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FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de revalidatiewetenschappen en de kinesitherapie

Masterproef
The influence of high intensity exercise on the energy metabolism in MS

Promotor :
Prof. dr. Bert OP 'T EIJNDE

Copromotor :
dr. Inez WENS

Sander De Groote , Ann-Sofie Salaets
Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

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We would also like to thank all persons with multiple sclerosis for their participation and commitment in this study. Finally we want to thank our family and friends for their help and support.

Neerpelt, juni 2015 SA

Scherpenheuvel, juni 2015 DS

Research context

Multiple sclerosis (MS) is a condition of the central nervous system in which insulating covers of nerve cells are damaged. This deficiency results in symptoms including loss of strength, fatigue, spasticity, cognitive dysfunctions,…These primary symptoms are associated with physical inactivity and consequently increase the risk to develop secondary conditions such as impaired glucose tolerance (IGT), type 2 diabetes (T2D), obesity and cardiovascular diseases (CVD).

This second part of our master thesis is a continuation on the literature search we conducted last year. In this literature search, evidence concerning high intensity interval training (HIIT) to improve several parameters within the metabolism of healthy and T2D individuals was reviewed. Results demonstrated no change in glucose tolerance and insulin sensitivity (IS) after HIIT in healthy individuals, however glucose tolerance improved in persons with T2D. In addition, these findings need to be extrapolated carefully to the MS population because of the pathological influence on the cell metabolism. The influence of HIIT on IGT was never investigated before in persons with MS.
A study of Wens et al. noted that a mild-to-moderate-intensity combined endurance and resistance training did not affect glucose tolerance but improved muscle strength and exercise tolerance. As HIIT appears to be a time efficient training modality to improve IGT and insulin sensitivity in individuals with T2D, this part of the master thesis will investigate changes in the cell metabolism following HIIT or high intense continuous training (CONT) combined with resistance training in MS patients.

This master thesis is part of the doctoral project of Dr. I. Wens, supervised by Prof. Dr. B. Op't Eijnde, who performs research in the fields of the rehabilitation of neurodegenerative diseases. " Exercise therapy in multiple sclerosis: the impact of exercise intensity on glucose disposal and muscle contractile properties." This study focuses on training modalities to improve secondary symptoms, metabolic properties and functional capacity in persons with MS and was conducted in the rehabilitation research center of Hasselt University.

Since our study was part of an ongoing research, our contribution to the investigation consisted of guiding training sessions. To gain more experience within the fields of research, we assisted in a clinical study of Prof. Dr. D. Hansen. However, data processing, statistics and interpretation of results were conducted independently.

1. Abstract

Background: MS often leads to a more inactive lifestyle, thereby increasing the risk of developing secondary conditions such as obesity, CVD and IGT. Studies have pointed out the beneficial effects of exercise to improve these health conditions in healthy subjects, however, in the MS population, moderate intensity training (MIT) did not result in improved glucose tolerance. Some studies suggest that high intensity training (HIT) has enhanced effects on glucose tolerance, however this has never been investigated before in MS.

Objective: The aim of this study was to determine the impact of a combined HIIT or CONT program on glucose tolerance and GLUT4 concentrations in persons with MS.

Design: 34 persons with MS were randomized to either HIIT (n=12), CONT (n=11) or a sedentary group (SED) (n=11). Glucose tolerance, GLUT4, body composition, muscle strength and aerobic performance were determined in all groups at baseline and after 12 weeks of exercise training.

Results: Plasma glucose concentrations significantly decreased in HIIT and CONT compared with baseline ($p<0.05$). Serum insulin only decreased significantly within CONT ($p<0.05$), while skeletal muscle GLUT4 protein content increased solely within HIIT. ($p<0.05$) No changes were observed within SED. Body composition was unaffected in all groups, whereas self-reported physical activity significantly increased in HIIT and CONT compared with baseline. ($p<0.05$)

Conclusion: Twelve weeks of combined CONT improved glucose and insulin concentrations in this randomized controlled trial, whereas combined HIIT improved glucose and GLUT4 concentrations. Both types of intervention were well tolerated in persons with MS.

Key words: Multiple sclerosis, glucose tolerance, GLUT4, high intensity training, resistance training, body composition, aerobic performance, muscle strength

2. Introduction

The inflammatory neurodegenerative disease of the central nervous system 'Multiple Sclerosis' [1] is a pathology with a prevalence of 4.3 cases per 100.000 in Europe [2]. It leads to symptoms such as fatigue, spasticity, loss of balance, weakness, reduced cognitive function and bladder dysfunction [3, 4] which contribute to a decrease in physical activity and health related quality of life (HRQOL) [5] . Physical inactivity can increase the risk of developing secondary conditions e.g., obesity, CVD and IGT that can accelerate MS-related functional decline [6, 7].

IGT is a result of peripheral insulin resistance and leads to a decreased glucose uptake in muscle cells, a less effective energy metabolism and precedes the development of T2D. [8, 9] The World Health Organization defines IGT as a fasting glucose concentration of 6.1- 6.9 mmol/l and two-hour-post-load glucose of 7.8- 11.1 mmol/l. [8]

It has already been shown that there is a decrease in the incidence of T2D and an improvement in IS among patients with IGT after MIT. [10, 11] The mechanisms of training effects by improved IS were part of a coherent increase of GLUT-4 translocation and regulated by AMP-activated protein kinase (AMPK) [11-13]. In persons with MS, MIT increases aerobic capacity and muscular strength. Mobility, extreme fatigue and health related quality of life might improve but evidence is conflicting [14]. Studies combining MIT with resistance training revealed improved strength, endurance, body composition and walking speed but no changes in insulin resistance, IGT, aerobic capacity, fatigue, depression and HRQOL were observed [15].

