2015•2016
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

Impact of high-intensity interval training on the glucose metabolism in MS

Promotor :
Prof. dr. Bert OP 'T EIJNDE

Copromotor :
dr. Inez WENS

Eline Emmers
Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

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Impact of High-Intensity Interval Training on the Glucose Metabolism in MS

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According to the guidelines of the "Multiple Sclerosis Journal"

https://uk.sagepub.com/en-gb/eur/journal/multiple-sclerosis-journal#submission-guidelines

Acknowledgement

I thank all persons who contributed to this master thesis. First of all my promotor Prof. Dr. Op't Eijnde Bert and co-promotor Dr. Ir. Wens Inez for their guidance to complete this master thesis. Furthermore, my gratitude goes out to all participants for their commitment to the research, and Hasselt University for the opportunity to perform this master thesis.

Finally I would like to thank my family and friends for all the help and support.

Lommel, juni 2016 E.E.

Research context

This study is part of the cardiometabolic and neurological subdomain of the rehabilitation sciences and physiotherapy department of Hasselt University. The purpose of this quasi-experimental study is to investigate the effect of high-intensity interval training (HIIT) on the glucose metabolism of multiple sclerosis patients.

Multiple sclerosis (MS) is a common worldwide neurodegenerative disease with various symptomes. Due the variating character of the disease the patient population is extensive, with multiple grades of disability. This is quantified by the Expanded Disability Status Scale (EDSS) based on a neurological examination, with scores ranging from 0.0 (normal neurological examination) to 10.0 (death due to MS). Although a large amount of research has been done on this disease, to date no cure has been found. Therefore, symptom prevention is often the main goal of the treatment. To help prevent symptoms, a wide array of therapies is available, including physical exercise. The effects of various exercise modalities have been investigated on MS patients, but less is known about the effect of high-intensity interval training. Therefore, in this study, a high-intensity form of physical exercise is used to investigate the effects on the glucose metabolism of MS patients.

This thesis is part of the PhD of Charly Keytsman with the topic "Multiple Sclerosis: associated cardiometabolic risks and impact of exercise therapy" and protocol number 4.84/cardio14.11, which is supervised by Prof. Dr. Bert Op 't Eijnde and Dr. Ir. Inez Wens.

The research topic and protocol were selected by promotor Prof. Dr. Bert Op 't Eijnde and co-promotor Dr. Ir. Inez Wens. Practical research and data-collection were performed by Dr. Ir. Inez Wens, Charly Keytsman and colleagues at REVAL center of Hasselt University Biomedical Research Institute. Master students assisted in the practical execution of the training protocol and in the data-collection in form of pre- and post-intervention tests. Statistical analysis was performed individually by each master student.

1. Abstract

Background: Previous research suggests an increased risk of impaired glucose tolerance (IGT) in Multiple Sclerosis (MS) patients. In healthy persons, physical training is proven to be beneficial to reduce this risk. In MS patients this effect was researched by Wens et al., demonstrating no improvement on the glucose metabolism after 24 weeks of combined resistance and endurance training. Interestingly, other research including high-intensity training demonstrated positive effects on the glucose metabolism.

Objective: The aim of this study was to investigate the effect of high-intensity interval training (HIIT) on the glucose metabolism of MS patients.

Methods: Baseline differences in body composition and glucose metabolism between MS patients (MS) (n=29) and healthy controls (HC) (n=26) were determined by OGTT and DEXA-scan. Subsequently, the MS group was separated into an intervention group (EX) (n=16) which completed a 12 week HIIT protocol, and a sedentary control group (SED) (n=13). Glucose metabolism and body composition were investigated in both groups at baseline and after twelve weeks.

Results: Baseline analysis showed significantly increased fasting serum insulin concentrations (p=0.0109) of the MS group compared to the HC group.

Surprisingly, glucose total area under the curve (tAUC) (p=0.0244) of SED was significantly decreased after twelve weeks. Within-group analysis of the EX group showed a significant decrease in fasting serum insulin (p=0.0495) and HOMA-IR (p=0.0245) concentrations.

