



Endurance and resistance training in rehabilitation of patients with multiple sclerosis

Aerobni trening i trening sa progresivnim opterećenjem u rehabilitaciji obolelih od multiple skleroze

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system, affecting 2.5 million people worldwide¹. It is the most frequent non-traumatic disabling neurological disorder among young adults². Despite a number of immunomodulatory agents and various symptomatic therapies, there is still a significant level of disability and reduction of quality of life in this population. Therefore, rehabilitation treatment seems to be a very important therapeutical approach, having the potential to reduce symptoms and signs of disease, diminish level of disability and improve independency of MS patients.

Rehabilitation of MS patients is multidisciplinary and consists of kinesiotherapy treatment, occupational therapy, speech therapy, psychological treatment and social worker counseling. Although kinesiotherapy represents an important part of rehabilitation, the intensity, frequency, duration and type of exercises, have not been precisely defined so far³. Exercise programs are mostly individually tailored and directed towards the actual neurological symptoms and signs, such as impaired balance, coordination, walking capacity and muscle weakness³. It has been shown that MS patients show a reduced aerobic capacity^{4,5} and diminished isometric^{6,7} and isokinetic⁸ muscle strength, not only due to insufficient activity and deconditioning⁶ but also due to neural mechanisms including inability to activate the entire motor unit and a reduced firing rate of motor units⁹.

Engaging MS patients into physically demanding activity has not been advised for a long time, because of fear that it could provoke worsening of symptoms and signs of disease¹⁰. Although more recent literature opposed that atti-

tude¹¹, it still seems to be one of the biggest obstacles for massive implementation of endurance and resistance training in kinesiotherapy programs in MS treatment. It is very often seen, that even when these two trainings are encompassed in rehabilitation program, they are not performed in accordance with recommendation on intensity and duration that are necessary to achieve specific positive effects¹². In such a way, many symptoms and consequences of the disease are left undertreated and rehabilitation potential is not fully utilized. Positive effects of endurance and resistance training are already well-studied in healthy population^{13,14}, but recently published results showed that similar effects could be obtained in persons with MS if adequate training regimen were used¹². Endurance and resistance training are well-known for its potential to improve muscle strength and condition. Resistance training improves muscle strength^{15–18} and is a result of two mechanisms: hypertrophy of muscle fibers¹⁹ and augmentation of efferent motor drive from spinal motor neurons to lower limbs²⁰. Endurance training, on the other hand, improves aerobic capacity by influencing physiological adaptation of the cardiorespiratory system^{21,22}. Effects of endurance and resistance training on different symptoms and signs of MS, as well as on activity and quality of life, are much more studied in recent time and have promising results in many of these domains^{17,18,21}.

The aim of this paper was to review available scientific evidence regarding the effects and safety of endurance and resistance training in patients with MS and bring out current recommendations on their prescription. For this purpose we reviewed randomized control trials (RCT) and review articles that investigated the effects of endurance and resistance training in MS patients.

Effects of endurance and resistance training in MS patients

Effects on functional capacity

This is the most studied domain of physical functioning, which represents the ability to perform activities of daily living¹². Outcome measures used for this purpose vary across different studies, so it is very difficult to draw out solid conclusions regarding which kind of exercise better influence this function.

Resistance training showed favorable results in activities such as transfers from sitting to standing position or stair climbing^{23, 24}. Positive effects on gait performance were seen only at high intensity resistance training regimens^{23, 25} (Table 1).

Aerobic training influences greatly walking distance and speed, even when comparing to classical kinesiotherapy treatment^{23, 26, 27} (Table 2). Its effects on other measures of functional capacity have been rarely investigated¹². Analysis of different intensities of endurance training revealed that

Table 1
Effects of resistance training on muscle strength, functional capacity, fatigue, balance and quality of life in patients with multiple sclerosis (MS)

