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Increased insulin-stimulated glucose uptake in both leg and arm muscles after sprint interval and moderate intensity training in subjects with Type 2 Diabetes or Prediabetes

High-intensity training and type 2 diabetes

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ABSTRACT

We investigated the effects of sprint interval (SIT) and moderate intensity continuous training (MICT) on glucose uptake (GU) during hyperinsulinemic euglycemic clamp and fatty acid uptake (FAU) at fasting state in thigh and arm muscles in subjects with type 2 diabetes (T2D) or prediabetes.

Twenty-six patients (age 49, SD 4; 10 women) were randomly assigned into two groups: SIT (n=13), and MICT (n=13). The exercise in the SIT group consisted of 4–6 x 30 s of all-out cycling with 4 min recovery and in the MICT group 40–60 min cycling at 60% of VO_{2peak}. Both groups completed six training sessions within two weeks. GU and FAU were measured before and after the intervention with positron emission tomography in thigh (quadriceps femoris, QF; and hamstrings) and upper arm (biceps and triceps brachii) muscles.

Whole-body insulin-stimulated GU increased significantly by 25% in both groups and this was accompanied with significantly increased insulin-stimulated GU in all thigh and upper arm muscles and significantly increased FAU in QF. Within QF, insulin-stimulated GU improved more by SIT than MICT in rectus femoris (p=0.01), but not differently between the training modes in the other QF muscles.

In individuals with T2D or prediabetes, both SIT and MICT training rapidly improve insulin-stimulated GU in whole body and in the thigh and arm muscles as well as FAU in the main working muscle QF. These findings highlight the underused potential of exercise in rapidly restoring the impaired skeletal muscle metabolism in subjects with impaired glucose metabolism.

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INTRODUCTION

Prevalence and incidence of type 2 diabetes (T2D) is increasing throughout the world (Danaei *et al.*, 2002). It is well known that regular exercise is an effective, though underused method for the prevention and treatment of T2D (Colberg *et al.*, 2010). Emerging research in healthy subjects shows that not only moderate intensity continuous training (MICT), but also more vigorous high-intensity interval training (HIIT) causes health-enhancing changes in the body, such as increased VO_{2peak} (Milanovic *et al.*, 2015;Sloth *et al.*, 2013;Gist *et al.*, 2014), improved whole-body insulin sensitivity (Eskelinen *et al.*, 2015;Jelleyman *et al.*, 2015), and increased skeletal muscle (Burgomaster *et al.*, 2008) and whole-body fat oxidation (Astorino *et al.*, 2013).

The current recommendations for physical activity for people with T2D include moderate intensity aerobic exercise at least three times a week, totally for 150 minutes. This kind of exercise training benefits glucose control in T2D patients at least as effectively as drug therapy or diet (Snowling & Hopkins, 2006). Interestingly, recent studies with different HIIT protocols and large range of intensities show that HIIT can have at least equivalent health-enhancing effects also in subjects with T2D or prediabetes. For example, VO_{2peak} (Karstoft *et al.*, 2013;Robinson *et al.*, 2015;Tjønna *et al.*, 2008;Mitranun *et al.*, 2014) and whole-body insulin sensitivity (Mitranun *et al.*, 2014;Tjønna *et al.*, 2008) have increased, and fasting plasma glucose concentration (Karstoft *et al.*, 2013;Mitranun *et al.*, 2014) decreased at least equally after HIIT as MICT intervention in subjects with T2D or prediabetes, with some exceptions (Robinson *et al.*, 2015). Plasma glycated hemoglobin (HbA1c) concentration has decreased more by HIIT than MICT intervention in one study (Mitranun *et al.*, 2014), but the improvement has not been evident in all studies (Karstoft *et al.*, 2013;Terada *et al.*, 2013). On the other hand, HIIT has also effectively reduced body mass (Mitranun *et al.*, 2014), body mass index (BMI) (Karstoft *et al.*, 2013;Mitranun *et al.*, 2014) and body fat content (Mitranun *et al.*, 2014;Terada *et al.*, 2013;Karstoft *et al.*, 2013) in patients with T2D.

