extracellular portion of AChR itself or membrane proteins that interact with AChR, such as muscle-specific kinase (MUSK) or lipoprotein-related protein 4 (LRP4). Muscle weakness and easy fatigability are the main clinical manifestations of MG[2], and easy fatigability is currently believed to be caused by disease-specific

autoantibodies. Currently, first-line treatment for MG focuses on selecting the optimal immunosuppressive drug therapy regimen, including glucocorticoids, immunosuppressants, and novel molecular targeted drugs. However, in daily practice, supportive treatment regimens such as ptosis surgery[2,3], weight reduction[2], and comorbidity management are also very important for improving patients' quality of life.

Traditional theory suggests that MG patients should not engage in exercise. However, some studies have shown that most MG patients often face restrictions in engaging in social activities[4], and physical exercise can effectively improve patients' social functioning levels[5]. With a deeper understanding of MG among researchers and the publication of relevant randomized double-blind study findings, it is now believed that moderate exercise can benefit stable MG patients. This article will review four aspects: baseline exercise levels in MG patients, the safety of exercise, the benefits of exercise for MG patients, and currently published studies on exercise in MG patients.

BASELINE EXERCISE LEVELS IN MG PATIENTS

The baseline exercise levels of MG patients are generally lower than those of healthy controls. A study published in 2019 by Swedish scientists explored the baseline exercise levels of MG patients[6]. This study used wearable accelerometers to assess differences in daily exercise volume, sedentary time, physical activity levels, daily step count, and sedentary time between MG patients, a healthy control group, and a Chronic Obstructive Pulmonary Disease (COPD) control group. The study found that, from the perspective of baseline exercise levels, most MG patients primarily engage in sedentary behavior. Compared with healthy individuals, MG patients are generally less physically active[6].

A study published in 2022 assessed the baseline exercise levels of patients in the Danish MG Cohort, which found that 46%-48% of patients did not meet the WHO's recommended minimum exercise levels[7]. Another study that assessed the baseline exercise levels of MG patients through online questionnaires found that over half of the participants (62.4%) achieved the minimum daily exercise standards for healthy individuals, with an average of 9 hours of sedentary time per day[8].

POTENTIAL BENEFITS OF EXERCISE FOR MG PATIENTS

Exercise reduces inflammation levels in the body

MG is an autoimmune disease primarily involving cellular immunity. Multiple studies have confirmed that patients with MG exhibit high expression levels of IL-6, CRP, TNF-α, and IL-17 in their peripheral blood[9]. Moreover, the expression levels of these inflammatory indicators are positively correlated with the Quantitative Myasthenia Gravis Score (QMGS), suggesting that an inflammatory storm plays a role in the pathogenesis of MG[10]. In studies on autoimmune diseases, researchers have found that exercise can inhibit the active inflammatory state in the body [11,12]. In studies on neuromuscular diseases, particularly involving patients with polymyositis and dermatomyositis, exercise has been shown to improve muscle function and reduce disability rates by enhancing the muscle's oxygen-carrying capacity[13]. Additionally, exercise can increase muscle strength in patients with chronic inflammatory polyneuropathy[13,14]. For patients with facioscapulohumeral muscular dystrophy type 1, exercise can alleviate their chronic fatigue symptoms[15]. In the case of MG patients, a pilot study has confirmed that exercise can reduce the levels of microRNAs in peripheral blood, suggesting a potential mechanism by which exercise improves muscle function in these patients[16].

Exercise improves mental health status

Patients with MG may exhibit depression, anxiety, and frustration[17]. Therefore, improving quality of life and mental health should be prioritized in the long-term management strategy for MG patients. Currently,

multiple studies have confirmed the value of exercise in improving mental health. Physical exercise may play a significant role in the treatment of mild or moderate mental health disorders[18]. Research on suicide rates and mental health among college students has shown that regular exercise is negatively correlated with the risk of related events, with a certain dose-related effect[5]. For the elderly population, researchers have found that physical exercise may serve as an adjunctive therapy for neuropsychiatric and cognitive disorders during aging, helping to improve late-life depression[19]. In the context of patients with myasthenia gravis, a case report following up on a female MG patient confirmed that exercise increased her confidence in independent living[20]. Currently, studies on the correlation between mental health status and exercise among MG patients are relatively scarce.

