ACKNOWLEDGEMENTS

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SITUATING STUDY

This study is a part of a new project of the Hasselt University, Faculty of Medicine and Life Sciences (Hasselt, Belgium), in collaboration with 'Department of Human Movement Sciences, NUTRIM School for Nutrition, Toxicology and Metabolism', Maastricht University Medical Centre (Maastricht, the Netherlands) and 'Rehabilitation Sciences and Physiotherapy', Gent University (Gent, Belgium). This study has been granted by the Yvonne and Jacques François-de Meurs fund from the King Baudouin Foundation.

The purpose of our master's thesis is to investigate whether exercising in the fasted state has a superior effect on glycemic control, oxidative capacity, blood parameters and muscle metabolism, as opposed to training in the fed state in type 2 diabetes mellitus (T2DM) patients. The proper timing of exercise training in T2DM patients has not yet been investigated. To limit the uprising prevalence, enhance the treatment of this syndrome and improve quality of life as efficiently as possible, timing of exercise can be of great importance.

Exercise training in the fasted vs. postprandial state to augment the clinical benefits in type 2 diabetic patients

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ABSTRACT

Exercise training is a key treatment, besides pharmacological or dietary interventions. However the optimal treatment for type 2 diabetes mellitus (T2DM) patients remains unknown. Therefore we investigated whether exercise training in the fasted (before breakfast) or fed (after breakfast) state is more beneficial for improving exercise capacity, body composition and most importantly glucose tolerance and insulin sensitivity in T2DM patients. 28 male patients were randomly assigned, by envelope, to 3 months of exercise training for 3 times/week for 45minutes/session (cycling and walking). The entire exercise training protocol was completed by 18 patients, 8 patients trained in the fast group (age 61,8 ± 12,6 years; BMI 30,9 ± 5,2) and 10 patients trained in the fed group (age 62,8 ± 6,9 years; BMI 29,1 ± 1,5). Exercise training improved blood glycated hemoglobin (HbA_{1c}), glucose disposal rate (GDR), metabolic flexibility, total fat mass and lean arm mass ($p<0,05$). Only the rates of perceived exertion (BORG-score) were significantly lower after exercise training in the fasted state as opposed to exercise training in the fed state ($p=0,008$). We conclude that exercise training in the fasted and fed state are equally effective to improve insulin sensitivity in T2DM patients.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is defined as 'a subclass of diabetes mellitus that is not insulin-responsive or insulin-dependent'. It is initially characterized by insulin resistance and hyperinsulinemia resulting into glucose intolerance, and progressively evolving to hyperglycemia and overt diabetes.

In the care of T2DM exercise is a key treatment, besides glucose lowering pharmacological interventions and dietary interventions (1). Participation into exercise training leads to a decrease in adipose tissue mass and waist circumference (2), an improvement in glycemic control (3, 4) insulin sensitivity, cardiovascular disease risk factors (5), physical fitness (6) and quality of life (7) in T2DM patients.

Official position statements therefore endorse the implementation of exercise intervention in the care of T2DM patients. According to these guidelines subjects with T2DM should exercise 3-5 times a week for a minimum duration of 150 min/week at 40-70% VO2peak, with the addition of resistance exercises (5-10 exercises/session, three series/exercise, 10-15 repetitions).

The optimal frequency, intensity and duration of exercise in T2DM patients has already been investigated in previous studies. However it is believed that the maximal clinical benefits of exercise training in T2DM has not been achieved yet. For example, the optimal timing of exercise training (before or after breakfast) in T2DM patients remains speculative.

Exercise training performed during high carbohydrate availability (after breakfast) in healthy subjects leads to energy uptake principally from carbohydrate degradation, as well as inhibition of intramuscular triglycerides (IMTG) degradation. On the other hand exercise training in the fasted state is characterized by elevated fatty acids degradation and facilitated IMTG use (8). For this reason exercise training in the fasted state seems an effective strategy to lower IMTG content (8). It is well known that IMTG accumulation is associated with the development of insulin resistance. Therefore exercise training in the fasted state could be a more effective rehabilitation strategy for treatment of T2DM, when compared to exercise training in the fed state.

Indeed, Van Proeyen et al. have shown that exercise training in the fasted state during a high-fat diet is more effective to enhance whole-body glucose tolerance as opposed to exercise training in the fed state in healthy subjects (9). However the impact of long term exercise training in fed vs. fasted state in T2DM patients is unknown.

In this study we examined the impact of a long term exercise intervention in which training sessions were executed in fasted vs. fed state in T2DM patients. We hypothesized that exercise training in the fasted state will establish a greater improvement in glycemic control as opposed to exercise training performed in the fed state in T2DM patients.

METHODS

Subjects

For the complete study, twenty-eight T2DM patients (male) were included. Sample size was based on a previous study of van Proeyen, (n=10 (FED), n=10 (FAST), n=7 (control)). Participants volunteered for this study through advertisements published in local newspapers. For our master's thesis, results of only eighteen participants were available because the study was still ongoing.

Subjects with the following characteristics were included: male, age 40-80 years, sedentary lifestyle, treated by oral blood glucose lowering medication, no exogenous insulin therapy, no history of coronary events/revascularization, absence of chronic pulmonary, renal and/or orthopedic diseases that interfere with exercise training, no involvement in exercise training and/or caloric restriction program for at least one year. Patients were primarily matched for age and BMI, baseline characteristics are shown in table 1. 10 patients dropped out of the study. A flowchart of the complete study is displayed in figure 1.