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Improved whole-body insulin-stimulated glucose uptake (GU) after training can be due to an effect in many tissues, but is mostly attributed to skeletal muscle (Dela *et al.*, 1992;Dela & Stallknecht, 2010;Reichkendler *et al.*, 2013). We recently showed that GU increases in the main working muscle, quadriceps femoris (QF) muscle group, at least as effectively after a short-term very intense sprint interval training (SIT) as MICT in healthy men (Eskelinen *et al.*, 2015). On the other hand, we did not observe any significant changes in GU in upper body muscles or in fatty acid uptake (FAU) in any of the studied muscles (Eskelinen *et al.*, 2015). The feasibility and the effects on glucose and fat metabolism of such a demanding SIT intervention in subjects with T2D or impaired glucose metabolism are unknown.

In the present study we used positron emission tomography (PET) combined with fluorine-18 labelled tracers, 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) and 14(R,S)-[^{18}F]fluoro-6-thia-heptadecanoic acid ([^{18}F]FTHA), to measure glucose and free fatty acid uptake in the thigh and arm muscles in response to SIT and MICT training performed by leg cycling exercise. In our previous study we found no significant difference in GU after SIT and MICT in healthy subjects, but a more extensive meta-analysis shows that whole-body insulin sensitivity has increased more by HIIT than MICT in both healthy and diabetic or metabolic syndrome patients (Jelleyman *et al.*, 2015). Thus we tested the hypothesis that insulin-stimulated GU would be increased in the QF more after SIT than MICT. In addition, as patients with T2D or prediabetes consistently have poor physical fitness (Reusch *et al.*, 2013) and training can thus induce more profound metabolic changes in patients with T2D or prediabetes compared to healthy subjects, we also hypothesized that GU would be improved in these patients also in other muscles than just the main working muscle QF, and that the training would also improve muscle FAU.

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MATERIALS AND METHODS

Subjects

Fifty-seven subjects were screened, and eligible twenty-six sedentary [age 49 (SD 4) years], individuals (10 female) with either non-insulin-treated T2D or prediabetes (impaired glucose tolerance, IGT and/or impaired fasting glucose, IFG) were admitted into this study. The recruitment was done with newspaper advertisements, using personal contacts, and by using electronic and traditional bulletin boards. The inclusion criteria were age of 40-55 years and a good treatment balance in case of T2D. The exclusion criteria were as follows: any other chronic disease or defect which hinder daily life, smoking or use of narcotics, history of anorexia nervosa or bulimia, history of asthma, current or history of regular and systematic exercise training, VO_{2peak} > 40 $ml \cdot kg^{-1} \cdot min^{-1}$, or any other condition that in the opinion of the investigator could create a hazard to the participant's safety, endanger the study procedures, or interfere with the interpretation of the study results. According to the diagnostic criteria of WHO (World Health Organisation, 2006), seventeen of the subjects had T2D, seven had both IGT and IFG, and two had IFG. Nine of the subjects in the SIT group and four in the MICT group were treated by oral hypoglycemic agents (table 1). The subjects were instructed not to alter their eating habits or daily activities during the intervention.

Previously we observed that GU was increased in the QF by 53% after SIT and by 28% after MICT in healthy subjects undergoing the same training protocols as in the present study. As patients with T2D generally have poorer physical fitness, we assumed that the training responses and the difference in training response between the groups would be even larger in these patients. We calculated that a sample size of 10 subjects per group with the increases of 60% and 30% for HIIT and MICT would give > 90% power of detecting significant difference in the training response between the groups with a level of significance at 5% (two-tailed). To allow possible drop-outs and possible technical problems in acquiring or in the analyses of the data, three extra subjects were recruited for both groups. During the intervention, two participants from the SIT group dropped out, one due to migraine

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headache during the first exercise session, and one due to claustrophobic sensation in the MR scanner. Three participants from the MICT group dropped out due to personal reasons.

The health status of the subjects was determined by a thorough physical examination. The purpose, nature, and potential risks were verbally and literally explained to the subjects before they gave their informed consent to participate. The study was performed according the Declaration of Helsinki and was approved by the Ethical Committee of the Hospital District of South-Western Finland (decision 95/180/2010 §228). The present study is a part of a larger study entitled: ''The Effects of Short-Term High-Intensity Interval Training on Tissue Glucose and Fat Metabolism in Healthy Subjects and in Patients with Type 2 Diabetes'' (NCT01344928).

