Impact of high-intensity exercise on endurance capacity and muscle strength in persons with Multiple Sclerosis.

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Research context

The present research was performed at the REVAL Rehabilitation Research Center of the Biomedical Research Institute of Hasselt University. It is situated within the domain of ‘rehabilitation in neurodegenerative diseases’, specifically multiple sclerosis (MS) and investigated the effects of a supervised high intensity endurance and resistance training program on muscle strength and endurance/aerobic capacity in people with MS. Physical therapy is known to have several positive effects in people with MS, ranging from improvements in quality of life to walking capacity and especially in exercise capacity and muscle strength, which are important to decrease possible comorbidities (1, 2). A guideline of Latimer-Cheung et al (2013) stated the need to train at a moderate intensity to improve fitness, mobility, fatigue and health-related quality of life (QoL) and most studies followed these guidelines in investigating exercise programs. Therefore high intensity programs have been avoided in people with MS to minimize possible side effects such as extreme fatigue and low adherence (1). However, a study of Wens et al (2015) warranted to investigate the influence of higher intensities to find possible effects on blood glucose and serum insulin, which could not be detected by using moderate intensity exercise programs (2). At present, there is a lack of consensus concerning the most optimal intensity to obtain positive results and minimize the possible side effects in people with MS.

The aim of this study was to determine the effects of a high intensity supervised endurance and resistance exercise program on aerobic capacity and muscle strength in people with MS. This study is part of a doctoral research entitled ‘the influence of rehabilitation on cardiometabolic risk factors in people with multiple sclerosis’, investigating the effect of a high intensity exercise program on various cardiometabolic risk factors in people with multiple sclerosis. The study was conducted at the REVAL Rehabilitation Research Center of the Biomedical Research Institute of Hasselt University led by Prof. Dr. Bert Op ‘t Eijnde, Dr. Inez Wens and drs. Charly Keytsman. Although the doctoral research consists of four master theses, Zeelmaekers Kimberly and Rihon Mathias investigated the effects of a supervised high-intensity rehabilitation program on muscle strength and aerobic capacity.

The contribution of the students consisted of several parts: since this was an ongoing study, the research design and methodology were already determined. However during the data acquisition, both students participated in the execution of the testing protocols, as well as the guidance of the participants during the intervention program. Next, each student acquired the data independently and conducted their own data processing. Afterwards, results were compared and if dissimilarities were found, data was checked for errors. Finally, the students worked together on writing the academic thesis, which in retrospect was controlled for grammatical faults and enhancements by the co-promoters.

Abstract

Background: Multiple sclerosis (MS) is a chronic neurodegenerative disease characterized by progressive demyelination of the central nervous system. The heterogeneous symptoms, such as deterioration of muscle strength and endurance capacity, lead to a predisposition of a sedentary lifestyle. To diminish these symptoms, exercise therapy is indicated, preferably a combined strength and endurance training program. However, research tends to focus on low-to-moderate intensities and only one study demonstrates the effects of a combined high intensity exercise program.

Objectives: To determine whether a 12-week combined high intensity interval program has an impact on muscle strength, endurance capacity and body composition in people with MS.

Participants: Thirty-one people with MS were selected based on inclusion and exclusion criteria and divided into an experimental or control group.

Measurements: Exercise capacity and muscle strength were considered as primary outcome measures, whilst body composition was considered as a secondary outcome measure.

Results: After 12 weeks of training workload, VO2max, mean ventilatory exchange (VE) and muscle strength improved in the intervention group, especially for the weakest leg. In contrast, the control group remained stable or deteriorated over time. No changes in body composition were detected in both groups.

Conclusion: People with MS benefit from a 12-week combined high intensity exercise program, concerning exercise capacity and muscle strength compared to usual care.

