Impact of high-intensity concurrent training on cardiovascular risk factors in persons with multiple sclerosis - pilot study

Peer-reviewed author version

KEYTSMAN, Charly; HANSEN, Dominique; WENS, Inez & OP 'T EIJNDE, Bert (2019) Impact of high-intensity concurrent training on cardiovascular risk factors in persons with multiple sclerosis - pilot study. In: DISABILITY AND REHABILITATION, 41(4), p. 430-435.

DOI: 10.1080/09638288.2017.1395086
Handle: http://hdl.handle.net/1942/30006

Impact of high intensity concurrent training on cardiovascular risk factors in persons with Multiple Sclerosis – pilot study

Charly Keytsman, Dominique Hansen, Inez Wens and Bert O. Eijnde

REVAL Rehabilitation Research Center, BIOMED Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Agoralaan Building A, Diepenbeek, Belgium

Word count: 2824

Running head: Concurrent training in Multiple Sclerosis

Article type: Research paper

Correspondence:

Charly Keytsman

Agoralaan Building A, 3590 Diepenbeek, Belgium.

Email: charly.keytsman@uhasselt.be

Tel: +32477/61 11 22

ABSTRACT

Purpose. High intensity concurrent training (HICT) positively affects important cardiovascular risk factors. Because this was never investigated in MS, the present pilot study explored the impact of combined high intensity endurance interval and strength training on cardiovascular risk factors in this population.

Methods. Before (PRE) and after (POST) 12 weeks of HICT (endurance interval and strength, 5 sessions per 2 weeks, n=16) body composition (DEXA), resting blood pressure and heart rate, 2h oral glucose tolerance (OGTT, HbA1c, $[glucose]_{blood}$, $[insulin]_{blood}$), blood lipids (HDL, LDL, total cholesterol, triglyceride levels) and C-reactive Protein (CRP) were analyzed.

Results. Twelve weeks of HICT appears to be well tolerated and significantly improved resting heart rate (MD 4 bpm, 95% CI 2 to 7) , 2h $[glucose]_{blood}$ (MD 1 mmol/l, 95% CI -1 to 2) and HOMA index (MD 0.5, 95% CI 0 to 1). Blood pressure, body composition, blood lipids and CRP however did not seem to be affected.

Conclusion. Under the conditions of the present pilot study, 12 weeks of concurrent high intense endurance interval and strength training improved resting heart rate, 2h glucose and HOMA index in MS, but did not affect blood CRP levels, blood pressure, body composition and blood lipid profiles. This data warrants further, larger and controlled research investigating the effects of HICT on cardiovascular risk factors in MS.

Key words: multiple sclerosis, cardiovascular diseases, HICT exercise, rehabilitation

1. INTRODUCTION

Decreased exercise capacity, post-exercise fatigue and reduced muscle contractile functioning are frequently occurring comorbidities in Multiple Sclerosis (MS) that lead to an inactivity-related physiological profile and thus more associated (secondary) health risks than provided by the disease *per se* [1, 2, 3, 4]. Furthermore, and similar to other populations, such sedentary lifestyle is associated with an increased risk for the development of cardiovascular diseases (CVD) [5] such as hypertension, overweight/obesity, type 2 diabetes mellitus and dyslipidemia [5, 6].

Low-to-moderate intensity exercise therapy (cardiovascular and resistance training) has become an important part of overall symptom management in MS [7] leading to improved exercise capacity, muscle strength and various functional measures [8]. In HC, moderate intensity exercise training clearly affects various cardiovascular risk factors such as whole body glycemic control [9]. Consequently, we previously investigated its effectiveness on glucose tolerance in persons with MS [10] but, surprisingly, were unable to show any effects [10]. It is difficult to explain this discrepancy. Possibly, in persons with MS higher exercise intensities may be required to induce positive effects. This was already demonstrated in healthy controls, obese subjects and in stroke/cardiac patients were a wide range of high intensity interval training modes (HIIT; 1-5 high intensity exercise bouts ranging from 6s-4min interspersed by recovery periods of 30s-4min, intensities of 90-100% heart rate or VO_{2max}) substantially improve exercise performance and muscle strength [11] but also various cardiovascular risk factors such as body composition (subcutaneous and abdominal fat) [12], blood glucose and insulin sensitivity [13], functional recovery (improved cardiorespiratory fitness, reduced effort of walking) [14], intrinsic heart pump activity [15] and systemic cytokine balance. In keeping with this, we recently evaluated the impact of both moderate (24w, 5 sessions per 2 weeks, 50-70% HR max) and high intensity training (12w, 5 sessions per 2 weeks, 90-100% HR max) on various cardiovascular risk factors in MS [16] and reported substantially greater improvements in exercise capacity, muscle contractile characteristics and in glucose tolerance following 12 weeks of HIIT compared to 24 weeks of moderate intensity training [10, 16]. Interestingly, in healthy subjects and compared to HIIT alone high intensity concurrent training (HICT) that combines high intense endurance and strength training has been shown to further improve body composition, muscle strength, overall health and cardiovascular fitness [17, 18, 19]. Consequently, in this population the combined effects of HIIT and resistance training on important cardiovascular risk factors appear to be worthwhile investigating. The effects of high intensity concurrent training on various cardiovascular risk factors in MS however have not been investigated yet.