Exercise and drug-related complications

Most MG patients require long-term oral administration of low-dose glucocorticoids to maintain disease stability during the stable phase. However, glucocorticoids may lead to metabolic drug-related side effects such as obesity, osteoporosis, and diabetes. Regarding obesity, the World Health Organization recommends at least 150 min of moderate-intensity or 75 min of high-intensity aerobic exercise per week, along with two sessions of resistance/muscle-strengthening activities per week[21]. For osteoporosis, current research generally agrees that both self-weight aerobic training and weight-bearing strength training have effects on increasing bone density[22]. Additionally, multiple studies have emphasized the important role of exercise in the treatment of diabetes[23,24]. In summary, for stable MG patients, exercise can ameliorate the related side effects caused by glucocorticoids.

SUMMARY OF PUBLISHED STUDIES ON MG AND EXERCISE

Studies focusing on exercise intervention in MG patients were searched in the PubMed database using the keywords “myasthenia gravis” + “exercise” or “myasthenia gravis” + “physical training” or “myasthenia gravis” + “physical activity” or “myasthenia gravis” + “respiratory training”. The identifiable published literature currently includes only a few randomized controlled trials (3 studies), cohort studies (2 studies), pilot studies (4 studies), or case reports (5 studies). Additionally, 3 studies specifically focused on respiratory training in MG patients. Due to the limited number of studies on exercise intervention in MG patients, these studies are discussed and summarized in relatively greater detail below [Table 1].

Safety and adherence of exercise in patients with myasthenia gravis

Existing studies have confirmed that MG patients exhibit high safety and adherence to exercise[40,41]. Researchers assessed adherence by studying dropout rates and protocol adherence rates. A study published enrolled 15 MG patients and observed a dropout rate of less than 10%[25]. In a pilot study published by Westerberg *et al.* in 2017, the protocol adherence rate of the remaining patients was as high as 95%[16]. In terms of safety, researchers evaluated it through self-assessment or assessor-reported Myasthenia Gravis Foundation of America (MGFA) classifications, QMG scores, disease exacerbation, and adverse reactions.

Characteristics of patients enrolled in relevant studies

The patients enrolled in these studies are primarily those with mild to moderate generalized MG or clinically stable MG. Some studies assess the severity of illness in enrolled patients using the Osserman classification[38]. Patients with mild to moderate generalized MG are generally classified according to the MGFA grading system, specifically including those with MGFA grades II/III. Some study protocols also include patients with ocular MG (MGFA grade I). The definition of clinically stable MG varies in different literature. In a prospective cohort study published in 2022, clinically stable MG was defined as patients whose MG treatment had not been adjusted within six months[29]. In another study, clinically stable MG was simply defined as patients who were regularly followed up, had well-controlled symptoms as assessed by clinicians, and still required treatment[16]. Birnbaum *et al.* also defined clinically stable MG as patients with

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Table 1. Summary of active physical exercise intervention studies in myasthenia gravis

