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

Masterproef

Impact of a high intensity training program on glucose tolerance in people with multiple sclerosis

Promotor :
Prof. dr. Bert OP 'T EIJNDE

Copromotor :
Mevrouw Inez WENS

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

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WOORD VOORAF

Allereerst zou ik graag mijn oprechte dank willen betuigen aan mijn promotor, Prof. Dr. Bert Op ‘t Eijnde, en co-promotor Dra. Inez Wens. Zij hebben mij gedurende dit tweejarig proces uitstekend begeleid met het schrijven van mijn masterthesis. Zonder hun ervaring en kennis had ik dit eindresultaat nooit kunnen bekomen.

Bovendien wil ik alle deelnemers van de studie oprecht bedanken. Zonder hun gedrevenheid en volharding had deze studie nooit kunnen plaatsvinden. Eveneens wil ik mijn collega studenten bedanken voor de hulp die ze geboden hebben.

Tenslotte wil ik mijn familie en vrienden bedanken voor de steun en toeverlaat die ze tijdens deze periode voor mij waren.

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SITUERING

Multiple sclerosis (MS) is een degeneratieve aandoening van het centraal zenuwstelsel (CZS) die gekenmerkt wordt door een afbraak van de myelinescheden en de axonen. Dit leidt tot een vertraagde zenuwgeleiding met een variëteit van symptomen als gevolg[1].

De meest voorkomende kenmerken in MS zijn krachtsverlies, vermoeidheid en een verminderd sensorisch gevoel[2]. Al deze symptomen kunnen leiden tot fysieke inactiviteit en deconditionering[3, 4]. Dit gaat gepaard met een verhoogd risico op secundaire aandoeningen zoals diabetes mellitus, hartproblemen en obesitas[1].

Deze masterproef was een onderdeel van de reeds lopende doctoraatsstudie van Dra. Inez Wens, getiteld 'Exercise therapy in multiple sclerosis: the impact of exercise intensity on glucose disposal and muscle contractile properties', met als promotor Prof. Dr. Bert Op't Eijnde. De studie vond plaats op REVAL, de revalidatie onderzoeksgroep van de Universiteit Hasselt, waar het nodige materiaal en infrastructuur beschikbaar was. Omwille van de bovengenoemde kenmerken en gevolgen van de ziekte is het belangrijk om een trainingsmodaliteit te vinden die een positief effect heeft op deze parameters, met het oog op de verbetering van de kwaliteit van leven, de functionele capaciteit en het reduceren van secundaire gezondheidsproblemen.

Deel één van deze masterproef bestond uit een literatuurstudie omtrent de wetenschappelijke evidentie rond de effecten van een gecombineerd oefenprogramma op glucose intolerantie en de klinische parameters bij MS patiënten zoals kracht, inspanningscapaciteit en lichaamssamenstelling. Op basis van de literatuuranalyse kon worden geconcludeerd dat het effect van gecombineerde training op klinische parameters beperkt werd onderzocht, terwijl onderzoek naar glucose intolerantie in MS nooit eerder werd uitgevoerd. Recent onderzoek rapporteerde een verhoogde prevalentie van glucose intolerantie in MS[5]. Ongepubliceerd werk (Wens I, persoonlijke communicatie) toonde aan dat een gecombineerd oefenprogramma van matige intensiteit een positief effect heeft op spierkracht, uithoudingscapaciteit en lichaamssamenstelling maar geen invloed heeft op glucose intolerantie. Aangezien hoge intensiteitstraining vaak als primaire behandelingsmethode wordt gebruikt bij andere populaties met glucose intolerantie, werd in het tweede deel van deze masterproef onderzocht of zowel Hoog Intensieve Intervaltraining (HIIT) als een hoog intens continue oefenprogramma, beide gecombineerd met krachttraining, een effect hebben op glucose tolerantie, spierkracht, lichaamssamenstelling, inspanningscapaciteit en spiervezels. Enkel de eerste 3 parameters worden besproken in deze masterproef. Er werd gekozen voor twee trainingsmodaliteiten om te kijken welke modaliteit het beste resultaat geeft om op die manier in de praktijk de meest optimale behandeling te kunnen bieden aan MS patiënten.