Figure 1: Flowchart

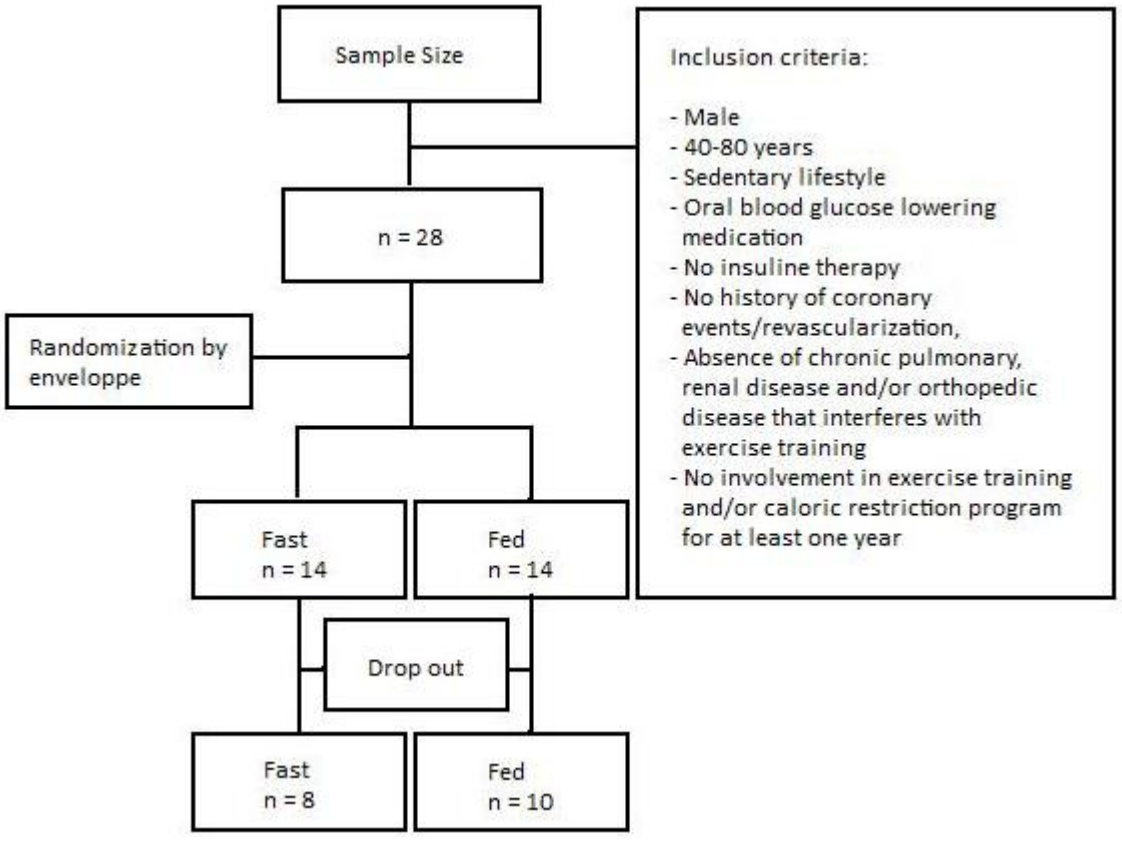


Table 1: Participant charasteristics

Characteristics	FAST	FED
n	8	10
Age (years)	61,8 ± 12,6	62,8 ± 6,9
Weight (kg)	97,6 ± 16,5	93,2 ± 9,2
BMI (kg/m²)	30,9 ± 5,2	29,1 ± 1,5
Insuline sensitivity		
HbA1c (%)	6,7 ± 0,5	7,4 ± 1,1
GDR (mg/m/kg)	10,7 ± 10,9	10,0 ± 8,6
Peak Exercise capacity		
VO_{2peak} (ml/min)	2414 ± 617	2269 ± 627
HR_{peak} (bpm)	150 ± 23	151 ± 19
RER_{peak}	1,16 ± 0,05	1,21 ± 0,08
Submaximal exercise capacity		
VO_{2rest} (ml/min)	257 ± 70	258 ± 51
VO_2 at 20% VO2peak (ml/min)	874 ± 178	778 ± 256
VO_2 at 40% VO2peak (ml/min)	1084 ± 301	978 ± 518
VO_2 at 60% VO_{2peak} (ml/min)	1450 ± 414	1541 ± 476
HR_{rest} (bpm)	70 ± 8	65 ± 7
HR at 20% VO2peak (bpm)	92 ± 7	78 ± 10
HR at 40% VO2peak (bpm)	101 ± 8	90 ± 17
HR at 60% VO2peak (bpm)	117 ± 15	97 ± 18
RER_{rest}	0,86 ± 0,07	0,92 ± 0,12
RER at 20% VO2peak	0,86 ± 0,06	0,83 ± 0,10
RER at 40% VO2peak	0,93 ± 0,04	0,90 ± 0,11
RER at 60% VO2peak	1,01 ± 0,07	0,96 ± 0,08
Body composition		
Fat mass Arms (g)	1716 ± 627	1508 ± 434
Fat mass Legs (g)	4449 ± 1018	4069 ± 807
Fat mass Trunk (g)	17860 ± 5308	17139 ± 3964
Fat mass Total (g)	31919 ± 8514	29718 ± 6104
Lean mass arms (g)	3528 ± 739	3514 ± 509
Lean mass Legs (g)	9514 ± 1080,2	9706 ± 1126
Lean mass Trunk (g)	30571 ± 3987	30352 ± 2321
Lean mass Total (g)	60695 ± 7321	60898 ± 5480

Study design

This study is a randomized trial executed in an university rehabilitation centre. Subjects were randomly assigned by envelope to three months of exercise training in the fasted state (n=8) and exercise training in the fed state (n=10).

At entry and after 3 months of intervention, following measurements were executed: fasting blood sample collection (for assessment of glucose content and blood glycated hemoglobin (HbA_{1c}), hyperinsulinemic euglycemic clamp test (clamp) (for assessment of insulin sensitivity), maximal cardiopulmonary exercise test (for assessment of peak oxygen uptake (VO_{2peak}) and maximal heart rate (HR_{max})), submaximal exercise test (for assessment of RER, VO_2 and HR at rest, at 20%, at 40% and at 60% of VO_{2peak}), a dual x-ray absorptiometry scan (for assessment of body composition). One day prior to the clamp, maximal and submaximal exercise test patients abstain from taking oral blood-glucose, all other types of medications were allowed.