Publication year	Authors	Study design	Sample Size	Participant characteristics	Outcome measures	Exercise mode	Results
2017	Rahbek *et al.*[25]	Randomized stratified	15 cases	MGFA II/III	1. Evaluation of exercise safety and changes in QMG score; 2. Effects of exercise on muscle strength, oxygen consumption, functionality, MG-QoL15r, MDI, MFIS	AT protocol (6 patients, moderate to high-intensity aerobic training): incremental cycling trial over 8 weeks, reaching 75%-80% of maximum heart rate. RT protocol (6 patients): progressive whole-body resistance training, e.g., leg press, bench press	Exercise is safe for most stable, mild MG patients; the RT group showed improvements in knee extension and shoulder abduction strength; the AT group experienced deterioration in MG-QoL scores
2021	Birnbaum *et al.*[26]	Randomized controlled Trial	43 cases (23 in exercise group, 20 in routine group)	Stable generalized MG patients, female, no exercise contraindications	1. Evaluation of exercise tolerance and safety; 2. HRQoL score assessment	Over 3 months, unsupervised, moderate-intensity rowing exercise, 3 times per week, 40 min per session	Good exercise tolerance: no significant improvement in HR-QoL compared to the routine care group
2021	Misra *et al.*[27]	Randomized controlled trial	40 cases, open-label study, randomized into 2 groups	Mild to moderate generalized MG patients	1. MG-QoL score; 2. MMS, MG-ADL, grip strength, 6 min walk test distance, trapezius RNS amplitude decrement, prednisone and pyridostigmine doses	Over 3 months, 30 min daily walking	Good exercise tolerance; daily 30 min exercise improves quality of life and 6 min walk test distance in mild and moderate MG patients compared to rest
2018	Westerberg *et al.*[28]	Cohort study, prospective	11 cases	Mild to moderate generalized MG patients	1. Electrophysiological measures: CMAP amplitude; 2. Grip strength; 3. Muscle thickness by ultrasound; 4. 30-second sit-to-stand time; 5. MGC score	12-week aerobic + strength training under professional supervision	Rectus femoris parameters improved: CMAP amplitude, muscle strength, and muscle thickness increased. Clinical improvements in MGC score and the 30-second chair stand test. No improvement in biceps muscle function parameters
2021	Chang *et al.*[29]	Cohort study, prospective	34 cases	Clinically stable MG patients, MGFA II/III	1. QMG score, HR-QoL score; 2. Grip strength, walking speed; 3. Body composition	1. QMG score, HR-QoL score; 2. Grip strength, walking speed; 3. Body composition	Good exercise tolerance; arm muscle mass declined in the high-intensity exercise group, but forced vital capacity, walking speed, and symptom severity improved; significant improvement in walking speed for the low QMG score group
2018	Farrugia *et al.*[30]	Pilot study, prospective	10 cases	Clinically stable MG patients with persistent fatigue complaints	1. MGC, MGADL, MG-QoL15r; 2. Modified Fatigue Impact Scale (MFIS), Visual Analog Fatigue Scale (VAFS), Fatigue Severity Scale (FSS); 3. HADS	10-week exercise + psychotherapy	Mild improvement in MFIS physical and psychosocial subscales. Significant improvement in VAFS at the end of the program ($P < 0.01$). No improvement in FSS. Fatigue scores reduced to baseline after three months
2017	Westerberg *et al.*[16]	Pilot study, prospective	10 cases	Clinically stable MG patients, MGFA grade I-II	1. MGC score; 2. Electrophysiological indicators: CMAP, RNS; 3. Muscle strength; 4. 6 min walk test;	12-week aerobic + strength training under professional supervision	Good exercise tolerance; increased CMAP amplitude and muscle strength in biceps and rectus femoris; normal muscle enzyme levels; decreased disease-specific miR-150-5p and miR-21-5p post-training

					5. Serum inflammatory markers (IL-6, microRNAs), muscle enzymes		
2014	Wong *et al.*[31]	Pilot study, prospective	7 cases	Clinically stable MG patients	1. QMG score; 2. 6 min walk test; 3. Balance function (TUG and foamEC)	16 sessions, balance strategy training including balance strength and endurance exercises	Most measures continued to improve at follow-up. Significant clinical improvement in QMG, TUG, and foamEC (> 15%)
1993	Lohi *et al.*[32]	Pilot study, prospective	11 cases	Mild-to-Moderate MG	1. Active muscle strength of three muscle groups; 2. Degree of fatigue	10 weeks, 27-30 sessions of strength training;	Good exercise tolerance. Improved knee extension strength on the trained side compared to the untrained side
2018	Birnbaum *et al.*[33]	Case report	1 case	36-year-old female, Generalized MG, AchR antibody (+)	1. Muscle strength; 2. MGQol score; 3. Medication status	Marathon, running 5-10 km per week, continued for 2 years after MG diagnosis	Stable MG status; Discontinued azathioprine; Normal respiratory function; Stable lower limb muscle strength; Improved MGQoL score
2012	Scheer *et al.*[34]	Case report	1 case	55-year-old male, Generalized MG	-	Marathon, 220 km	Stable MG; Symptom fluctuations during the race, improved with rest or oral pyridostigmine
2007	Lucia *et al.*[20]	Case report	1 case	29-year-old female, Generalized MG, McArdle's disease, thymoma	1. Exercise capacity; 2. Ability to live independently	12-week aerobic exercise training program	Significant improvement in exercise capacity and regained ability to live independently
2001	Stout *et al.*[35]	Case report	1 case	26-year-old male, Generalized MG, athlete	1. Body weight; 2. Body fat percentage; 3. Muscle strength	15-week strength training program	Increased body weight; Decreased body fat percentage; Increased lower limb flexor and extensor strength
2000	Leddy *et al.*[36]	Case report	1 case	17-year-old male; Generalized MG, rugby player	-	Regular rugby training	Retired from rugby; Engaged in other recreational sports activities
2005	Fregonezi *et al.*[37]	Randomized controlled trial	27 cases	Generalized MG	1. Lung function; 2. Respiratory pattern; 3. Respiratory muscle strength; 4. Respiratory endurance; 5. Chest mobility	Interval-based inspiratory muscle training (IMT) combined with breathing retraining (BR) for 8 weeks	The training mode is safe and effective; Improvements in respiratory muscle strength, chest mobility, respiratory pattern, and respiratory endurance
2007	Rassler *et al.*[38]	Pilot study	10 cases	Mild-to-moderate generalized MG, Osserman types 2-4; No history of respiratory diseases	1. Bessinger score; 2. Lung function; 3. Respiratory muscle endurance	Normocapnic hyperventilation training; 20 training sessions over 4-6 weeks	Significantly improved respiratory endurance and total ventilation; Approximately 25% of the gains were lost after a 3-5 month detraining period
2018	Freitag *et al.*[39]	Case-control study	12 cases	MGFA II MG patients	1. Respiratory endurance (RE); 2. MG symptoms; 3. Lung function; 4. Impact on physical fitness	Long-term respiratory muscle endurance training (RMET) based on normocapnic hyperventilation. Four weeks of intensive training (IT; 5 × 30 min per week), 12 months of maintenance training (MT; 5 × 30 min within two weeks)	Increased time to fatigue (Tlim), MG score; Increased number of squats per minute; No changes in lung function during training, prolonged exhalation time, changes in breathing pattern at rest. Subjective improvements in MG symptoms, respiratory symptoms, and physical fitness scores