In keeping with the above line of reasoning, the present pilot trial therefore explores the effects of a 12-week HICT intervention on various cardiovascular risk factors, such as body composition, blood pressure and heart rate, blood lipid profiles, whole body glucose disposal and C-reactive protein (CRP) levels in a small sample of persons with MS. We hypothesize that HICT improves these cardiovascular parameters in persons with MS.

2. METHODS

2.1 Subjects

Following local advertisement and written informed consent, sixteen persons with MS (mean EDSS 2.6±0.2) were included. Subjects were excluded if they were pregnant, aged <18 years, participated in another study, experienced an acute exacerbation 6 months prior to the start of the study, had contraindications to perform physical exercise, or had an EDSS score >6. Use of disease-modifying therapy and other medication intake was inventoried. Subjects were asked to maintain their usual medication intake constant throughout the study course. All data was collected at the Rehabilitation Research Centre of Hasselt University. The study was approved by the local Ethical Committee of the Jessa hospital and Hasselt University, and was performed in accordance with the Declaration of Helsinki of 1975. This study was registered at ClinicalTrials.gov (NCT02466165).

2.2 Study Design

At baseline, body composition, resting blood pressure and heart rate, blood sample analysis (detection of HDL, LDL, total cholesterol, triglyceride levels, CRP, glucose- and insulin concentrations), exercise capacity (maximal graded exercise test) and muscle strength (isometric/isokinetic dynamometry) were assessed. Furthermore, previous cardiovascular problems, smoking and any antihypertensive medication were registered. Following baseline screening persons with MS were enrolled in a 12-week high intensity concurrent training (HICT) program under a one on one supervision of a physiotherapist to increase compliance and adherence. Hereafter, baseline measurements were repeated.

2.3 Measurements

2.3.1 Body composition:

Whole body fat and lean tissue mass were obtained using Dual Energy X-ray Absorptiometry scan (DEXA) (Hologic Series Delphi-A Fan Beam X-ray Bone Densitometer, Vilvoorde, Belgium). A calibrated analogue weight scale (Seca®) was used to measure total body mass.

2.3.2 Blood pressure and heart rate:

Resting blood pressure and heart rate were measured with an automatic blood pressure cuff (Omron M4-I, Omron Healthcare Europe B.V., Hoofddorp, The Netherlands) in a supine position (7 min) immediately following the DEXA scan (to prevent orthostatic influence).

2.3.3 Oral glucose tolerance test:

Glycemic control of persons with MS was investigated using an oral glucose tolerance test (OGTT). Following a 10h overnight fasting period, all participants received a 1g glucose/kg body weight solution. Before and after glucose administration, capillary blood samples were collected from a hyperaemic earlobe at 30min intervals during a 2h period, to measure whole-blood glucose concentrations immediately (Analox GM7 Micro-stat, Analox instruments Ltd, London, UK). Whole-blood glucose concentrations were converted to plasma concentrations using a multiplier of 1.11 [20]. To determine serum insulin levels, 4cc of venous blood was collected in serum separation tubes (SST, BD Vacutainer®, Becton Dickinson, Erembodegem, Belgium) at 1h intervals. After 30min, allowing blood coagulation, samples were centrifuged during 10min at 3500 rpm. The obtained serum was frozen and stored at -80°C for batch analysis of serum insulin levels (Mercodia Insulin ELISA, Uppsala, Sweden).