HIT programs are known to lead to faster and larger physical fitness improvements [15] and appear to be a time efficient means in subjects with T2D to improve IGT, IS and GLUT4 concentrations but can be perceived as more stressful. [16-18]. Although the responses to exercise training in persons without a neurological disease are relatively well defined, the metabolic responses and adaptations in persons with MS during HIIT remain unexplored. Considering the impact of MS on a number of body systems, evaluation of metabolic responses and adaptations during HIIT is an important and necessary aspect in the development of exercise recommendations.

Based on the above line of reasoning, the main objective of this study is to examine the effectiveness of HIT on glucose metabolism (Insulin-, glucose- and GLUT4 concentrations) in persons with MS. Secondary we aimed to investigate the effect of HIT on abdominal fat, physical activity, endurance and strength of knee flexors and extensors.

3. <u>Methods</u>

Participants

12 men and 22 women (mean 46 years, range 29 – 62 years) diagnosed with MS according to the McDonald criteria with an expanded disability status scale (EDSS) between 0.5 and 6 agreed to participate in the study [19] **.** Participants were recruited from the MS rehabilitation center in Overpelt or by means of a folder. Eligible participants received a written consent explaining the procedures and possible associated risks of the study, according to the declaration of Helsinki and approved by the Ethical Committee of Jessa Hospital and Hasselt University (protocol number 13.20/reva13.02). Exclusion criteria were glucose lowering medication, pregnancy, other comorbidities (cardiovascular-, pulmonary-, orthopaedic-, metabolic- , renal and mental disorders or cancer), exacerbations less than six months prior to the beginning of the study. Subjects participating in other studies were also excluded. Subject characteristics are presented in Table 1.

Study design

The subjects were randomly divided into three groups: a group that performed HIIT (n=12), a CONT group (n=11) and a SED group performing no physical training (n=11). The participants in the two training groups completed a 12 week training period as described below, whereas participants in SED continued their habitual physical activities during the period. The intervention took place at the research center of Hasselt University (REVAL), with a frequentation of 5 sessions/ 2 weeks. To prevent Uhtoff's phenomena, training room temperature was kept at 19°C [20]. All training sessions were supervised by a physical coach. Missing training sessions were accomplished during subsequent weeks so that the total required amount of training sessions was reached.

Exercise protocols

HIIT

The training consisted of a brief 5-min warm-up on a leg cycle ergometer at an intensity of 50% of heart rate maximum (HRmax) followed by a training session composed of 5 x 1 min intervals at 100% HRmax, interspersed with 1 min rest between intervals. Interval duration gradually increased to two minutes. Workload increased to maintain the intensity of 100% HRmax.

CONT

Subjects also started with a 5 min warm up at 50% HRmax on a leg cycle ergometer.
Following the warm up, two 5 min bouts on a cycle ergometer and treadmill were performed at an intensity of 80% HRmax and interspersed with 1 min rest. Duration of each bout was increased gradually to 2x10 min/bout.

Strength training

Both HIIT and CONT were followed by the same unilateral strength-endurance training for upper and lower limbs. Exercises were performed on six different weight machines (leg curl, leg extension, leg press, chest press, arm curl and vertical traction) progressing from one set of ten repetitions (10RM) to two sets of twenty repetitions (20RM) of each exercise. Subjects were instructed that the duration of the eccentric movement phase has to be three times as long as the concentric phase. Each training session was ended with a cool down of 5 min on a leg cycle with an intensity of 50% HRmax and stretching exercises.

Testing

Before and after the 12 week intervention period, subjects completed a series of tests that consisted of an oral glucose tolerance test (OGTT) and strength assessment (day 1), a maximal oxygen uptake test (VO2max) and measurement of body composition (day 3), a muscle biopsy (day 5) and an assessment of physical activity. Subjects were instructed to refrain from alcohol and caffeine consumption before tests.

Measurements

Primary outcomes

OGTT

An OGTT was used to determine the extent to which the body can maintain a homeostasis of blood glucose. After an overnight fast, a glucose load of 1-g glucose/kg body weight was administered at 8 o'clock in the morning. Capillary blood samples were collected from the earlobe at 0, 20, 40, 60, 80, 100 and 120 min and whole blood glucose concentrations were assessed directly (Analox-GM7 Micro-stat). To determine plasma glucose, whole blood glucose concentrations were converted to plasma glucose by multiplying whole blood glucose with a factor of 1.11. (D'Orazio P. ea, 2005) Furthermore, venous blood samples were obtained at 0-, 1- and 2h to determine serum insulin. Serum concentrations of insulin were assessed using a commercially available ELISA (Mercodia Insulin Enzyme-linked Immunosorbent assay, Uppsala, Sweden). Total area under the curve (tAUC) for plasma glucose and serum insulin was calculated using the trapezoidal model.