Introduction

Multiple sclerosis (MS) is a chronic neurodegenerative autoimmune disease characterized by progressive demyelination of the central nervous system. The heterogeneous symptoms, like increased fatigue and decreased quality of life (QoL), result in the predisposition of a sedentary lifestyle, which in turn can negatively affect muscle strength and endurance capacity. The latter one can possibly lead to secondary health-related problems such as development of an elevated cardiovascular risk profile and metabolic diseases (3-5). Other therapies are used, such as medication, but they only affect these health-related symptoms. In contrast, exercise therapy is preferred because of its influence on these impairments and the minimal of side-effects (6).

Evidence exists that endurance- and resistance training at low to moderate intensity benefits people with MS in terms of isometric muscle strength, QoL, risk for depression and resting heart rate (7). A guideline of Latimer-Cheung et al (2013) stated the importance of combining both endurance and strength modalities in exercise programs, by training endurance capacity at moderate intensity biweekly for a minimum of 30 minutes and performing resistance training for major muscle groups (1). Such combined exercise interventions would entail improvements in fatigue, mobility and QoL. Additionally, other studies demonstrate the positive effects of a combined mild- to moderate intensity program on MS related symptoms, such as muscle weakness and exercise intolerance (1, 2, 7, 8).

High intensity exercise programs have been avoided in people with MS because of their possible side effects, such as increased fatigue and lower adherence. Consequently, previous research shows the tendency to investigate the effects of low to moderate intensity training programs in people with MS. However, exercise intervention programs consisting of high intensity interval training (HIIT) are widely investigated in healthy persons providing good results in muscle strength and fitness (9). Similarly, a review by Raymond et al (2013) showed more improvement in older people when performing training at high intensities regarding lower-limb strength compared to lower intensities (10). It is suggested that programs focusing at moderate intensity are sufficient to improve muscle endurance and power without causing injuries in people with MS (11). Nevertheless, some authors suggested that people with MS could also benefit from a higher intensity endurance or resistance exercise program (8, 12). High intensity exercise programs can be used to investigate the impact on several secondary health problems like a disturbed serum insulin sensitivity and blood glucose intolerance, factors which can contribute to elevated cardiovascular risk profiles in people with MS (2, 3).

The study of Wens et al (2015) was the first to show improvements in mild to moderately impaired people with MS (mean EDSS 3.25) by using a combined high intensity exercise program consisting of both endurance and strength training (2). As promising as these results seem, from a scientific point of view solely one study is not sufficient for application in practice. Therefore, the purpose of this research is to confirm the effects of a combined high intensity exercise program on muscle strength, exercise capacity and body composition in mild to moderate disabled people with MS.

Hypothesis

Expectations of the study are a significant improvement of exercise capacity and strength in the intervention group compared to the control group. Furthermore, we believe that the intervention group will show a higher decrease in fat mass and increase in lean body mass compared to the control group. Additionally, the intervention group will show a significant improvement for all parameters after 12 weeks of training.

Methods

Participants

Thirty-one people with MS diagnosed according to the McDonald criteria (13), EDSS < 6 and older than 18 years were included following written informed consent. Subjects were excluded if they fulfilled one of the exclusion criteria (Table 1). Subsequently, participants were divided into an experimental or control group (Figure 1). After approval by the ethical committee of the Jessa Hospital (protocol number 4.84/cardio14.11) and Hasselt University, the training intervention program started in April/May 2015.

Study design

After group allocation, baseline measurements such as age, gender, height, weight, BMI, EDSS score, type MS, physical activity, DEXA scan, maximal cardiopulmonary exercise test and BIODEX, were performed in April / May 2015, one month prior to the start of the intervention program. During the study, the control group was asked to continue their usual care, while the experimental group participated in a 12-week high-intensity exercise program. All post measurements were performed similarly to baseline procedures within two weeks after the last training session. The purpose of the baseline measurements was to investigate the training effect in the intervention group. To prevent muscle exhaustion, participants were instructed to not perform physical activity within 48 hours prior to the test. For the same reason, performance of the BIODEX and the maximal cycle ergometry were scheduled with separation of at least 48 hours between. Strength measurements were performed with both legs separately, respectively first with the right leg and afterwards the left leg.