2.3.4 Blood analysis

Following an overnight fasting period (10h), a venous blood sample was collected and centrifuged at 2000 rpm for 10min. Plasma was frozen immediately in liquid nitrogen and stored at -80°C until further analysis. Plasma samples were analyzed for total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), plasma triglycerides, C-reactive protein (CRP) (Beckman Synchron LX 20 Analyzer®,

Beckman Coulter Inc., Diamond Diagnostics, USA), and glycosylated haemoglobin (HbA1c) (Hi-Auto A1c Analyzer®, Menarini Diagnostics Inc., Florence, Italy). Whole-body insulin sensitivity was calculated by the homeostasis model assessment (HOMA: [fasting plasma glucose (mmmol/l) x fasting serum insulin (mU/l)]/22,5) [21].

2.3.5 Physical activity

Participants were asked to report their physical activity level (Physical Activity Scale for Individuals with Physical Disabilities, PASIPD) of the previous 7 days [22].

2.3.6 Maximal exercise test

During the exercise test to volitional fatigue, an electronically braked cycle ergometer (eBike Basic®, General Electric GmbH, Bitz, Germany) with pulmonary gas exchange analysis (Jaeger Oxycon®, Erich Jaeger GmbH, Germany) was used (cycling frequency: 70 rpm). This test was performed at least 48 hours separated from the isometric muscle strength test to exclude interference of muscle fatigue. Female and male persons with MS started at 20W and 30W, respectively, during the first minute. Hereafter, workload increased, respectively, 10W and 15W per minute [23]. Oxygen uptake (VO_2), expiratory volume (VE), and respiratory exchange ratio (RER) were collected breath-by-breath and averaged every minute. Using a 12-lead ECG device, heart rate (HR) was monitored every minute. At the end of the test RER values were evaluated to verify whether the test was maximal. In addition, maximal cycling resistance (W_{max}), maximal heart rate (HR_{max}), test duration and VO_{2max}, defined as the corresponding load, heart rate, minutes and oxygen uptake measured at the level of exhaustion, were reported.

2.3.7 Isometric/isokinetic strength test

After five minutes of warming-up on a cycle ergometer maximal voluntary isometric muscle strength of the knee extensors and flexors (45° and 90° knee angle) was measured, using an isokinetic dynamometer (System 3, Biodex®, ENRAF-NONIUS, New York, USA). Two maximal isometric extensions (4s) and flexions (4s), followed by a 30s rest interval, were performed . The highest isometric extension and flexion peak torques (Nm) were selected as the maximal isometric strength. Baseline results were used to classify the legs of each patient as the

weakest or strongest leg. This subdivision was maintained in further analysis, replacing a conventional left-right classification. The isokinetic test was initiated following 3 submaximal trial contractions. Subjects performed 20 maximal dynamic knee-extensions/flexions at a velocity of 180°/s to assess strength endurance of the knee muscles. Extension of the knee was initiated at a joint angle of 90° to an angle of 160°. Following each extension the leg was returned actively to the starting position from which the next contraction was immediately initiated. Throughout the range of movement, workload was kept constant during both extension and flexion. To determine muscle strength endurance, the average work (J) of the first 6 contractions was compared with the last 6 contractions and expressed as a percentage decrease.

2.3.8 High intensity concurrent training (HICT)

HICT consisted of combined endurance interval and resistance training. High intensity endurance interval training was performed on a cycle ergometer under close supervision at a frequency of 5 sessions per 2 weeks, throughout the 12-week program. During the first 6 weeks of training, cycle exercise duration gradually increased from 5x1min bouts of high intense endurance exercise followed by 1min rest intervals, to 5x2min exercise bouts with 1min rest intervals. Exercise intensity was 100% of the maximal workload (obtained during the exercise test), corresponding to 85-90% of the maximal heart rate. During the second 6 week training cycle, duration remained stable at 5x2min exercise bouts with 1min rest intervals and the workload increased to 100% of maximal heart rate. The second part of the training session consisted of resistance training for upper (vertical traction, arm curl and chest press) and lower (leg press, leg extension and leg curl) limbs. Training intensity and volume were adjusted throughout the intervention program from 1x10 repetitions to 2x20 repetitions at an individual maximal attainable load for each subject. To exercise at similar relative workloads and to compensate for frequently occurring bilateral strength differences between the legs of persons with MS , resistance training of the lower limbs was performed unilaterally.

3. Statistical Analysis

All data were analyzed using SPPS v. 22.0 (IBM). Pre-post differences within groups were analyzed using paired t-tests. All data are presented as means ± SD's or mean difference (MD) with accompanying confidence interval (CI) and the threshold for statistical significance was set at $p<0.05$.