De afgelopen twee jaar bestond mijn taak hoofdzakelijk uit het rekruteren van proefpersonen, het uitvoeren van de metingen en het begeleiden van de patiënten tijdens de trainingen. Tijdens de zomervakantie volgde ik in het Universitair Ziekenhuis van Antwerpen de insulinemetingen, aan de hand van ELISA protocollen. Ondanks dat de methode van het onderzoek reeds grotendeels bepaald werd voor aanvang van mijn masterproef, werd mij gevraagd de wetenschappelijke evidentie hieromtrent op te zoeken en hierover kritisch na te denken. Na het verwerven van alle data werd de dataverwerking geheel zelfstandig uitgevoerd en werden de resultaten, evenals de andere onderdelen van deze masterproef autonoom beschreven.

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Impact of a high intensity training program on glucose tolerance in people with multiple sclerosis

Drawn up according to the guidelines of the Multiple Sclerosis Journal

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Abstract

Background: Recent research reported a higher prevalence of impaired glucose tolerance (IGT) in MS patients than in healthy people. The influence of high intensity exercise on IGT in MS was never investigated before.

Objective: To investigate the effect of high intensity aerobic interval (HIIT) or continuous endurance (CT) training, both in combination with resistance training, on glucose tolerance muscle strength and body composition.

Methods: 34 subjects were randomly assigned to a control group (n=11), to a group who received a combined cardiovascular and resistance training program (n=11) or to a group who received a combined high-intensity interval training (HIIT) and resistance training program (n=12). At baseline and after 12 weeks, glucose tolerance was measured using an Oral Glucose Tolerance Test, muscle strength was measured using an isokinetic dynamometer and the DEXA was used to measure body composition.

Results: A significant decrease of glucose concentration was seen in both groups. Furthermore, muscle strength and body composition improved in both exercise groups, whereas all outcome measures remained stable in the sedentary control group.

Conclusion: Twelve weeks of high intensity aerobic exercise in combination with resistance training was safe and well tolerated and induced changes in glucose tolerance in MS patients.

Introduction

Multiple sclerosis (MS) is a chronic degenerative disease that effects the central nervous system (CNS), leading to destruction of myelin, oligodendrocytes and axons as a result of the fact that T-cells cross the blood-brain barrier into the CNS[1].

With a prevalence of 1 per 1000 adults in the USA[6] and a total prevalence rate of 83 per 100 000 for the past three decades[7], it is demonstrated that MS is a common disease mostly seen in young and middle-aged women of European origin[6]. Sufficient knowledge about the symptoms and possible treatments of these are essential to positively affect the functioning of daily living of patients with MS. But till today, there is no exact etiology known[8].

MS is a complex disease with an unpredictable course. Several patterns of progressions, or subtypes, have been established. Most of the MS patients, approximately 85%, are diagnosed with relapsing-remitting MS (RRMS). These patients gave attacks or relapses followed by subsequent improvement. A second subtype is the secondary progressive MS (SPMS). In this case, the patient develops a progressive deterioration after many years. There are no attacks or relapses. The difference with primary progressive MS (PPMS) is that this subtype has a progressive course from the beginning, also without any attacks or relapses. At last, there is progressive relapsing MS, a subtype characterized by a steady decline over time, with relapses later in de disease[2, 9].

The physiological process mentioned earlier will lead to a wide range of symptoms such as ataxia, spasticity, sensory disturbance and loss of strength[10], especially in the lower limbs[11]. There are also less notable symptoms like fatigue, bladder dysfunction, depression and cognitive impairment[11]. Owing to these symptoms, MS patients often get a sedentary lifestyle with the subsequent deficits like disuse atrophy[3] and a reduced physical activity level [4] with de-conditioning as a result[10]. This inactivity is a risk factor for developing impaired glucose tolerance since movement is an important factor to transport glucose into a muscle cell[12]. Wens et al. reported that there is a higher prevalence of impaired glucose tolerance in MS patients than in healthy people[5].

Today, there is a general agreement that physical exercise has a positive effect on clinical parameters in MS. Unlike before when researchers thought that exercise could worsen the symptoms or could lead to fatigue[13].

Several studies demonstrated the effect of strength and endurance training on muscle strength[14-19] and physical endurance[20-22], which will secondarily lead to improved walking capacity, better balance and reduced fatigue[1, 23].

Regarding the effect of combined therapy, there are two studies that investigated this kind of exercise program in MS patients. Surakka et al. concluded none or only a small improvement in knee flexion strength or knee extension strength and a decrease in motor fatigue[24] whereas Wens et al. defined a significant increase of maximal isometric muscle strength for both knee flexion and extension (Inez Wens personal communicated unpublished data).