Procedure

Primary outcome measures

Exercise capacity

To evaluate exercise capacity, subjects performed a maximal cardiopulmonary exercise test on an electronic cycle ergometer (eBike Basic, General Electric GmbH, Bitz, Germany). Prior to initiation of the test, participants were asked to cycle 10 minutes without resistance as a warming up. During the test, participants were instructed to cycle at an average speed of 70 rounds per minute (rpm). The test was stopped when the participant could not maintain at least 50 rpm or when the point of exhaustion was reached. Female participants began at a resistance of 20W with an addition of 10W per minute. Male participants, in contrast, started at 30W with an addition of 15W per minute. During execution of the test, pulmonary gas exchange (Jaeger Oxycon, Erich Jaeger GmbH, Germany) was continuously measured. Every minute, mean ventilatory exchange (VE) (l/min), VO2max (ml/kg/min) and respiratory exchange rate (RER) were determined. Examiners executed a Jaeger calibration every testing day. Mean heart rate per minute was assessed using a 12 lead ECG. HR max was determined as the heart rate at the time the participant ceased the exercise test. Furthermore, every 2 minutes blood samples from the earlobe were obtained to assess the blood lactate concentrations (mmol/l) using a portable lactate analyzer (AccuTrend) (14).

Strength

Both isometric and isokinetic muscle strength were measured using an isokinetic dynamometer (BIODEX REVAL, UHasselt). First, maximal voluntary isometric strength (Nm) was measured. Participants were seated upright with the hips in a 90° angle, where between tests knee angle differed from 45° and 90°. Participants were instructed to perform two maximal isometric extensions and flexions alternated by a 30 second rest interval. The highest value of each attempt was considered as the maximal voluntary isometric muscle strength of the m. Quadriceps and m. Hamstrings.

Secondly, isokinetic strength (Nm/s) was determined in the same position by executing one set of 20 repetitions as fast and hard as possible. The highest values of flexion and extension were considered as the maximal voluntary isokinetic muscle strength.

Secondary outcome measures

Body composition

Fat mass (kg), lean body mass (kg), total mass (kg) and fat percentage (%) were determined using a Dual Energy X-ray Absorptiometry (DEXA) scan. Participants were allowed to eat prior to testing. The DEXA scan was performed at REVAL (UHasselt).

Intervention protocol

The exercise intervention program consisted of progressive endurance high-intensity interval training and strength training, which consisted of 5 training sessions per 2 weeks. Endurance training was a high intensity interval training program on a cycle ergometer which was individualized based on the results of the maximal exercise test. Participants cycled 5 x 1 minute on a high resistance level matching 100% of the maximal workload, which corresponds with approximately 80-90% of the maximal heart rate, alternated by a low resistance during the rest intervals. During the first 6 weeks, the rest intervals lasted 1 minute, whilst high resistance cycling progressed to 2 minutes by adding 10 seconds every week. For week 7-12, the same training program of week 6 was used, with adjustment of resistance levels to compensate when maximal heart rate could not be reached anymore. Strength training focused on 6 major muscle groups and progressed from 10 repetitions to 2 times 20 repetitions at a maximal attainable load. The strength training program consisted of 3 exercises for both the upper and lower extremities. A target BORG score of 14-16 was considered ideal to determine exercise intensity. Both strength- and endurance training were performed under supervision of a therapist, who guided the patients and recorded possible problems.

Statistical analysis

All data were analyzed using JMP Pro 12 software (SAS Institute Inc, Cary, NC). Since parametric testing was not allowed as the group number is lower than 30, baseline differences and group differences between MS groups were analyzed using the Wilcoxon test. Possible changes over time in the experimental and control group were evaluated by a Wilcoxon signed rank test. All data are presented as mean ± SEM and $p < 0.05$ was set as statistical significant threshold.

Results

Baseline characteristics

At baseline, the control group consisted of more women than men and subjects with primary progressive MS. However, no differences in baseline measurements were found between groups (Table 2).