Exercise training intervention

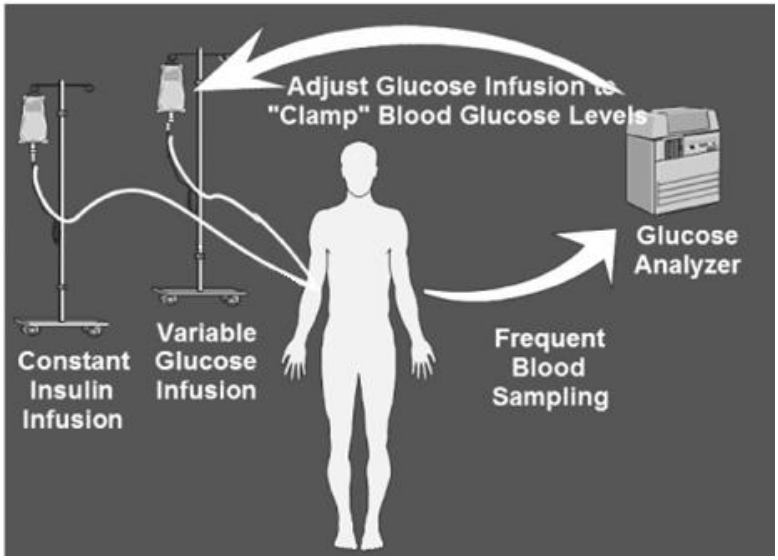
All participants performed three individually supervised, endurance exercise sessions per week for a three-month during intervention period. During each training session, walking and cycling is performed, for a total duration of 45 min, at exactly 65% of VO_{2peak} reserve. The corresponding heart rate of 65% VO_{2peak} reserve was assessed. This intensity was the participant's target heart rate. Cycle ergometers and treadmills were all equipped with a heart rate feedback system, this means that the target heart rate of the subject's 65% VO_{2peak} reserve is entered in the ergometer or treadmill, when a subject's heart rate is lowered or raised the system adjusts the speed or inclination of the treadmill and the resistance (Watt) of the cycle ergometer according to the target heart rate. The exercise training intensity was standardized by continuous heart rate monitoring (Polar, Oy, Finland). Subjects randomized to the fasted state exercise training group exercised between 07.00-10.00 AM, followed by breakfast within 60 min after exercise. Subjects randomized to the fed state exercise training group exercised between 08.30-11.00 AM, after having consumed a breakfast <60 min ago. During the 45-minutes during exercises session, it was only allowed to drink water. Administration of monosaccharides was only allowed in case of hypoglycemic symptoms. According to Colberg et al. (10) exercise training in fasted state for T2DM patients is safe.

Measurements

Hyperinsulinemic Euglycemic Clamp

An hyperinsulinemic euglycemic clamp was executed prior and after the 12-week during training program. The clamp test is a test to assess the sensitivity to insulin. The complete deployment of the hyperinsulinemic euglycemic clamp is shown in figure 2.

Figure 2: Hyperinsulinemic Euglycemic Clamp test



First a fasted blood sample is collected to measure blood glucose and blood HbA_{1c} level. Blood glucose was assessed by the use of an Analox apparatus. At the start of the clamp test Actrapid, which is a rapidly working type of insulin, was injected into a peripheral vein of the right arm. The amount of insulin injected was determined according to the body surface area. At beginning of the test (the first 5 min) Actrapid was injected at a rate of 103MIu/m2/min, after which a lower dose was injected for the rest of the test (40MIu/m2/min). Every five minutes blood glucose levels were assessed by blood samples to adjust the rate of glucose injection (20%-50% glucose solution). Blood samples were taken from the left arm which was placed in a hot box. The purpose of this hot box was to imitate the arterial blood characteristics. When blood is heated the blood glucose will not be dispersed from the blood capillaries into the neighboring tissue. Blood glucose injection was adjusted with the aim of reaching a steady state of 5 mmol/L. The duration of this hyperinsulinemic euglycemic clamp test was maximally 2 hours. The amount of glucose needed to restore the increased blood insulin level determines the sensitivity to insulin. After completing the test, the glucose disposal rate (GDR) was calculated. This provided us a marker for the improvement or worsening of the insulin sensitivity of each participant.

Maximal Cardiopulmonary Exercise Test

All subjects underwent a maximal cardiopulmonary exercise test on an electronically braked cycle ergometer (eBike Basic, General Electric GmbH, Bitz, Germany) using a 1-min work stage protocol. Starting load was set at 40W and incremental work stage was 20W. Patients were asked to cycle at a frequency of 70 rpm. Pulmonary exchange analysis (Jaeger Oxycon, Erich Jaeger GmbH, Germany), respiratory exchange ratio (RER) and VO_{2peak} were assessed. Before each maximal cardiopulmonary exercise test a gas and volume calibration was executed. Maximal heart rate was assessed with constant heart function monitoring using a 12-lead ECG device. If there were signs of dangerous cardiac arrhythmias the test was stopped immediately. During the test environmental temperature was kept stable to 19-21°C (11).

Submaximal Exercise Test

Metabolic flexibility was measured prior to the exercise program and after completion of the program. This was established on the basis of a submaximal cardiopulmonary exercise test. Participants were instrumented to rest for 15 minutes for the assessment of resting data. RER, VO_2 and HR at 20%, at 40% and at 60% of VO_{2peak} were assessed during a submaximal exercise test on an electronically braked cycle ergometer (eBike Basic, General Electric GmbH, Bitz, Germany).

Dual-energy X-ray Absorptiometry

Body composition was assessed using whole body dual-energy X-ray absorptiometry (DXA; Lunar DPXL, WI, USA). Segmental (arms, legs and trunk) and whole body fat-free and fat mass were assessed. (12)

Statistical analysis

Statistical analysis was performed with SPSS 22.0. To test for normality of the different intervention groups, a Shapiro-Wilk test was used. This test has shown that our population groups are distributed normally. To test whether there was a true difference between groups on a certain variable (VO_{2max}, blood glucose level), a parametrical analysis of variance with repeated measures (one-way ANOVA) was performed (with time and group as interaction factors). A p-value lower than 0,05 was considered significant. Mean values of each variable were noted with the corresponding standard deviation (SD)

