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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 worldwide [1]. It is the most frequent non-traumatic disabling neurological disorder among young adults [2]. 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 far [3]. Exercise programs are mostly individually tailored and directed towards the actual neurological symptoms and signs, such as impaired balance, coordination, walking capacity and muscle weakness [3]. It has been shown that MS patients show a reduced aerobic capacity [4, 5] and diminished isometric [6, 7] and isokinetic [8] muscle strength, not only due to insufficient activity and deconditioning [6] but also due to neural mechanisms including inability to activate the entire motor unit and a reduced firing rate of motor units [9].

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 disease [10]. Although more recent literature opposed that attitude [11], 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 effects [12]. 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 used [12]. 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 fibers [19] and augmentation of efferent motor drive from spinal motor neurons to lower limbs [20]. 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.

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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 living [12]. 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 investigated [12]. Analysis of different intensities of endurance training reveled 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: duration (weeks)	Training: frequency (days/week)	Training: intensity	Training effect on study outcomes
Dodd et al, 2011 [18]	36/35**	RCT	NR	RR	10	2	10RM/2ST	muscle strength: ↑↑ WHOQOL bref: ↑↑ MFIS: ↑↑
Learmonth 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 – Expended 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: duration (weeks)	Training: frequency (days/week)	Training: intensity	Training effect on study outcomes
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]	36/24/19/16**	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 – Expended 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 outs [27].

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 approach [28]. 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 use [31]. 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 symptom [33] Nowadays, it is well-known that exercises are safe and that they can even lessen fatigue [12] 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 training [33].

The influence of resistance training on fatigue was examined in a limited number of studies [36]. Although not generated on large number of patients, effects of this kind of exercise are promising [36] (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 regime [38]. 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 impairment [41]. 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 improvement [42]. Although researches on population of MS patients demonstrated a correlation between aerobic capacity and cognitive status, causal relationship has yet to be proven [43].

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 cytokines [44], 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 domain [47].

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 time [48]. 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 inconsistent [45] (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 patients [50]. On the other hand, many other rehabilitation approaches, including multidisciplinary 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 possible [12]. 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 training [12].

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 effects [55].

Recommendations on endurance training

Recommendations on endurance training in MS patients are in accordance with those for healthy adults [53], 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) method [53]. 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 establishing 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 HRR [53]. For patients with MS it is shown that moderate intensities of training (40–60% HRR) are safe and effective [27]. 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 acid [53]. 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 period [12].

There are no consistent recommendations on combined training prescription. Insufficient scientific evidences regarding this type of training allows us only to claim its safety [56]. This kind of training is most often prescribed as a combination of two trainings, performed on alternate days [56]. 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 efficiently [12].

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.

R E F E R E N C E S

1. Neurological disorders: Public health challanges. Geneva: World Health Organization; 2006.
2. *Alonso A, Hernán MA.* Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurology 2008; 71(2): 129−35.
3. *Wiles CM.* Physiotherapy and related activities in multiple sclerosis. Mult Scler 2008; 14(7): 863−71.
4. *Tantucci C, Massucci M, Piperno R, Grassi V, Sorbini CA.* Energy cost of exercise in multiple sclerosis patients with low degree of disability. Mult Scler 1996; 2(3): 161−7.
5. *Mostert S, Kesselring J.* Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. Mult Scler 2002; 8(2): 161−8.
6. *Garner DJ, Widrick JJ.* Cross-bridge mechanisms of muscle weakness in multiple sclerosis. Muscle Nerve 2003; 27(4): 456−64.
7. *Kent-Braun JA, Ng AV, Castro M, Weiner MW, Gelinas D, Dudley GA*, et al. Strength, skeletal muscle composition, and enzyme activity in multiple sclerosis. J Appl Physiol 1997; 83(6): 1998−2004.
8. *Armstrong L, Winant DM, Swasey PR, Seidle ME, Carter AL, Gehlsen G.* Using isokinetic dynamometry to test ambulatory patients in multiple sclerosis. Phys Ther 1983; 63: 1247−9.
9. *Rice CL, Vollmer TL, Bigland-Ritchie B.* Neuromuscular responses of patients with multiple sclerosis. Muscle Nerve 1992; 15(10): 1123−32.