Regarding a possible effect of physical exercise on insulin resistance, there are several studies that demonstrate a positive effect in people with impaired fasting glucose and overweight individuals[25, 26]. However, this effect is not yet thoroughly researched in people with MS. Only one study concluded that physical training at moderate intensity does not affect the altered glucose tolerance seen in MS patients (Inez Wens personal communicated unpublished data).

The positive effects of HIIT on VO2, muscle strength, insulin resistance and bodyweight are already demonstrated in various populations, like healthy persons, obese people and patients with cardiovascular or respiratory problems[27, 28]. Yet, evidence for HIIT in MS patients remains un-existed.

In accordance with the above line of reasoning, the current study aims to investigate the effect of combined movement therapy on impaired glucose tolerance and clinical parameters in MS.

Material and methods

Study design

A randomized controlled trial was used to investigate the effect of physical exercise on glucose tolerance, muscle strength, physical endurance and body composition. The study started with a baseline measurement (M1) of these four parameters and a muscle biopsy of the vastus mediales muscle, followed by a 12-week training program of resistance training (RT) combined with continuous endurance training (CT) or high-intensity interval training (HIIT). There were measurements again after 12 weeks to determine possible evolutions.

Subjects

The study recruited a total of 34 patients. Patients met the following inclusion criteria: male or female; older than 18 years; physician-diagnosed MS with an EDSS score between 0.5-6, and they had to be available and prepared to participate for 12 weeks.
Patients were excluded if they had physician-diagnosed diabetes mellitus, had other serious disorders (like cancer), were pregnant, participated in another study, had contra-indications to do physical exercise or if they had an acute exacerbation of their MS symptoms within the last month.

Before the study, participants were extensively informed about the course of the study and possible risks and they all had to sign an informed consent.
The study was approved by the ethical committee of Hasselt University and Jessa Hospital and it was registered as protocol number 13.20/reva13.02. The study was conducted in accordance with the Declaration of Helsinki of 1964.

Oral Glucose Tolerance Test

The Oral Glucose Tolerance Test (OGTT) was used to evaluate the whole body glucose tolerance.
The test was administered at 8 o'clock in the morning when the subjects received one gram of glucose per kilo body weight. Every 20 minutes, a capillary blood sample was taken from the ear to immediately measure the blood glucose concentration (Analox-GM7 Micro-stat). According to the World Health Organization, impaired glucose tolerance corresponds with a fasting plasma glucose concentration of 6.1-6.9 mmol/l and a two-hour post-load plasma glucose of 7.8-11.1 mmol/l[5].

A venous blood sample was collected every hour (0h-1h-2h), processed and stored at -80°C, to determine serum insulin levels. The method used was ELISA (Mercodia Insulin enzyme-linked immunosorbent assay) and was administered in the University Hospital in Antwerp. The normal amount of insulin in venous blood is 110 mmol/l or lower.

According to the trapezoidal rule, the total area under the curve (tAUC) was measured to express glucose and insulin responses. A higher tAUC value means that there is a higher glucose/insulin value in serum[5].

Muscle strength

Using an isokinetic dynamometer (System 3; Biodex Medical Systems, New York, USA), the maximal voluntary unilateral strength of both legs was measured. Research has shown that this method is safe and reliable to determine torque, work and power in ambulatory patients with MS[29, 30]. The following protocol is based on the used protocol of Broekmans et al.[31]. The subjects first performed a four-minute warm-up on a leg cycling ergometer after which they took place in the Biodex. The test was performed on a backward inclined (5°) chair in seated position.
The dynamometer rotational axis was aligned with the transverse knee-joint axis and it was connected to the distal end of the tibia through a length-adjustable lever arm. Safety belts were used to stabilize the upper leg, hips and shoulders[31].

Maximal isometric torque was measured by one submaximal trial contraction followed by two maximal isometric contractions by knee extensors and flexors at knee angles of 45° and 90°. The 4-second contractions were paused by 30-second rest intervals[31].

A second measurement was the maximal isokinetic torque. After three sub-maximal trial contractions, the subject had to perform 30 maximal serial isokinetic knee extensions. The used velocity was 60°/sec. The knee extension started at a joint angle of 90° going to an angle of 160°. The leg was returned passively to the starting position after every extension, from which the next contraction was immediately initiated. The highest of 30 isokinetic extension torques (Nm) determined the maximal dynamic torque[31]. The supervisor provided verbal encouragement during the entire test.