Study design

The measurements and the training intervention were conducted at the Turku PET Centre, Turku, Finland. VO_{2peak} and body composition were measured at The Paavo Nurmi Centre, University of Turku, Turku, Finland. The measurement procedures were similar to our previous study in healthy subjects (Eskelinen *et al.*, 2015). Pre-training oral glucose tolerance test (OGTT) was performed during the screening day as previously described (Eskelinen *et al.*, 2015). This was followed by a VO_{2peak} test on the same or one of the next few days (see more details below). At least a week later, a [^{18}F]FTHA-PET study was performed to measure FAU in different muscles in the fasting state (see more details below). Before the [^{18}F]FTHA-PET study, myocardial perfusion was measured with [^{15}O]H_2O-PET in the basal state and during adenosine stress. These results are not reported in the present paper. On the next day, a [^{18}F]FDG-PET study under hyperinsulinemic euglycemic clamp was performed to measure insulin-stimulated GU in different muscles (see more details below) as previously described for the healthy subjects (Eskelinen *et al.*, 2015). Subjects were required to have fasted for at least 10 h before the OGTT and PET measurement days. They were also instructed to abstain from caffeinated drinks and to avoid exhausting exercise 48 h prior to the studies. After all

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the pre-training measurements, the subjects were randomly allocated into two training groups: either into the SIT or MICT group. Randomization was performed in random permuted blocks of four subjects with 1:1 ratio.

All the measurements were repeated after the training interventions starting on the second day (about 48 hours) after the last training session. The post-training measurements were started with the [^{18}F]FTHA-PET study, followed by the hyperinsulinemic euglycemic clamp and the [^{18}F]FDG-PET study on next day, and completed with OGTT and VO_{2peak} tests on the fourth post-training day.

Training interventions

Similarly to our previous study (Eskelinen *et al.*, 2015;Kiviniemi *et al.*, 2014) both groups (SIT and MICT) trained six sessions within two weeks in controlled laboratory conditions. The progressive SIT training included 4–6 × 30 s of all-out cycling efforts with 4 min of recovery between the bouts, during which participants were allowed to remain still or do unloaded cycling (Monark Ergomedic 894E; Monark, Vansbro, Sweden) as based on the protocol originally described by Burgomaster et al. (2005). The initial number of bouts was 4 and it was increased by one after every other session. Each bout started with about a five-second acceleration to maximal cadence without any resistance, followed by a sudden increase of the load (10% of the fat free body mass in kg) and continued by maximal cycling for 30 seconds. The participants were shortly familiarized with the SIT training protocol during the screening phase (2 x 30 s bouts). A session of MICT group consisted of 40-60 min of cycling at an intensity of 60% of VO_{2peak} with an electrically-braked ergometer (Tunturi E85, Tunturi Fitness, Almere, the Netherlands). The duration of cycling was initially 40 min, and it was increased by 10 min after every other session until 60 min was reached during the last two sessions. 5 min low-intensity warm-up and cool-down periods were included in both training modes before and after each session.

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PET measurements

The GU and FAU measurements were performed as previously described (Eskelinen *et al.*, 2015). The PET and CT imaging was performed with GE Advance PET/CT scanner (General Electric Medical System, Milwaukee, WI, USA).

FAU was measured using [^{18}F]FTHA (half-life 110 min) that was produced as previously described (DeGrado, 1991;Maki *et al.*, 1998). The tracer [155 (SD 9) MBq] was injected into the vein and scanning of the thoracic region (biceps and triceps brachii muscles) was started simultaneously and continued for 40 minutes in 4 x 15 s, 6 x 20 s, 2 x 60 s, 2 x 150 s and 6 x 300 s time frames. The femoral region (quadriceps femoris and hamstring muscle groups) was scanned starting approximately at 65 minutes after the tracer injection in 3 x 300 s time frames. Starting at 4 min after the tracer injection, blood samples for plasma radioactivity determination (Wizard 1480 3; Wallac, Turku, Finland) and calculation of input function were collected at approximately (exact timing was recorded) 4, 5, 7.5, 10, 20, 30, 55, and 70 min time points. As the heart was in the imaging area, the activity in the LV chamber in the first ten time frames (first 3 min) in PET image set were used for determination of input function for that period. Additional blood samples were collected to measure the metabolites of the [^{18}F]FTHA to make pure plasma [^{18}F]FTHA input function.