RESULTS

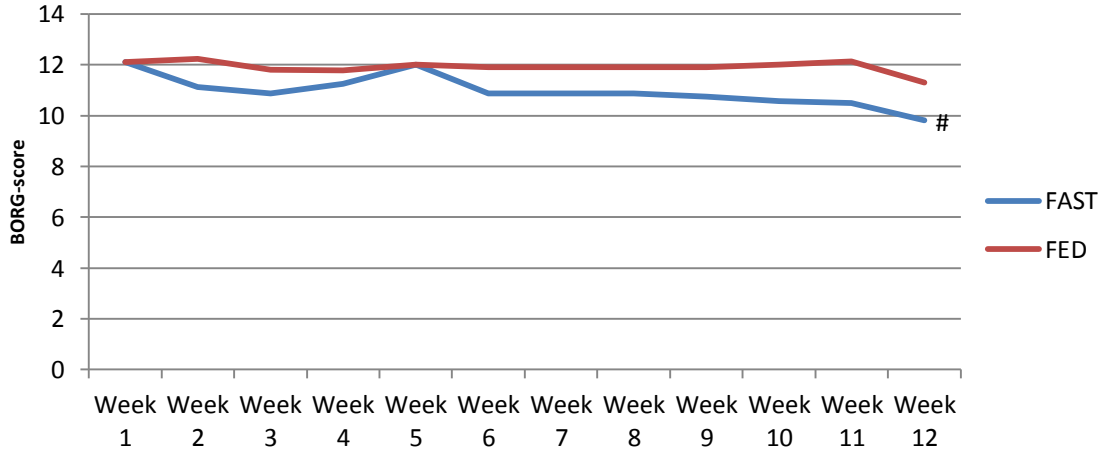
Subjects

Eighteen T2DM patients (age 62,3 years ± 9,6, BMI 30,2 ± 4,2) were randomly assigned to exercise training in the fasted state (n=8) or exercise training in the fed state (n=10) (see table 1 for subject characteristics). Groups were significantly different for HbA_{1c} ($p<0,05$)

Exercise intervention

Baseline BORG-scores were similar between both groups at entry of intervention (FAST, 12,1 ± 1,9; FED, 12,1 ± 1,4), but ratings of perceived exertion became significantly lower for the fast group as opposed to the fed group after 3 months of exercise training ($p<0,01$) (see figure 3)

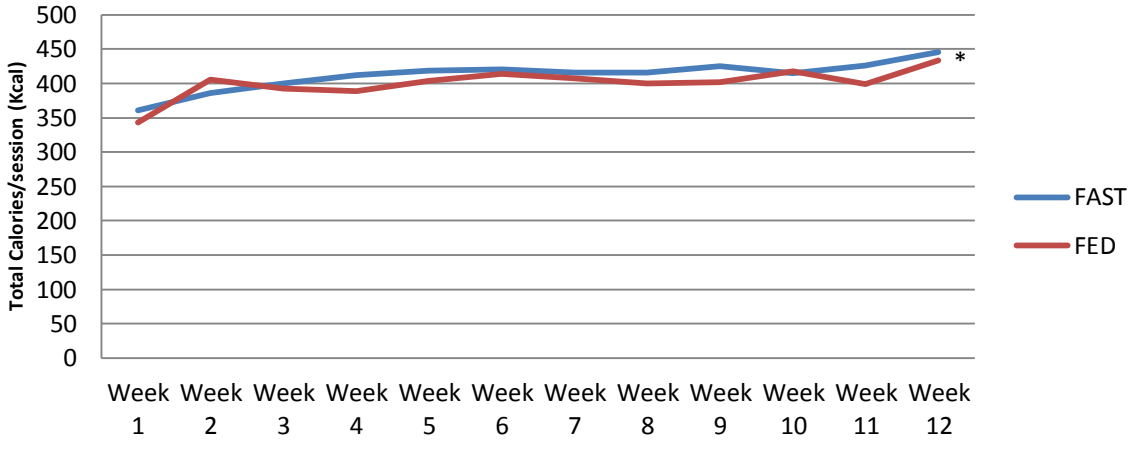
Figure 3: BORG-scores



 # significant interaction effect after 12 weeks of exercise training (p<0,01)

There was a significant increase in caloric expenditure during exercise training in both groups (FAST, from 360kcal ± 110 to 445kcal ± 74; FED from 343kcal ± 124 to 433kcal ± 94; $p<0,01$). But the caloric expenditure during exercise training was comparable between groups over the 12-week period (see figure 4) ($p=0,92$).

Figure 4: Caloric expenditure during training sessions

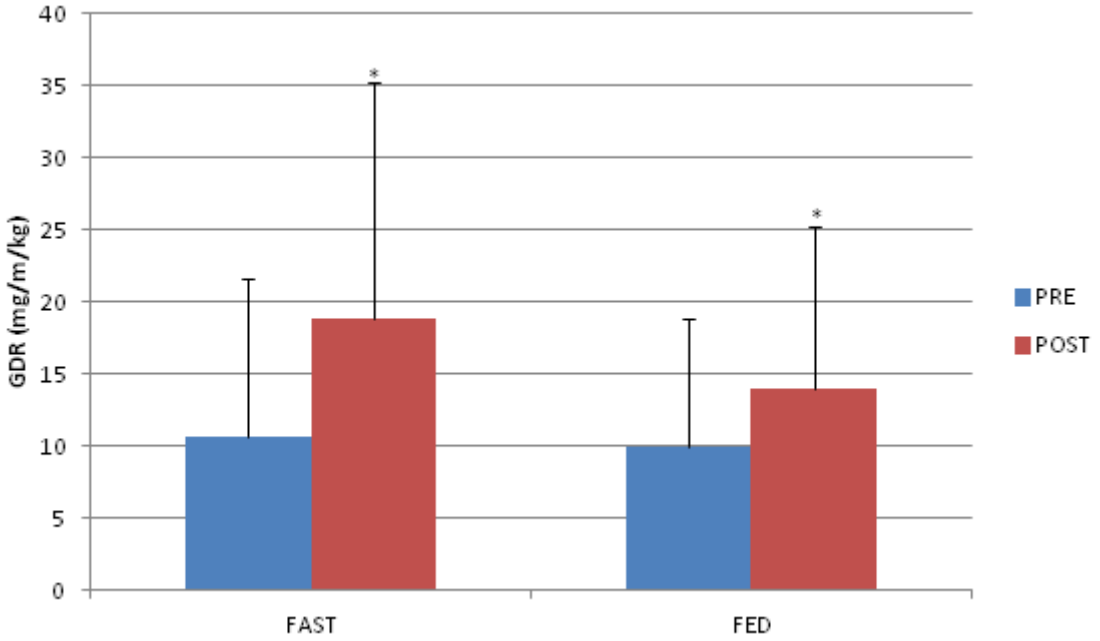


** significant training effect after 12 weeks of exercise training in total group (p<0,01)*

Insulin sensitivity and glucose tolerance

12 weeks of exercise training induced a significant increase of GDR in both groups (FAST, from 10,7mg/m/kg ±10,9 to 18,9mg/m/kg ± 16,3; FED, from 10,0mg/m/kg ± 8,6 to 14,0mg/m/kg ± 11,0; p=0,04), without significant interaction effects between groups (p=0,41). (See figure 5)