When al the measurements were done, a distinction was made between a strong and a weak leg by determining a cut-off score. If the strength rate was higher than the cut-off score, it was classified as a strong leg. If the strength rate was lower than the cut-off score, it was classified as a weak leg. Following this reasoning, it was possible that a subject had two weak legs, or two strong legs.

Body composition

The participants were scanned with a whole body dual energy x-ray absorptiometry (DEXA) system (Hologic Series Delphi-A Fan Beam X-ray Bone Densitometer, Vilvoorde, Belgium). The outcomes of interest were the amount of fat and the amount of muscle in the body. The subjects had to lie supine with the arms along the body and were instructed to lie still throughout the entire procedure.

Training

The intervention consisted of two types of training: Endurance training followed by resistance training or high-intensity interval training (HIIT) followed by resistance training. Two types of training were chosen to see which protocol had the most beneficial effects on impaired glucose tolerance. In both interventions, the subjects had to train three times a week, for 12 weeks.

The combined training was based on the recommendations for the application of resistance-, endurance- and combined training of Dalgas et al.[23]. The training included two parts: an aerobic training (running and cycling) followed by resistance training. The participants did a five-minute warm-up at 50% of VO2max on a leg cycling ergometer or a treadmill. Afterwards, they had to perform two cycles of five minutes, with one minute of rest in between, on both the cycling ergometer and the treadmill. This was at an intensity of 80% of the wattage that corresponds to 100% of the VO2max. This was gradually increased up to two cycles of 10 minutes with one minute of rest in between.

For the resistance training, the subjects did one set of 15 repetitions at an intensity of 15 RM. Through the training program, this was progressively increased to two sets of 20 repetitions at an intensity of 20 RM. Exercises for the lower body were always executed alternately left and right to avoid compensation of the preferred leg. The patients were communicated that the eccentric phase should last about twice the time of the concentric phase. There was always a physical trainer to supervise the sessions and to encourage the patients to fully perform their sets.

The whole resistance program contained six exercises using the following machines: Leg curl, leg extension, leg press, chest press, arm curl and vertical traction. Hereby, the following muscles were trained: m. biceps femoris, m. rectus femoris, m. vastus lateralis, m. vastus medialis, m. gluteus maximus, m. pectoralis major, m. biceps brachii and m. trapezius pars transversus.

Each session was completed with a five-minute cool down.

The HIIT protocol started with a five-minute warm-up on a leg cycling ergometer at 50% of the VO2max. The first 2 weeks, the participants had to cycle five bouts of one minute, separated by one minute of rest. This was at an intensity of 100% of VO2max. The duration of the cycling periods was slowly increased with 10 seconds every week up to two minutes. Afterwards, the wattage was increased every two weeks. After a five-minute cool down at 50% of the VO2max, they had to do the same resistance training as the other intervention group.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) was used for statistical analyses. Shapiro-Wilk test was used to check normality. For comparison of data between two groups, an unpaired t-test was performed. A paired t-test was used to compare data within a group. A mixed-model repeated-measures analysis of variance (ANOVA) was used to compare data between multiple groups, three groups in this case.

Results

Participants

The characteristics of the subjects who completed the study are shown in table 1. No differences were observed between the control group and the exercise groups at baseline.

There was no dropout during the study. All patients completed the training programme with full adherence. They attended for 83% of the training sessions. There were no side effects reported by any of the participants during the twelve-week training program.

	Control	CT	HIIT	p Value
Number (M/F)	11(2/9)	11(5/6)	12(5/7)	
Age (y)	47,9(41,2-54,6)	46,5(39,9-53,1)	43,0(36,8-49,3)	NS
Height (cm)	167,7(162,4-173,0)	169,5(164,1-175,0)	171,2(166,0-176,5)	NS
Weight (kg)	75,8(67,7-83,9)	70,2(61,9-78;5)	76,9(67,7-86,1)	NS
BMI (m/kg2)	27,0(23,9-30,1)	24,4(21,7-27,1)	26,1(23,5-28,6)	NS
EDSS	2,5(1,7-3,3)	2,7(2-3,5)	2,3(1,6-3,1)	NS

Table 1. Demografic data at baseline. Values are means and confidence interval

BMI = Body Mass Index; EDSS = Expanded Disability Status Scale; NS = not significant

Glucose concentration

There were no differences between the areas under the curve (AUC) for glucose comparing the groups at baseline. After 12 weeks of training, the AUC of both the HIIT group and the CT group decreased significantly ($p<0,05$) (see figure 1). A little increase of the AUC was noticed in the control group but this was not significant ($p<0,05$).