10. *Petajan JH, White AT*. Recommendations for physical activity in patients with multiple sclerosis. Sport Med 1999; 27(3): 179−91.
11. *Smith RM, Adeney-Steel M, Fulcher G, Longley WA*. Symptom change with exercise is a temporary phenomenon for people with multiple sclerosis. Arch Phys Med Rehabil 2006; 87(5): 723−7.
12. *Dalgas U, Stenager E, Ingemann-Hansen T*. Multiple sclerosis and physical exercise: recommendations for the application of resistance-, endurance- and combined training. Mult Scler 2008; 14(1): 35−53.
13. *Jones AM, Carter H*. The effect of endurance training on parameters of aerobic fitness. Sport Med 2000; 29(6): 373−86.
14. *Kraemer WJ, Ratamess NA*. Fundamentals of resistance training: progression and exercise prescription. Med Sci Sports Exerc 2004; 36(4): 674−88.
15. *Harvey L, Smith A, Jones R*. The effect of wighted leg raises on quadriceps strenght, EMG parameters and functional activities in people with multiple sclerosis. Phys Ther 1999; 85: 154−61.
16. *Dodd KJ, Taylor NF, Denisenko S, Prasad D*. A qualitative analysis of a progressive resistance exercise programme for people with multiple sclerosis. Disabil Rehabil 2006; 28(18): 1127−34.
17. *Debolt LS, McCubbin MJ*. The effects of home-based resistance exercice on balance, power and mobility in adults with multiple sclerosis. Arch Phys Med Rehabil 2004; 85(2): 290−7.
18. *Dodd KJ, Taylor NF, Shields N, Prasad D, McDonald E, Gillon A*. Progressive resistance training did not improve walking but can improve muscle performance, quality of life and fatigue in adults with multiple sclerosis: a randomized controlled trial. Mult Scler 2011; 17(11): 1362−74.
19. *Dalgas U, Stenager E, Jakobsen J, Petersen T, Overgaard K, Ingemann-Hansen T*. Muscle fibre size increases following resistance training in multiple sclerosis. Mult Scler 2010; 16(11): 1367−76.
20. *Fimland MS, Helgerud J, Gruber M, Leivseth G, Hoff J*. Enhanced neural drive after maximal strength training in multiple sclerosis patients. Eur J Appl Physiol 2010; 110(2): 435−43.
21. *Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW*. Impact of aerobic training on fitness and quality of life in multiple sclerosis. Ann Neurol 1996; 39(4): 432−41.
22. *Ponichtera-Mulcare JA, Mathews T, Barrett PJ, Gupta SC*. Change in aerobic fitness of patients with multiple sclerosis during a 6 month training program. Sports Med Train Rehabil 1997; 7(3−4): 265−272.
23. *Dalgas U, Stenager E, Jakobsen J, Petersen T, Hansen HJ, Knudsen C,* et al. Resistance training improves muscle strength and functional capacity in multiple sclerosis. Neurology 2009; 73(18): 1478−84.
24. *Taylor NF, Dodd KJ, Prasad D, Denisenko S*. Progressive resistance exercise for people with multiple sclerosis. Disabil Rehabil 2006; 28(18): 1119−26.
25. *Çakt BD, Nacir B, Genç H, Saraçoğlu M, Karagöz A, Erdem HR,* et al. Cycling Progressive Resistance Training for People with Multiple Sclerosis. Am J Phys Med Reh 2010; 89(6): 446−57.
26. *Dettmers C, Sulzmann M, Ruchay-Plössl A, Gütler R, Vieten M*. Endurance exercise improves walking distance in MS patients with fatigue. Acta Neurol Scand 2009; 120(4): 251−7.
27. *Collett J, Dawes H, Meaney A, Sackley C, Barker K, Wade D*, et al. Exercise for multiple sclerosis: a single-blind randomized trial comparing three exercise intensities. Mult Scler 2011; 17(5): 594−603.
28. *Romberg A, Virtanen A, Ruutiainen J, Aunola S, Karppi SL, Vaara M*, et al. Effects of a 6-month exercise program on patients with multiple sclerosis: a randomized study. Neurology 2004; 63(11): 2034−8.
29. *Sabapathy NM, Minahan CL, Turner GT, Broadley SA*. Comparing endurance- and resistance-exercise training in people with multiple sclerosis: a randomized pilot study. Clin Rehabil 2010; 25(1): 14−24.
30. *de Bolt LS, McCubbin JA*. The effects of home-based resistance exercise on balance, power, and mobility in adults with multiple sclerosis. Arch Phys Med Rehabil 2004; 85(2): 290−7.
31. *Buchner DM, Cress ME, Lateur BJ, Esselman PC, Margherita AJ, Price R,* et al. A comparison of the effects of three types of endurance training on balance and other fall risk factors in older adults. Aging 1997; 9(1−2): 112−9.
32. *Learmonth YC, Paul L, Miller L, Mattison P, McFadyen AK*. The effects of a 12-week leisure centre-based, group exercise intervention for people moderately affected with multiple sclerosis: a randomized controlled pilot study. Clin Rehabil 2012; 26(7): 579−93.
33. *Andreasen AK, Stenager E, Dalgas U*. The effect of exercise therapy on fatigue in multiple sclerosis. Mult Scler 2011; 17(9): 1041−54.
34. *Oken BS, Kishiyama S, Zajdel D, Bourdette D, Carlsen J, Haas M,* et al. Randomized controlled trial of yoga and exercise in multiple sclerosis. Neurology 2004; 62(11): 2058−64.
35. *Rasova K, Havrdova E, Brandejsky P, Zálišová M, Foubikova B, Martinkova P*. Comparison of the influence of different rehabilitation programmes on clinical, spirometric and spiroergometric parameters in patients with multiple sclerosis. Mult Scler 2006; 12(2): 227−34.
36. *Dalgas U, Stenager E, Jakobsen J, Petersen T, Hansen HJ, Knudsen C,* et al. Fatigue, mood and quality of life improve in MS patients after progressive resistance training. Mult Scler 2010; 16(4): 480−90.
37. *Andreasen AK, Jakobsen J, Petersen T, Andersen H*. Fatigued patients with multiple sclerosis have impaired central muscle activation. Mult Scler 2009; 15(7): 818−27.
38. *Gandevia SC, Allen GM, Butler JE, Taylor JL*. Supraspinal factors in human muscle fatigue: evidence for suboptimal output from the motor cortex. J Physiol 1996; 490(Pt 2): 529−36.
39. *Gold SM, Schulz K, Hartmann S, Mladek M, Lang UE, Hellweg R,* et al. Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. J Neuroimmunol 2003; 138(1−2): 99−105.
40. *Castellano V, Patel DI, White LJ*. Cytokine responses to acute and chronic exercise in multiple sclerosis. J Appl Physiol 2008; 104(6): 1697−702.
41. *Chiaravalloti ND, DeLuca J*. Cognitive impairment in multiple sclerosis. Lancet Neurol 2008; 7(12): 1139−51.
42. *Colcombe S, Kramer AF*. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 2003; 14(2): 125−30.
43. *Motl RW, Sandroff BM, Benedict RH*. Cognitive dysfunction and multiple sclerosis: developing a rationale for considering the efficacy of exercise training. Mult Scler 2011; 17(9): 1034−40.
44. *Dalgas U, Stenager E*. Exercise and disease progression in multiple sclerosis: can exercise slow down the progression of multiple sclerosis? Adv Neurol Disord 2012; 5(2): 81−95.
45. *Sprangers MA, De Regt EB, Andries F,van Agt HM, Bijl RV, De Boer JB*, et al. Which chronic conditions are associated with better or poorer quality of life. J Clin Epidemiol 2000; 53(9): 895−907.
46. *Drulovic J, Pekmezovic T, Matejic B, Mesaros S, Manigoda M, Dujmovic I,* et al. Quality of life in patients with multiple sclerosis in Serbia. Acta Neurol Scand 2007; 115(3): 147−52.
47. *Zwibel HL, Smrtka J*. Improving quality of life in multiple sclerosis: an unmet need. Am J Manag Care 2011; 17(Suppl 5): 139−45.
48. *Motl RW, Gosney JL*. Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis. Mult Scler 2008; 14(1): 129−35.