Insulin-stimulated GU was measured using [^{18}F]FDG (half-life 110 min) that was produced as previously described (Hamacher *et al.*, 1986;Lemaire *et al.*, 2002). The tracer [157 (SD 10) MBq] was injected into the vein and similar scans with similar framing from thoracic and femoral regions were performed as in the [^{18}F]FTHA-study. Also plasma radioactivity samples for input function were taken similarly, but no other samples were needed as [^{18}F]FDG is not metabolized. Due to technical issues some of the PET measurements were unsuccessful. The [^{18}F]FTHA study was successfully completed for 25 subjects (12 SIT, 13 MICT) pre- and for 17 subjects (8 SIT, 9 MICT) postintervention. The [^{18}F]FDG study was successfully completed for 24 subjects (11 SIT, 13 MICT) pre- and for 19 subjects (9 SIT, 10 MICT) postintervention.

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PET data analysis

All PET image data were corrected for dead time, decay, and photon attenuation and reconstructed using 3D-OSEM reconstruction method. Carimas software (version 2.9, Turku PET Centre, Turku, Finland, www.turkupetcentre.fi/carimas) was used in the image analysis. Regions of interest (ROIs) were drawn manually into the CT images and copied into the PET images for the data analysis. Femoral region ROIs encompassed the four heads of QF individually (rectus femoris, RF; VL; vastus medialis, VM; vastus intermedius, VI) and the hamstring muscle group (semitendinosus, semimembranosus, and biceps femoris) in five cross-sectional mid-thigh planes (5 x 3.3 mm thick). For the QF as a whole, the weighted average according to cross-sectional area of the four heads of QF was calculated. For the upper arm muscles, ROIs were drawn into the biceps and triceps brachii muscles on three subsequent cross-sectional mid-muscle planes. Using these ROIs, tissue time activity curves (TACs) were extracted from the PET data.

Fractional rate of tracer uptake was calculated using graphical analysis using tissue and plasma TACs as previously described (Eskelinen *et al.*, 2015). The rate of glucose (GU) and fatty acid uptake (FAU) was calculated by multiplying the fractional tracer uptake rate by the average plasma glucose or plasma free fatty acid concentration of the study subjects from the repeated samples during the PET scan. With GU this was further divided by the lumped constant value of 1.2 (Peltoniemi *et al.*, 2000). Analyses of plasma glucose concentrations were performed at the Turku PET Centre laboratory and analyses of plasma FFAs as well as hemoglobin (Hb) and hematocrit (Hct) at the laboratory of Turku University Hospital using standard assays.

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Hyperinsulinemic euglycemic clamp

The hyperinsulinemic euglycemic clamp study was performed as previously described (Eskelinen *et al.*, 2015). It was performed after at least 10 hours of fasting. A primed-constant insulin (Actrapid, 100 U · ml^{-1}, Novo Nordisk, Bagsvaerd, Denmark) infusion was started with the rate of 40 mU · m^2 of body surface area in minutes during the first 4 min. From 4 to 7 min, infusion rate was reduced to 20 $mU \cdot m^{-2} \cdot min^{-1}$, and, from 7 min to the end of the clamp, it was kept constant at 10 $mU \cdot m^{-2} \cdot min^{-1}$. Exogenous glucose infusion was started 4 min after the start of the insulin infusion with a rate of subject's weight (kg) · $0.1^{-1} \cdot g^{-1} \cdot h^{-1}$. At 10 min, glucose infusion was doubled, and after that further adjusted according to blood glucose concentration to keep it as closely as possible to the level of 5 mmol · l^{-1}. Arterialized venous blood samples were collected before the clamp and every 5 min during the first 30 min of the clamp and later every 10 minutes to determine the glucose concentration for adjusting the glucose infusion rate. Whole body insulin-stimulated GU rate was calculated from the measured glucose values collected during the PET scan that was started 95 min (SD 20) after the start of the clamp. FDG-PET study was performed when the subject had reached the stable glucose concentrations at the level of 5 mmol · l^{-1} (within 5% range for at least 15 min) after positioning into the PET scanner (table 2).