Muscle biopsy

A tissue sample from the vastus lateralis muscle of the weakest leg was obtained under local anesthesia. A piece of muscle was dissected free of blood and connective tissue, freeze dried and powdered to determine the occurrence of metabolic adaptations. Measurement of GLUT4 concentrations was assessed by ELISA (BlueGene).

Secondary outcomes

Body composition

Fat, lean, total and percentage fat mass of the trunk, as well as total body mass measurements were assessed by a whole dual energy x-ray absorptiometry (DEXA) system (Hologic Series Delphi-A Fan Beam X-ray Bone Densitometer). All body composition measurements were performed by the same investigator throughout the study period.

Aerobic performance

A graded exercise test was performed on a bicycle ergometer to determine VO2max as well as aerobic and anaerobic thresholds. Male subjects started at a workload of 30 watt and female subjects at 20 watt. Workloads respectively increased with 15 and 10 watt every minute until exhaustion. Oxygen uptake, heart rate (HR), continuous electrocardiogram (ECG), blood pressure and blood lactate were monitored during the test, which was supervised by a physician. The subjects were encouraged to continue cycling until voluntary exhaustion or difficulties in maintaining adequate revolutions per minute, or until interrupted by a physician for medical reasons (Pathological changes in ECG).

Muscle strength

Before strength testing, subjects performed a warm up of 5 min on a cycle ergometer and 2 x 10 reps on a leg extension and leg press. Unilateral muscle strength of both legs was determined by an isokinetic dynamometer (Biodex system 3). Subjects were positioned on a chair with an posterior inclination of 5°. The axis of rotation was positioned perpendicularly on the knee joint. Maximal isometric torque (Nm) was assessed by a submaximal trial flexion/extension contraction at 45 and 90°, followed by two maximal contractions of 4 sec, interspersed with 30s rest between each contraction. Thereafter, maximal isokinetic peak torque (Nm) was determined by three submaximal trial isokinetic extension contractions, followed by 30 maximal contractions, starting at 90° knee flexion to 180° at a speed of 180°/sec [21-23].

Statistical analysis

For the statistical analysis, the software package IBM SPSS Statistics 22 was applied. Differences in baseline characteristics, body composition, physical activity, insulin AUC, glucose AUC, GLUT4, VO2max and leg strength between groups were assessed by the Kruskal-Wallis one-way analysis of variance. The Wilcoxon signed-rank test was applied to observe significant differences within groups. The level of statistical significance was set at $p<0.05$ for all analyses.

4. **Results**

Results

Subject characteristics

Subject characteristics are presented in table 1. Groups were comparable at baseline (Pre) with respect to sex, age, length, mass, EDSS and smoking behavior. All participants completed their experimental treatment with an adherence of 80-100%. No exacerbations occurred during training sessions. There were no differences between groups in medication use except for antidepressants, anti-epileptic drug, muscle relaxing and PPI (proton pump inhibitor) which showed significant differences. ($p<0.05$)

Table 1. Subject characteristics

	SED	HIIT	CONT	p-value
No. (M/F)	11 (2/9)	12 (5/7)	11 (5/6)	NS
Age	47,90 ±9,97	43,0±9,81	46.45±9,80	NS
Length (m)	1,68 ±0,078	1,71±0,08	1,70±0,081	NS
Mass (kg)	74,44±11,46	75,83±14,22	68,95±11,99	NS
BMI	26,55±4,42	25,76±3,88	23,96±3,88	NS
Smoker (Y/N)	3/8	4/8	1/10	NS
EDSS	2,5±0.78	2,3±0,46	2,7±0,26	NS
METs	13.96±8,78	25.86±22,97	14,74±8,89	NS
Antidepressant	63%	8%	9%	S
Magnesium	9%	8%	0%	NS
Immunosuppressant	9%	17%	36%	NS
Statins	18%	8%	0%	NS
Anti-epileptic drug	27%	0%	45%	S
Diuretics	0%	0%	0%	NS
Muscle-relaxing drug	45%	0%	9%	S
Analgesics	0%	16%	0%	NS
Beta-blocker	9%	0%	0%	NS
Immunomodulant	45%	50%	45%	NS
NSAIDs	9%	0%	0%	NS
PPIs	27%	0%	0%	S
Anticholinergic drug	27%	0%	8%	NS

male (M), female (F), body mass index (BMI), metabolic equivalent (MET), yes (Y), no (N), non-steroidal anti-inflammatory drugs (NSAID), non significant (NS), significant, $p<0.05$ (S)

Primary outcomes

OGTT

Glucose tAUC between groups were comparable at baseline. No differences were found between groups in the change of glucose tAUC after 12 weeks. A significant decrease within HIIT ($p<0.05$) and CONT ($p<0.05$) was observed compared with Pre, while SED showed a non-significant change (Fig 1/3).

No significant differences in insulin tAUC were seen between groups at baseline and following training. Compared with Pre, insulin tAUC significantly decreased within CONT ($p<0.05$), a similar trend was found within HIIT but values did not reach statistical significance. In contrast, insulin tAUC increased within SED compared with Pre but changes were not significant (Fig.2/3).