Conclusions: Due to the inconsistent results, no clear conclusion can be drawn about the effect of HIIT on the glucose metabolism of the MS patients in this cohort.

2. Introduction

Multiple sclerosis (MS) is a neurodegenerative auto-immune disease of the central nervous system causing irreversible lesions of the insulating myelin sheet of nerve fibres. These lesions lead to difficulties in nerve conduction which results in a wide range of symptoms including fatigue, muscle weakness and cognitive decline.[1] Furthermore, MS patients are often more physically inactive due to their symptoms. In healthy persons, physical inactivity is a risk factor for the development of secondary diseases such as hypertension, obesity and type II diabetes.[2],[3] Wens et al. investigated the precursor of type II diabetes, impaired glucose tolerance (IGT), in MS patients and reported a higher prevalence compared to healthy controls.[4]

In healthy persons, physical activity is an essential factor to reduce the risk of these secondary diseases[2], whereby a variety of training modalities are appropriate such as endurance training, muscle power training, combination training, etc.[5] Physical training was contra-indicated in MS patients for many years. However, in the last decade more research has demonstrated the beneficial effects of physical exercise in this population.[6] Despite this growing research, less is known about the effects of physical exercise on the glucose metabolism of MS patients. Recently, Wens et al. investigated the effect of twenty-four weeks of mild-to-moderate intensity combined resistance and endurance training on the glucose metabolism of MS patients and concluded no improvement in the glucose tolerance.[7] Interestingly, in a following study of the same authors, an improvement in glucose tolerance was demonstrated after a high-intensity interval training protocol.[8]

The present study is a continuation of the research of Wens et al., investigating the effect of high-intensity interval training on multiple parameters of the glucose metabolism of MS patients, such as glucose and insulin total area under the curve (tAUC). Furthermore, correlations between fat mass and glucose parameters are investigated. Research has shown a strong correlation between abdominal fat mass and insulin resistance in healthy persons, leading to a higher risk of metabolic syndrome.[9],[10] However, less is known about this relationship in MS patients.

Based on the findings of previous research, it is hypothesized that a twelve week high-intensity interval training protocol has a positive effect on the glucose metabolism of MS patients, which is demonstrated by a decrease in the glucose and insulin total area under the curve (tAUC) and HOMA-IR concentration. Furthermore, a positive correlation between fasting insulin and fat mass is hypothesized.

3. Method

Participants

Group allocation is presented in figure 1.

A total of twenty-nine MS patients participated in the study. They were recruited from databases of Dr. Ir. Inez Wens and Charly Keytsman based on former research. Furthermore, patients from Rehabilitation and MS center Overpelt (Belgium) were invited to participate in the study.

All MS patients attended to an information session about the study before onset.

After recruiting and informing the patients, participants were included according to the following criteria; multiple sclerosis diagnosed according to McDonald criteria (EDSS 1.0-6.0) and age of eighteen years or older. Exclusion criteria were; other chronic diseases (cardiovascular, metabolic, etc.), an acute MS exacerbation three to six months before the start of the study, type II diabetes mellitus, pregnancy, medication affecting the glucose metabolism and participation in other studies. Additionaly, twenty-six healthy persons were recruited to investigate the baseline differences between MS patients and healthy controls. All healthy persons received detailled information about the study. After signing informed consents, participants were divided into three groups. One MS intervention group (EX) consisting of sixteen participants, one sedentary control group (SED) consisting of thirteen participants and one healthy control group (HC) consisting of twenty-six participants.

The study was approved by the ethics committee, performed in accordance with the Declaration of Helsinki in December, 2014.

