A Narrative Review of Respiratory Impairment, Assessment, and Rehabilitation in Multiple Sclerosis

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Keywords

Multiple sclerosis · Respiratory dysfunction · Assessment · Rehabilitation

Abstract

Background: Respiratory impairment is a problem seen in people with multiple sclerosis (pwMS) from the early stages of the disease but not frequently recognized by clinicians until the later stages. It is seen in different ways, such as respiratory muscle weakness, change in pulmonary volumes, and decrease in cough efficiency. This situation has consequences affecting individuals' physical fitness, participation in daily life, and quality of life. **Summary:** This review explains possible respiratory impairment mechanisms, related problems, assessment, and rehabilitation approaches in pwMS. **Key Messages:** It is recommended a comprehensive assessment of respiratory functions in pwMS regardless of the disease severity and stage. In addition, pulmonary rehabilitation and other exercises can have positive effects on the respiratory functions of pwMS. In future studies, specific training parameters should be determined for pwMS to achieve optimal benefits. There is also a need for studies

that apply respiratory muscle training in pwMS who have a high disease severity and limited participation in the activities of daily living.

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Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system predominantly diagnosed in young adults [1]. It is estimated globally to be about 2.8 million people with MS (pwMS) [2]. These individuals are confronted with various serious symptoms such as spasticity, muscle weakness, gait disturbance, cognitive impairment, swallowing problems, and bladder-bowel dysfunction [3, 4]. In addition, the pulmonary system can be impaired, but healthcare providers usually overlook its assessment due to the high prevalence of other MS symptoms. However, respiratory functions and respiratory muscle strength have been altered even in the early stages of MS, and these changes become exacerbated by the increased disability [5]. The risk of respiratory death is almost 12 times higher, and this rate ac-

Fig. 1. Pulmonary system affecting mechanism in MS: the function of respiratory muscles is deteriorated primarily by the formation of demyelinated plaques in the central nervous system and accompanied by secondary factors (drugs, fatigue, increased body temperature, sedentary lifestyle, and deconditioning). This impairment manifests in different ways, such as decreased respiratory muscle strength, lung volumes, and cough efficiency.

counts for approximately 47% of all causes of death in MS [6]. The pulmonary system's involvement which is generally observed deterioration in diffusion capacity (DLCO), respiratory muscle strength, and ventilation-perfusion ratio (V/Q) [7] leads to exercise intolerance, hospitalization, and morbidity in pwMS. As a result, the physical fitness level of pwMS deteriorates, and it becomes more difficult for them to participate in daily activities [8].

Previous research has compiled information about pulmonary dysfunction, assessment, and treatment in MS [9]. Due to substantial developments that have been achieved on this topic, it is thought that a current review will contribute to studies related to MS. The current narrative review aimed to explain respiratory involvement, including respiratory failure, respiratory muscle weakness, cough inefficacy, sleep breathing disorders, and respiratory dysfunction during exercise. Furthermore, it is

aimed to present respiratory assessment tools and the results of rehabilitation programs for the pulmonary system in pwMS.

Underlying Mechanisms of the Respiratory Impairment

The brain stem and spinal cord contain relevant centers that generate signals to regulate respiratory muscles' functioning. Depending on the size and area of demyelinating plaques that develop in these respiratory centers, respiratory muscle-related impulses could be disrupted in pwMS [10]. Therefore, one or more symptoms such as respiratory muscle weakness, dyspnea, ineffective cough, bulbar dysfunction, and decreased respiratory control are seen in varying severity [11]. Although pulmonary in-

involvement in the early stages of MS is uncommon, pulmonary issues' prevalence increases with exacerbated disease severity [10]. Medication, fatigue, and high body temperature leading to interruption of nerve conduction may adversely affect the respiratory muscles and enhance the possibility of respiratory dysfunctions. The occurrence of pulmonary system impairment and resulting problems in MS are summarized in Figure 1.

