2013•2014
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

The effect of a Combined Training Protocol on Glucose Tolerance and Endurance Capacity in patients with Multiple Sclerosis

Promotor :
Prof. dr. Bert OP 'T EIJNDE

Copromotor :
Mevrouw Inez WENS

Maartje Krekels

Proefschrift ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

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KNOWLEDGE IN ACTION

Universiteit Hasselt | Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Universiteit Hasselt | Campus Diepenbeek | Agoralaan Gebouw D | BE-3590 Diepenbeek

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Woord vooraf

Het voorleggen van een masterproef ter afsluiting van een universitaire studie is een ideaal moment voor mij om mijn dankbaarheid uit te drukken ten aanzien van een aantal personen die mij in de loop der jaren en in het bijzonder bij het tot stand komen van dit proefschrift gesteund hebben. Allereerst dank ik hiervoor mijn promotor Prof. Dr. Bert Op 't Eijnde en mijn copromotor Dra. Inez Wens voor de begeleiding gedurende deze twee jaren. Het is mede dankzij de diepgaande en omvangrijke kennis van deze personen dat ik deze thesis tot een goed eindproduct heb kunnen brengen. Verder wil ik ook nog de deelnemende participanten van de studie bedanken voor hun aanzienlijke inzet. Zonder hun medewerking had dit relevante onderzoek nooit plaats kunnen vinden. Ook wil ik mijn ouders bedanken voor de steun en het vertrouwen: zij gaven mij de kans om verder te studeren.

Reusel, 12 mei 2014 M.K

Outline

Multiple Sclerosis (MS) is a common neurological disorder. Pathophysiologically, MS is characterized by an impairment of saltatory conduction leading to several symptoms [1]. Symptom presentation is extremely variable ranging from spasticity, fatigue and pain to sexual-, bladder- and cognitive dysfunction and to depression and is characterized by the possible presence of exacerbations and remission [1]. These symptoms often result in an decreased daily physical activity leading to a reduction in muscle strength, endurance capacity and associated secondary health problems such as an increased risk of cardiovascular disease (CVD), obesity and impaired glucose tolerance (IGT) that precedes type-II diabetes [1-4]. Furthermore, data already indicated significant higher insulin and glucose concentrations in MS patients compared to healthy controls [5].

The effect of exercise therapy on IGT has been repeatedly investigated in healthy subjects, indicating enhanced glucose and insulin profiles after physical training, including endurance or resistance exercises [6-10]. However, unpublished data of Dra. Inez Wens investigated already the effect of continuous aerobic exercise, at a moderate intensity, combined with resistance training on IGT in MS patients, resulting in no significant changes in glucose or insulin values. Since high intensity interval training (HIIT) resulted in promising improvements in glucose and insulin values in other populations [11, 12], and its effect in MS patients has not been investigated previously, the first aim of the current investigation is to examine the effect of HIIT combined with resistance training on glucose tolerance in MS patients. In addition, HIIT will be compared with continuous aerobic training.

So far, it is also clear that resistance training improves many aspects of muscle strength and overall functionality in MS patients. The additional impact of aerobic training, however, is not clear. Therefore, the second goal of this study is to examine the effect of a combined training protocol, including both resistance and endurance training, in MS patients on a variety of parameters such as aerobic capacity and body composition. Because HIIT in healthy subjects also provides improvements in endurance capacity, expressed in VO2max[13, 14], this study will examine whether this also applies to MS patients.

The present study is part of the doctoral project of Dra. Inez Wens, investigating the impact of different exercise modalities and intensities on muscle contractile properties and functional capacity in MS. The investigation was conducted in the REVAL Rehabilitation Research Center of Hasselt University. The REVAL center of Hasselt has training and rehabilitation facilities and features measurement instruments to assess cardiorespiratory fitness (Jaerger, Oxycon), muscle strength (Biodex isokinetic dynamometer) and body composition (DEXA scan).

The study design was developed within an ongoing research project, whereby no contribution can be made in the determination of the used methods. My contributions to the investigation consisted of guiding training sessions, assisting data acquisition and supporting the execution of tests during training sessions and measurements. Data processing and specific statistics are also performed independently, followed by writing part 2 of the Master Thesis.