4. RESULTS

4.1 Subject characteristics

Subjects characteristics are displayed in Table 1. Thirteen persons with MS were on disease-modifying therapy of which 2 on teriflunomide, 6 on interferon-beta, 1 on dimethyl fumarate, 1 on glatiramer acetate and 3 on natalizumab. Furthermore, 1 person was on ACE-inhibitors, 1 on beta-blockers, 1 on statins and 1 on biguanides. Subjects scored 18.3±11,7 on the PASIPD (data not shown).

4.2 Adherence and adverse events

No drop-outs or adverse events were reported during the course of the study

INSERT TABLE 1 HERE

4.3 Cardiovascular risk factors

In MS, resting heart rate (MD 4bpm, 95% CI 2 to 7), 2h glucose (MD 1 mmol/l, 95% CI -1 to 2) and HOMA index (MD 0.5, 95% CI 0 to 1) improved significantly ($p<0.05$) during the study course. Other cardiovascular risk factors did not differ.

INSERT TABLE 2 HERE

4.4 Maximal cardiopulmonary exercise test and isometric/isokinetic dynamometry

Following 12 weeks of HICT workload capacity (MD 25W, 95% CI -34 to -16), time to exhaustion (MD 2min, 95% CI -3 to -1), VE max (MD 15l/min, 95% CI -23 to -7) significantly increased (Table 3). Furthermore, isometric and isokinetic muscle strength of the quadriceps and hamstrings of both legs improved (e.g. +14% extension 45° weakest leg, MD 14 Nm, 95% CI -23 to -6) significantly after the 12-week HICT intervention (Table 4).

INSERT TABLE 3 HERE

INSERT TABLE 4 HERE

5. DISCUSSION

Twelve weeks of high intensity concurrent training (HICT) in multiple sclerosis (MS) substantially improved exercise capacity and leg muscle strength as well as resting heart rate and 2h blood glucose and HOMA index. In contrast to larger (n=8-84) controlled studies applying high intensity exercise in healthy controls [11, 12, 13], older subjects, persons with overweight, type 1 diabetes [12, 24] and heart disease [14, 15, 25], the present pilot study, not including a control group, did not demonstrate comparable effects on most cardiovascular risk factors in persons with MS.

To date exercise therapy has become an important part of MS rehabilitation, leading to improvements in various health related parameters [7]. To optimize therapy adherence and avoid complications, exercise interventions in this population so far have mainly focused on low to moderate intensity rehabilitation training. In other populations however higher intensity exercise therapy clearly further improves therapy outcome. In keeping with this, our research group was the first to perform a well-tolerated HIIT program in this population, presenting substantial improvements in endurance capacity and muscle contractile characteristics [16] as well as whole body glucose disposal [23]. The present pilot study confirms this showing improved exercise capacity (oxygen uptake, time to exhaustion, workload, Table 3) and muscle strength (Table 4) as well as reduced 2h blood glucose and HOMA index (Table 2). Similar to our previous work, subjects did not report exercise-induce side effects or discomfort and safely tolerated HIIT.

HICT has been shown to be an efficient strategy to improve cardiovascular fitness, aerobic capacity, body composition and muscle strength in healthy (older) adults [17, 18, 19]. Because persons with MS also present elevated cardiovascular risk factors [4] the present pilot study investigated the impact of an HICT intervention on several of these cardiovascular risk factors in MS. As described above and similar to our previous HIIT study 2h blood glucose, HOMA index and resting heart rate improved. In contrast to other comparable studies (1-5 high intensity exercise bouts ranging from 6s-4min interspersed by recovery periods of 30s-4min, at intensities of 90-100% heart rate or VO_{2max}, 8 to 12 weeks of training, n=8 to 84) in other populations [11, 12, 13, 14, 24, 25] blood lipid profile (total cholesterol, HDL, LDL), body composition (fat and lean tissue mass) and hemodynamic parameters (systolic and diastolic blood pressure) however were not affected. It is difficult to explain the latter but despite the fact that we and others previously successfully performed HIIT protocols in MS to improve exercise