Respiratory Failure

Respiratory failure occurs as a consequence of demyelinated plaque formation at the cervical spinal cord, as well as in the terminal stage of MS when respiratory muscles and cough efficiency are severely affected. Even if an acute respiratory failure is seen rarely in MS, it is quite common in quadriplegic and paraplegic pwMS. Moreover, the risk of acute respiratory failure enhances in relapsing-remitting MS following new, large plaque formation in the brain stem [12]. Individuals with relapsing-remitting MS can develop dyspnea, orthopnea, confusion within hours and minutes, or rapid, shallow breathing associated with diaphragm weakness. The vital capacity (VC) also decreases by more than 30% during the transition from lying down to sitting upright [12]. Chronic respiratory failure is seen at the advanced stages of MS or pwMS who use wheelchair with weak upper extremities and respiratory muscles [11, 13].

Respiratory Muscle Weakness

Respiratory muscle weakness is the most common respiratory problem in pwMS, especially in bedridden people or people who use wheelchairs [14]. Even if respiratory muscle weakness is more common in advanced stages of MS, respiratory muscles weaken asymptotically from the early stage. Expiratory muscle weakness is more predominant in MS because expiratory muscles are primarily involved [15]. Although respiratory muscle strengths are normal in pwMS with moderate disease severity, these values can differ greatly between individuals, indicating lower respiratory muscle strength in some individuals [16]. pwMS with significant expiratory muscle weakness have lower functional exercise capacity and higher disability levels [16].

Multiple factors are influential to the detriment of the respiratory muscles in MS; however, the corruption of the neural tract related to respiratory muscles is most effective. In addition, sedentary lifestyle, deconditioning, fatigue, malnutrition, steroid-related myopathy, disrupted respiratory activation and coordination, bulbar dysfunction, and facial paralysis contribute to weakness [15, 17].

The progression of paralysis from distal to proximal in MS causes weakness of the expiratory muscles, the rectus abdominis, and transversus abdominis, before the diaphragm and intercostal muscles [18]. Likewise, respiratory muscle endurance and maximum inspiratory muscle strength progressively decline in line with the patient's ambulation ability [13].

Weakened respiratory muscle leads to general muscle weakness, spasticity, fatigue, and cognitive dysfunction [11, 19], except for issues associated with the pulmonary system like decreased lung volumes, ventilation-cough inefficiency, inadequate airway clearance, and sleep-disorder breathing [6]. It has also been reported that respiratory muscle endurance is significantly related to sleep quality and functional exercise capacity in pwMS [19].

The pelvic floor, the diaphragm responsible for inspiration, and the abdominal muscles responsible for expiration generate the trunk stabilizing system. This system provides postural adjustments by regulating intra-abdominal pressure during static and dynamic activities [20]. It has been reported that urinary and gait functions are more impaired in pwMS whose respiratory muscle strength and respiratory functions are affected. In particular, a higher correlation was found between expiratory muscle strength and urinary incontinence and physical dysfunctions [21]. The simultaneous activation of these muscle groups and the presence of a biomechanical connection among trunk stabilizing system components explain the relation between respiratory muscle strength and urinary incontinence [21].

Decreased Cough Efficiency

Cough efficiency is a vital function responsible for the clearance of secretions in airways. Bulbar dysfunction, delayed glottis closure, and decreased intrathoracic pressure accordingly with expiratory muscle weakness reduce cough efficiency in pwMS. Cough inefficiency accumulates secretions in their airways, and therefore, it might lead to atelectasis and pneumonia in the future [22]. It has been shown that there is a correlation between peak cough flow (PCF), which is a parameter for indicating cough efficiency, and disease severity in pwMS [22]. A study examining pwMS who use wheelchairs found that PCF was reduced in 61.6% of these individuals, and PCF was severely affected in 37% of them [23].

Impaired Respiratory Control

Respiratory control is provided by respiratory centers located in the pons and medulla. There are two respiratory centers called dorsal and ventral groups controlled

by the pneumotoxic and apneumatic respiratory centers in the pons. While the dorsal respiratory center is responsible for inspiration and respiratory rhythm, the ventral respiratory center is responsible for active expiration in conditions where ventilation must be increased, like physical exercise. When one of those respiratory centers is affected by MS, respiratory control is destroyed, and then respiratory control difficulties might emerge as paroxysmal ventilation, loss of voluntary or autonomic respiratory control, or apneumatic breathing [13, 24].