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The effect of a Combined Training Protocol on Glucose Tolerance and Endurance Capacity in patients with Multiple Sclerosis

Opgesteld volgens de richtlijnen van *Multiple Sclerosis Journal*
http://www.uk.sagepub.com/msg/msj.htm#MSprep

Abstract

Background: Exacerbations and symptoms in multiple sclerosis, leading to decreased physical activity, can possibly be linked to reduced endurance capacity and impaired glucose tolerance.

Objective: This study aims to investigate the effect of combined exercise training on glucose tolerance and endurance capacity in patients with multiple sclerosis.

Methods: Thirty-six patients with multiple sclerosis completed 12 weeks of continuous aerobic endurance training or high intensity interval training; both combined with resistance training or continued their habitual lifestyle. At baseline and post intervention, glucose tolerance was measured with an oral glucose tolerance test. In addition, endurance capacity was measured with a maximal exercise test.

Results: A training protocol consisting of continuous aerobic endurance training combined with resistance training ensures decreased insulin (20%) and glucose (11%) values in response to glucose load. Thereby, endurance capacity improved by means of increased peak power and peak time reached during an exercise test. High intensity interval training combined with resistance training ensures decreased glucose values (7%) and in addition improved endurance capacity with enhanced VO2peak, peak power and peak time values.

Conclusion: A combined protocol, consisting of endurance and resistance training is effective for improvement of glucose tolerance and endurance capacity in patients with multiple sclerosis.

Introduction

Multiple Sclerosis is a demyelinating central nervous system disorder that affects approximately 2.1 million people worldwide, mainly young to middle aged adults [15]. The pathophysiology of MS can be described as an impairment of saltatory conduction [1], based on plaques of demyelination and axional damage in relationship to demyelination and inflammation. Immune cells, and their activity, are the basis of the pathology [15].
MS is characterized by the possible presence of exacerbations and remission and different symptoms, including spastic paraparesis or hemiparesis, frequently combined with ataxia, sensory impairments, neurogenic bladder, flexor and extensor spasm, visual disturbances and cognitive impairments [1]. Furthermore, general fatigue, muscular weakness and reduced muscle strength are also prevalent symptoms in MS. As a consequence of the latter, MS patients are often more inactive than matched healthy controls [1-3], leading to a reduced aerobic capacity and muscle strength [2], which is reported as an important characteristic of MS.
Another feature of MS patients is a reduction in maximal aerobic capacity, also described as a decreased maximal oxygen consumption (VO2max), reflecting the physical fitness of an individual [2]. A reduction of VO2max can be explained by MS related muscle weakness on respiratory surface, together with neurological impairments, duration of illness and fatigue [4].
Previously mentioned symptoms of MS, often leading to physical inactivity, can be firmly linked to an increased risk of secondary health problems, including CVD, osteoporosis, obesity and cancer [2]. Besides, this association also applies to type-II diabetes, preceded by IGT [2], with already demonstrated significant higher insulin and glucose concentrations in MS patients compared to healthy controls [5].

Furthermore, the influence of exercise therapy on IGT has already been demonstrated in healthy subjects, indicating enhanced glucose and insulin profiles after physical training, including endurance or resistance exercises [6-10]. However, unpublished data of Dra. Inez Wens investigated the effect of continuous aerobic exercise, at a moderate intensity, combined with resistance training on IGT in MS patients, resulting in no significant changes in glucose or insulin values. Since high intensity interval training (HIIT) resulted in promising improvements in glucose and insulin values in other populations [11, 12], and its effect in MS patients has not been investigated previously, the first aim of the current investigation is to examine the effect of HIIT with resistance training on glucose tolerance in MS patients. In addition, HIIT will be compared with continuous aerobic training.

Endurance and resistance training, which are important aspects of the non-pharmacological rehabilitation of MS, has been studied previously, with several benefits already demonstrated [2]. This is in contrast with earlier beliefs when MS patients have been advised to avoid exercise because of excessive fatigue and thermo sensitivity, since symptoms could temporarily worsen on exposure to heat or during physical exercise [1]. However, there is lack of studies that examine the effect of a combined training protocol in MS. The second goal of this study will therefore investigate the effect of combined training on physical parameters, including aerobic capacity and body composition, in MS.