capacity and glucose tolerance, it is possible that persons with MS cannot reach the required maximal exercise intensities to affect other cardiovascular parameters. Some recently published findings support this hypothesis. First, MS is associated with cardiovascular autonomic dysfunction leading to impaired carotid baroreflex control [26], attenuated elevations in blood pressure [27] and disturbed increases in heart rate [28] during exercise. As a result, subjects probably did not reach near maximal heart rates during HIIT. In other populations [29], cardiovascular autonomic dysfunction often induces chronotropic incompetence (inability of the heart rate to increase proportionally to an increase in activity or metabolic demand). Whether persons with MS also exhibit such abnormality is presently unknown but the obtained maximal heart rates of the HIIT group during the exercise test in the current study may indirectly confirm this hypothesis (PRE: 161±3.5 bpm vs. POST:162±4.8 bpm). Second, abnormal muscular energy metabolism in MS has been demonstrated involving reduced Krebs cycle and complex I and II activities [30], overproduction of reactive oxygen species (ROS [31]), increased basal AMP-activated protein kinase phosphorylation [32] and delayed phosphocreatine resynthesis after exercise [30, 32, 33]. This suggests higher basal and exercise related energy expenditure and increased exercise-induced intramyocellular lactate accumulation, and thus greater muscle fatigue, as recently evidenced by increased basal [34] serum lactate concentrations. Therefore impaired energy supply may attenuate adequate exercise therapy response in MS. Although Amorini et al [34] only reported elevated serum lactate levels under resting conditions this again may indicate that, in the present pilot study, maximal exercise intensity was not reached as evidenced by the lower maximal blood lactate concentrations (Table 3), despite high post exercise muscle fatigue and overall perceived exertion rates (BORG: 14.7±1.5).

5.1 Study limitations

The present study warrants future research but it is clear that to better differentiate between high intensity interval therapy alone and high intense concurrent training, future intervention studies in this population should include a control group performing other exercise intervention types. Furthermore, under the conditions of the present pilot study effects on cardiovascular parameters seem limited. Despite the fact that similar training regimens in our previous training intervention study [16, 23] affected exercise capacity, muscle strength and glucose tolerance, longer training program duration may be required to improve other cardiovascular effects. Finally, this pilot study explored the impact of HICT on cardiovascular risk factors in a small sample size of persons with MS. Consequently, these data need confirmation in a larger scale study.

6. CONCLUSION

Under the conditions of the present pilot study, 12 weeks of high intensity concurrent training improved exercise capacity and muscle strength but does not appear to affect important cardiovascular risk factors such as blood pressure, body composition, blood lipid profiles and CRP levels in MS. The present findings warrant further, larger and controlled studies.

Declaration of interest

The authors report no conflicts of interest.

Reference List

1. Ellis T, Motl RW. Physical activity behavior change in persons with neurologic disorders: overview and examples from Parkinson disease and multiple sclerosis. J Neurol Phys Ther. 2013 Jun;37(2):85-90. doi: 10.1097/NPT.0b013e31829157c0. PubMed PMID: 23632452; eng.
2. Ng AV, Kent-Braun JA. Quantitation of lower physical activity in persons with multiple sclerosis. Med Sci Sports Exerc. 1997 Apr;29(4):517-23. PubMed PMID: 9107635; eng.
3. Wens I, Dalgas U, Vandenabeele F, et al. Multiple sclerosis affects skeletal muscle characteristics. PLoS One. 2014;9(9):e108158. doi: 10.1371/journal.pone.0108158. PubMed PMID: 25264868; PubMed Central PMCID: PMCPMC4180259. eng.
4. Keytsman C, Eijnde B, Hansen D, et al. Elevated cardiovasuclar risk factors in multiple sclerosis. Mult Scler Relat Disord2017. p. 220-223.