Sleep-Disordered Breathing

pwMS experience three different respiratory disorders during sleep: obstructive sleep apnea (OSA), central sleep apnea linked with demyelination in the medulla, and nocturnal hypoventilation linked with decreased tidal volume (V_t) in REM sleep. Obstructive and central sleep apneas usually occur in cases with brain stem involvement [25, 26].

Sleep-disordered breathing might conclude inability to fall asleep, insomnia, daytime sleepiness, loss of concentration, and tiredness. It is important to note that sleep disorder breathing-related fatigue should be distinguished from MS-related fatigue [25, 26]. It has also been reported that perceived fatigue is a substantial predictor of OSA in pwMS [27].

OSA, which is estimated to be about 33% in pwMS, is a potential risk factor for cognitive dysfunction [28]. A study investigated the potential impact of OSA treatment on cognition and concluded that verbal learning significantly improved in pwMS who received treatment [29]. Given these outcomes, there is a need to further investigation for improvement of cognitive function and fatigue in MS through the treatment of sleep-disordered breathing.

Neurogenic Pulmonary Edema

Neurogenic pulmonary edema, which occasionally emerges as the first symptom, is a rare condition in pwMS. Although the pathophysiology of neurogenic pulmonary edema has not been precisely explained, it has been reported that it may be associated with a defect in the tractus solitarius, which is responsible for pulmonary hydrostatic pressure [30]. The affected tractus solitarius induces pulmonary hydrostatic pressure via increasing sympathetic impulses and resulting in pulmonary edema [30].

Deterioration in Lung Volumes

Alteration in pulmonary volumes usually occurs following respiratory muscle weakness [13]. While respira-

tory muscle strength is affected mildly or moderately, these volumes could be at normative values in MS [13]. It has been reported that resting pulmonary volumes are associated with exercise tolerance in MS [31], but similarly, pulmonary volumes are not associated with disability levels [16].

The VC can vary depending on postural changes and disability levels in pwMS. For instance, the VC value decreases by 10–30% when shifting from upright to supine; it is about 102% of the predicted VC in pwMS with a lower disability [13]. Besides, this value is lower than both bedridden people (62% predicted) and (82% predicted) pwMS who use wheelchairs [13]. The current research has reported a decrease of VC in 72.6% of wheelchair-bounded pwMS and a significant correlation between VC and disease severity [23].

Respiratory Function during Exercise

During submaximal or endurance exercise, remarkable alteration occurs in the respiratory functions of pwMS, such as an impaired pulmonary gas exchange. The carbon dioxide ventilation equivalent and the oxygen ventilation equivalent values which are the indicators of pulmonary gas exchange are enhanced during submaximal exercise. Change in these values means ventilatory gas exchange is reduced. The end-tidal oxygen pressure value rises through the endurance exercise, and the end-tidal carbon dioxide pressure value declines. This stands for that the V/Q is disturbed. Apart from these, the physiological dead space/ V_t ratio increases, and oxygen saturation and DLCO decrease during exercise [31].

When pulmonary system issues (related to diffusion, ventilatory gas exchange, diaphragm function, and respiratory rhythm) are accompanied by cardiovascular dysfunction, the V/Q is impaired, resulting in lower oxygen levels in pwMS throughout physical exercise. It has also been reported that these respiratory dysfunctions are associated with perceived exertion, exhaustion, and exercise tolerance [32].

Outcome Measures Evaluating the Respiratory Function

Pulmonary function tests, which could guide the physician by providing information about the pulmonary system's components, include assessment methods for monitoring and managing pwMS who are diagnosed or not [33]. To provide a better viewpoint, the pulmonary system evaluation in pwMS is categorized according to

Fig. 2. Respiratory system assessment in pwMS according to the ICF: an overview of each component of ICF (body structure and function; activity and participation) under the subheadings of clinician-rated measures, self-reported measures, and performance-based measures. TLC, total lung capacity; FEV₁/FVC, the ratio of the FEV₁ to FVC volumes; FEF_{25-75%}, maximum flow rates between 25 and 75% of VC; ICF, International Classification of Functioning, Disability, and Health.

the International Classification of Functioning, Disability, and Health framework (Fig. 2).