Because HIIT in healthy subjects provides improvements in endurance capacity, expressed in VO2max [13, 14], this study will also examine whether these results also applies to MS patients.

Methods

Participants/Subjects:

Thirty-six participants, 18 years or older, diagnosed according to the McDonald criteria (EDSS ≤ 7) and available for a minimum of four months, participated. Exclusion criteria where comorbidities or presence of other disorders, exacerbations one month prior to the study, contra-indications for physical activity, pregnancy, previously diagnosed diabetes mellitus type II and participations in other studies. Full written informed consent was obtained before enrolment, in accordance with the Declaration of Helsinki.

Experimental design:

The present study is a 12-week randomized controlled trial. All participating subjects were tested at baseline before the trial. Subsequently, an independent researcher randomly assigned participants to various groups, consisting of resistance-and continuous aerobic endurance training (COMB), high intensity interval training combined with resistance exercises (HIIT) or the control group (CTR). The control group continued their previous daily activity level during the trial period. Anew, all groups where evaluated after 12 weeks, to compare various groups, assessing the impact of the potential intervention. The primary outcome measures were changes of glucose and/or insulin values, with endurance capacity and body composition as secondary outcome measures.

Training program:

The experimental period lasted 12 weeks with a training frequency of 2-3 times a week. For resistance training, the use of training machines was preferred, exercising the major muscle groups of upper and lower limbs. During the initial training phase, 1 set of 10 repetitions was maintained, increasing toward 2 sets of 20 repetitions in the more advanced phase, always at a maximal attainable load, individually adapted. The total resistance program contained 6 exercises, existing of 3 upper limb and 3 lower limb exercises.

For the continuous aerobe endurance exercises, including cycling and treadmill training, an intensity of 80-90% of VO2-max, based on the heart rate during the maximum endurance test, is detained with the exercise duration starting on 6 minutes, evaluating to 2 sets of 10 minutes. The high intensity interval training consisted of a cycling program, starting with 5 sets of 1 minute on 100% of the maximum achievable wattage, gradually building up to 5 sets of 2 minutes, interspersed with rest intervals of 1 minute.

Outcome measures

Insulin and Glucose concentrations:

The primary outcome is IGT. The subjects received an OGGT after at least 3 days of unrestricted diet, usual physical activity and an overnight fasting period of 8-14 hours. The mention of influencing factors, such as medication, inactivity or infections, is recommended. First, a fasting blood sample was collected. After this, the subject drunk 1 gram of glucose per kg of body weight in 250-300 ml water. Venous blood samples were drawn at 0, 60 and 120 minutes to determine serum insulin (Mercodia inulins ezyme-linked immunosorbent assay (ELISA)). Capillary blood samples were obtained at 20 minutes intervals to directly measure blood glucose levels (Analox-GM7 Micro-stat). Glucose and insulin levels where then expressed as the total areas under the curve (tAUC), calculated using the conventional trapezoid rule.

Endurance Capacity:

A maximal protocol was applied with the advantage of a direct measurement of VO2peak and monitoring the heart rate of the participants. The protocol for males started at 30 Watt with an addition of 15 Watt per minute. The females started at 20 Watt and raising 10 Watt per minute. Other parameters, including respiratory exchange ration (RER) peak and lactate peak, were also measured to ensure maximal exertion.

Body composition:

The participants underwent dual-energy X-ray absorptiometry (DEXA) for this purpose, measuring parameters including fat mass and lean body mass.

Statistics

Standard statistical methods are used to compute average values and standard deviations. More specific statistical analyses were performed using the SPSS program. Normality was evaluated using the Shapiro-Wilk test for all variables. Additionally, before data analysis, homogeneity of variances was checked. In order to determine possible differences after the various 12-week interventions, the parametric test for independent samples was used (1-way ANOVA). When normality or homogeneity of the variances was not demonstrated, the nonparametric test for independent samples was used (Kruskal-Wallis 1-way ANOVA). Significantly different outcomes where further evaluated with Bonferroni post-hoc analysis to describe where the differences were located exactly. To evaluate a possible intervention effect over time, variables were analyzed by a paired t-test. All data are presented as mean ± SEM and the statistical significance was adjusted to $p<0,05$.