VO_{2peak} test and body composition

Similarly to the previous description of the study in the healthy subjects (Eskelinen *et al.*, 2015;Kiviniemi *et al.*, 2014), the subjects with T2D or prediabetes in this study performed an exercise test (VO_{2peak} test) on a bicycle ergometer (Ergoline 800s; VIASYS Healthcare, Germany) to determine peak oxygen consumption. The participants were asked to abstain from eating and drinking at least for 2 hours before the testing. The test was started at 50 W and followed by an increase of 30 W every 2 minutes until volitional exhaustion. Ventilation and gas exchange (Jaeger Oxycon Pro; VIASYS Healthcare) were measured and reported as the mean value per minute. The peak respiratory

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exchange ratio was at least 1.17 and the peak blood lactate concentration, measured from capillary samples obtained immediately and 1 min after exhaustion (analyzed using YSI 2300 Stat Plus; YSI Incorporated Life Sciences, Yellow Springs, OH), was at least 7.4 $mmol \cdot l^{-1}$ for all the tests. The highest 1-min mean value of oxygen consumption was used as VO_{2peak}. The test was performed for each participant before the intervention and 4 days after the last training session at approximately the same time of day at the test laboratory of the Paavo Nurmi Centre, University of Turku, Turku, Finland. Body composition was measured also at the Paavo Nurmi Centre using a bioimpedance monitor (InBody 720, Mega Electronics Ltd., Kuopio, Finland).

Statistical analysis

All the data are presented as mean (95% confidence interval, CI). Normal distribution of the variables was evaluated visually and tested using Shapiro-Wilk test. Logarithmic transformations were done to achieve the normal distribution assumption for all GU data, for FAU in the hamstrings, as well as for insulin concentrations, insulin AUC, glucose (FTHA), and body fat percentage.

The difference between the groups at the baseline was tested using t-test for age and height and Fisher's exact test for the diabetes status (T2D or prediabetes) and gender. For all other parameters reported in tables 1 and 2 and figures 1 and 2 we used a hierarchical linear mixed model including one within-factor (time) and one between-factor (group). Compound symmetry covariance structure was used for time. The diabetes status (T2D/prediabetes) and gender were used as additional factors for all the analyses. Subjects with one value, but another missing (drop outs, technical problems) are included in this model and therefore model-based mean (SAS least square means) values are reported for all the parameters. Comparisons between the changes in GU and blood glucose variables were performed by Pearson's correlation coefficient (r) and by Spearman's rank correlation coefficient (ρ) for non-normally distributed data.

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All the tests were performed as two-sided with a significance level set at 0.05. The analyses were performed using SAS System, version 9.3 for Windows (SAS Institute Inc., Cary, NC, US).

RESULTS

Subjects characteristics and whole-body findings

At the baseline, the two training groups did not differ according to any of the characteristics reported in this study (by t-test or Fisher's exact test). Over the study, fat percentage decreased (p=0.018 for the time effect) in both training groups, but body weight, BMI, and fat free mass (FFM) only tended to change (all p≤0.11 for the time effect). VO_{2peak} changed differently between the groups (p=0.0495 for the group*time interaction), increasing by 5.0%, 1.3 (0.3, 2.3) $ml \cdot kg^{-1} \cdot min^{-1}$ (p=0.013 for the time effect) in the SIT group and remaining unchanged in the MICT group, -0.2 (-1.3, 0.9) $ml \cdot kg^{-1} \cdot min^{-1}$ (p=0.75 for the time effect). In both groups HbA1c decreased (p=0.002 for the time effect), Hb and Hct decreased (p<0.001 and p<0.001), 2-h glucose OGTT tended to decrease (p=0.089), and whole-body insulin-stimulated GU (M-value in the hyperinsulinemic euglycemic clamp) increased (p=0.001) during the intervention, whereas there was no change in the fasting glucose or insulin levels. When Hb was added to the model, the decrease in HbA1c was no longer significant (p=0.22 for the time effect, p=0.74 for group*time interaction).