Insulin concentration

At baseline, the area under the curve (AUC) for insulin did not differ between groups. There is a significant decrease of the AUC in the CT group ($p< 0,05$) after 12 weeks of training (see figure 2). The same decrease was seen in the HIIT group but wasn't significant ($p>0,05$). The opposite happened in the control group where the AUC increased after 12 weeks.

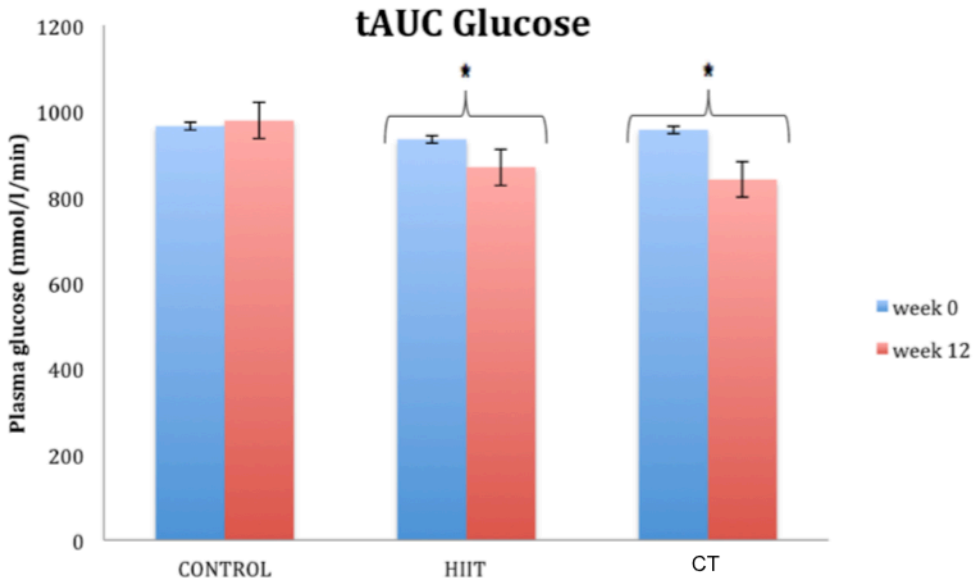

Fig 1. Total area under the curve (tAUC) for glucose expressed in mean ±SEM at baseline and 12 weeks. Significant ($p<0,05$) difference compared to baseline

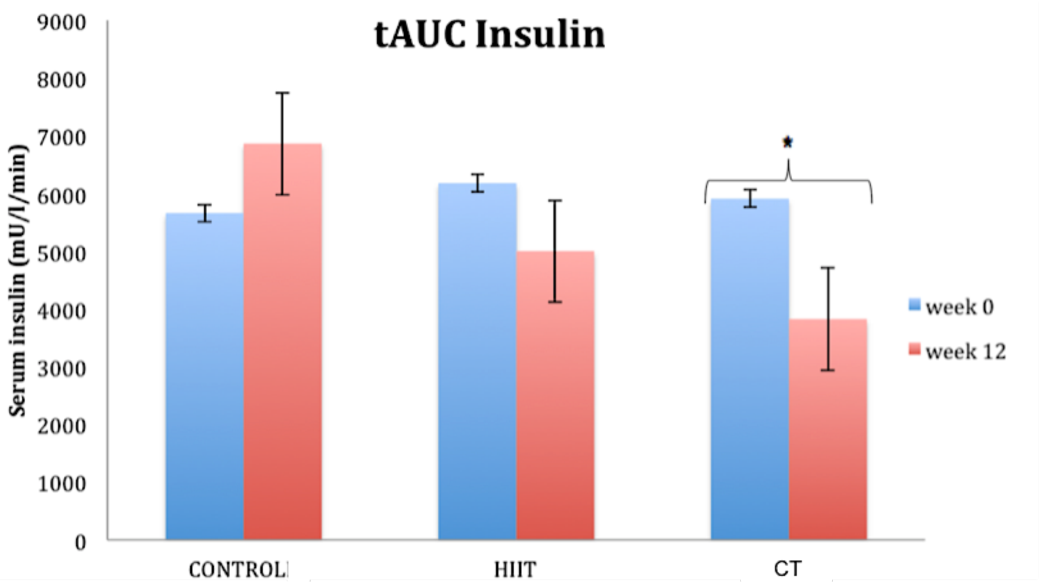

Fig 2. Total area under the curve (tAUC) for insulin expressed in mean ±SEM at baseline and 12 weeks.
* Significant ($p<0,05$) difference compared to baseline

Muscle strength

<u>Maximal isometric muscle strength</u>

No differences of isometric peak torque could be demonstrated between groups at baseline. After 12 weeks of training, all data of the control group were significantly different from those of the HIIT group ($p<0,05$), except for the extension of the left leg at 90°.