Respiratory Muscle Function

Respiratory muscle function is commonly assessed by maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) in pwMS. Inspiratory mouth pressure is a method that requires generating as much pres-

sure as possible against a closed mouthpiece and reflects the inspiratory muscle function. Expiratory mouth pressure, created by the Valsalva maneuver against the closed mouthpiece in total pulmonary capacity, is a method that reflects expiratory muscle function. The strength of the abdominal, auxiliary respiratory muscles and the lung's elastic recoil affect the expiratory mouth pressure value [18].

Compared with the values expected from the healthy general population, MIP decreased significantly by 77% (± 23) and MEP by 60% (± 13) in pwMS [14]. When pwMS with low (0–2) and moderate (2.5–4.5) disability levels were compared with healthy individuals, it was observed that MEP was significantly reduced in pwMS with low (112.43 ± 23.33 cm H₂O) and moderate (98.89 ± 27.81 cm H₂O) disability. On the other hand, although MIP decreased in all patients compared to healthy individuals, MIP value decreased significantly only in patients with moderate disability (84.00 ± 17.06 cm H₂O) [5]. In a recent study, it has been reported that respiratory muscle strength was normal on a group level in pwMS with a moderate disease course (4.0–6.5), but these values differed largely between individuals. The MIP values ranged from 26 to 143 (mean 80 ± 28) cm H₂O ($98 \pm 31\%$ predicted), and the MEP values ranged from 43 to 166 (mean 97 ± 25) cm H₂O ($104 \pm 29\%$ predicted) in this study [16].

It has been reported that there is a moderate correlation between respiratory muscle strength and urinary function, more in expiratory muscle strength. In addition, a similar relation was found between expiratory muscle strength and physical functions evaluated with the timed up and go test and Barthel Index in pwMS [21].

Spirometry Test

The spirometry test, which is a more utilized method for lung function assessment, is easily performed by an exhalation as quickly as possible following maximum inhalation. The forced expiratory volume in 1 s (FEV₁), the forced VC (FVC), and the ratio of FEV₁ to FVC are used to determine obstructive or restrictive ventilation problems [33]. Other tests are the peak expiratory flow (PEF) during expiration, maximum flow rates between 25 and 75% of VC that reflect the condition of small airways, and the maximum voluntary ventilation (MVV), stating the respiratory muscle endurance [33]. MVV is also used in estimating breathing reserve during maximal exercise. There is a significant correlation between MVV and FEV₁; therefore, MVV might not be included in the set of lung function parameters [34]. In case of a disproportionate decrease in MVV relative to FEV₁ [34], both parameters should be included in the spirometry test in MS.

A study has reported that obstructive pulmonary disorder, a condition in which the ratio of FEV₁ to FVC or maximum flow rate value between 25 and 75% of VC decreased, was seen in 52.17% of pwMS without disability or with minimal disability and 50% of pwMS with mild to severe disability. Likewise, it has been determined that participants' PEF values decreased [5]. A recent study

presented a significant positive correlation between pulmonary function variables (VC, FVC, FEV₁, and PEF) and respiratory muscle strengths, besides moderate correlation between PEF and the 6-min walk distance in pwMS with moderate disability [16]. Although VC and FEV₁ were normal in these patients, PEF was in the lower limit of normal [16].

Lung Volumes

The residual volume (RV), briefly defined as the dead air space, reflects the volume of air remaining in the lungs at the end of maximum expiration [33]. RV can be increased significantly in pwMS in case if the air in the lungs is not completely discharged [13]. The total lung capacity, the sum of RV and VC, is recognized as the total air volume at the end of maximum inspiration [33]. As with restrictive pulmonary disorders, total lung capacity tends to decrease in MS [13].