Glucose, FFA, and insulin concentrations during the PET studies

The glucose and FFA concentrations during both PET measurements were similar between the groups and did not change during the intervention (Table 2). The insulin levels during the FAU measurements decreased (p=0.002 for the time effect) with no difference between the groups (p=0.54 for the group*time interaction, Table 2).

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GU and FAU in different lower and upper body muscles

The insulin-stimulated GU increased statistically significantly in QF, hamstrings, and biceps and triceps brachii in both training groups without statistically significant difference between the groups (see Fig. 1 for statistics). In the QF the GU increased by 3.35 (2.45, 4.59) µmol·100 g^{-1}·min^{-1} in the SIT group ($p<0.001$), and by 1.70 (1.27, 2.29) µmol·100 g^{-1}·min^{-1} in the MICT group ($p<0.001$), which correspond to 138% and 93% changes in average, respectively.

Within QF, RF responded differently to training interventions ($p=0.010$ for the group*time interaction) so that GU increased significantly more in the SIT group (Fig. 2). However, in the vasti muscles (VL, VM and VI) GU increased after both training modes (all $p<0.001$ for the time effect), but not differently between the groups (all $p>0.26$ for the group*time interaction, Fig. 2).

The change in the 2-h glucose OGTT correlated strongly with the change in GU in the QF ($\rho=-0.87$, $p=0.002$) and triceps brachii ($\rho=-0.83$, $p=0.005$) in the SIT group, but not significantly in the MICT group. The changes in fasting glucose or glucose AUC in the OGTT did not correlate significantly with the changes in GU in any of the investigated muscles.

The FAU increased statistically significantly in the QF, but not in hamstrings, biceps, or triceps brachii. Training interventions increased FAU in all the four heads of QF (all $p\leq0.036$ for the time effect), but not statistically differently between the groups (all $p>0.60$ for group*time interaction).

DISCUSSION

Both SIT and MICT have been shown to be effective in improving insulin-stimulated glucose uptake in the main working muscle, QF in healthy subjects (Eskelinen *et al.*, 2015). Here we show that these training modes are even more effective in the subjects with T2D or prediabetes, as only six session of SIT or MICT within two weeks induced dramatic 138% and 93% increases in QF GU compared to 53%

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and 28% increase previously observed in healthy subjects. Furthermore, in contrast to healthy subjects, GU increased significantly also in the hamstrings and arm muscles and also FAU increased in the QF. Correspondingly with the findings in healthy subjects, GU in the RF increased significantly more after SIT than after MICT. These findings underscore the remarkable possibilities that exercise training - either SIT or MICT - has to restore impaired skeletal muscle insulin-stimulated glucose uptake and insulin sensitivity even in a very short time frame.

In the present study, in subjects with T2D or prediabetes, both SIT and MICT training increased whole-body insulin sensitivity (M-value) similarly by 25% on average. This finding agrees well with the previous findings, although the changes were larger here than in our previous study with healthy subjects after similar training interventions (Eskelinen *et al.*, 2015). Also other studies have shown markedly improved insulin sensitivity in subjects with T2D or prediabetes after HIIT and/or MICT interventions (Mitranun *et al.*, 2014;Tjønna *et al.*, 2008). Interestingly, training also decreased HbA1c significantly in both groups even though fasting glucose values remained unchanged. One potential explanation for decreased HbA1c could be decreased postprandial plasma glucose levels (Praet *et al.*, 2006), as it has been shown that even a single session of HIIT or MICT leads to significantly attenuated postprandial plasma glucose levels and 24-hour glucose profiles (Francois *et al.*, 2014;Gillen *et al.*, 2012;Little *et al.*, 2011) and HbA1c is more closely related to postprandial than fasting glucose levels (Ketema & Kibret, 2015). Another potential and even more likely explanation considering the short intervention could be the observed hemodilution. Hb and Hct decreased significantly after the training in the present study, probably due to increased plasma volume as typically observed after training. When Hb was added into the analysis as covariate the changes in HbA1c were no longer statistically significant. It is possible that at least a part of the decreases in HbA1c observed in previous studies with relatively short training interventions have been due to the same mechanism, but have not been considered.