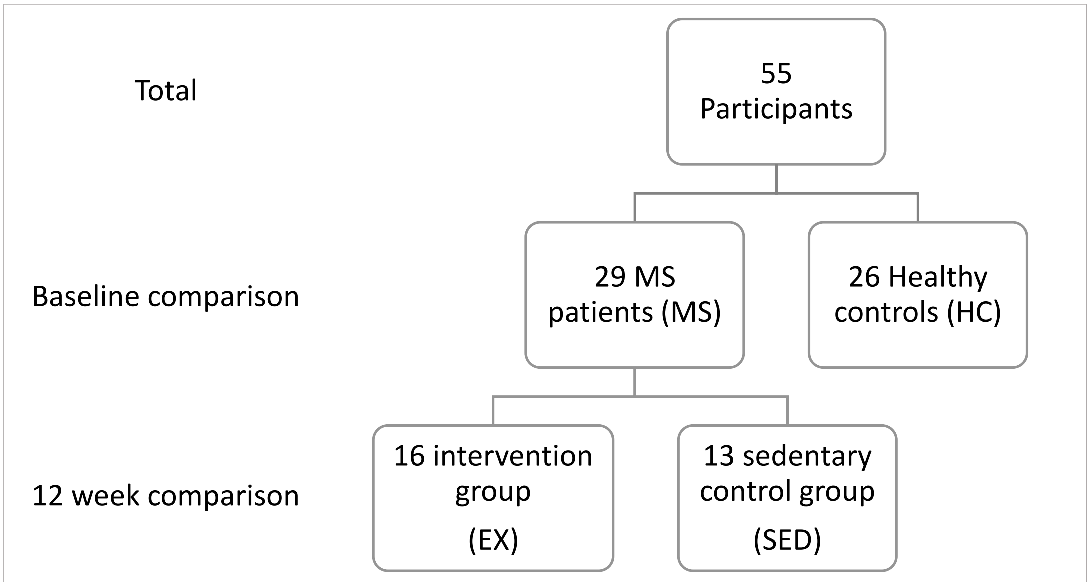

Fig. 1 Flowchart of group allocation

Procedure

Two weeks prior to the start of the intervention, all participants were invited to the rehabilitation research center (Reval) of Hasselt University (Belgium) for baseline testing. Measurements consisted of an oral glucose tolerance test (OGTT) and DEXA-scan.

An OGTT is a two-hour test to detect impaired glucose tolerance (IGT) by plasma glucose and serum insulin concentrations. After a 10-hr overnight fasting period, participants received a glucose bolus of 200 ml containing 1g/kg body weight glucose.

Measurements

Plasma glucose

Plasma glucose concentrations were determined by capillary blood samples from the earlobe which were collected during two hours, starting at fasted state followed by every 30 minutes after administration of the glucose bolus.[4] (Analox-GM7 Micro-stat; Analox Instruments Ltd, London, UK). These whole-blood glucose concentrations were converted to plasma glucose concentrations using a multiplier of 1.11.[7]

Serum insulin

Serum insulin concentrations were determined by venous blood which was collected at fasted state, at 60 minutes and at 120 minutes post administration. These samples were collected by a trained nurse using serum separation tubes (BD Vacutainer; Becton Dickinson, Erembodegem, Belgium). After collection, a 30 minute waiting period was provided to allow blood coagulation. Subsequently, the serum samples were centrifuged for 10 minutes at 3500 rpm.[7] The obtained serum was frozen and stored at -80°C for analysis of serum insulin levels (Mercodia Insulin enzyme-linked immunosorbent assay (ELISA)).[11]

Body composition

A dual-energy X-ray absorptiometer (DEXA) scan (Hologic Series Delphi-A Fan Beam X-ray Bone Densitometer, Vilvoorde, Belgium) was used to determine body composition of all participants. The scan measured whole-body fat mass, lean soft tissue mass and fat percentage.[7] These outcome measures were used to search for correlations with the primary outcome measures of the OGTT.

All tests were repeated after 12 weeks.

Exercise protocol

The training group program consisted of a cardiovascular cycling part (Technogym) and a strengthening part (Technogym). Both parts were included in every session. The participants trained five times in two weeks at the Reval center, alternately three and two times per week. All training sessions were supervised by a physiotherapist and two master students and were initiated by a ten minute warming-up period on the cycle ergometer.