Primary outcome measure

Exercise capacity

After 12 weeks of training, the intervention group improved significantly for workload (144.06 watt vs. 168.44 watt), VO2max (26.77 ml/kg/min vs. 32.66 ml/kg/min) and VE (82.6 L/min vs. 99.4 L/min) compared to baseline measurements (Table 3). The control group however deteriorated significantly over time for workload (114.62 watt vs. 100.77 watt) and RER (1.18 vs. 1.09).

For pre measurements, there was a significant difference in VO2max (26.77 ml/kg/min vs. 20.78 ml/kg/min) between the intervention and control group, which remained significant in the post measurements (32.66 ml/kg/min vs. 21.24 ml/kg/min). After 12 weeks, the same applies to workload (168.44 watt vs. 100.77), HRmax (162.25 bpm vs. 140.23 bpm), lactate (5.756 mmol/L vs. 4.618 mmol/L), VE (99.4 L/min vs. 59.77 L/min), RER (1.18 vs. 1.09) and recovery lactate (10.547 mmol/L vs. 6.391 mmol/L) between groups. The latter one deteriorated (8.2 mmol/L vs. 10.547 mmol/L) over time for the intervention group, however not significantly.

Strength

Strongest leg

Both groups differed significantly over time for both 45° isometric flexion (80.25 Nm vs. 90.06 Nm; 69.08 Nm vs. 62.92 Nm) and extension (111.63 Nm vs. 123.25 Nm; 109.67 Nm vs. 98.17 Nm), however when comparing means, the intervention group demonstrated an improvement while the control group showed a deterioration (Table 4). The same deterioration was detected for isometric 90° extension in the control group (133.75 Nm vs.

122.5 Nm). For isokinetic strength (Table 5), the intervention group showed a significant effect for extension (83.88 Nm/s vs. 89.56 Nm/s).

When comparing baseline and post-measurements, no significant group effects were established for the strongest leg, except for 45° isometric flexion in favor of the intervention group after 12 weeks (90.06 Nm vs. 62.92 Nm). In the intervention group the isokinetic extension improved significantly over time.

Weakest leg

No changes were found over time for the control group. The intervention group on the other hand increased significantly for isometric 45° flexion (63.69 Nm vs. 75.19 Nm) and extension (101.13 Nm vs. 116.13 Nm), isometric 90° flexion (50.38 Nm vs. 60.5 Nm) and extension (111.75 Nm vs. 127.63 Nm) (Table 6) and isokinetic extension (74.13 Nm vs. 80.94 Nm/s) (Table 7). In the intervention and control group, no changes across groups for both baseline and post-measurements were found.

Secondary outcome measure

Body composition

After 12 weeks, no changes were established in the intervention and control group separately (Table 8). When comparing baseline measurements between groups, fat mass (17,8 kg vs. 23,1 kg) differed significantly in favor of the intervention group. The same results apply for the post measurements (17,0 kg vs. 23,2 kg) and total mass (61,2 kg vs. 70,3 kg) after 12 weeks. Furthermore, no group effects were found for lean mass and fat percentage, however, the latter did show a positive trend (28.15625% vs. 33.030769%).

Discussion

This study shows that people with MS can also benefit from a 12-week combined high intensity training program in terms of endurance capacity and muscle strength. It is well known that these patients have health-related symptoms such as elevated levels of fatigue and decreased muscle strength and exercise capacity. Literature states that low to moderate exercise therapy has a positive influence on these negative consequences. Nevertheless, at present, only one other study demonstrated the effects of a high-intensity endurance and strength exercise program (2).

The influence of high-intensity interval training in MS

Exercise capacity (workload, VO2max, VE, lactate and recovery lactate) remained stable or improved over time in the intervention group, demonstrating that training is effective to prevent the deterioration of exercise capacity. In contrast, usual care postulates deterioration.