MG: Myasthenia gravis; QMG: quantitative myasthenia gravis; MGFA: myasthenia gravis foundation of America; RT: resistance training; AT: aerobic training; MFIS: modified fatigue impact scale; HR-QoL: health-related quality of life; MG-QoL: myasthenia gravis quality of life; CMAP: compound muscle action potential; MGC: myasthenia gravis composite; MG-ADL: myasthenia gravis activities of daily living; HADS: hospital anxiety and depression scale.

stable symptoms, as assessed by clinicians[26]. In a study published in 2014, clinically stable MG was defined in detail, requiring the patient's attending physician to confirm that the patient's MG was controlled and clinically stable, and that the MG treatment regimen would not be adjusted during the study[31]. However, some studies still lack a precise definition of clinically stable MG[30]. In addition, some studies have accurately characterized whether the enrolled patients exhibited symptoms of fatigue[30]. In a study published in 2018, the Modified Fatigue Impact Scale (MFIS), Fatigue Severity Scale (FSS), and Visual Analog Fatigue Scale (VAFS) were administered to patients at baseline, and the scores from these scales were used to assess their baseline susceptibility to fatigue[30]. Furthermore, to minimize baseline bias, Birnbaum's study published in 2021 restricted enrollment to female patients[26].

Outcome variables involved in related studies

Various research methodologies have been employed in different studies, leading to a certain degree of heterogeneity among their conclusions. The outcome variables involved in these related studies include:

(a) MG-related scale scores: MG-related self-assessed or externally assessed scales can comprehensively reflect the objective clinical manifestations of MG patients and their subjective feedback on the disease. The scientific selection of relevant rating scales is conducive to a comprehensive assessment of the efficacy of specific treatment methods for MG patients. MG-related self-assessed scales primarily include Myasthenia Gravis Quality of Life (MG-QoL) and Myasthenia Gravis Activities of Daily Living skills (MG-ADL) scores. For MG, the specificity, sensitivity, and consistency with objective scale scores of self-assessed scales have gradually been recognized by researchers and institutions. Due to their simplicity and convenience, the application of self-assessed scales has gradually been widely promoted[42]. The MG-QoL score is an adapted Health-Related Quality of Life (HR-QoL) score for MG patients, focusing on their subjective perception and tolerance of MG and the disability it causes[17,42,43]. Studies by Misra *et al.*[27], Birnbaum *et al.*[33], and Farrugia *et al.*[30] have used the MG-QoL score as a primary or secondary study endpoint, while Chang *et al.* and Birnbaum *et al.*[29,44] have used HR-QoL as a secondary endpoint for assessment. The MG-ADL score focuses on the daily living abilities of MG patients and has been used as a primary outcome variable in multiple randomized controlled trial (RCT) studies related to MG treatment[42]. In RCTs on myasthenia gravis and exercise, MG-ADL has been used as a secondary outcome variable in individual studies[27]. Besides self-assessed scales, the QMG score, which quantitatively assesses the fatigue tolerance of sentinel muscle groups, is a key objective rating scale for MG treatment outcomes recommended in the MG clinical research guidelines issued by the MGFA in 2000[45]. The QMG score demonstrates high consistency with patients' MGFA classifications and Post Intervention Status (PIS) status, and its inter-rater reliability has been confirmed[45]. Studies by Wong[31] *et al.* and Chang[29] *et al.* have used the QMG score as the primary outcome variable. The minimal manifestation status (MMS) scale, developed by Gasdoj in 1983, mainly assesses trunk muscle strength, limb muscle strength, and cranial nerve muscle strength and shows a high degree of consistency with the QMG score. However, its clinical application is currently limited due to the lack of respiratory muscle assessment. In studies related to MG and exercise, Misra[27] *et al.* used the MMS score as a secondary outcome variable. The Myasthenia Gravis Composite (MGC) score, derived