5. Warren TY, Barry V, Hooker SP, et al. Sedentary behaviors increase risk of cardiovascular disease mortality in men. Med Sci Sports Exerc. 2010 May;42(5):879-85. doi: 10.1249/MSS.0b013e3181c3aa7e. PubMed PMID: 19996993; PubMed Central PMCID: PMCPMC2857522. eng.
6. Wens I, Dalgas U, Stenager E, et al. Risk factors related to cardiovascular diseases and the metabolic syndrome in multiple sclerosis - a systematic review. Mult Scler. 2013 Oct;19(12):1556-64. doi: 10.1177/1352458513504252. PubMed PMID: 24048545; eng.
7. Motl RW, Gosney JL. Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis. Mult Scler. 2008 Jan;14(1):129-35. doi: 10.1177/1352458507080464. PubMed PMID: 17881388; eng.
8. Kjolhede T, Vissing K, Dalgas U. Multiple sclerosis and progressive resistance training: a systematic review. Mult Scler. 2012 Sep;18(9):1215-28. doi: 10.1177/1352458512437418. PubMed PMID: 22760230; eng.
9. Rankin AJ, Rankin AC, MacIntyre P, et al. Walk or run? Is high-intensity exercise more effective than moderate-intensity exercise at reducing cardiovascular risk? Scottish medical journal. 2012 May;57(2):99-102. doi: 10.1258/smj.2011.011284. PubMed PMID: 22194404; eng.
10. Wens I, Hansen D, Verboven K, et al. Impact of 24 Weeks of Resistance and Endurance Exercise on Glucose Tolerance in Persons with Multiple Sclerosis. Am J Phys Med Rehabil. 2015 Mar 12. doi: 10.1097/phm.0000000000000257. PubMed PMID: 25768064; Eng.
11. Sloth M, Sloth D, Overgaard K, et al. Effects of sprint interval training on VO2max and aerobic exercise performance: A systematic review and meta-analysis. Scandinavian journal of medicine & science in sports. 2013 Dec;23(6):e341-52. doi: 10.1111/sms.12092. PubMed PMID: 23889316; eng.
12. Boutcher SH. High-intensity intermittent exercise and fat loss. Journal of obesity. 2011;2011:868305. doi: 10.1155/2011/868305. PubMed PMID: 21113312; PubMed Central PMCID: PMCPMC2991639. eng.
13. Sandvei M, Jeppesen PB, Stoen L, et al. Sprint interval running increases insulin sensitivity in young healthy subjects. Archives of physiology and biochemistry. 2012 Jul;118(3):139-47. doi: 10.3109/13813455.2012.677454. PubMed PMID: 22540332; eng.
14. Boyne P, Dunning K, Carl D, et al. High-intensity interval training in stroke rehabilitation. Topics in stroke rehabilitation. 2013 Jul-Aug;20(4):317-30. doi: 10.1310/tsr2004-317. PubMed PMID: 23893831; eng.
15. Kemi OJ, Wisloff U. High-intensity aerobic exercise training improves the heart in health and disease. Journal of cardiopulmonary rehabilitation and prevention. 2010 Jan-Feb;30(1):2-11. doi: 10.1097/HCR.0b013e3181c56b89. PubMed PMID: 20040880; eng.
16. Wens I, Dalgas U, Vandenabeele F, et al. High Intensity Exercise in Multiple Sclerosis: Effects on Muscle Contractile Characteristics and Exercise Capacity, a Randomised Controlled Trial. PLoS One. 2015;10(9):e0133697. doi: 10.1371/journal.pone.0133697. PubMed PMID: 26418222; PubMed Central PMCID: PMCPMC4587912. eng.
17. Cadore EL, Pinto RS, Bottaro M, et al. Strength and endurance training prescription in healthy and frail elderly. Aging and disease. 2014 Jun;5(3):183-95. doi: 10.14336/ad.2014.0500183. PubMed PMID: 24900941; PubMed Central PMCID: PMCPMC4037310. eng.
18. Salom Huffman L, Foote SJ, Hyatt H, et al. The Effect of a Sprint Interval and Resistance Concurrent Exercise Training Program on Aerobic Capacity of Inactive Adult Women. J Strength Cond Res. 2017 Aug 02. doi: 10.1519/jsc.0000000000002013. PubMed PMID: 28777244; eng.
19. Garcia-Pinillos F, Laredo-Aguilera JA, Munoz-Jimenez M, et al. Effects of 12-week concurrent high-intensity interval strength and endurance training programme on physical performance in healthy older people. J Strength Cond Res. 2017 Mar 13. doi: 10.1519/jsc.0000000000001895. PubMed PMID: 28301438; eng.