Diffusion Capacity

DLCO, reflecting the gas dispersed across the alveolar membrane, provides knowledge about the alveolar membrane's integrity and dimension. It is determined by calculating the remaining carbon monoxide amount because of exhaling whole air after taking a rapid breath. It has been stated that DLCO can be impaired with respiratory muscle and other lung volumes or decreased due to fingolimod medication in MS [35].

Peak Cough Flow

PCF is directly related to expiratory muscle strength and cough effectiveness [36]. It has been reported that in pwMS who have both pulmonary dysfunction and cough inefficacy, PCF value improves, and the decline rate of FVC and PCF slows down after lung volume recruitment [37].

Neurophysiologic Procedures

Magnetic transcranial-cervical stimulation and electrical stimulation are the tools employing motor evoked potentials of the phrenic nerve to evaluate pulmonary functions. Central motor conduction time between cortex and diaphragm can be measured by this method. Despite the absence of respiratory disturbance, the diaphragm's electrophysiological evaluation can surprisingly result in increment motor evoked potential and central motor conduction time in pwMS [38].

Diaphragmatic Ultrasound

Diaphragmatic ultrasound is a practical, noninvasive technique to assess diaphragm thickness and mo-

Table 1. Overview of the studies on RMT in pwMS

Study	Sample size	MS course	EDDS score	Interventions	Intensity, frequency, and duration	Main results
Gosselink et al. [42] (RCT)	28 pwMS Intervention (n = 9) Control (n = 9)	NR	Range: 6.5–9.5 Median: 8.5	EMT (control group: breathing exercise)	60% MEP 3 sets 15 repetitions 2 times/day	MIP, MEP ↑ (more in the EMT group than control) Cough efficiency (PI) ↑ (more in EMT group than control)
Chiara et al. [41] (RCT)	pwMS (n = 17) Healthy control (n = 14)	NR	Range: 1.5–6.5 Mean (SD): 3.62 (1.31)	EMT	40–80% MEP 4 sets 6 repetitions 5 days/week 8 weeks training 4 weeks detraining	MEP, PEF ↑ (in pwMS) Maximal voluntary cough ↔ (in pwMS)
Pfalzer and Fry [47] (RCT)	46 pwMS Intervention (n = 20) Nontreatment control (n = 19)	RRMS (n = 22) PPMS (n = 5) SPMS (n = 5) PRMS (n = 3) Unknown (n = 4)	Intervention group = Range: 2.0–6.5 Mean (SD): 4.1 (1.9) Control group = Range: 2.0–6.5 Mean (SD): 3.2 (1.2)	IMT	60% MIP 3 sets 15 repetitions 10–15 min/day 10 weeks home-based training	MIP ↑ (more in the IMT group than control) MEP, MVV ↑ (no group difference) Timed balance scores ↑ (more in the IMT group than control) 6-MWT ↑ (no group difference)
Ray et al. [40] (RCT)	21 pwMS Intervention (n = 11) Nontreatment control (n = 10)	NR	Intervention group = Range: 1.0–6.5 Mean (SD): 3.2 (1.9) Control group = Range: 1.0–6.0 Mean (SD): 4.4 (2.1)	IMT + EMT	25–50% MIP-MEP 30 min/session 3 days/week (only 1 day at the clinic) 5 weeks training	MIP, MEP ↑ (more in the RMT group than control) MFIS ↓ (more in the RMT group than control) 6-MWT, timed stair climb, PADS, and MSSE ↔ (neither group showed changes) SF-36 (decreased emotional well-being and general health in the control group; increased energy/fatigue and general health in RMT)
Silverman et al. [44] (RCT)	42 pwMS Intervention (n = 20) Sham (n = 14)	NR	Intervention group = Range: 2.5–8.0 Mean (SD): 5.5 (1.5) Sham group = Range: 2.0–8.5 Mean (SD): 5.48 (1.7)	EMT	75% MEP (sham: 0% MEP) 5 sets 5 repetitions 20 min/day 5 days/week 5 weeks training	MEP ↑ (no group difference) SWAL-QOL ↑ (except for burden and pharyngeal swallow symptom status, no group difference) PAS ↓ (more in the EMT group than sham)
Huang et al. [43] (within-subjects design)	37 pwMS	NR	Range: 8.0–9.5 Mean (SD): 8.5 (0.4)	IMT	%30 MIP 3 sets 15 repetitions 7 days/week 10 weeks training	MIP ↑ MEP ↔
Martin-Sanchez et al. [45] (non-randomized, double-blind, controlled trial)	67 pwMS Intervention (n = 36) Respiratory exercise group (n = 31)	RRMS (n = 49) PPMS (n = 2) SPMS (n = 16)	Range: 2.0–8.5 Median: 6 Mean (SD): 5.35 (2.30) Intervention group = Mean (SD): 5.21 (2.36) Control group = Mean (SD): 5.51 (2.31)	IMT (control group: nasal breathing and maximum exhalation)	%20 MIP (during the first 2-week) %30 MIP (after the second week) 8 sets (in the morning) and 7 sets (in the afternoon) of 1 min breathing exercises 15 min/day 5 days/week 12 weeks training	MIP ↑ (more in the IMT group than control) MEP ↑ (no group difference) MVV, PEF ↑ (no group difference) TV ↑ (only in the IMT group) MBORG ↓ (more in the IMT group than control) FEV1, FEF _{25–75} , VC, FVC ↔ SF-12 ↔