from the QMG, MG-Manual Muscle Testing (MMT), and MG-ADL scales, combines self-assessment and physician evaluation items[17]. It is characterized by ease of operation and a combination of subjective and objective evaluations. In a small-scale pilot study, Westerberg[16] *et al.* utilized the MGC score as the primary outcome variable. Some studies have demonstrated improvements in MG-QoL or HR-QoL scores before and after interventions, yet the improvement in QMG scores was not significant. On the one hand, this is related to the fact that most of the patients enrolled in these studies were clinically stable MG patients. On the other hand, it also suggests that exercise may have a greater impact on improving the subjective perception of the disease among MG patients.

(b) Fatigue-Related Scale Scores: MG is primarily characterized by muscle weakness and easy fatigability. In some patients, the characteristic of easy fatigability may not show significant improvement with traditional immunotherapy[40]. Farrugia *et al.*[30]primarily investigated the degree of improvement in the clinical characteristic of easy fatigability among MG patients through exercise. In addition to the MGC, MG-QoL15r, and MG-ADL scores, their study also included assessments using the MFIS, VAFS, and FSS within the evaluation scope. Similarly, Rahbek[25] *et al.* also incorporated the MFIS as a secondary outcome variable in their study. While subjective fatigue scales capture patients' perceived exertion, they may conflate psychological and physiological dimensions. Future studies could integrate repetitive task performance (e.g., 6-min walk distance) with real-time biomarker monitoring (e.g., salivary cortisol) to disentangle these components.

(c) Psychological Scales: Some studies on exercise in MG have also included psychological scales and balance function scales in their assessments. Farrugia[30] *et al.*'s study focused on the impact of exercise on the psychological state and degree of fatigability among MG patients, and accordingly incorporated the Hamilton Anxiety Scale for assessment. In a randomized stratified study designed by Rahbek[25] *et al.*, the Major Depression Inventory was included as a secondary outcome variable.

(d) Functional Assessment: Pre- and post-intervention muscle strength assessments have been addressed in multiple studies[16,25,27,29,32]. In Rahbek *et al.*'s study, researchers objectively assessed patients' muscle strength in knee extension, knee flexion, shoulder abduction, elbow flexion, and hip flexion using an isokinetic dynamometer[25]. Most studies assessed patients' grip strength using a grip dynamometer[27,28]. Additionally, some studies evaluated the 6 min walk test distance and 30 s chair stand time before and after intervention and obtained positive results[16,27,28,31].

(e) Laboratory Tests and Examinations: In their 2017 pilot study, Westerberg[16] *et al.* assessed the levels of IL-6 and disease-related microRNAs before and after intervention. Compared to pre-intervention levels, disease-specific miR150-5p and miR21-5p showed significant decreases post-intervention. These microRNAs are currently considered specific indicators for anti-AchR antibody-positive myasthenia gravis patients, suggesting that regular exercise may reduce the level of inflammatory responses in MG patients. The study also included assessments of creatine kinase (CK), electrolyte levels, and IL-6 levels, which did not show significant changes before and after intervention. Some studies explored neurophysiological examination indicators before and after intervention. Misra[27] *et al.* investigated the degree of decrement in the Repeated Nerve Stimulation (RNS) amplitude of the trapezius muscle before and after exercise and obtained negative results, consistent with the findings reported by Westerberg[16] *et al.* in 2017. Westerberg[16,28] *et al.* also investigated changes in the Compound Muscle Action Potential (CMAP) amplitude of proximal limb muscles before and after intervention. Both studies found significant increases in the CMAP amplitude of the quadriceps femoris muscle before and after intervention.

(f) Treatment: Adjustments in the frequency and dosage of therapeutic drugs, including glucocorticoids, non-hormonal immunosuppressants, and cholinesterase inhibitors, are important outcome variables commonly assessed in studies related to MG treatment. Some studies on the correlation between exercise and MG[27,44] have also included these indicators as secondary outcome variables. However, relevant studies have not found statistically significant positive results.