In the first week a familiarization period was provided for the participants to habituate with the devices and the protocol. In this week the training consisted of five bouts of one minute cycling. Intensity was determined by the heart rate corresponding to 100% of the maximal workload. This heart rate was comparable to 80%-90% of the maximal heart rate. The training bouts were interspersed with one minute of active rest. During the rest period patients cycled at a lower resistance level to prevent blood pooling and hypotension. From week two to week six the duration gradually increased to five bouts of two minutes cycling at the same intensity, interspersed with one minute active rest.

From week seven until week twelve, intensity was further increased to 100%-120% of the maximal workload, corresponding with 90%-100% of the maximal heart rate. Although duration was kept at five bouts of two minutes, resistance was increased in order to reach the target heart rate.

The second part of the protocol consisted of resistance training. This program contained six exercises; arm curl, chest press and vertical traction for the upper extremity and leg press, leg curl and leg extension for the lower extremity (Technogym). In the first week the participants performed one bout of ten repetitions, which was gradually increased over the next weeks until two bouts of twenty repetitions were performed. Exercise intensity was set at the maximal attainable load, this was determined by the maximal load a participant could sustain. After the training session, participants were asked to score each exercise with the BORG-scale of perceived exertion. The scores ranged from score one, “no exertion” to score 20, “maximal exertion”. The aim of the protocol was to reach a BORG-score of 14 to 16, when this score decreased intensity was increased by the physiotherapist.

At the end of each training session participants received six stretching exercises to facilitate recovery and prevent muscle soreness. These exercises focused on the main muscle groups according to the strengthening exercises.

Statistical analysis

Statistical analysis was performed with the software SAS JMP PRO 12. All data were assessed by non-parametric tests after checking the normality. Baseline differences in all primary and secondary outcome measures between groups were investigated using the Mann-Whitney test. Within-group analysis of all data was performed by the Wilcoxon signed-rank test.

Level of significance for all analysis was set at $p<0.05$.

4. Results

Baseline results

Subject characteristics

Subject characteristics of the MS and HC group are presented in table 1.a.

Both groups were comparable at baseline for age, gender, height and length. As hypothesized, a baseline difference in fasting serum insulin concentration was found. This was significantly higher in the MS group compared to the HC group (p=0.0109).

Table 1.a. Subject characteristics MS and HC

	MS	HC	*P*
Sex, M/F	13/16	10/16	NS
Age, mean ± SEM, yr	53 ± 8	49 ± 11	NS
Height, mean ± SEM, m	1.7 ± 0.08	1.6 ± 0.01	NS
Weight, mean ± SEM, kg	72.3 ± 13.2	70.6 ± 13.7	NS
BMI, mean ± SEM, kg/m²	24.7 ± 3.6	24.3 ± 2.6	NS
Fasting insulin, mean ± SEM, pmol/l	72 ± 47.9	50.8 ± 27.8	S
Insulin, mean ± SEM, tAUC	50625 ± 37970	41930,76 ± 25502	NS
Fasting glucose, mean ± SEM, mmol/l	5.6 ± 0.9	5.1 ± 0.6	NS
Glucose, mean ± SEM, tAUC	1198,5 ± 300	1101,5 ± 161	NS
HOMA, mean ± SEM	2.5 ± 1.8	1.7 ± 0.9	NS
HbA1c, mean ± SEM, %	5.3 ± 0.3	5.2 ± 0.2	NS
Fat mass, mean ± SEM, g	20175.1 ± 6212	18141 ± 4854.3	NS
Lean mass, mean ± SEM, g	45606.4 ± 10044.1	46273.2 ± 11394.7	NS
Fat, mean ± SEM, %	30.7 ± 7.1	28.4 ± 6.7	NS

SEM, standard error of mean; BMI, body mass index; M, male; F, female; HbA1c, haemoglobin A1c; tAUC, total area under curve; NS, not significant; S, significant

Subject characteristics of the EX and SED group are presented in table 1.b.
Baseline differences were found between groups for glucose tAUC (p=0.0213), Hba1c (p=0.0461) and fat mass (p=0.0168). These were significantly higher in the SED compared to the EX group.