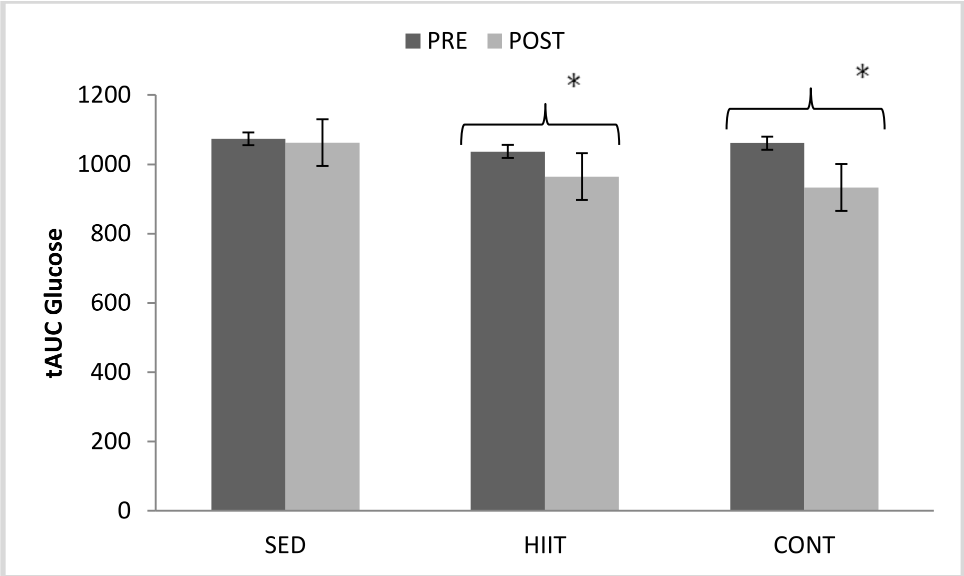

Fig 1. tAUC for glucose before and after 12 wk . Data are given as mean ± SD (standard deviation). Significantly different from Pre, * $p<0.05$.

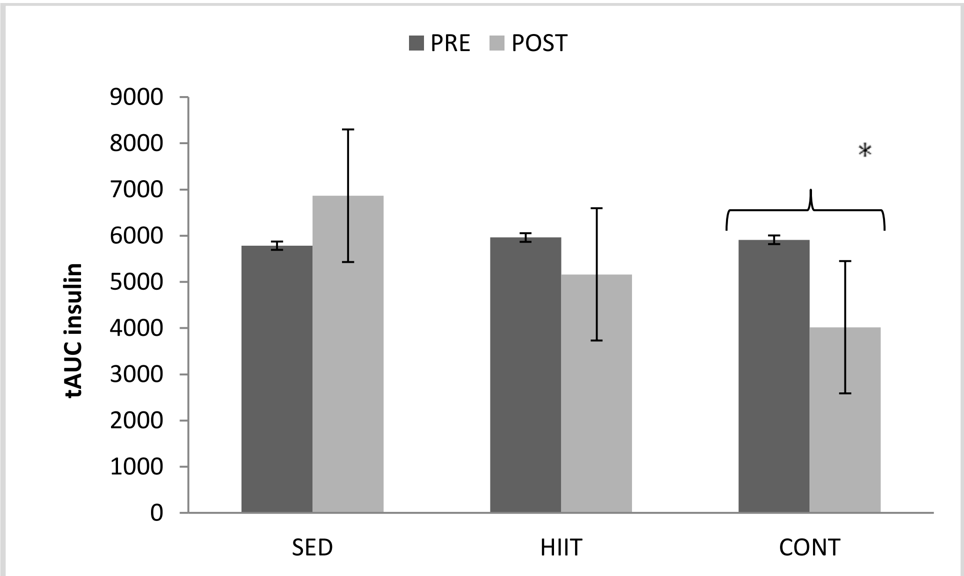

Fig 2. tAUC for insulin before and after 12 wk. Data are given as mean ± SD. Significantly different from Pre, *$p<0.05$.