49. *Asano M, Dawes DJ, Arafah A, Moriello C, Mayo NE*. What does a structured review of the effectiveness of exercise interventions for persons with multiple sclerosis tell us about the challenges of designing trials. Mult Scler 2009; 15(4): 412−21.
50. *Middel B, van Sonderen E*. Statistical significant change versus relevant or important change in (quasi) experimental design: some conceptual and methodological problems in estimating magnitude of intervention-related change in health services research. Int J Integr Care 2002; 2: e15.
51. *Khan F, Turner-Stokes L, Ng L, Kilpatrick T*. Multidisciplinary rehabilitation for adults with multiple sclerosis. Cochrane Database Syst Rev 2007; (2): CD006036.
52. *Rietberg MB, Brooks D, Uitdehaag BM, Kwakkel G*. Exercise therapy for multiple sclerosis. Cochrane Database Syst Rev 2005; (1): CD003980.
53. *American College of Sports Medicine*. ACMS's guidelines for exercise testing and prescription. 6th ed. Philadelphia: Lippincot Williams and Wilkins; 2000.
54. *Kraemer WJ, Adams K, Cafarelli E, Dudley GA, Dooly C, Feigenbaum MS,* et al. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sports Exerc 2002; 34(2): 364−80.
55. *Jones DA, Rutherford OM, Parker DF*. Physiological changes in skeletal muscle as a result of strength training. Q J Exp Physiol 1989; 74(3): 233−56.
56. *Romberg A, Virtanen A, Ruutiainen J, Aunola S, Karppi SL, Vaara M*, et al. Effects of a 6-month exercise program on patients with multiple sclerosis: a randomized study. Neurology 2004; 63(11): 2034−8.

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