Results

Subjects

Of the 36 selected patients, 2 subjects were excluded for reasons not associated with the investigation and MS. Data from 34 participants remained for statistical analysis. Subject characteristics at baseline are summarized in table 1. Disparities between groups were not statistically significant for any of these variables.

Table 1. Demographic data at baseline

	CTR (n=11)	COMB (n=11)	HIIT (N=12)	p Value
Age (y)	47,91 ± 9,51	46,54 ± 9,41	43,08 ± 9,43	NS
Height (m)	1,68 ± 0,07	1,70 ± 0,07	1,71 ± 0,08	NS
Weight (kg)	75,84 ± 11,5	70,25 ± 11,74	76,93 ± 13,88	NS
BMI (kg/m^2)	27,05 ± 4,41	24,42 ± 3,82	26,11 ± 3,80	NS
EDSS	2,5 ± 1,07	2,77 ± 1,07	2,33 ± 1,14	NS
Gender F=1	0,82 ± 0,39	0,55 ± 0,50	0,58 ± 0,49	NS
Smoker Yes = 1	0,27 ± 0,45	0,09 ± 0,29	0,33 ± 0,47	NS

Data are given as mean ± SD.
NS = not significant, BMI = Body Mass Index, EDSS = Expanded Disability Status Score.

Impaired Glucose Tolerance

Insulin

The values of insulin tAUC are shown in figure 1. At baseline, no significant differences in insulin tAUC were found between the various groups. Compared to the CTR group, insulin values of the HIIT or COMB group, after the 12-week training period, where not significantly declined. However, insulin values post intervention were significantly lower than at baseline within the COMB group (p<0,05) with an average decrease of 20%. Moreover, the HIIT and CTR group remained stable.

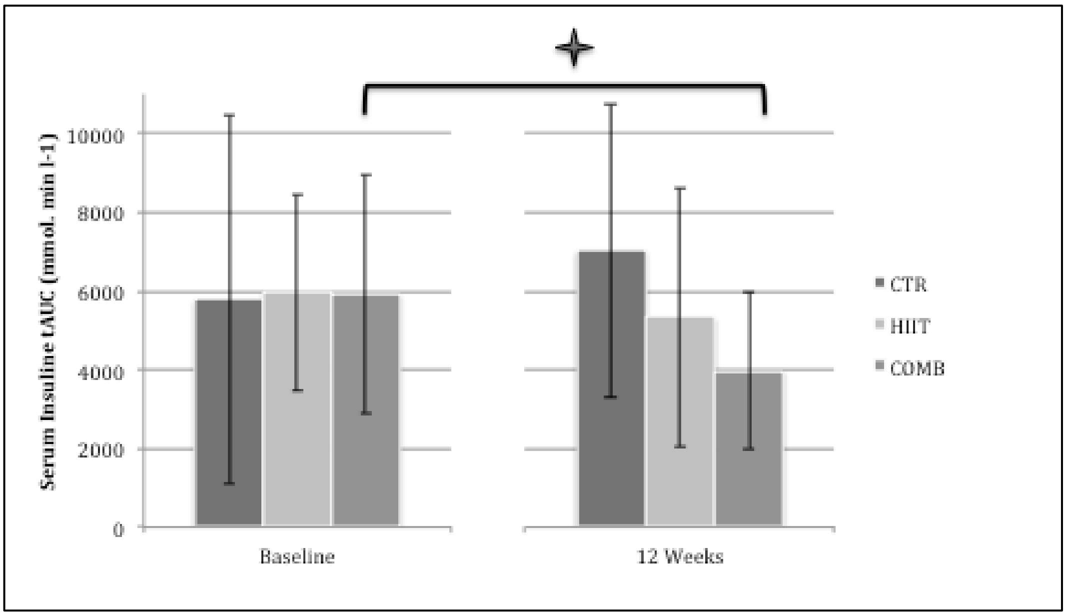

Figure 1: Insulin response (AUC) to an oral glucose load pre- and post 12 Week intervention

Glucose

The values of glucose tAUC are shown in figure 2. At baseline, no differences in glucose tAUC were found between the various groups. Furthermore, no significant reduction was found after the training period in the COMB or HIIT group, when compared to the CTR. However, a significant decreased glucose tAUC was demonstrated, post intervention compared with baseline, within the HIIT group (p<0,05) and within the COMB group (p<0,05), respectively with an average decrease of 7% and 11%. The CTR group remained stable.