Study (references)	Sample size TG/CG	Study design	Disability (EDSS score)	MS course	Training			Training effect on study outcomes
					duration (weeks)	frequency (days/week)	intensity	
Dodd et al, 2011 ¹⁸	36/35**	RCT	NR	RR	10	2	10RM/2ST	muscle strength: ↑↑ WHOQOL bref: ↑↑ MFIS: ↑↑
Leamonth et al, 2012 ³²	20/12	RCT	< 5.5	NR	12	2	40 min circuit training + balance exercises	TUG: ↑↑ ABCQ: ↑↑ 6MWT: Ø BBS: Ø
Dalgas et al, 2009 ²³	19/19	RCT	< 5.5	RR	12	2	15–8RM	muscle strength: ↑↑ FC: ↑↑
Dalgas et al, 2012 ³⁶	16/15	RCT	3.0–5.5	RR	12	2	15–8RM/3–4ST	FSS: ↓↓ MDI: ↑↑ PCS-SF36: ↑↑ MCS-SF: 36↑↑
Fimland et al, 2012 ²⁰	7/7**	RCT	< 5.0	NR	3	5	4RS/4RS	MVC: ↑↑ EMG activity: ↑↑
Cakt et al, 2012 ²⁵	15/15/15***	RCT	< 6.0	RR; SP	8	2	TG(1) bicycle ergometer + balance exercises TG(2) strength + balance CG: NI	TUG: ↑↑, DGI: ↑↑, FSS: ↑↑ FR: ↑↑, FES-↑↑ RPSF36 – ↑↑, BDI: ↓↓ 10MWS – Ø

**Different procedures; ↑↑ – significantly improved; ↓↓ – significantly decreased; Ø – a non-significant change; EDSS – Expanded Disability Status Scale; RCT – randomized controlled trial; RR – relapsing remitting MS; NR – not reported; TG – training group; CG – control group; RM – repetition maximum; ST – set; WHOQOL bref – World Health Organization Quality of Life shorter version; MFIS – Modified Fatigue Impact Scale; FC – functional capacity; FSS – Fatigue Severity Scale; MDI – Major Depression Inventory; PCS – SF36 – Physical Component Score SF36; MCS-SF36 – Mental Component Score; NI – no intervention; FR – functional reach; TUG – Timed Up and Go test; DGI – Dynamic Gait Index; 10MWT – 10 minute walk test; RPSF36 – Role Physical SF36; BDI – Beck Depression Inventory; FES – Fall Efficacy Scale; ABCQ – Activity Balance Confidence Questionnaire.

Table 2
Effects of endurance training on walking distance, fatigue, and quality of life in patients with multiple sclerosis (MS)

Study (references)	Sample size TG/CG	Study design	Disability (EDSS score)	MS course (patient number)	Training			Training effect on study outcomes
					duration (weeks)	frequency (days/week)	intensity	
Collet et al, 2011 ²⁷	20 /21/20*	RCT	NR	RR 22	12	2	TG(1) continuous TG(2) intermittent TG(3) combined	2MWT: ↑↑ muscle strength: ↑↑ TUG: Ø, FSS: Ø, SF36: ↓
Dettmers et al, 2009 ²⁶	15/15**	RCT	< 3.0	PP3 SP4	3	3	NR	walking distance: ↑↑ MFIS: Ø, BDI: Ø, HAQUAMS: Ø
Oken et al, 2004 ³⁴	14/10/9* *	RCT	< 6.0	NR	26	1	ergometer bicycle-until fatigue	MFIS: ↓↓ SF36: ↑↑
Rasova et al, 2006 ³⁵	36/24/19/1 6**	RCT	< 6.5	NR	8	2	ergometer bicycle 60% VO2 max, 30 min	MFIS: ↓↓ MSQOL: ↑↑ BDI: ↑↑
Sabapath et al, 2011 ²⁹	16/16**	RCT	NR	RR10 PR 3 SP 3	8	2	ET: NR RT: 6–8 RM, 2ST	6MWT: Ø MFIS: Ø, FSST: Ø BDI: Ø, FR: Ø SF36: Ø, TUG: Ø

*Different training intensity; **different procedures; ↑↑ – significantly improved; ↓↓ – significantly decreased; Ø – a non-significant change; EDSS – Expanded Disability Status Scale; RCT – randomized controlled trial; RR – relapsing remitting MS; NR – not reported; TG – training group; CG – control group; RM – repetition maximum; ST – set; WHOQOL bref – World Health Organization Quality of Life shorter version; MFIS – Modified Fatigue Impact Scale; FC – functional capacity; FSS – Fatigue Severity Scale; MDI – Major Depression Inventory; PCS – SF36 – Physical Component Score SF36; MCS-SF36 – Mental Component Score; NI – no intervention; FR – functional reach; TUG – Timed Up and Go test; DGI – Dynamic Gait Index; 10MWT – 10 minute walk test; RPSF36 – Role Physical SF36; BDI – Beck Depression Inventory; FES – Fall Efficacy Scale; ABCQ – Activity Balance Confidence Questionnaire.

higher intensities had a better influence on gait parameters, but have been connected with a higher number of injuries and dropping outs²⁷.