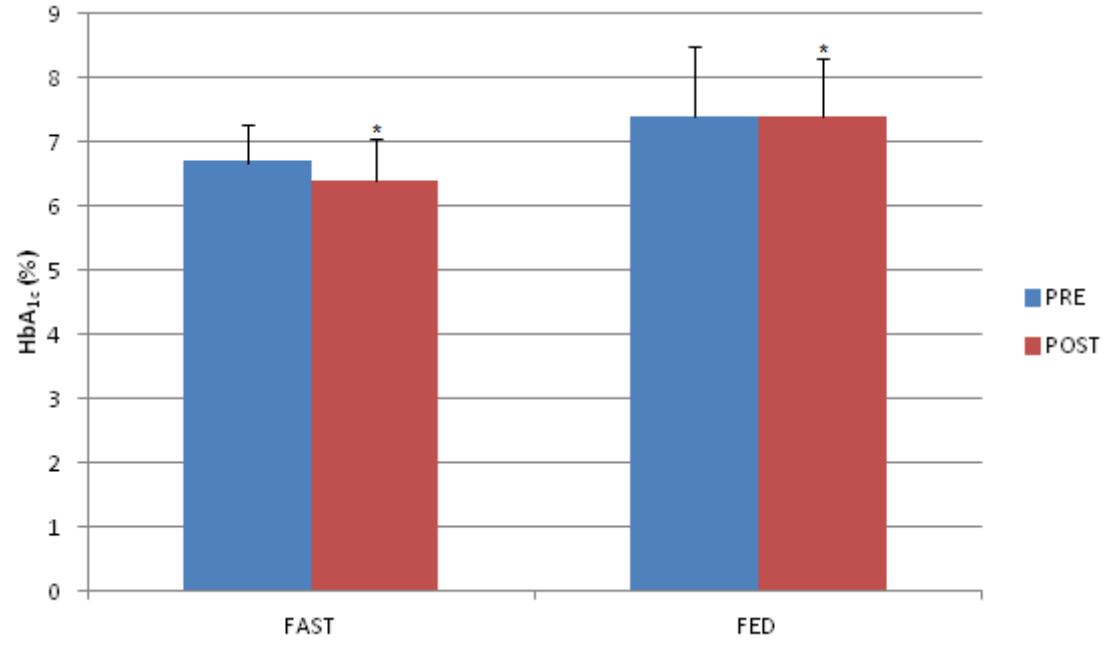
Figure 5: GDR



** significant training effect after 12 weeks of training in total group (p=0,04)*

Three months of exercise training led to a significant decrease in blood HbA1c levels in total group (FAST, from 6,7% ± 0,5 to 6,4% ± 0,6; FED, from 7,4% ± 1,1 to 7,4% ± 0,9; (p=0,04)) without significant interaction effects (p=0,20). (see figure 6)

Figure 6: HbA_{1c} levels

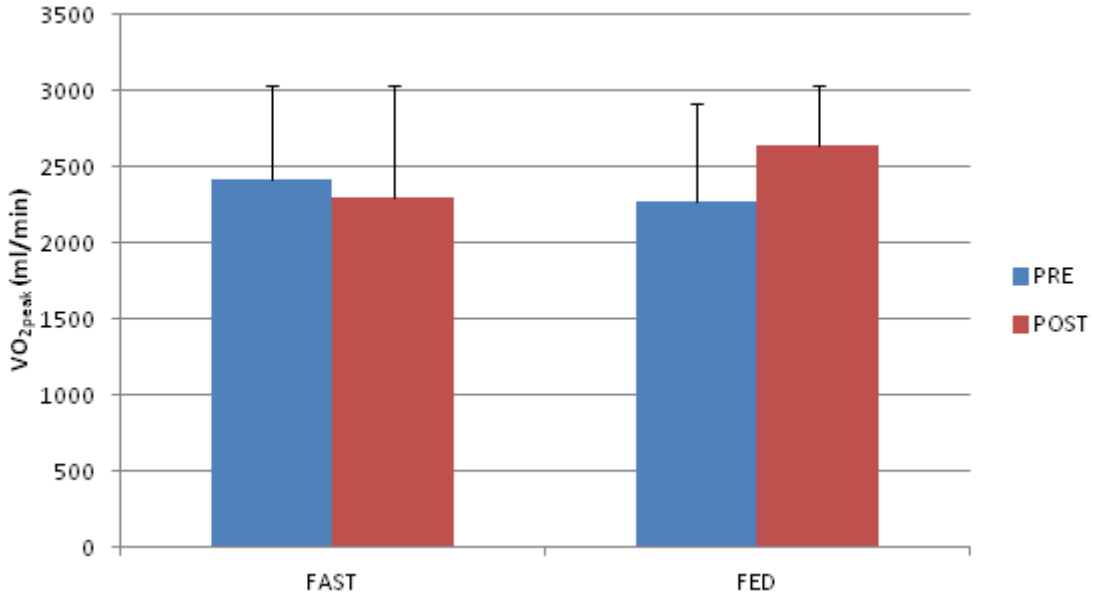


** Significant training effect after 12 weeks of training in total group (p=0,04)*

Maximal exercise capacity

No significant change in VO_{2peak} was assessed after 12 weeks of exercise training in both training groups (FAST; from 2414ml/min ± 617 to 2295,0ml/min ± 747; FED, from 2269ml/min ± 627 to 2644ml/min ± 410(p=0,93), without significant interaction between groups (p=0,14) (see figure 7). No significant change in RER_{peak} was found for both training groups after 12 weeks of exercise training (FAST, from 1,16 ± 0,05 to 1,18 ± 0,09; FED, from 1,21 ± 0,08 to 1,22 ± 0,09; (p=0,27)), without significant interaction effect between groups (p=0,54). No significant change in HR_{peak} was found after 12 weeks of exercise training (FAST, from 149bpm ± 23 to 141bpm ± 28; FED from 151bpm ± 19 to 156bpm ± 21; (p=0,07)), without significant interaction effects between groups (p=0,68).