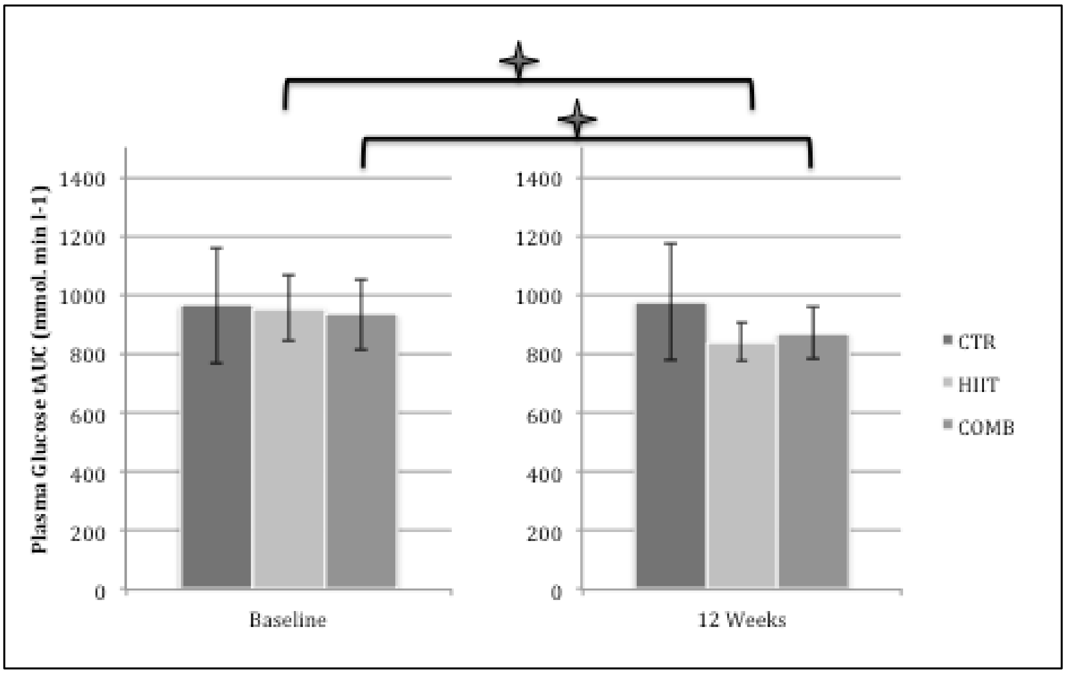

Figure 2: Glucose response (AUC) to an oral glucose load pre- and post 12 Week intervention

Endurance Capacity

At baseline, no significant differences were found in endurance capacity between the various groups. However, the treatment protocol resulted in significantly improved measurements of endurance capacity (table 2).

Firstly, compared to the CTR group, VO2peak values of the HIIT group were significantly higher after the 12-week intervention, indicating a training effect (p<0,05). Thereby, a significant increase over time is demonstrated in the HIIT group (p<0,05), with a VO2peak improvement of 18%. The COMB group enhanced 11%, but that difference appeared not to be significant (p>0,05). Secondarily, the HIIT group also improved their percentage VO2peak relative to the predicted VO2peak, based on age and weight in healthy individuals. The values increased from 96% to 107%, with an average improvement of 18%, indicating a better VO2peak after training than would be predicted (p<0,05). The CTR group remained stable in all of the variables.

A significant higher value of maximum workload achieved during an exercise test was also demonstrated in the HIIT group, compared to the CTR group, after 12-weeks of training (p<0,05). The wattage that could be accomplished improved with 25%, compared to baseline (p<0,05). The COMB group enhanced with an average of 12% (p=0,057) and was borderline different from the CTR, after the intervention (p=0,054).