Likewise, Schmidt et al (2014) investigated the effect of a combined endurance and interval training at 65-70% and 70-80% of the participants' peak HR respectively, on peak oxygen consumption and observed a significant improvement after 12 months, proving that the decline in exercise capacity due to the progressive character of the disease cannot only be prevented, but can also be reversed (15).

Recovery lactate however, increased unexpectedly but not significantly in the intervention group after 12 weeks. A possible hypothesis is that the participants can tolerate a higher level during exercise, whereas before the intervention program patients had to cease training at lower levels. Another potential explanation is the enhanced processing of a higher amount of lactate after exertion.

As mentioned in the results, isometric muscle strength of the weakest leg increased significantly in the experimental group as expected, however flexion/extension ratios did not. Furthermore, the control group deteriorated in general over time.

In addition to this study, Dalgas et al (2009) showed that 12 weeks of high intensity progressive resistance training had a significant effect on knee extensor isometric muscle strength (16). Thus, it can be established that exercise at high intensities can improve

isometric muscle strength in people with MS.
In contrast, the flexion/extension ratios did not alter which can be explained by an increase in both flexion and extension isometric strength.
In general, it could be stated that the weakest leg improved more than the stronger leg in the intervention group. Likewise, Wens et al (2015) reported the same differences between both legs after a 24-week resistance and endurance training program (2). Possible explanations for bilateral differences in the present study could be that the weakest leg has more room for improvement compared to the stronger leg or that the training program accounts for bilateral differences.

In the present study, both isokinetic extensor and flexor strength improved in the intervention group, however this increase was only significant for the extensors. Similarly, Souza-Teixeira et al (2008) reported that an eight-week low to moderate progressive resistance training has a positive effect on muscular endurance of the knee extensors (11). This is possibly due to the fact that the exercise program consisted of two exercises for the extensors and only one for the flexors. The flexion/extension ratio did not change as anticipated. The same statement applies to the isokinetic muscle strength of the strong leg.

In general, it could be stated that the intervention program had no effect on body composition which is surprising since high intensity interval training is proven to have a positive effect on fat mass in healthy adolescents (17). This could be explained by the high intensity of the training program in which alterations in body composition are not the mean purpose. Furthermore, baseline differences in fat mass make interpretation between group differences at 12 weeks difficult. Nevertheless, total mass improved after 12 weeks in favor of the experimental group. Wens et al (2015) on the other hand reported a significant increase in lean tissue mass after 24-weeks of combined training. Other outcome parameters such as total mass, adipose and lean tissue mass remained stable (2).
Overall, the effects of combined high intensity interval training in people with MS on muscle strength, endurance capacity and body composition are scarcely investigated. In this study, participants did not have injuries related to the exercise program and it can be stated that the combined high intensity program was well tolerated.

One of the limitations of the present study was the lack of randomization into groups; the enrollment was based on the choice of the participants. This can account for a self-selection bias, nevertheless, baseline characteristics did not differ between groups. During the study, one participant changed groups because of breathing difficulties during exercise and one decided to quit for personal reasons. Also, participants, therapists and assessors were not blinded.

In contrast, DEXA scan, which is commonly referred to in literature as the golden standard to evaluate body composition, is proven to be highly accurate in measuring fat-free mass and muscle mass (18-23). In addition, BIODEX and maximal cycle ergospirometry tests were used to respectively measure muscle strength and endurance capacity, which are proven to be valid and reliable measurement techniques (24, 25). Finally, to interpret the results of muscle strength, a distinction was made between isometric and isokinetic strength in order to be thorough. However, some results were not as expected. Therefore, further research is needed to investigate the effect of a long-term combined exercise program.