RCT, randomized controlled trial; RRMS, relapsing-remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PRMS, progressive relapsing multiple sclerosis; MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure; FEF_{25–75}, mean expiratory flow; MFIS, Modified Fatigue Impact Scale; SWAL-QOL, swallow-related quality of life; PAS, abnormal airway penetration and aspiration; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; SF-12, Medical Outcomes Study 12-Item Short-Form Health Survey; PADS, Physical Activity Disability Scale; MSSE, Multiple Sclerosis Self-Efficacy Scale; PI, pulmonary index; MBORG, Modified Borg Dyspnea Scale; NR, not reported; ↑, increased; ↓, decreased; ↔, no significant change.

bility during quiet-deep breathing. Diaphragmatic mobility and the thickening rate evaluated by this method are reduced, and they are significantly associated with the disability of pwMS [39]. Surprisingly, diaphragm thickness is similar in pwMS to healthy individuals [39].

Rehabilitation Interventions to Improve Respiratory Function

Respiratory muscle training (RMT) is considered a promising approach for pwMS suffering from respiratory dysfunction [7]. It could be applied in the form of inspiratory muscle training (IMT), expiratory muscle training (EMT), and their combination that has advantages like taking less time, not aggravating symptoms, and easy adaptation [40]. Short and long-term RMT provides positive improvements in respiratory muscle strength, spirometry parameters, cough efficiency, swallowing, fatigue, and dyspnea in pwMS [41–45]. Benefits from RMT are greater in pwMS whose disease severity was lower [46]. However, RMT could also be applied to nonambulated pwMS, and its effects continue even after 8 weeks of training [43]. Moreover, a study showed that RMT affected aerobic capacity and physical performance [47]; another study stated it was not substantially effective [40]. According to a Cochrane review, including a limited number of studies, there was low-quality evidence that IMT was moderately effective at prescribed MIP, while EMT had no significant effect in pwMS with mild to moderate disease severity. The sustainability of IMT's positive effect, clinical significance, reflection on the quality of life, pulmonary complication, and antibiotic use are uncertain due to the large differences in follow-up periods. Therefore, it has been suggested that randomized controlled studies investigate the effectiveness of various RMT (e.g., IMT, EMT, or their combination; supervised and unsupervised; and telemedicine), determining its effectiveness according to disease severity and applying long-term measurements [48]. Table 1 presents the available studies in pwMS in detail.