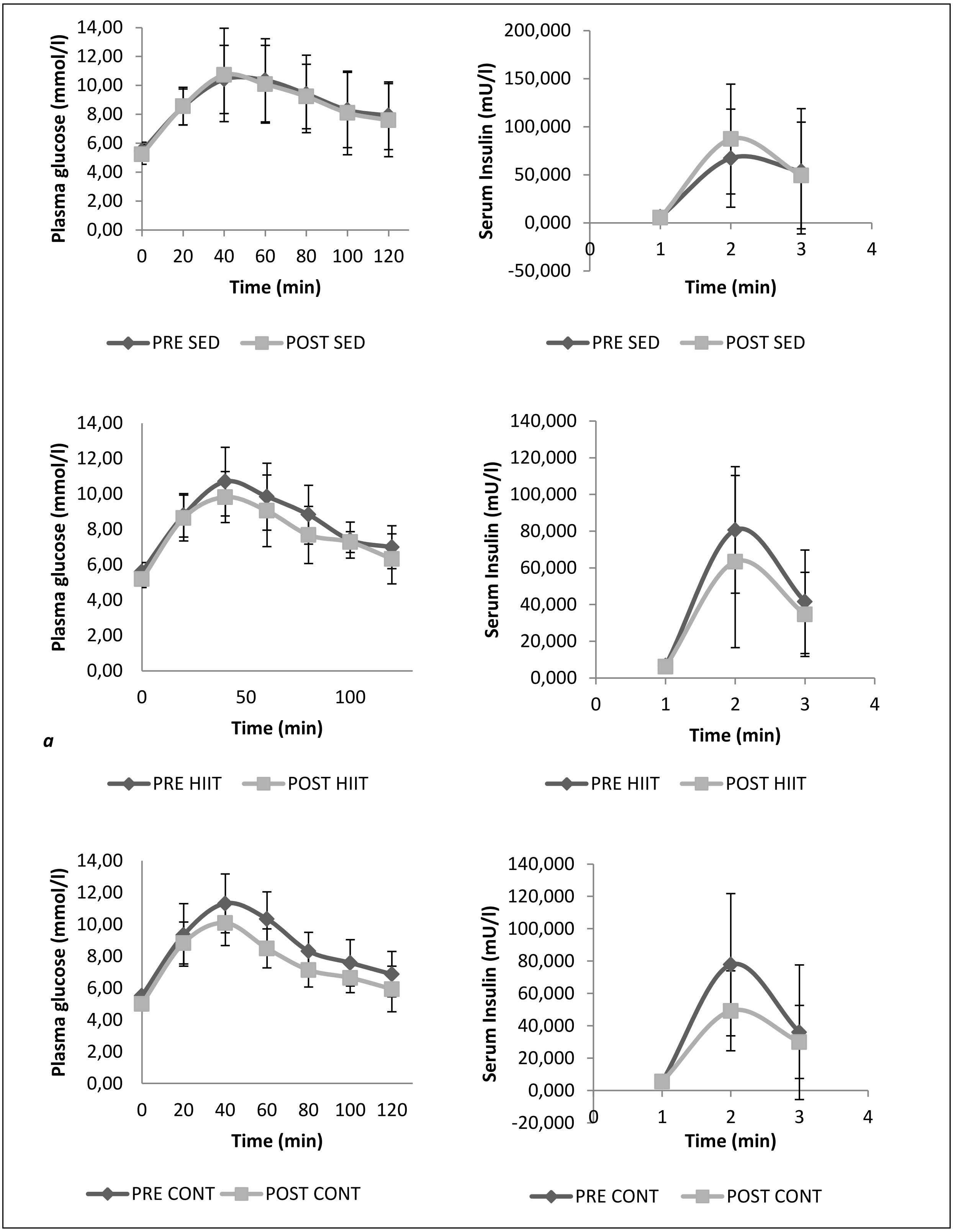

Fig 3. Plasma glucose (a) and serum insulin (b) concentration pre- and post profiles responses to an OGTT in SED, HIIT and CONT (± SD).

GLUT 4

At baseline, no differences existed between groups. There were no significant changes observed in GLUT4 concentrations between groups after 12 weeks of training. Muscle GLUT4 content was significantly increased within HIIT compared with Pre ($p<0.05$) Furthermore, protein concentrations increased within CONT and decreased within SED, however, values did not differ significantly from Pre (fig4).

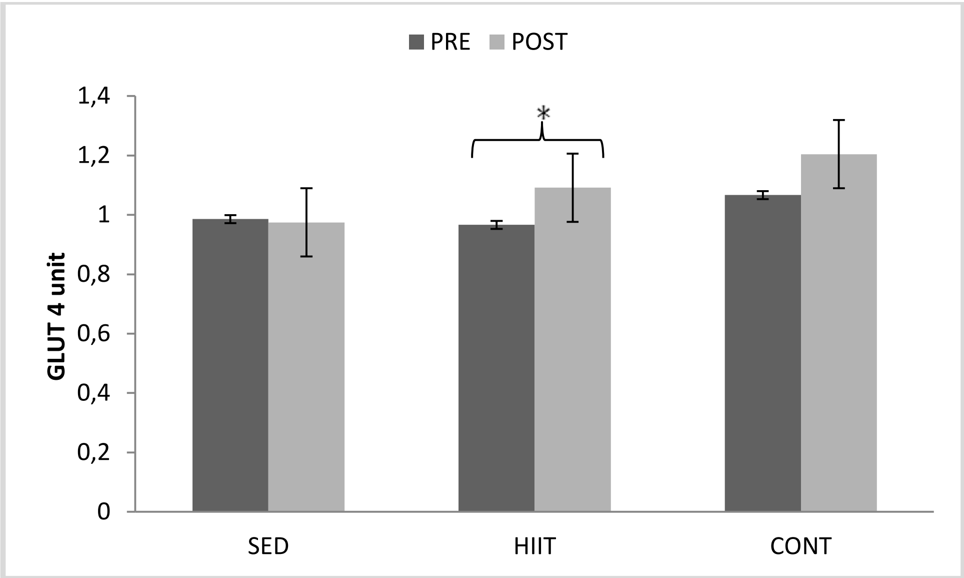

Fig 4. GLUT-4 unit before and after 12 wk . Data are given as mean ± SD. Significantly different from Pre, *$p<0.05$.

Secondary outcomes

Body composition

The DEXA scans revealed no significant differences at baseline. There were no significant changes in total body mass, fat-, lean-, total abdominal mass or percentage abdominal fat in any group after 12 weeks (Table 2).