The maximum number of minutes that could be reached during an exercise test was also higher in the HIIT group, compared to the CTR group, after the intervention period (p<0,05). In addition, HIIT values were significantly different compared to the values of the COMB group (p<0,05), whereas no dissimilarity was established between the COMB and CTR groups. The average significant improvements of the number of minutes in the HIIT and COMB group were respectively 27% and 15%, compared to baseline, whereby the outcome measures of the CTR group remained stable.

Additional measurements, including maximum heart rate, lactate values and RER were not significant from each other in the various groups after 12-week intervention. However, the maximum heart rate in the COMB and HIIT group increased significantly (p<0,05), when compared to baseline, with respectively 3% and 6%.

Body composition

No significant differences were found in any of the body composition measurements between the groups at baseline assessment and post intervention. After the training period, significant changes were seen in relation to pre-training values in lean body mass, in the HIIT group (p<0,05) with an average increase of 1,4%, and in body fat percentage, in the COMB group (p<0,05) with an average decrease of 4%. Other parameters, including total body mass and fat mass remained stable in all groups.

Table 2. Endurance capacity at baseline and after the trial

	HIIT Group		COMB Group		CTR Group	
Parameter	**Baseline**	**Posttest**	**Baseline**	**Posttest**	**Baseline**	**Post**
VO2peak (mL, min)	2031,2 ± 615,8	2378,9 ± 653,3*^	1870,1 ± 751,4	2004,3 ± 703,5	1648,3 ± 460,9	1575,4 ± 564,3
%VO2 predicted	96.1 ± 21,1	107,3 ± 16,1*	89,3 ± 26,6	99,5 ± 25,2	93,1 ± 26,3	88,5 ± 25,4
Peak power (Watt)	155,4 ± 48,4	191,4 ± 52,9*^	125,5 ± 60,6	135,0 ± 54,4*	109,1 ± 32,9	108,9 ± 39,3
Peak time (Min)	11,8 ± 2,9	14,6 ± 3,3*^§	8,8 ± 3,3	9,8 ± 2,9*	9,3 ± 3,3	9,0 ± 3,4
HR max (bpm)	160,0 ± 21,1	168,1 ± 17,5*	153,5 ± 17,9	161,6 ± 18,1	145,4 ± 20,9	146,0 ± 26,7
RER	1,2 ± 0,1	1,2 ± 0,1	1,2 ± 0,1	1,2 ± 0,1	1,2 ± 0,15	1,2 ± 0,13
Lactate	6,9 ± 1,7	7,5 ± 1,7	5,8 ± 1,3	6,8 ± 1,3*	5,5 ± 1,7	5,8 ± 1,6

Data are given as mean ± SD.
*Significant higher than baseline value (P<0,05).
^ Significant higher compared to CTR (P<0,05).
§ Significant higher compared to COMB (P<0,05).

Discussion

Physical inactivity is a hallmark symptom of MS and is associated with fatigue, muscle weakness and reduced aerobe capacity. In addition, physical inactivity may contribute to an increased risk of diabetes type 2, which is preceded by IGT [2]. In this study, we hypothesized that individuals with MS would increase muscle strength (data not shown) and aerobe capacity in response to a 12-week training program, consisting of resistance training in combination with continuous moderate intensity exercises or HIIT. Furthermore, we speculated that increases in physical activity would be associated with improved IGT and a reduction in insulin and glucose levels during the OGTT in MS subjects.

Impaired Glucose Tolerance

The first aim of this study was to examine the effects of different training modalities on glucose tolerance in MS patients. After the 12-week intervention, no overall interaction effect could be demonstrated in insulin and glucose profiles between the HIIT-, COMB- and CTR group. However, insulin and glucose values were significant lower post intervention compared to baseline as a result of resistance training combined with moderate intensity endurance training. This average reduction was as much as 20% for insulin tAUC and 11% for glucose tAUC, meaning that habitual endurance training of moderate intensity combined with resistance training ensures a reduced insulin response to an OGTT with additional lower blood glucose levels. These findings correspondent with the results of Poehlman et al., also demonstrating improved insulin sensitivity, exclusively after endurance- or resistance training, measured with the hyperinsulinemic-euglycemic clamp technique [9]. The unchanged insulin values after resistance training combined with HIIT are in contrast with the results of Brabaj et al., demonstrating a significant reduced tAUC of 37% [11]. This discrepancy can be explained by a lower average age and BMI of their participating healthy subjects, indicating a possibly lower fat percentage that can be associated with less resistance to insulin [6, 8]. However, the results of significant decreased glucose levels are congruent [11]. The effects of a combined protocol consisting of endurance- and resistance training on insulin and glucose levels have not been investigated. Furthermore, the total endurance training volume, being lower in the HIIT group, could perhaps explain the unchanged insulin levels compared to the reduced insulin tAUC in the COMB group. This suggests that the total exercise duration should be considered when designing training programs with the intent of improving insulin action.