Figure 7: VO_{2peak} levels

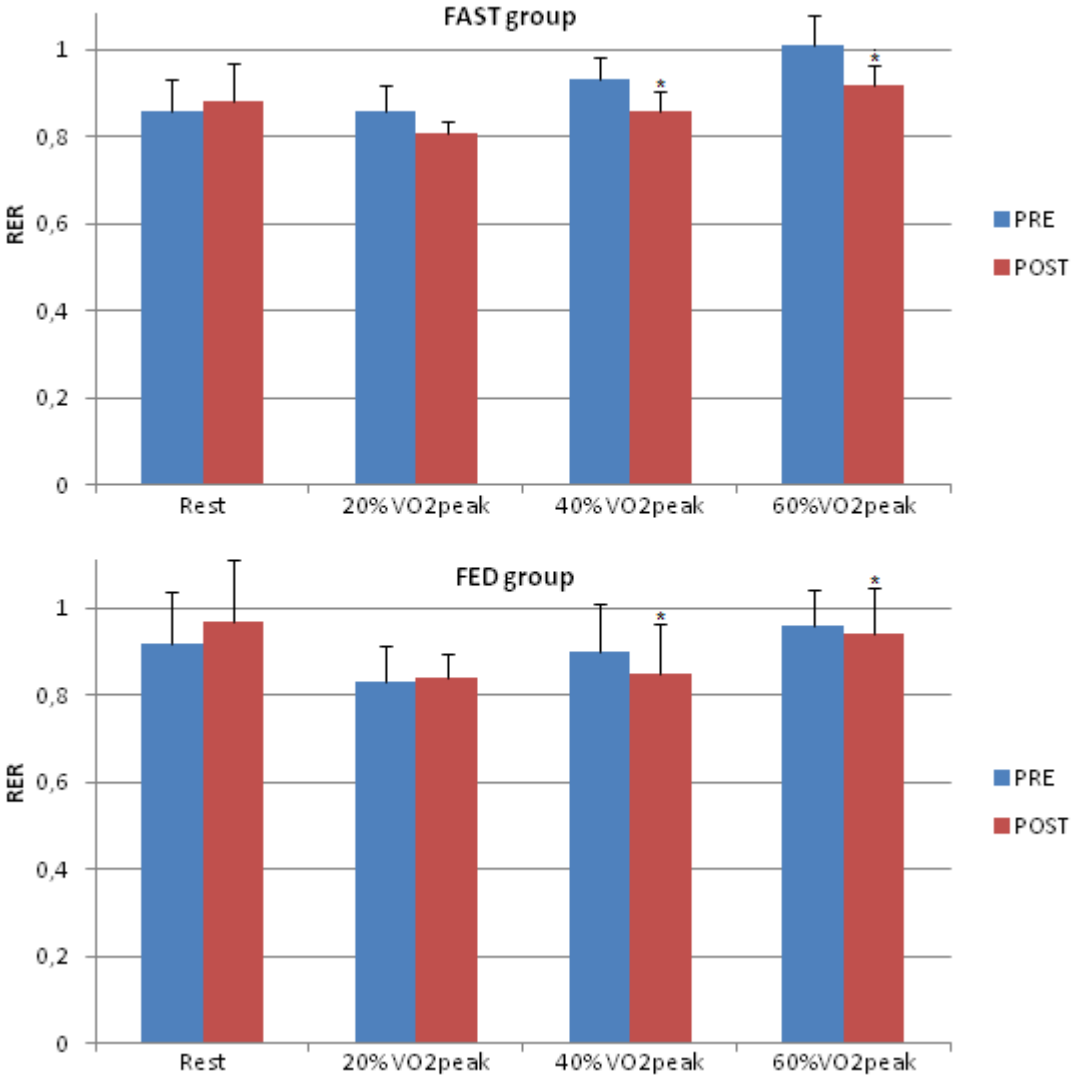


No significant effects

During the submaximal exercise test, RER, VO_2 and HR were analyzed at rest, at 20% VO_{2peak}, at 40% VO_{2peak} and at 60% VO_{2peak}. No significant exercise training effect was found for VO_{2rest} after 12 weeks (FAST, from 257ml/min ± 70 to 313ml/min ±73; FED, from 258ml/min ± 51 to 285ml/min ± 48; (p=0,06)), with no significant interaction effect between both intervention groups (p=0,32). No significant exercise training effect was found for VO_2 at 20% of VO_{2peak} (FAST, from 874ml/min ± 178 to 954ml/min ± 182; FED, from 778ml/min ± 256 to 758ml/min ±254; (p=0,50)), with no significant interaction effect between groups (p=0,52). 12 weeks of exercise training did not induce a training effect for VO_2 at 40% VO_{2peak} (FAST, from 1084ml/min ± 301 to 1224ml/min ± 260; FED from 978ml/min ± 518 to 1101ml/min ± 250; (p=0,71)), with no significant interaction effect for both groups (p=0,55). No significant exercise training effect was found for VO_2 at 60% VO_2peak (FAST, from 1450ml/min ± 414 to 1663ml/min ± 442; FED, from 1541ml/min ± 476 to 1631ml/min ± 276; (p=0,74)), with no significant interaction effect between groups (p=0,52). No significant change was found for HR_{rest} after 12 weeks of exercise training (FAST, from 70bpm ± 8 to 67bpm ± 7; FED, from 65bpm ±7 to 64bpm ± 9; (p=0,21)), with no significant interaction effect between groups (p=0,96). No significant change in HR at 40% VO_{2peak} was found after 12 weeks of exercise training (FAST, from 92bpm ± 7 to 90bpm ± 5; FED, from 78bpm ± 10 to 84bpm ± 18; (p=0,29)), with no significant interaction effect between groups (p=0,96). 12 weeks of exercise training