Physical activity

Self- reported physical activity was similar at baseline. After 12 weeks of training, a near- significant trend ($p=0.067$) was observed between groups. Subjects in HIIT demonstrated higher activity levels than SED. In comparison with Pre, physical activity increased significantly within HIIT ($p<0.01$) and CONT ($p<0.01$), while no significant difference was seen within SED. (Table 2).

Aerobic performance

VO2max

At baseline, no significant differences were seen between groups. After 12 weeks of training, VO2max values approached statistical significance between groups ($p=0.051$), indicating a larger VO2max increase in HIIT compared with SED. In comparison with Pre, VO2max increased within HIIT and

CONT but only HIIT showed a significant result (p=0.05). Conversely, a decrease in VO2max was seen within SED, but observations were not significant compared with Pre (table 2).

HR

No significant difference existed between groups at baseline and post-intervention.

Compared with Pre, HR increased in all groups, however only significantly within HIIT ($p<0.05$) and SED ($p<0.05$) (table 2.)

Table 2. DEXA measurements (trunk fat mass, lean+ BMC, total mass and fat%) and graded exercise test measurements (VO2max/HRmax) expressed in progress % and physical activity measurements (MET) after 12 wk ± SD. Significantly different from Pre *(p<0.05), ** (p<0.01)

Characteristic Variable	Result variable	SED	HIIT	CONT
Trunk fat mass (g)	Progression (%)	-1.67±11.80	-3.29 ±14.45	-2.95±6.98
Trunk Lean + BMC (g)	Progression (%)	0.43±3.33	0.28±2.5	0.12±3.96
Trunk total Mass (g)	Progression (%)	-0.21±4.42	-0.94±4.15	-1.05±4.09
Trunk fat (%)	Progression (%)	-1.64±8.54	-2.69±10.8	-1.84±4.92
VO2max (ml/O2/min)	Progression (%)	0.084±15.31	18.39±15.324 *	7.39±19.85
HRmax (Beats/min)	Progression (%)	6.54±8.44 *	6.18±7.75	3.72±5.09
METs	Pre	13.96±8,78	25.86±22,97	14,74±8,89
	Post	15.99±13,5	37,96±24,98**	23,86±14,73**

Muscle strength

Isometric strength

There were no differences between groups at baseline. For both legs, a significant increase in peak torque isometric knee flexion and –extension at 45° and 90° was observed between HIIT and SED ($p<0.05$).

Compared with Pre, knee flexor strength at 45° significantly increased within HIIT ($p<0.05$) and tended towards significance at 90° of knee flexion (p=0.08). Peak torque extension of the knee did not reach significant results within HIIT. Increases of isometric hamstrings strength were also seen within CONT but only 45° flexion of the right leg showed a statistical significant change. ($p<0.05$) An overall decrease in peak torque isometric strength was observed within SED ($p<0.05$) (Fig. 6).

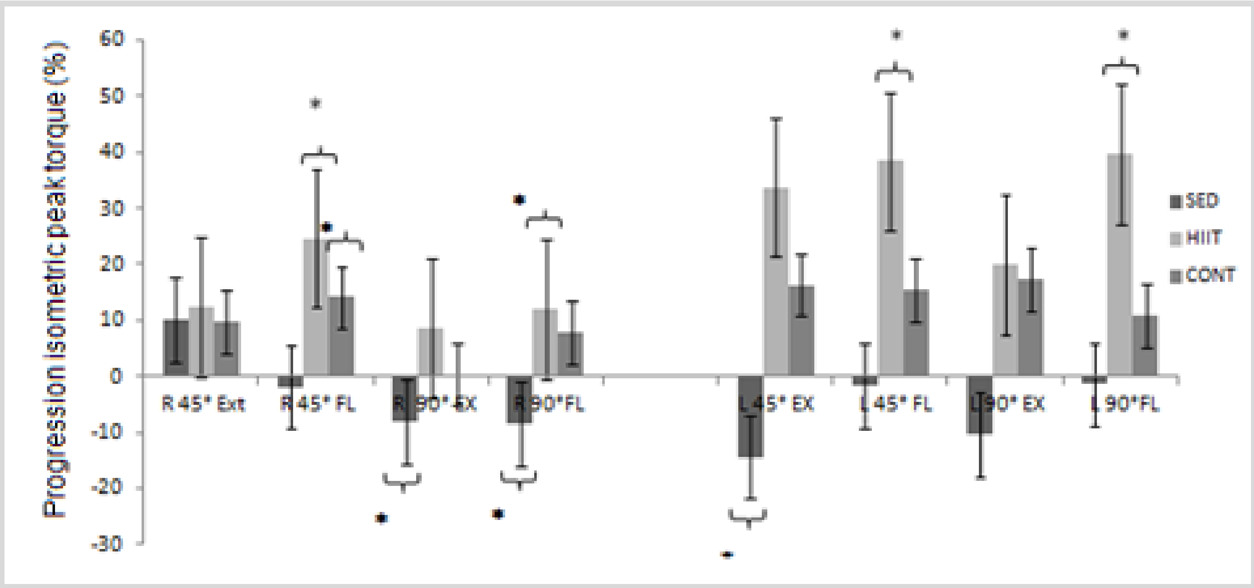

Fig 5. Isometric peak torque flexion and extension progression in % after 12 wk at an angle of 45° and 90° ± SD. Significantly different from Pre, * p<0.05, Flexion (FL) / Extension (EX)/ Left (L)/ Right (R).