It has been reported that low-intensity IMT practiced in people with chronic spinal cord injury has a protective effect on cardiac function with a contribution of the autonomic nervous system [49]. IMT manages to prevent cardiovascular diseases with increasing parasympathetic activity. It stimulates baroreflex activity by increasing venous return with enhanced intrathoracic pressure and metaboreflex threshold, leading to a decrease in the

heart's sympathetic activity during rest. It also creates an oscillation effect in the V_t of the lung. The primary component that supports IMT's effect on autonomic control is the resistance of training. Thus, IMT is more supportive than nonresistance breathing exercises [50]. It has been reported that IMT improves both respiratory muscle strength and respiratory muscle endurance which is associated with functional capacity and physical performance [50]. Low-intensity IMT applied in pwMS increases inspiratory-expiratory strength more than combined RMT. In addition, this training improves respiratory functions and dyspnea more than conventional breathing exercises [45]. The reason for the decrease in dyspnea is the slowing of respiratory rate and decline in carbon dioxide production due to the improvement of respiratory-related parameters [51]. The most practical point of low resistance IMT enhances the respiratory system without causing fatigue [45]. This is valuable in terms of compliance and adherence in RMT. Further research is needed to explain the potential treatment mechanisms of IMT for pwMS.

Respiratory muscle endurance training applied in people with stroke and spinal cord injury improves respiratory muscle strength, lung volumes, cough efficiency, dyspnea, as well as aerobic capacity, exercise performance [52, 53]. Nonetheless, similar to these studies, no research examines the effects of respiratory muscle endurance training in pwMS.

It has not been accurately explained to treatment mechanisms of the exercise training, which is necessary for MS management, on pulmonary function in pwMS. However, the most probable mechanism can be the indirect and direct anti-inflammatory effect controlling neuroinflammation. The reduction of visceral adiposity, which is a crucial source of inflammation, reveals the indirect effect. On the other hand, the increase in T-cells responsible for the formation of interleukin-10 and transforming growth factor beta in the immune system reveals the direct effect [54]. Exercise training provides a recurrent and short-term inflammatory stimulus that induces the body to increase T-cell production during and after exercise. Provided that exercise is done regularly, the body can adapt to this condition and result in chronically increased T-cells [55]. Besides, it has been reported that exercise training increases oxygen distribution by regulating vasodilation and angiogenesis [56], and high-repetition low-intensity resistive and aerobic exercise positively influence heart rate variability [57, 58]. However, it is not known whether this training conduces to alteration of the pulmonary system.

Complementary and alternative treatment approaches are also performed to improve pulmonary dysfunction in pwMS. It has been reported that 8-week pilates training can improve aerobic capacity, balance, cognitive function, and respiratory muscle strength [59], and 16-week yoga training can also increase cough efficiency [60]. A recent study comparing the effects of yoga and pilates training in pwMS found that both methods can improve respiratory muscle strength without any significant difference [61].

It has been reported that continuous positive airway pressure, which is used in the treatment of OSA, can improve fatigue in pwMS with OSA [62], and it may have a significant effect on somnolence and sleep quality [63]. It has been shown recently that continuous positive airway pressure applied at 6 months in pwMS with fatigue and nonsevere OSA did not significantly reduce fatigue severity but significantly improved the fatigue severity and sleepiness at 3 months [64].

Limitation and Recommendation

Various exercise types that positively affect respiratory muscle strength, cough efficiency, and pulmonary volumes should be investigated to demonstrate their impact on physical performance, life expectancy, quality of life, and long-term outcomes in MS. Since RMT differs from previous studies regarding duration, intensity, and frequency, it would be helpful to determine training parameters for optimum benefits. Further studies should investigate pwMS who are wheelchair-bounded or bedridden as well as pwMS who can independently walk. In addition, no studies are comparing IMT and EMT that can be

performed as a combination or separately in pwMS. Therefore, comparing these two interventions in this population of patients requires further investigation.

Conclusion

Pulmonary function is significantly affected in pwMS from the early stages of the disease and leads to respiratory muscle weakness, ineffective cough, dyspnea, and pneumonia. Exercise training, RMT, and complementary and alternative treatments such as pilates and yoga may potentially reduce respiratory problems in pwMS. However, further studies with high methodological quality and larger sample sizes are highly warranted.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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