induced a significant training effect for HR at 40% VO_{2peak} (FAST, from 101bpm ± 8 to 98bpm ± 4; FED, from 90bpm ± 17 to 90bpm ± 19, (p=0,01), with no significant interaction effect between groups (p=0,48). A significant change after 12 weeks of exercise training was found for HR at 60% of VO_{2peak} (FAST, from 117bpm ± 15 to 112bpm ± 8; FED, from 97bpm ± 18 to 110bpm ± 25; (p=0,02)), with no significant interaction effect between groups (p=1,00). No significant change in RER_{rest} was found after 12 weeks of training (FAST, from 0,86 ± 0,07 to 0,88 ± 0,09; FED, from 0,92 ± 0,12 to 0,97 ± 0,14; (p=0,05)), with no interaction effect between both groups (p=0,57). No change in RER at 20% VO_{2peak} was found after 12 weeks of training (FAST, from 0,86 ± 0,06 to 0,81 ± 0,03; FED, from 0,83 ± 0,10 to 0,84 ± 0,06; (p=0,69)), with no significant interaction effect between groups (p=0,70). 12 weeks of exercise training induced a significant change in RER at 40% VO_{2peak} (FAST from 0,93 ± 0,04 to 0,86 ± 0,05; FED, from 0,90 ± 0,11 to 0,85 ± 0,12; (p=0,02)), with no significant interaction effect between groups (p=0,76). 12 weeks of exercise training also induced a significant effect for RER at 60% VO2peak (FAST, from 1,01 ± 0,07 to 0,92 ± 0,06; FED, from 0,96 ± 0,08 to 0,94 ± 0,09; (p=0,007)), with no significant interaction between both groups (p=0,57). RER values at rest, 20%, 40% and 60% VO_{2peak} are shown in Figure 8.

Figure 8: RER values at 20%, 40% and 60% VO_{2peak}



** significant training effect after 12 weeks in total group (RER 40%VO2peak, p=0,02; RER 60% VO2peak, p<0,01)*

Body composition

12 weeks of exercise training did not induce a significant change in arm adipose tissue mass (FAST, from 1716g ± 627 to 1524g ± 553; FED, from 1508g ± 434 to 1319g ± 347; (p=0,22), with no significant interaction effect for both groups (p=0,19). No significant change in leg adipose tissue mass was found after 12 weeks of exercise training (FAST, from 4449g ± 1018 to 3397g ± 1636; FED, from 4069g ± 807 to 3549g ± 1155; (p=0,12), with no significant interaction effect for both groups (p=0,80). 12 weeks of exercise training induced a significant effect for trunk adipose tissue (FAST, from 17860g ± 5308 to 15077g ± 5460; FED, from 17139g ± 3964 to 16313g ± 4689; (p=0,04)), with no significant interaction effect between both groups (p=0,24). We found a significant exercise training effect for total body adipose tissue (FAST, from 31919g ± 8514 to 27032g ± 9041; FED, from 29718g ± 6104 to 27412g ± 7538; (p=0,002)), with no significant interaction effect for both groups (p=1,00).

12 weeks of exercise training induced a significant effect for lean arm mass (FAST, from 3528g ± 739 to 3296g ± 397; FED, from 3514g ± 509 to 3400g ± 578; (p=0,03)), with no significant interaction effect between groups (p=0,90). No significant exercise training effect was found for lean leg mass (FAST, from 9514g ± 1080 to 9887g ± 1038,9; FED, from 9706g ± 1126 to 9354g ± 1507; (p=0,30)), with no significant interaction effect between groups (p=0,06). No significant change was found for lean trunk mass after 12 weeks of exercise training (FAST, from 30571g ± 3987 to 30176g ± 2867; FED, from 30352g ± 2321 to 29812g ± 4058; (p=0,92)), with no significant interaction effect between groups (p=0,90). No change was found for total lean mass after 12 weeks of exercise training (FAST, from 60695g ± 7321 to 60122g ± 5789; FED, from 60898g ± 5480 to 59208g ± 8325; (p=0,93)), with no significant interaction effect between both groups (p=0,30).

Table 2: Pre and Post test measurements

Variable	FAST		FED		Effect of training (*p* value)	Interaction between FAST and FED (*p* value)
	PRETEST	**POSTTEST**	**PRETEST**	**POSTTEST**		
Insuline sensitivity						
HbA_{1c} (%)	6,7 ± 0,5	6,4 ± 0,6	7,4 ± 1,1	7,4 ± 0,9	0,04*	0,41
GDR (mg/m/kg)	10,7 ± 10,9	18,9 ± 16,3	10,0 ± 8,6	14,0 ± 11,0	0,04*	0,20
Exercise capacity						
VO_{2peak} (ml/min)	2414 ± 617	2295 ± 747	2269 ± 627	2644 ± 410	0,93	0,14
HR_{peak} (bpm)	149 ± 23	141 ± 28	151 ± 19	156 ± 21	0,07	0,68
RER_{peak} (VCO_2/VO_2)	1,16 ± 0,05	1,18 ± 0,09	1,21 ± 0,08	1,22 ± 0,09	0,27	0,54
VO_{2rest} (ml/min)	257 ± 70	313 ± 73	258 ± 51	285 ± 48	0,06	0,32
VO_2 20% VO_{2peak} (ml/min)	874 ± 178	954 ± 182	778 ± 256	758 ± 254	0,50	0,52
VO_2 at 40% VO_{2peak} (ml/min)	1084 ± 301	1224 ± 260	978 ± 518	1101 ± 250	0,71	0,55
VO_2 60% VO_{2peak} (ml/min)	1450 ± 414	1663 ± 442	1541 ± 476	1631 ± 276	0,74	0,52
HR_{rest} (bpm)	70 ± 8	67 ± 7	65 ± 7	64 ± 9	0,21	0,96
HR at 20% VO_{2peak} (bpm)	92 ± 7	90 ± 5	78 ± 10	84 ± 18	0,29	0,96
HR at 40% VO_{2peak} (bpm)	101 ± 8	98 ± 4	90 ± 17	90 ± 19	0,01*	0,48
HR at 60% VO_{2peak} (bpm)	117 ± 15	112 ± 8	97 ± 18	110 ± 25	0,02*	1,00
RER_{rest}	0,86 ± 0,07	0,88 ± 0,09	0,92 ± 0,12	0,97 ± 0,14	0,05	0,57
RER at 20% VO_{2peak}	0,86 ± 0,06	0,81 ± 0,03	0,83 ± 0,10	0,84 ± 0,06	0,69	0,70
RER at 40% VO_{2peak}	0,93 ± 0,04	0,86 ± 0,05	0,90 ± 0,11	0,85 ± 0,12	0,02*	0,76
RER at 60% VO_{2peak}	1,01 ± 0,07	0,92 ± 0,06	0,96 ± 0,08	0,94 ± 0,09	0,007*	0,57
Body composition						
Fat mass Arms (g)	1716 ± 627	1524 ± 553	1508 ± 434	1319 ± 347	0,22	0,19
Fat mass Legs (g)	4449 ± 1018	3397 ± 1636	4069 ± 807	3549 ± 1155	0,12	0,80
Fat mass Trunk (g)	17860 ± 5308	15077 ± 5460	17139 ± 3964	16313 ± 4689	0,04*	0,24
Fat mass Total (g)	31919 ± 8514	27032 ± 9041	29718 ± 6104	27412 ± 7538	0,002*	1,00
Lean mass arms (g)	3528 ± 739	3296 ± 397	3514 ± 509	3400 ± 578	0,03*	0,90
Lean mass Legs (g)	9514 ± 1080	9887 ± 1038	9706 ± 1126	9354 ± 1507	0,30	0,06
Lean mass Trunk (g)	30571 ± 3987	30176 ± 2867	30352 ± 2321	29812 ± 4058	0,92	0,90
Lean mass Total (g)	60695 ± 7321	60122 ± 5789	60898 ± 5480	59208 ± 8325	0,93	0,30
Training intensity						
Kcal/session (kcal)	360 ± 74	445,5 ± 112	343 ± 110	433 ± 110	<0,01*	0,92
BORG-score	12,1 ± 1,9	11,3 ± 2,1	12,1 ± 1,4	9,8 ± 1,6	0,28	0,008#