Isokinetic strength

No significant differences were observed at baseline. A significant increase in isokinetic peak torque knee flexion and –extension was found in HIIT compared with SED for both legs after 12 weeks ($p<0.05$). Isokinetic work fatigue was not significantly different between groups. Compared with Pre, increases in peak torque flexion and extension for both legs were seen within HIIT and CONT, but only knee flexion showed significant results within both groups. ($p<0.05$) Contrarily, isokinetic peak torque decreased within SED. All over, work fatigue did not decrease significantly within any group.

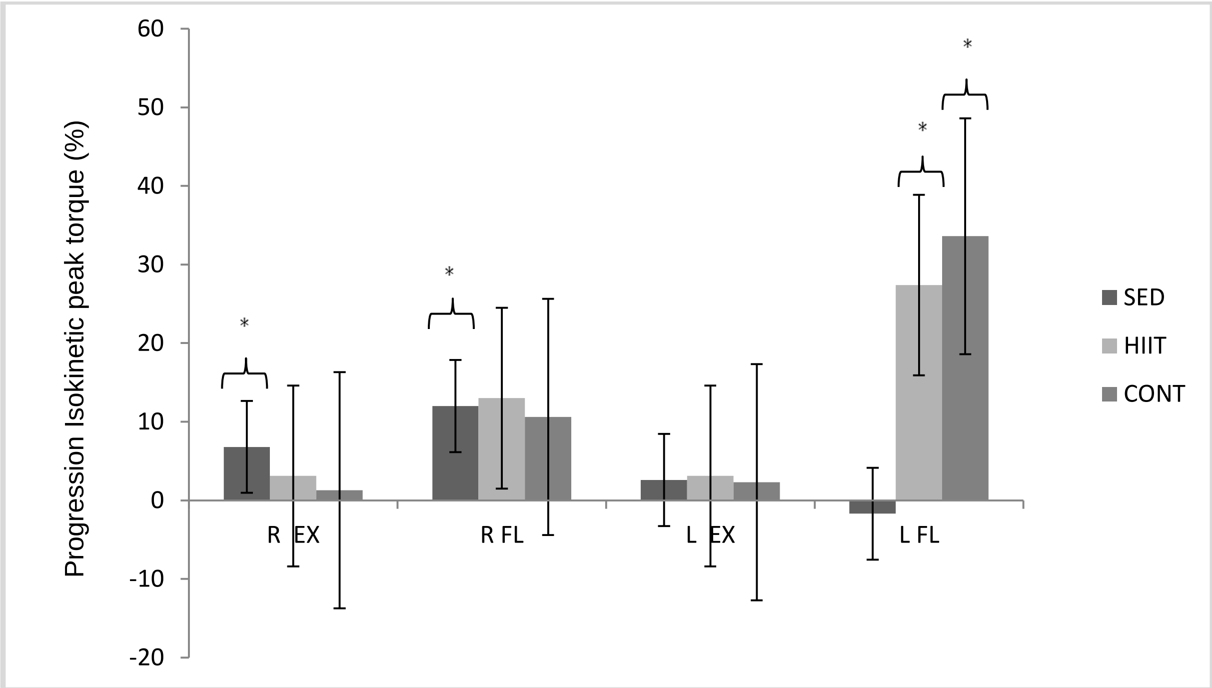

Fig 6. Isokinetic peak torque (FL and EX) mean progression in % after 12 wk at velocity of 60°/sec. ± SD. Significantly different from Pre, *p<0.05.