Within the CT group, a significant increase of the isometric peak torque was seen for flexion and extension of the right leg at an angle of 45° (p<0,05) (see figure 3). This increase was also noticed in the HIIT group for flexion of the right and left leg at an angle of 45° and flexion of the left leg at an angle of 90° (p<0,05).

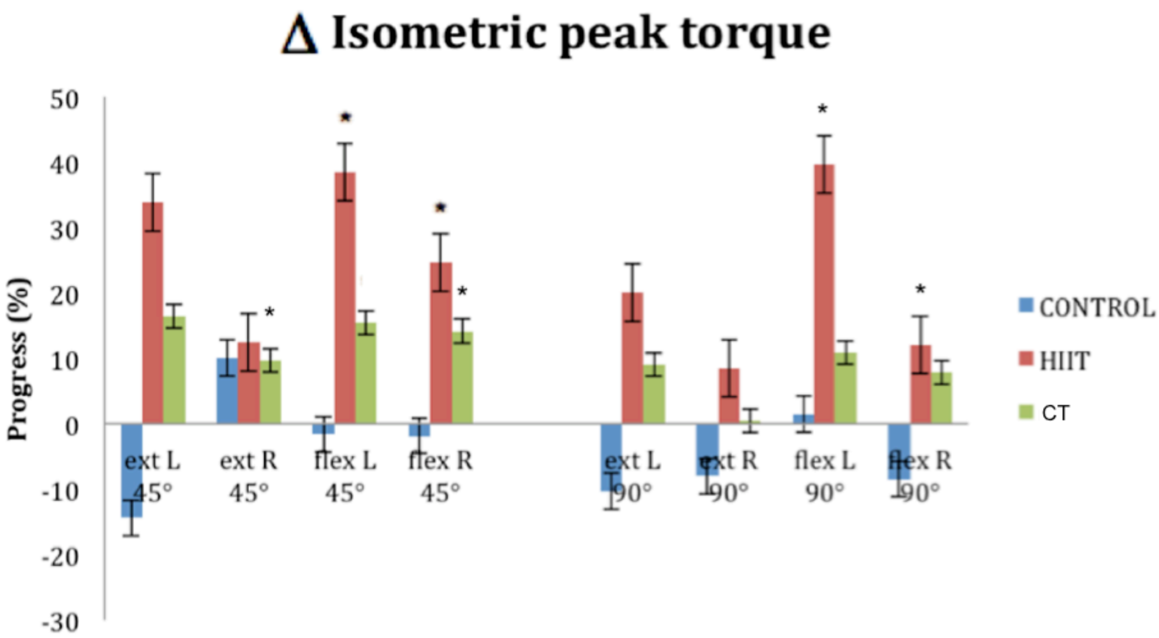

Fig 3. Delta isometric peak torque at a an angle of 45° and 90° expressed in mean ±SEM
ext = extension; flex = flexion; L = left; R = right
* Significant (p<0,05) difference compared to baseline

<u>Isokinetic strength</u>

There were no significant differences at baseline between groups, except for the average power extension of the right leg. This measurement was significantly different between the control group and the HIIT group (p<0,05). The extension in both the left and right leg was significantly different between the control group and the HIIT group when it came to the peak torque, total work and the average power (p<0,05). On top of that, a significant difference was seen between the control group and the HIIT group for the peak torque of the left leg in flexion (p<0,05). No significant difference between groups was seen for work fatigue.

After 12 weeks of training, a significant increase was seen in the CT group for flexion peak torque of the left leg (see figure 4) and extension work fatigue of both legs (p<0,05). Within the HIIT group, a significant increase was seen for the flexion peak torque of the left leg (see figure 4) (p<0,05).

A positive evolution, seen for both isometric and isokinetic strength, was that in all cases a greater mean increase of muscle strength in the weak leg of the patients was observed.