Table 1.b. Subject characteristics EX and SED

	EX	**SED**	***P***
Sex, M/F	8/8	5/8	NS
Age, mean ± SEM, yr	52 ± 7	53 ± 10	NS
Height, mean ± SEM, m	1.7 ± 0.08	1.7 ± 0.07	NS
Weight, mean ± SEM, kg	68.7 ± 13.1	76.8 ± 12.2	NS
BMI, mean ± SEM, kg/m²	23.6 ± 3	26.2 ± 3.8	NS
MS type, RR/SP/PP	11/4/0	9/2/1	NS
EDSS, mean ± SEM	2.6 ± 1.5	3.5 ± 1.4	NS
Fasting insulin, mean ± SEM, pmol/l	61.3 ± 29.8	86.2 ± 90	NS
Insulin, mean ± SEM, tAUC	44870 ± 25397	58472 ± 50832	NS
Fasting glucose, mean ± SEM, mmol/l	5.4 ± 1	5.9 ± 1	NS
Glucose, mean ± SEM, tAUC	1064,39 ± 206	1363,70 ± 322	S
HOMA, mean ± SEM	2.1 ± 1.1	3.2 ± 3.2	NS
HbA1c, mean ± SEM, %	5.2 ± 0.2	5.4 ± 0.4	S
Fat mass, mean ± SEM, g	17820.3 ± 5109.8	23073.3 ± 9045.5	S
Lean mass, mean ± SEM, g	44543.9 ± 10690.4	46914 ± 13355.4	NS
Fat, mean ± SEM, %	28.8 ± 6.6	33.1 ± 10.3	NS

SEM, standard error of mean; BMI, body mass index; M, male; F, female; RR, relapse remitting; SP, secondary progressive; PP, primary progressive; EDSS, expanded disability status scale; HbA1c, haemoglobin A1c; tAUC, total area under curve; NS, not significant; S, significant

Primary outcome measures

OGTT

Results are presented in table 2.

After twelve weeks, between-group analysis demonstrated a significant larger decrease of the glucose tAUC in SED compared to EX (p=0.0244) (Fig. 2). Within the EX, fasting serum insulin (p=0.0495) and HOMA-IR (p=0.0245) concentrations were significantly decreased after twelve weeks of HIIT (Fig. 3).

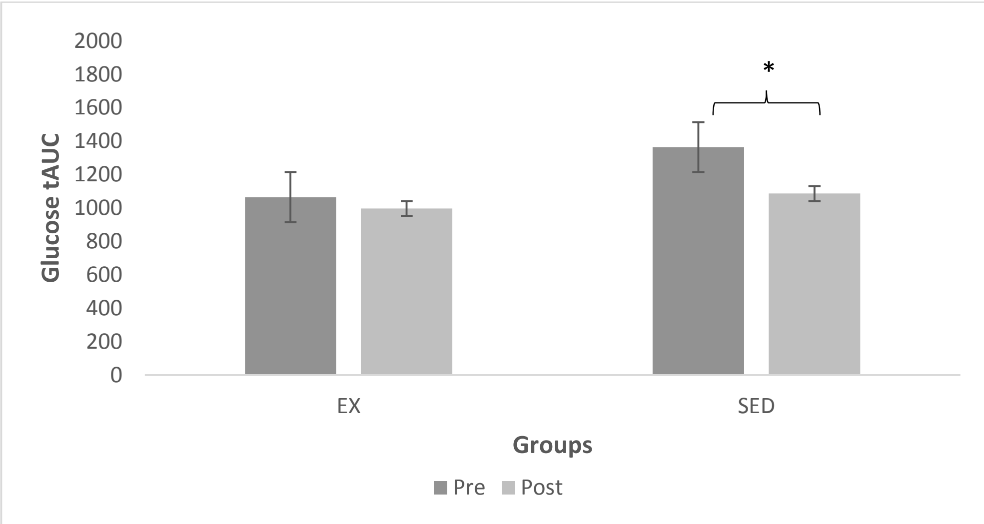

Fig. 2 Glucose total area under the curve (tAUC) before and after twelve weeks for EX and SED. Data are given in mean and ± SD. Significant difference, * p<0.05