New perspectives

In the present study, people with MS benefit from a combined 12-week high-intensity interval and strength exercise program in terms of endurance capacity and muscle strength. However, no conclusions can be made concerning the maintenance of effects or possible deterioration on the long term as post measurements were assessed immediately at the end of the intervention protocol. Furthermore, a study by Medina-Perez et al (2014) reported that resistance training followed by a period of detraining, both lasting 12 weeks, returned maximal voluntary isometric contraction to pre-training values (26). Consequently, other training strategies are needed to sustain the established effects. Home-based therapy programs may be useful to prevent relapses or deterioration. However, research is scarce and there is lack of consistent knowledge of the impact of a home-based training program on muscle strength, exercise capacity, quality of life and fatigue because most studies in people with MS are hospital-based or concern an in- or outpatient rehabilitation. The disadvantages of a supervised program in persons with a long-term disease are higher costs and the need for transportation (27). In order for home-based therapy to be effective, high adherence rate and a standardized rehabilitation program is essential. Social contact with the therapist by combining a diary with video or telephone calls is also important and gives the opportunity to assess progression. This could give a new perspective and chance for patients to maintain their results at home. However, further research is indicated to investigate the possible effects, but also other aspects like cost-effectiveness.

Conclusion

In conclusion, people with MS benefit from a combined endurance and strength high-intensity program concerning exercise capacity and muscle strength compared to usual care. Further research is indicated to investigate whether longer training periods have stronger effect and whether these positive effects can be maintained during a home based high-intensity program.

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Appendix

Table 1 Exclusion criteria
MS relapse within 6 months prior to the study
Contra-indications for increased physical activity diagnosed by a medical professional
Pregnancy
Inadequate comprehension of the Dutch language
Participation in another study