20. D'Orazio P, Burnett RW, Fogh-Andersen N, et al. Approved IFCC recommendation on reporting results for blood glucose: International Federation of Clinical Chemistry and Laboratory Medicine Scientific Division, Working Group on Selective Electrodes and Point-of-Care Testing (IFCC-SD-WG-SEPOCT). Clin Chem Lab Med. 2006;44(12):1486-90. doi: 10.1515/cclm.2006.275. PubMed PMID: 17163827; eng.
21. Sarafidis PA, Lasaridis AN, Nilsson PM, et al. Validity and reproducibility of HOMA-IR, 1/HOMA-IR, QUICKI and McAuley's indices in patients with hypertension and type II diabetes. Journal of human hypertension. 2007 Sep;21(9):709-16. doi: 10.1038/sj.jhh.1002201. PubMed PMID: 17443211; eng.
22. Washburn RA, Zhu W, McAuley E, et al. The physical activity scale for individuals with physical disabilities: development and evaluation. Arch Phys Med Rehabil. 2002 Feb;83(2):193-200. PubMed PMID: 11833022; eng.
23. Wens I, Dalgas U, Vandenabeele F, et al. High Intensity Aerobic and Resistance Exercise Can Improve Glucose Tolerance in Persons With Multiple Sclerosis: A Randomized Controlled Trial. Am J Phys Med Rehabil. 2016 Jun 29;[Epub ahead of print]. doi: 10.1097/phm.0000000000000563. PubMed PMID: 27362697; Eng.
24. Raymond MJ, Bramley-Tzerefos RE, Jeffs KJ, et al. Systematic review of high-intensity progressive resistance strength training of the lower limb compared with other intensities of strength training in older adults. Arch Phys Med Rehabil. 2013 Aug;94(8):1458-72. doi: 10.1016/j.apmr.2013.02.022. PubMed PMID: 23473702; eng.
25. Guiraud T, Nigam A, Gremeaux V, et al. High-intensity interval training in cardiac rehabilitation. Sports Med. 2012 Jul 1;42(7):587-605. doi: 10.2165/11631910-000000000-00000. PubMed PMID: 22694349; eng.
26. Huang M, Allen DR, Keller DM, et al. Impaired Carotid Baroreflex Control of Arterial Blood Pressure in Multiple Sclerosis. Journal of neurophysiology. 2016 Apr 13:jn.00003.2016. doi: 10.1152/jn.00003.2016. PubMed PMID: 27075533; Eng.
27. Huang M, Jay O, Davis SL. Autonomic dysfunction in multiple sclerosis: implications for exercise. Autonomic neuroscience : basic & clinical. 2015 Mar;188:82-5. doi: 10.1016/j.autneu.2014.10.017. PubMed PMID: 25458432; PubMed Central PMCID: PMCPMC4852554. eng.
28. Hansen D, Wens I, Dendale P, et al. Exercise-onset heart rate increase is slowed in multiple sclerosis patients: does a disturbed cardiac autonomic control affect exercise tolerance? NeuroRehabilitation. 2013;33(1):139-46. doi: 10.3233/nre-130938. PubMed PMID: 23949040; eng.
29. Keytsman C, Dendale P, Hansen D. Chronotropic Incompetence During Exercise in Type 2 Diabetes: Aetiology, Assessment Methodology, Prognostic Impact and Therapy. Sports Med. 2015 Jul;45(7):985-95. doi: 10.1007/s40279-015-0328-5. PubMed PMID: 25834997; eng.
30. Kent-Braun JA, Ng AV, Castro M, et al. Strength, skeletal muscle composition, and enzyme activity in multiple sclerosis. J Appl Physiol (1985). 1997 Dec;83(6):1998-2004. PubMed PMID: 9390973; eng.
31. Haider L, Fischer MT, Frischer JM, et al. Oxidative damage in multiple sclerosis lesions. Brain. 2011 Jul;134(Pt 7):1914-24. doi: 10.1093/brain/awr128. PubMed PMID: 21653539; PubMed Central PMCID: PMCPMC3122372. eng.
32. Hansen D, Wens I, Vandenabeele F, et al. Altered signaling for mitochondrial and myofibrillar biogenesis in skeletal muscles of patients with multiple sclerosis. Transl Res. 2015 Jul;166(1):70-9. doi: 10.1016/j.trsl.2015.01.006. PubMed PMID: 25666356; eng.
33. Kent-Braun JA, Sharma KR, Miller RG, et al. Postexercise phosphocreatine resynthesis is slowed in multiple sclerosis. Muscle Nerve. 1994 Aug;17(8):835-41. doi: 10.1002/mus.880170802. PubMed PMID: 8041390; eng.
34. Amorini AM, Nociti V, Petzold A, et al. Serum lactate as a novel potential biomarker in multiple sclerosis. Biochim Biophys Acta. 2014 Jul;1842(7):1137-43. doi: 10.1016/j.bbadis.2014.04.005. PubMed PMID: 24726946; eng.

Tables

Table 1. Baseline subject characteristics.

Age (years)	52.8 (7.2)
Weight (kg)	68.7 (13.2)
Height (m)	1.71 (0.1)
Sex (f/m)	9/7 (56/44%)
Smoking (y/n)	4/12 (25/75%)
Medication (y/n)	3/13 (19/81%)
BMI (kg/m²)	23.5 (3.3)
EDSS	2.6 (1.5)

Data are expressed as means (SD's) and represent baseline characteristics of the MS subjects (n=16). Abbreviations: f, female; m, male; y, yes; n, no; Medication, antihypertensive medication; BMI, Body Mass Index; EDSS, Expanded Disability Status Scale.