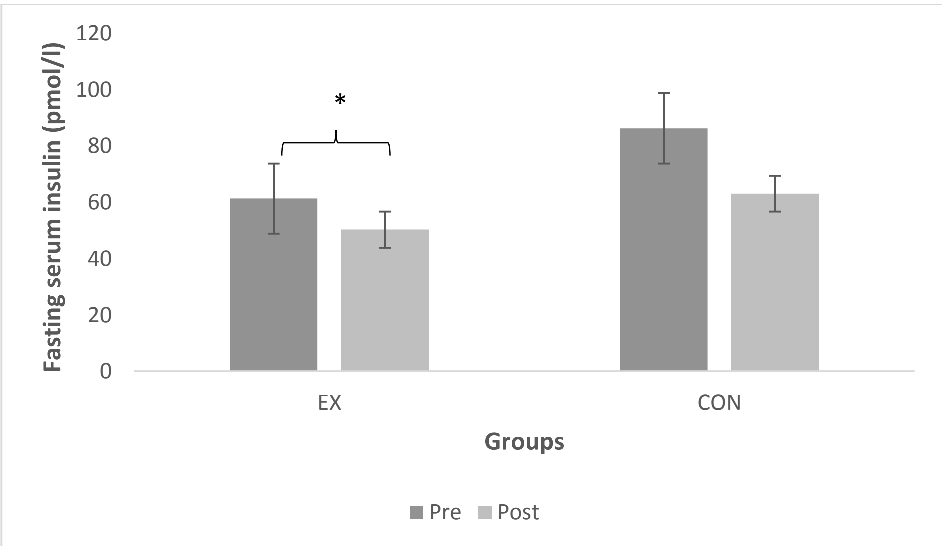

Fig. 3 Fasting serum insulin (pmol/l) before and after twelve weeks for EX and SED. Data are given in mean and ± SD. Significant difference, * p<0.05

Secundary outcome measures

Body composition

Results are presented in table 2.

No significant difference was found for whole-body lean mass, fat mass or fat percentage between EX and SED after twelve weeks. Within-group analysis also showed no significant differences.

Table 2. Results

	EX	**SED**	***P***
Height, mean ± SEM, m	-0.03 ± 1.6	1.2 ± 4.1	NS
Weight, mean ± SEM, kg	-0.8 ± 3.5	0.2 ± 2.7	NS
BMI, mean ± SEM, kg/m²	-0.3 ± 1	-0.07 ± 1.8	NS
Fasting insulin, mean ± SEM, pmol/l	-11 ± 24.7	-22.1 ± 70.9	NS
Insulin, mean ± SEM, tAUC	5266 ± 25605	-1360 ± 24478	NS
Fasting glucose, mean ± SEM, mmol/l	-0.2 ± 0.9	-0.1 ± 1.2	NS
Glucose, mean ± SEM, tAUC	-66,8 ± 180	-278,7 ± 267	S
HOMA, mean ± SEM	-0.5 ± 0.9	-0.9 ± 2.9	NS
HbA1c, mean ± SEM, %	0.01 ± 0.1	-0.08 ± 0.4	NS
Fat mass, mean ± SEM, g	-808.7 ± 2634.1	94.5 ± 1615.9	NS
Lean mass, mean ± SEM, g	-485.3 ± 1337.3	170.7 ± 1820.2	NS
Fat, mean ± SEM, %	-0.5 ± 2.6	-0.08 ± 1.9	NS

SEM, standard error of mean; BMI, body mass index; M, male; F, female; HbA1c, haemoglobin A1c; tAUC, total area under curve; NS, not significant; S, significant

Correlations

Baseline fasting serum insulin level and fat mass showed a significant low-to-moderate positive correlation (0.398; p=0.003). No further correlations were found between primary and secondary outcome measures of the pooled data.

5. Discussion

The present study investigated the effect of twelve weeks high-intensity interval training (HIIT) on the glucose metabolism of MS patients. Primary outcome measures were fasting serum insulin, fasting plasma glucose, serum insulin tAUC and plasma glucose tAUC. These parameters were measured by an oral glucose tolerance test (OGTT). To validate the measurements, Hba1c and HOMA-IR were used. Body composition was determined as secondary outcome measure, whereby whole-body fat mass, lean mass and fat percentage were determined by a DEXA-scan. These parameters were used to search for correlations with the primary outcome measures.