Although the combination of endurance and resistance training seems to be logic therapeutic choice, its effect has not been extensively studied. Surprisingly, the existing literature does not reveal effects on muscle strength and aerobic capacity when two training modalities (aerobic or resistance) were combined of singular training approach²⁸. Data on effects of kinesiotherapy programs which would combine specific exercises addressing actual neurological problem with resistance and endurance training are still missing. However, this approach, which can potentially influence all components of impairment, seems promising in an effort to improve functional capacity in MS patients.

Effects on balance

Several studies investigated the effects of resistance training on balance^{29, 30} (Table 1). Regarding endurance training, it is important to include some kind of activity that constantly provokes balance maintenance. That means that treadmill as a therapeutic device can be utilized, whereas stationary bicycle or machines for elliptical training are of no use³¹. To our best knowledge, RCT evaluating effect of endurance training on balance in MS are still missing. On the other hand, there is a sufficient evidence showing that resistance training in combination with balance exercises is much more effective than balance exercises alone^{25, 32}.

Effects on fatigue

Fatigue represents one of the most frequent and most disabling symptoms. In previous decades it was believed that physical activity worsens fatigue and patients were suggested to rest in order to diminish this symptom³³. Nowadays, it is well-known that exercises are safe and that they can even lessen fatigue¹². However, the intensity, duration and type of exercises that could have the most beneficial influence on fatigue still need to be determined. The majority of studies published to date have examined the effects of endurance training on fatigue (Table 2), but only few of them showed some reduction of fatigue, although without significant difference compared to other interventions^{34, 35}. They showed that training of moderate intensity and longer duration give better results than high intensity/low duration endurance training³³.

The influence of resistance training on fatigue was examined in a limited number of studies³⁶. Although not generated on large number of patients, effects of this kind of exercise are promising³⁶ (Table 1). It is believed that possible effects of resistance training on fatigue could be explained through central motor activation which was found to be decreased in MS patients with fatigue^{20, 37}. A connection between fatigue and suboptimal cortical output has also been found, which can explain worsening of symptoms and signs of disease after excessive training regime³⁸. Possible physiological effects of exercises on fatigue also include neural growth factor stimulation and its effect on plasticity, as well as stimulation of anti-inflammatory cytokine production^{39, 40}.

Effects on cognitive status and disease progression

Cognitive dysfunction is seen in 43–65% of MS patients and is characterized by decreased mental processing speed and memory impairment⁴¹. As similar changes are seen in elderly persons, cognitive impairment in people with MS can be understood as an accelerated process of aging. Some studies on elderly population showed positive effects of endurance and combined training on cognitive function improvement⁴². Although researches on population of MS patients demonstrated a correlation between aerobic capacity and cognitive status, causal relationship has yet to be proven⁴³.

Another interesting finding is a possible relationship between exercises and disease progression. Preliminary reports on this subject show a correlation between exercising and functional and structural changes in the brain. Possible underlying mechanisms include increase in neurotrophic factors and cytokines⁴⁴, but further longitudinal studies are needed to better elucidate this relationship.

Effects on quality of life

Quality of life is a very important dimension of health, especially for people with chronic diseases. It has been shown that people with MS have poorer quality of life compared to persons suffering from many other chronic diseases^{45, 46}. In recent past, many trials addressed this specific topic in order to influence improvements in this domain⁴⁷.

Evidence regarding effects of exercises presented in recently published meta analysis showed that endurance training for a period of 3 months had greater influence on quality of life compared to those performed over a longer time⁴⁸. This is probably due to easier motivation of the patient over a shorter period of time. Evidences regarding the effects of other type of exercises on quality of life are still inconsistent⁴⁵ (Tables 1, 2).