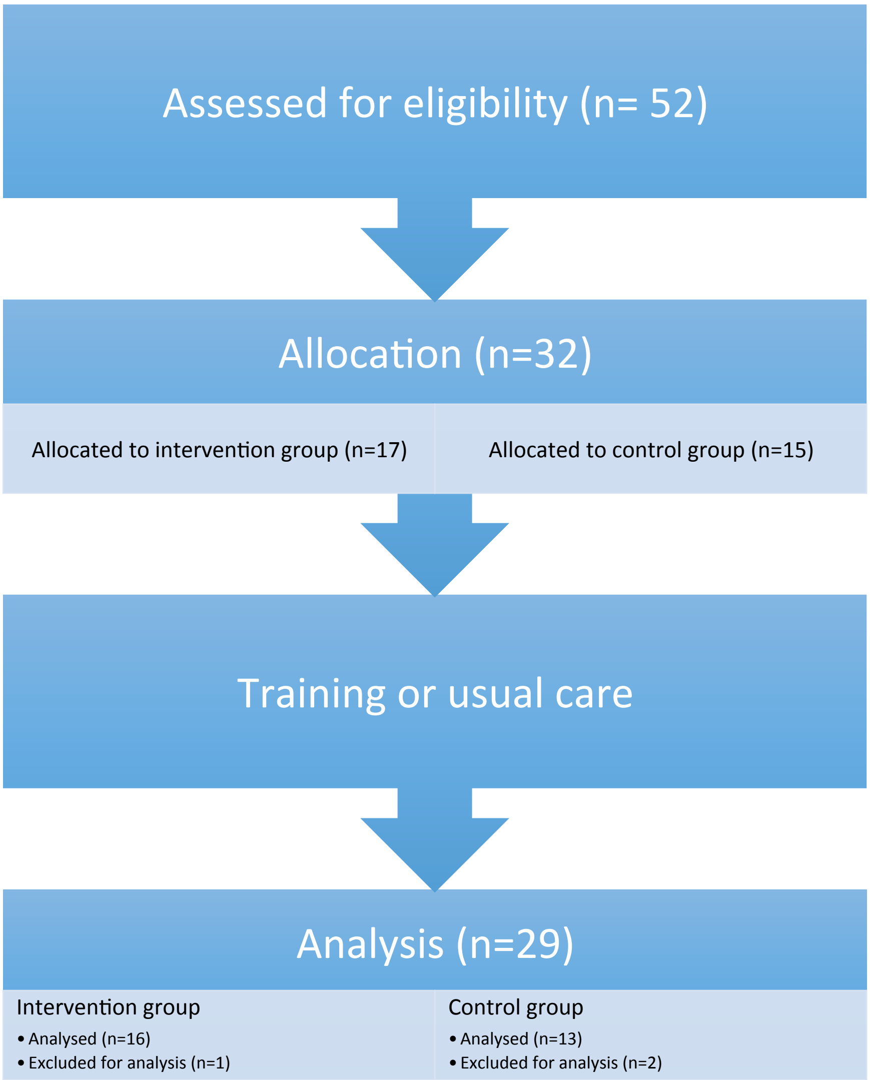

Figure 1: flowchart

TABLE 2 Baseline subject and disease characteristics			
	Intervention group	Control group	P
Age (years)	52 ± 7	53 ± 10	NS
Gender (M/F)	8/8	4/9	NS
Height (m)	170,7 ± 0,1	170,6 ± 0,1	NS
Weight (kg)	68,8 ± 13,2	76,6 ± 12,2	NS
BMI	23,5 ± 3,1	26,3 ± 3,7	NS
EDSS	2,5	3,3	NS
Type MS			NS
RR	11	9	
SP	5	2	
PP	0	2	
PA	18,3 ± 11,7	22,9 ± 16,5	NS

Data presented as mean ± SEM; SEM, standard error of mean; NS, not significant; S, significant; BMI, body mass index; EDSS, expanded disability status scale; MS, multiple sclerosis; RR, relapse remitting; SP, secondary progressive; PP, primary progressive; PA, physical activity

Table 3 Exercise capacity				
	Intervention group (n=16)		Control group (n=13)	
	Pre	Post	Pre	Post
VO2max (ml/kg/min)	26,8±8,6[a, c]	32,7±11[b]	20,8±6,6	21,2±7,5
HRmax (bpm),	160,6±13,6	162,3±17,9[b]	145,3±22,2	140,2±22,5
RER	1,2±0,1	1,2±0,2[b]	1,2±0,1[c]	1,1±0,1
Workload (W)	144,1±68,4[c]	168,4±74,8[b]	114,6±43,7[c]	100,8±38,7
VE	82,5±30,3[c]	99,4±37,3[b,1]	68,2±20,7	59,8±22,5
Lact (mmol/l)	5,8±1,7[3]	5,8±1,4[b]	5,2±2,1[1]	4,6±1,3[2]
Recovery HR (bpm)	117,6±19,3	122,9±18,6	106,7±14,6[1]	108,2±20,3
Recovery lactate (mmol/l)	8,2±3[3]	10,5±10,6[b, 1]	7,4±2,3[1]	6,4±1,6[2]

Data presented as mean ± SEM; Measurements were performed at baseline and after 12 weeks to evaluate possible effects of usual care and a combined training program.

[a] = P<0,05, difference between intervention and control at baseline.

[b] = P<0,05, difference between intervention and control at 12 weeks.

[c] = P<0,05, difference baseline measurements and measurements at 12 weeks.

[1]= 1 missing value

[2]= 2 missing values

[3]= 3 missing values

SD, standard deviation; HRmax, maximum heart rate; RER, respiratory exchange ratio; VE, ventilatory exchange; Lact, lactate

Table 4 Isometric muscle strength strongest leg				
	Intervention group (n=16)		Control group (n=12)	
	Pre	Post	Pre	Post
Ext 45° (Nm)	111,6±35,1[b]	123,3±41,9	109,7±27,3[b]	98,2±39,9
Flex 45° (Nm)	80,3±26,6[b]	90,1±30,7[a]	69,1±22[b]	62,9±21,3
Flex/ext 45°	72,9±17,9	74,3±14,4	63,3±16,7	74,9±48,9
Ext 90°(Nm)	142,4±48,5	144,8±49,7	133,8±40,5[b]	122,5±39,1
Flex 90°(Nm)	62,1±19,7	69,1±22,0	57,3±14,9	53,2±19,2
Flex/ext 90°	45,1±11,1	49,6±11,9	44,2±9,6	43,9±10,7