Previous research of Wens et al. supports the baseline differences which were found between the MS group (MS) and the healthy control group (HC).[4] Furthermore, this research revealed elevated fasting plasma glucose concentrations, serum insulin tAUC and plasma glucose tAUC. These differences in results could be accounted to a larger sample size in the study of Wens et al.[4] The baseline differences between the intervention group (EX) and the control group (SED) could be explained by the non-randomized research protocol. Due to the need for motivation, which is essential in high-intensity interval training, it was not possible to randomize the participants between groups. Therefore, it is possible that the intervention group consisted of participants with a more active lifestyle prior to the intervention, which positively influenced the outcome measures.

Surprisingly, between-group analysis post-intervention showed a larger decrease of the plasma glucose tAUC in the control group (SED) instead of the intervention group (EX). The mean plasma glucose tAUC at baseline of SED was remarkably high, therefore measurement error was suspected. After analysing the individual data this hypothesis was rejected as the analysis in this group (SED) did not show one extreme value, but rather multiple higher values. Remaining possible explanations for the unexpected significant decrease could be a change of lifestyle of multiple participants in the SED group or the start of new medication which affects the glucose metabolism, although participants were instructed not to change medication during the study. However, if these explanations are correct, a significant decrease of insulin tAUC and Hba1c would be expected. During the intervention period the participants received no dietary restrictions, nor was their dietary intake documented in a diary. Therefore, it is possible that participants of the EX group overcompensated their training sessions with caloric intake, resulting in no significant alterations in the glucose tAUC, Hba1c concentrations or fat mass.

After analysing the within-group effect of EX after twelve weeks of HIIT, a significant decrease in fasting serum insulin concentrations was found. This may indicate an improvement in insulin resistance, which would be confirmed by the decrease of HOMA-IR concentrations. However, although it did not reach a significant level, the insulin tAUC within EX was increased.

Research demonstrated a strong correlation between abdominal fat mass and insulin sensitivity in healthy and obese persons.[9],[10] For whole-body fat mass a moderate-to-strong correlation with insulin sensitivity was found, concluding fat mass is a considerable determinant for insulin resistance.[9] Therefore, the correlation between whole-body fat mass and fasting insulin in the current research could suggest that fat mass is also an important marker for insulin resistance in MS patients.

Strengths and weaknessess

As mentioned above, the main weakness of this study is the non-randomized research protocol. The participants of the intervention group voluntarily chose to be allocated to this group. A major consequence of this non-randomization is that EX and SED were not comparable for all parameters at baseline, influencing the interpretation of the intervention effect. Furthermore, the non-randomisation leads to sampling bias, which negatively influences the external validity of this research.

Other weaknesses are the lack of blinding of the assessors and the fact that there was no control of dietary intake in both groups, while a potential discrepancy between dietary intake of the groups can be an important factor influencing the outcome measures.

A strength of this research is that all measurements and analyses were performed by the same researchers. Furthermore, the oral glucose tolerance test (OGTT), which was used for the measurement of fasting plasma glucose and serum insulin concentrations, is approved for the prediction of insulin sensitivity when applied in groups. Research has shown positive correlations between the results of the OGTT and the gold standard, euglycemic-hyperinsulinemic clamp technique.[12] Additionally, during the twelve weeks of training, training conditions were constant. This was achieved by a mechanical cooled training area and standardized training equipment.

6. Conclusion

In conclusion, twelve weeks of high-intensity interval training had a positive effect on fasting serum insulin concentration and HOMA-IR concentrations in the EX group. However, due to the inconsistent findings, no clear conclusion can be drawn about the effect of HIIT on the glucose metabolism of this cohort of MS patients. Further research on this topic is warranted.

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Impact of high-intensity interval training on the glucose metabolism in MS

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij neurologische aandoeningen**
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