Endurance Capacity

The second aim of this study was to examine the effect of resistance- and endurance training on cardiorespiratory fitness. The present results reveal that brief but intense training has the potential to alter VO2peak, peak power and peak time, reached during a maximal exercise test. This indicates that the 12-week HIIT intervention ensures an improvement of the above-mentioned parameters compared to the CTR group. These findings are consistent with the results of the study of Astorino et al., also indicating an enhanced peak power and a mean VO2 peak improvement of 6,3% in active young men and women [13]. The inclusion of solely less physically active MS patients in our trial and a longer intervention period with more sessions could explain a larger improvement of as much as 18%. The study of Nybo et al. also confirms an increased maximal oxygen uptake after 12 weeks of intense interval running, indicating an average improvement of 14% in untrained men [16]. Additional relevant is the significant improvement in the percentage of the measured VO2peak relative to the predicted VO2peak, based on age and weight. This increase induces and confirms the opportunity for MS patients to normalize their aerobic fitness to the level of healthy individuals. The effect of HIIT combined with resistance training in MS patients has not been investigated before, making it impossible to exactly compare different protocols.

However, the unimproved VO2peak values after moderate intensity endurance training in the COMB group are in contrast with the results of Mostert et al., investigating the effect of a short-term training program of 3-4 weeks on aerobic fitness of subjects with MS. A significant improved VO2peak of 13% was demonstrated, with an additional increased workload of 11% [17]. The difference in maximal oxygen uptake can be explained by a higher training frequency, namely 5 times a week and consequently an increased training volume per week. The fact that merely bicycle training was used can also have a major impact, since MS patients have occasionally problems with continuing walking on a prescribed intensity during treadmill training, based on a potential restricted gait pattern. Moreover, the study of Petajan et al. indicates also an increased VO2peak of 22% after 15 weeks of moderate intensity endurance training [18]. Despite not significant changed VO2 measurements, improvements in peak time and peak power during the maximal exercise test were demonstrated of respectively 15% and 12% as a result of moderate intensity training, indicating definitely an effect.

Strengths and Limitations

Our study has several strengths and limitations that should be kept in mind when interpreting the results. First, the participating subjects represent a selected group of patients with MS, and findings are not necessarily transferrable to more disabled patients. Another important limitation is the restricted blinding of participants and practitioners during the training intervention. However, it is difficult to blind participants and supervising investigators to an exercise intervention, because a placebo intervention will be easily revealed. Furthermore, we chose a design with treadmill training whereby a limited gait pattern may influence training intensity. Finally, social interaction between participating subjects could influence the effects of interventions.

Strengths of our study are characterized by proper supervision of the training sessions with clear agreements between the trainers. This implies an accurate and strict monitoring of the exercise sessions with immediate adjustment of intensity when possible, guaranteeing optimal training conditions.

Conclusion

We demonstrated for the first time that a combined training protocol of endurance and resistance exercises is sufficient to achieve significant improvements in glycemic control and endurance capacity in patients with multiple sclerosis. A protocol, consisting of moderate intensity endurance training and resistance training ensures reduced insulin and glucose levels in response to an oral glucose load. In addition, it provides improvements in peak power and peak time during a maximal exercise test, reflecting partially enhanced endurance capacity. A protocol consisting of high intensity interval training and resistance training only ensures a reduced glucose response by means of a decreased tAUC. However, outcome measures including VO2peak, peak power and peak time reached during the maximal exercise test are auspicious, indicating major improvements in endurance capacity.

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