Data presented as mean ± SEM; Measurements were performed at baseline and after 12 weeks to evaluate possible effects of usual care and a combined training program.
[a] = P<0,05, difference between intervention and control at 12 weeks.
[b] = P<0,05, difference baseline measurements and measurements at 12 weeks.
SD, standard deviation; Flex, flexion; Ext, extension; Nm, newtonmeter;

Table 5 Isokinetic muscle strength strongest leg				
	Intervention group (n=16)		Control group (n=12)	
	Pre	Post	Pre	Post
Ext (Nm/s)	83,9±28,9[a]	89,6±35,5	73,2±20,6	68,8±19,1
Flex (Nm/s)	52,7±22,4	55,9±22,9	44,6±13,4	42,5±10,6
Ext/flex	62,6±13,3	62,6±9,1	61,2±10,4	62,9±10

Data presented as mean ± SEM; Measurements were performed at baseline and after 12 weeks to evaluate possible effects of usual care and a combined training program.
[a] = P<0,05, difference baseline measurements and measurements at 12 weeks.
SD, standard deviation; Flex, flexion; Ext, extension; Nm, newtonmeter; s, seconds;

Table 6 Isometric muscle strength weakest leg				
	Intervention group (n=16)		Control group (n=12)	
	Pre	Post	Pre	Post
Ext 45° (Nm)	101,1±45[a]	116,1±45,8	100±36	97,6±40,9
Flex 45° (Nm)	63,7±26,1[a]	75,2±24,9	61,7±28,3	57,1±29,5
Flex/ext 45°	65,2±18,3	68,2±18,2	60,8±15,4	56,8±18,4
Ext 90° (Nm)	111,8±49,4[a]	127,6±47,7	115,6±44,6	113,1±41,5
Flex 90° (Nm)	50,4±18,1[a]	60,5±21,8	51,5±20,1	47,8±22,9
Flex/ext 90°	51±24	49,6± 16,2	46±12,6	40,7±14,2

Data presented as mean ± SEM; Measurements were performed at baseline and after 12 weeks to evaluate possible effects of usual care and a combined training program.
[a] = P<0,05, difference baseline measurements and measurements at 12 weeks.
SD, standard deviation; Flex, flexion; Ext, extension; Nm, newtonmeter;

Table 7 Isokinetic muscle strength weakest leg

	Intervention group (n=16)		Control group (n=12)	
	Pre	Post	Pre	Post
Ext (Nm/s)	74,1±35,5[a]	80,9±37,2	69,5±22,1	67,2±23,7
Flex (Nm/s)	42,3±24,7	45,7±24,1	38,6±15,5	37,6±15,2
Ext/flex	56,3±19,8	56,9±20,7	54,7±11	56,3±18,7

Data presented as mean ± SEM; Measurements were performed at baseline and after 12 weeks to evaluate possible effects of usual care and a combined training program.
[a] = P<0,05, difference baseline measurements and measurements at 12 weeks.
SD, standard deviation; Flex, flexion; Ext, extension; Nm, newtonmeter; s, seconds;

Table 8 Body composition

	Intervention group (n=16)		Control group (n=13)	
	Pre	Post	Pre	Post
Fat M (kg)	17,8±4,7[a]	17±4,8[b]	23,1±6,4	23,2±6,2
Lean M (kg)	44,4±10,7	44,2±10,3	46,9±9,4	47,1±8,6
Total M (kg)	62,3±12,5	61,2±11,3[b]	70±11,6	70,3±10,6
% Fat	29±6,7	28,2±7,5	33,1±7,3	33±7

Data presented as mean ± SEM; Measurements were performed at baseline and after 12 weeks to evaluate possible effects of usual care and a combined training program.
[a] = P<0,05, difference between intervention and control at baseline.
[b]= P<0,05, difference between intervention and control at 12 weeks.
SD, standard deviation; g, grams; M, mass;

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