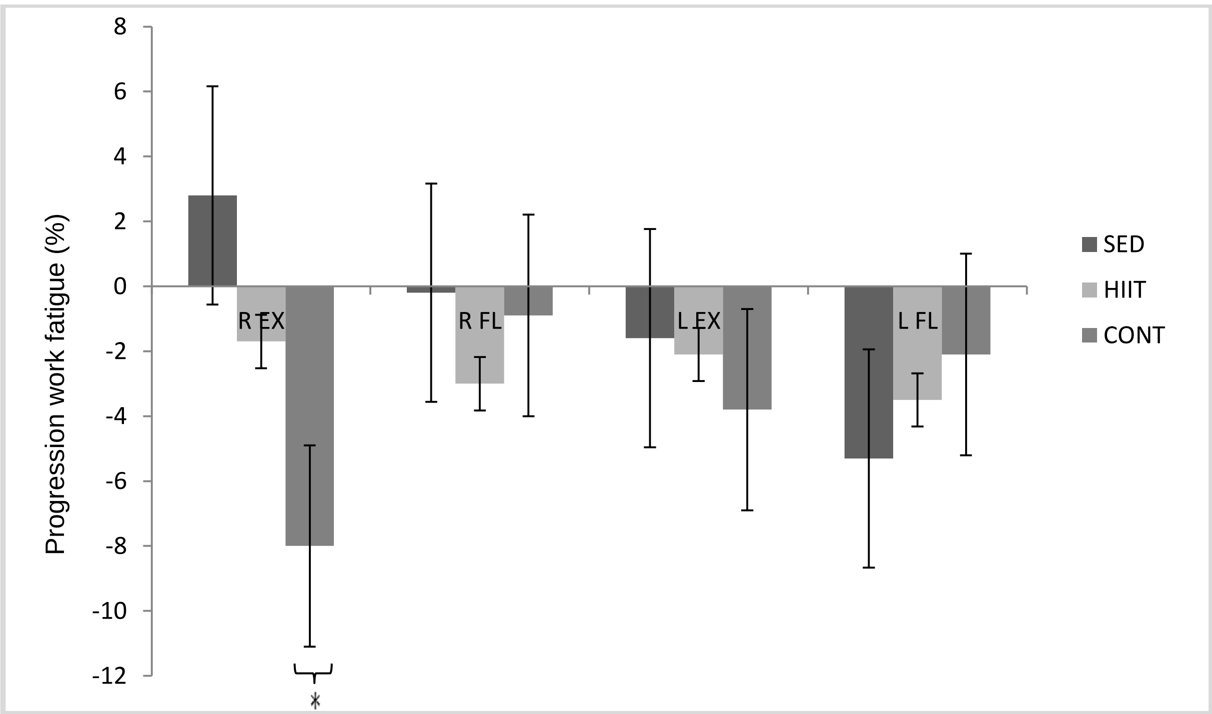

Fig 7. Work fatigue progression mean in % after 12 wk after isokinetic test. ± SD. Significantly different from Pre, *p<0.05.

5. Discussion

The present study investigated the effects of a 12 week combined HIIT and combined CONT program on glucose, insulin and GLUT4 concentrations. Body composition and physical activity were reported as secondary outcome measures. To validate the effect of 12 weeks combined HIIT or CONT, muscle strength and aerobic performance were assessed. The present study demonstrates that combined HIIT and CONT significantly reduce glucose tAUC. Moreover, only CONT seems to reduce insulin tAUC significantly in persons with MS as compared with baseline. GLUT 4 concentrations reduced in both intervention groups but only significantly in HIIT. Furthermore, muscle strength and aerobic performance improved substantially in HIIT and CONT, whereas it tended to deteriorate in SED.

To our knowledge, this is the first study investigating the effects of combined HIIT and CONT on glucose metabolism in persons with MS. Based on recent literature, we hypothesized that both combined HIIT and CONT lead to greater improvements in glucose and insulin levels compared with SED [16, 17, 18, 24, 25]. Interestingly, our findings suggest that only CONT has improved effects on insulin tAUC. However, several studies demonstrate a reduction of insulin levels after HIIT in sedentary and T2D subjects. [25-27] Discrepancies in results of our investigation and recent literature is possibly due to a difference in population sampling and different study interventions.

The mechanisms mediating the improvement in glycemic control following HIIT remain to be determined since serum insulin concentrations remained stable. Exercise had no effect on body composition, therefore, it is tempting to speculate that adaptations in skeletal muscle were involved. Previous studies observing the effects of HIIT in healthy and T2D subjects have shown beneficial effects on GLUT4 concentrations, indicating that a larger GLUT4 protein content could facilitate higher glucose uptake. [28-30]. Furthermore, Studies in rodents demonstrate that the exercise-induced increase in GLUT4 protein is directly related to an increase in muscle glucose uptake at any given insulin concentration [31]. Thus, even in the face of insulin resistance, the increased GLUT4 content might promote greater muscle glucose uptake and contribute to the improved glycemic regulation in HIIT.

Since only CONT improved serum insulin levels, duration is an important aspect in the design of an exercise program with the aim to improve serum insulin levels. This is in agreement with Houmard et al. [32], who reported improved IS with longer exercise durations in overweight and obese subjects, regardless of exercise intensity and volume. In contrast, Segerström noted an increase in IS, related to exercise intensity and not duration in persons with T2D [33] . This finding however, was not support by our HIIT group.

Several studies have demonstrated the benefits of HIT on abdominal fat loss in overweight and T2D subjects [34, 35]. In addition, it has been noted that reductions in abdominal fat correlate with improved glucose metabolism [36, 37]. Here, improvements in abdominal fat mass were not significant in HIIT or CONT. As subjects in our study possessed low to moderate levels of abdominal fat it is feasible that greater abdominal fat mass may show greater reductions after exposure to HIT.

Aerobic performance and muscle strength improved in HIIT and CONT emphasizing the validity of this trial. This is in agreement with previous studies demonstrating the beneficial effects of exercise on strength and aerobic performance in persons with MS. Overall, it is concluded that the applied HIIT and CONT was safe and well tolerated in MS [14, 38-40].

Limitations

This study had some limitations, resulting in recommendations for future research. Both normal and IGT persons with MS were included. This might explain the absence of some of the expected results on the insulin profile after 12 weeks of exercise. For future research, It would be interesting to have more than three measurements of serum insulin to obtain a more accurate insulin tAUC. Furthermore, due to the design of the study, subjects trained in group which could influence intervention outcomes as a result of social interaction. Finally, calorie intake was not taken into account, possibly explaining the absence of changes in body composition. Although subjects were asked not to change their eating habits, it would be convenient to use a food diary to acquire better control.

Conclusion

In conclusion, CONT improved glucose and insulin concentrations in this randomized controlled trial, whereas combined HIIT improved glucose and GLUT4 concentrations. Both types of training were not able to affect body composition in persons with MS. Self- reported physical activity increased in CONT and HIIT indicating a more active lifestyle.

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