Methodology: a continuing challenge

Current literature reveals a variety of effects of endurance and resistance training in patients with MS, varying from no effect to a variable degree of positive effects on different outcome measures (Tables 1, 2). Nevertheless, it is very difficult to draw out solid conclusion on exact training intensity and duration that would produce certain beneficial outcome. To show results of some intervention, it is advisable to present effect size (ES) of the intervention on outcome measures. Systematic review performed by Asano et al.⁴⁹ showed ES, a measure of an association between an intervention and an outcome, to vary in different studies from moderate to strong. However, due to a great diversity in implemented training protocols, different outcome measures, different number of studied patients with different disease phenotypes and different levels of disability, it is very difficult to draw out a definite recommendation on exact training intensity, duration and frequency that would produce certain beneficial outcome in MS patients⁵⁰. On the other hand, many other rehabilitation approaches, including multidisci-

plinary rehabilitation, comprehensive exercise, occupational therapy, are also without sufficient evidences to guide optimal rehabilitation treatment but are, nevertheless, regularly advised in routine work^{51, 52}.

Current recommendation for exercise prescription in MS patients

Exercises are always individually tailored in accordance with patient needs and possibilities. Thus, the recommendations based on current literature research^{11, 22, 53, 54}, which are listed below, are only a framework for an individually created program.

Recommendation for resistance training

It is advised that resistance training should start with closed kinetic chain exercises, using training machines, if possible¹². If this is not applicable, then the use of elastic bands or body weight as a load is recommended. Regarding patient's safety, it is better to include free weight exercises in later phases of training¹².

In the beginning, the target intensity should be 15 repetition maximum (RM), starting with 1 and increasing to 3 sets of exercises. After approximately 2 weeks, the load can be raised to 12 RM, with later possible increase in the number of sets to 4^{12, 53, 54}.

It is recommended to have 2–3 trainings weekly in a 12-week period to allow changes that could provide longer lasting effects⁵⁵.

Recommendations on endurance training

Recommendations on endurance training in MS patients are in accordance with those for healthy adults⁵³, but progression should be carefully monitored and increased depending on patient capacity. Practical indicators used to determine the intensity of endurance training are the target heart rate, and the level of perceived exertion. The most accurate way to establish targeted heart rate is the heart rate reserve (HRR) method⁵³. The level of perceived exertion (Borg scale) is a subjective measure which reflects patient's feeling of fatigue, and is frequently used in everyday clinical practice. Initial level of fitness is important in es-

tablishing minimum intensity of training. For sedentary people it is approximately 30% of HRR, while for patients with average to good fitness level, it is 45% of HRR⁵³. For patients with MS it is shown that moderate intensities of training (40–60% HRR) are safe and effective²⁷. Endurance training should start with a 5-minute warm-up, at low intensity training (20% HRR) to allow the cardiopulmonary system to adjust to the new demand. Then, a patient should easily progress towards the desired frequency, with work phase duration depending on the targeted frequency, or patient's perceived exertion. Following the work phase, the low intensity cool-down is performed for 5 minutes to prevent blood pooling, and to promote clearance of lactic acid⁵³. In the beginning, progression should be obtained by increasing training volume (frequency and duration) and later by increasing intensity. Appropriate duration of training may range from 20 (or even less at the beginning) to 40 minutes. Suggested frequency is 2–3 times weekly over a 12-week period¹².

There are no consistent recommendations on combined training prescription. Insufficient scientific evidences regarding this type of training allows us only to claim its safety⁵⁶. This kind of training is most often prescribed as a combination of two trainings, performed on alternate days⁵⁶. There are some suggestions that exercising should start with resistance training first, in order to improve muscle strength. Once a certain muscle strength is gained, endurance training could be performed more efficiently¹².

Conclusion

Current scientific evidence demonstrates that endurance and resistance training of moderate intensity are safe for patients with MS in whom these two training modalities show positive effects on muscle strength, condition, functional capacity, balance, fatigue and quality of life. In order to optimize rehabilitation effects in MS patients it is necessary to implement these two training modalities in everyday clinical practice. However, future research is needed to determine the optimal exercise treatment regimens for endurance and resistance training in MS patients with different disease phenotypes and different levels of disability.

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