Exercise modalities in related studies

Currently, intervention studies on MG and exercise have employed various exercise modality protocols. The training intensities range from moderate to high. The training is conducted regularly within a week, but the frequency of exercise adopted by different studies varies. The evaluations of resistance training, aerobic exercise, and broader exercise programs are based on a small number of patients, which hinders comparisons among different studies. It remains unclear whether any specific training program offers particular benefits for MG[41]. As noted by Rahbek *et al.*[25], the divergent results between the Aerobic Training (AT) and Resistance Training (RT) groups highlight the critical role of exercise modality selection. While the AT group showed a slight decline in MG-QoL scores, the RT group demonstrated stable or marginally improved outcomes. This suggests that RT protocols may be better tolerated by MG patients due to reduced neuromuscular fatigue accumulation. AT protocols could inadvertently exceed the metabolic thresholds of certain MG subgroups, particularly those with baseline bulbar or respiratory involvement. Currently, it is generally recommended that clinically stable MG patients engage in at least 150 min of moderate-intensity aerobic exercise per week. This aligns with the minimum physical activity recommendations for healthy older adults issued by the World Health Organization[46].

To date, studies investigating the relationship between exercise and MG remain relatively limited. Through a comprehensive literature search, we have systematically documented the study populations, outcome variables examined, and exercise protocols reported in existing research. However, substantial heterogeneity in methodological approaches has been observed across studies. This variability has resulted in marked variations in conclusions regarding exercise efficacy and safety in MG, significantly limiting the comparability of findings between studies. A stepwise algorithm integrating MGFA classification, antibody status, and fatigue severity should be introduced in future studies to guide exercise intensity adjustments.

RESPIRATORY MUSCLE-RELATED TRAINING

Three studies have explored the impact of respiratory muscle training on patients with MG, primarily focusing on those with mild to moderate disease severity. Respiratory muscle training (RMT) confers clinically meaningful benefits in MG by improving diaphragmatic endurance and cough efficacy[37]. Two of these studies included MG control patients who did not receive training[37,39]. The training lasted for 4 to 8 weeks, with one study incorporating a 12-month maintenance training phase[39]. The program included interval-based muscle endurance training and respiratory retraining. All three studies reported the adequate safety and feasibility of respiratory training and observed improvements in respiratory patterns and neuromuscular coordination. One study reported an improvement in MG scores[39], while another did not[38]. Two studies reported improvements in respiratory muscle strength and respiratory endurance[37,38]. Overall, patients' physical fitness and respiratory status improved after the training programs.

CONCLUSION

Research on exercise and MG is currently limited, with most studies being small-scale interventional or pilot studies. There are methodological differences among the studies, leading to some heterogeneity in their conclusions. While adherence rates in the reviewed RCTs were high, all three trials had small sample sizes. This restricts their ability to detect subtle but clinically meaningful changes in patient-reported

outcomes like MG-QoL. Current studies are limited by small sample sizes. Future trials should recruit ≥ 200 participants through international registries to stratify outcomes by MGFA class, autoantibody profiles, and immunotherapy regimens. To improve study design: (1) Standardizing baseline criteria will help reduce heterogeneity; (2) A Delphi consensus process is needed to define core variables for cross-study comparability; (3) Head-to-head comparisons of AT *vs.* RT in seropositive/seronegative subgroups may clarify dose-response relationships; (4) Wearable sensors could be used to enable real-time intensity titration.

Based on the existing research, it is evident that moderate physical activity is safe and potentially beneficial for clinically stable MG patients. However, further research is needed to determine the extent to which physical exercise should be incorporated into routine MG treatment protocols and whether there are specific training programs that are particularly beneficial for patients. Based on the literature reviewed in this review, we can conclude that clinically stable and well-controlled MG patients can be encouraged to initiate moderate physical activity programs.

DECLARATIONS

Authors' contributions

Conducted the literature review and wrote the manuscript: Shi J
Reviewed and edited the manuscript: Tan Y
Assisted with the literature review: Huang Y, Yan J
Conceptualized the research framework, reviewed, and approved the final manuscript: Guan Y

Availability of data and materials

Not applicable.

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Guan Y is the Guest Editor of the Special Issue titled "Advancements in Myasthenia Gravis Research: New Horizons in Treatment" in the journal *Rare Disease and Orphan Drugs Journal*. Guan Y was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, or decision making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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