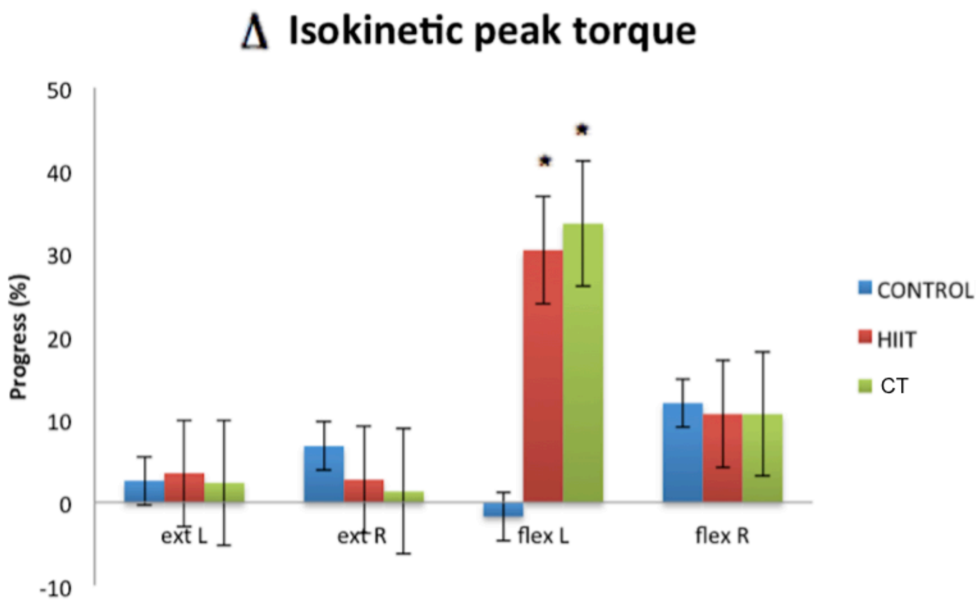

Fig 4. Delta isokinetic peak torque expressed in mean ±SEM

ext = extension; flex = flexion; L = left; R = right

* Significant ($p<0,05$) difference compared to baseline

DEXA

There were no significant differences between groups, neither at baseline nor after 12 weeks of training. The only result seen was a significant increase of the lean body mass in the HIIT group ($p<0,05$) (see figure 5).

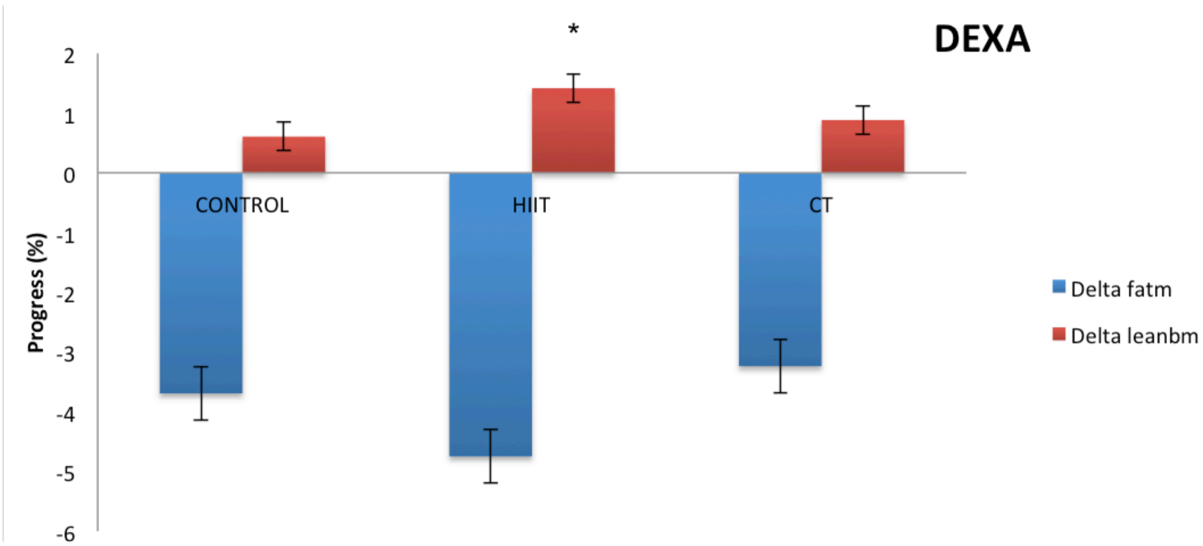

Fig 5. DEXA measurements (delta fat mass and delta lean body mass) expressed in mean ±SEM