Table 2. Cardiovascular risk factors and impact of high intensity concurrent training.

	PRE	POST
Total Mass (kg)	62.3 (12.5)	61.2 (11.4)
Fat Mass (kg)	17.8 (4.7)	16.9 (4.9)
Lean Body Mass (kg)	44.2 (10.7)	44.2 (10.2)
Fat percentage (%)	29 (6.7)	28.2 (7.5)
Systolic BP (mmHg)	130 (13.5)	129 (14.7)
Diastolic BP (mmHg)	81 (8.6)	82 (9.4)
HR rest (bpm)	68 (8.9)	64 (8.7)*
Total Cholesterol (mg/dl)	193.7 (29.8)	188.2 (28.5)
LDL (mg/dl)	110 (24.9)	106.9 (19.6)
HDL (mg/dl)	62.7 (21.5)	59.9 (18.8)
Triglycerides (mg/dl)	103.6 (54.9)	106.9 (46.5)
CRP (mg/l)	2.1 (2.7)	1.25 (1.1)
HbA1c (%)	5.2 (0.3)	5.3 (0.3)
Fasting glucose (mmol/l)	5.5 (1.0)	5.2 (0.6)
2h glucose (mmol/l)	7.8 (2.8)	6.8 (2.1)*
Fasting insulin (mU/l)	8.6 (4.2)	7.1 (2.4)
2h insulin (mU/l)	44.1 (33.1)	44.1 (25.1)
HOMA	2.1 (1.2)	1.6 (0.5)*

*Data are expressed as means (SD's) an represent cardiovascular risk factors before (PRE) and after (POST) 12 weeks of high intensity concurrent training (n=16). Abbreviations: BP, blood pressure; HR, heart rate. *p<0.05: significant difference between PRE and POST.*

Table 3. Cardiopulmonary exercise capacity and impact of high intensity concurrent training.

	PRE	**POST**
Workload (watt)	142.2 (66.4)	167.5 (75.4)*
Time to exhaustion (min)	10.3 (4.3)	12.3 (4.7)*
$VO2_{max}$ (ml/min/kg)	26.8 (8.6)	32.7 (11.4)*
VE_{max} (l/min)	82.3 (30.6)	99.4 (37.4)*
RER_{max}	1.24 (0.1)	1.2 (0.2)*
HR_{max} (bpm)	161 (13.6)	162 (18.5)
$Lactate_{max}$ (mmol/l)	5.8 (1.8)	5.7 (1.4)
$HR_{recovery}$ (bpm)	117.6 (19.3)	122.9 (18.7)
$Lactate_{peak}$ (mmol/l)	8.2 (2.8)	10.3 (2.2)*

*Data are expressed as means (SD's) and represent parameters of the maximal exercise test before (PRE) and after (POST) 12 weeks of high intensity concurrent training (n=16). Abbreviations: VE, expiratory volume; RER, respiratory exchange ratio; HR, heart rate.. * p<0.05: significant difference between PRE and POST.*

Table 4. Isometric/isokinetic strength and impact of high intensity concurrent training.

	PRE	POST
Isometric strongest leg		
Ext 45°	111.6 (35.1)	124 (42.9)*
Flex 45°	80.3 (26.6)	88.9 (31.2)
Ext 90°	142.4 (48.5)	144.8 (43.3)
Flex 90°	62.1 (19.7)	68.7 (22.1)*
Isokinetic strongest leg		
Ext 180°	83.9 (28.9)	89.9 (34.8)*
Flex 180°	52.7 (22.4)	56.9 (24.7)*
Isometric weaker leg		
Ext 45°	101.1 (45)	115.4 (45.3)*
Flex 45°	63.7 (26.1)	76.4 (27.1)*
Ext 90°	111.8 (49.4)	127.6 (46)*
Flex 90°	50.4 (18.1)	60.9 (22.9)*
Isokinetic weaker leg		
Ext 180°	74.1 (35.5)	80.6 (36.1)*
Flex 180°	42.3 (24.7)	44.7 (22.6)

*Data are expressed as means (SD's) and represent isometric and isokinetic flexion (Flex) and extension (Ext) strength (in Nm) before (PRE) and after (POST) 12 weeks of high intensity concurrent training (n=16). Abbreviations: VE, expiratory volume; RER, respiratory exchange ratio; HR, heart rate.. * p<0.05: significant difference between PRE and POST.*