DISCUSSION

In this study, it was found that 3 months of exercise training led to an improvement in blood HbA_{1c}, GDR, metabolic flexibility, total fat mass and lean arm mass ($p<0,05$) in patients with T2DM. However, the effects of exercise training in fasted or fed state were comparable between groups.

Caloric expenditure during training sessions were comparable between groups, therefore inconsistency in training results between fasted and fed group cannot be explained by a difference in caloric expenditure.

During the 3 month training period, a significantly lower rate of perceived exertion was observed in the fasted group as opposed to the fed group. This effect is somewhat remarkable because fasted exercise training is considered to be more challenging. However, our findings are in agreement with a previous study that examined exercise training in the fed or fasted state in competitive cyclist (13). The explanation behind this remarkable effect is still unknown. However, others found an increased blood epinephrine level during exercise training in the fasted state. (8) this could lead to lowered sensations of pain and exertion during exercise training. The latter hypothesis remains to be verified. A lower rating of perceived exertion during exercise training could enhance therapy compliance and lead to elevated and/or prolonged participation into training programs in T2DM patients, although this remains to be verified.

Low physical activity and persistent elevations in blood sugar (HbA_{1c}) increase the risk of cardiovascular mortality (14). We found that a 3-month exercise training program led to a significant reduction in blood HbA_{1c} levels ($p=0,04$). This finding is in line with previous studies reporting significant decrements in blood HbA1c levels in T2DM patients (15). Therefore exercise training may be of great importance in the treatment of T2DM. However, the impact of exercise training in fed or fast state on blood HbA1c seems comparable in T2DM. It thus follows that an equal improvement in glycemic control is achieved when exercising in the fed or fasted state.

We found a significant improvement of the glucose disposal rates after 3-months of exercise training in T2DM ($p=0,04$). However, the impact of exercise training in fed or fasted state on GDR seems comparable in T2DM, it thus follows that an equal improvement in glucose tolerance (GDR) is achieved by exercise training in the fasted or fed state. No significant interaction effect was found for fasted state exercise training as opposed to fed state exercise training for GDR. Our data seemed to contradict previous findings. Van Proeyen et al. found a significant improvement in insulin sensitivity in healthy subjects as a result of exercise training in the fasted state for 8 weeks, here a significantly smaller increase in insulin sensitivity was observed during exercise training in the fed state (9). However, we examined T2DM patients (as opposed to young healthy subjects in the study from Van Proeyen et al) (9) which may have an alteration in response to different training programs. Therefore, more studies in T2DM patients should be executed to verify our findings. On the other hand, our data on GDR are in line with the observed changes in blood HbA1c levels.

T2DM patients participating into long term training programs leads to adipose tissue mass loss. (14). In the present study, subjects lost ± 2000g of adipose tissue mass, predominantly in the trunk region, after three months of exercise training. Body weight loss of minimally 5% of body weight provide clinical benefits (insulin resistance, glycemia, lipemia, and blood pressure) in T2DM patients (16). It has been

proven that intra-abdominal fat distribution is a key factor contributing to the aggravation of insulin resistance in T2DM patients. On the contrary, peripheral fat distribution has shown to be less detrimental in case of insulin resistance in T2DM patients (17). Therefore we conclude that exercise training is important for intra-abdominal fat mass loss in T2DM patients to improve their insulin sensitivity. However, a similar adipose tissue mass loss was observed between the fed and fasted training group in the present study. Therefore, exercise in the fasted state does not lead to greater adipose tissue mass loss, even though the lipolytic response during exercise would be significantly greater.

In the present study, RER at 40% and at 60% of VO_{2peak} decreased significantly ($p<0,05$), without a different change between groups. These lower RER-values could lead to an increased fat oxidation capacity during exercise, which is important for T2DM patients as they suffer from metabolic inflexibility in oxidative fuel selection of skeletal muscles (18).

In this study certain limitations were present. We only studied males, a small sample size was examined and a relatively short training program was implemented. In addition, the food intake and physical activity level at home was not evaluated. On the other hand, many outcome parameters were measured by gold standard techniques: Dual X-ray absorptiometry for body composition, hyperinsulinemic euglycemic clamp test for insulin sensitivity and ergospirometric testing for the assessment of exercise tolerance.

CONCLUSION

We conclude that exercise training in the fasted state is equally effective as exercise training in the fed state to improve insulin sensitivity, exercise capacity and body composition in T2DM patients. Exercise training in the fasted state is experienced easier as opposed to exercise training in the fed state. Further research remains warranted to verify our findings.

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