DEXA = dual energy x-ray absorptiometry; fatm = fat mass; leanbm = lean body mass

* Significant ($p<0,05$) difference compared to baseline

Discussion

Loss of muscle strength[10, 11] and physical endurance[3] are two important symptoms in MS. They can lead to a reduced physical activity[4], which in turn is a risk factor for developing impaired glucose tolerance[12]. Unpublished data of Wens et al. reported no change in glucose and insulin concentrations after 24 weeks of mild-to-moderate intensity combined training (Inez Wens personal communicated unpublished data). Since Black et al. already reported, in healthy subjects, a dose-response-relationship between intensity and 24-hour post-exercise insulin resistance, concluding that high-intensity training gives better results than moderate-intensity training [25], we hypothesized that glucose intolerance would improve in MS patients after 12 weeks of high intensity combined exercise. Many studies already showed the positive effect of continues training on muscle strength[14-19] and physical endurance[20-22] in MS. However, the influence of high intensity exercise on these parameters was never investigated before. Therefore, we hypothesized that the muscle strength of MS patients would improve after a 12-week high intens combined strength/endurance exercise program. And that these results would even be better after a combined strength/HIIT exercise program.

Both the continuous and the HIIT training significantly decreased the tAUC of glucose. This in combination with only a significant decrease of the tAUC of insulin seen in the CT group requires us to reject our hypothesis that HIIT would be better than normal endurance training. This is not in accordance with the results of other studies. In other populations, several studies showed a significant (or at least a tendency to) decrease of the serum insulin levels[26, 32-34] and the HOMA-IR[26, 33-36] after HIIT. Only one study showed a decrease of the fasting glucose[34] while two studies did not see any difference in fasting glucose after training[32, 33]. The different populations and the differences in intervention can explain these conflicting results.

The results of our recent study suggest that duration of training should be considered when designing a training program for improving serum insulin levels, since only the CT group significantly influenced the insulin concentration. However, research is contradictory. Houmard et al. concluded that duration of training does play a role in insulin resistance in overweigh/obese patients[37], whereas Segerström et al. found the opposite in people with type 2 diabetes. They concluded that intensity of training is related to improvement of insulin resistance, not duration[38], warranting further research in the future.

This study showed a positive effect of physical exercise on glucose intolerance but an underlying cause has not been evaluated. Two possible underlying mechanisms are the translation of GLUT4 to the cell membrane and the decrease of insulin resistance. Assessment of these mechanisms should be taken into account in future studies.

Looking at other studies that investigated the effect of resistance training on muscle strength in MS patients, we see less or similar improvements[18, 19, 39], except for the study of Taylor et al. who concluded an improvement of 32,6% for muscle strength in knee extension after ten weeks of training. It should be mentioned that only the data of seven subjects were analysed[17].

The effect of HIIT training, in combination with resistance training, on muscle strength in MS patients has never been investigated before. In healthy subjects, conflicting results were found after HIIT. A study of Astorino et al. did not find any increase of peak torque after two weeks of HIIT without additional resistance training[40], whereas Wong et al. found a 15% increase of the peak torque after a 8-week HIIT training period with additional resistance training[41]. A difference in HIIT protocol should be mentioned. Nevertheless, both studies achieved a less favourable result than the 22,5% increase of peak torque in knee extension achieved in our present study. Our data also showed that only knee flexion had a significant difference with baseline, which was never the case for knee extension. This can be due to the fact that the hamstring muscle of MS patients was less strong than the quadriceps muscle at baseline, which is also concluded in other studies[42, 43]. This could explain why the relative increase was more pronounced for knee flexion after 12 weeks of training.

This study also had limitations. During the 12 weeks, there has always been trained in group. This could have altered the results because of the social interaction and peer pressure. To identify this social interaction, a questionnaire can be administered in which the subject's social behaviour and activities outside the study are questioned.
Although body composition was not a primary outcome, it should be noted that the study did not take into account the calorie intake. At baseline, the participants were asked not to chance their eating habit during the study. To obtain a better control on this eating habit, the subjects could be requested to fill out a food diary, in which all their meals can be registered.

In conclusion, the present study showed that a high intensity combined training program improved glucose concentrations, insulin concentrations and muscle strength in MS, whereas high intensity intermittent exercise improved glucose concentration and muscle strength. Furthermore, this study shows that high intensity training can be applied by MS patients, since it is found safe and well tolerated.

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