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Interestingly, despite the positive effects on whole body glucose metabolism, the training responses in VO_{2peak} differed significantly between the groups (p=0.0495). While VO_{2peak} improved after SIT, it remained essentially unchanged after MICT. This contrasts our previous findings of improved VO_{2peak} after both SIT and MICT in healthy subjects (Eskelinen *et al.*, 2015). The changes in VO_{2peak} have been similar (about 5 – 7%) after two weeks of SIT in other studies with healthy individuals (Sloth *et al.*, 2013), but the results in HIIT studies in subjects with T2D or prediabetes have been variable. HIIT has increased VO_{2peak} in these subjects similarly or even more than MICT, but the changes have not been statistically significant in all studies (Karstoft *et al.*, 2013;Robinson *et al.*, 2015;Terada *et al.*, 2013). Taken together these findings suggest that although HIIT and MICT may not improve physical fitness (measured by VO_{2peak}) as effectively in subjects with T2D as in healthy subjects, they both are very effective to rapidly improve whole body glucose metabolism.

It is therefore not surprising that both HIIT and MICT increased remarkably the insulin-stimulated GU in the main working muscle, QF. It is fascinating that despite the pre-intervention QF GU in the present study was less than half of the QF GU of the healthy middle-aged men in the previous study (Eskelinen *et al.*, 2015), after only two weeks of SIT training, QF GU was at the same level as in the healthy subjects at baseline (Eskelinen *et al.*, 2015). In the MICT group the increase was slightly smaller and the post-training values in the subjects in the present study did not quite reach the baseline level in healthy subjects, but most probably after a few more weeks of training they would have reached the same level. These findings emphasize the effectiveness of exercise training, especially high intensity exercise, on skeletal muscle glucose metabolism. Intriguingly, although impaired skeletal muscle insulin sensitivity is only one of the manifestations of T2D, it is also one of the most important; and based on our findings in the present study, and supported by other studies (Hussey *et al.*, 2012;Little *et al.*, 2011;Perseghin *et al.*, 1996), can easily be reversed with short training interventions.

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Previously we did not observe any significant changes in the other muscles than QF in the healthy subjects. Here we show that the early training adaptations in subjects with type 2 diabetes or prediabetes are more widespread as GU increased also in the posterior thigh and arm muscles suggesting a more general whole-body response to exercise. It is generally known that lower physical fitness prior to exercise intervention can cause greater responses and this may also be one of the reasons of the more pronounced effects observed in the subjects in the present compared to the previous study. It has been also shown that people with diabetes are less physically active than the general population and the majority of people with diabetes or at high risk for developing T2D do not engage in regular physical activity (Morrato *et al.*, 2007). Thus, even though the subjects in our present and previous study (Eskelinen *et al.*, 2015) were both physically inactive at baseline, the subjects in the present study may have been even less physically active than the healthy subjects in the previous study, and may therefore have had larger capacity to increase GU.

In concordance with the healthy subjects (Eskelinen *et al.*, 2015), HIIT and MICT caused different responses in GU in the RF so that the increase was larger after HIIT than MICT. In the vasti muscles this was not observed corresponding to the findings in healthy subjects (Eskelinen *et al.*, 2015). The possible explanations for these diverging responses between QF muscles were discussed in depth in the previous paper (Eskelinen *et al.*, 2015). The most plausible explanation is that the biarticular RF is fully activated only by a certain amount of force production that is not reached during moderate intensity exercise.

Previously, skeletal muscle FAU has been shown to be decreased in subjects with glucose intolerance (Turpeinen *et al.*, 1999) and T2D (Blaak *et al.*, 2000) and on the other hand, not different between healthy untrained and trained subjects (Hannukainen *et al.*, 2007). Also, in our previous study in healthy subjects two weeks of SIT or MICT did not change muscle FAU significantly (Eskelinen *et al.*, 2015). However, in the present study, in subjects with T2D and prediabetes FAU increased significantly, but only in the main working muscle QF. It should be noted that although the

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subjects in the present study were in the fasted state during the FTHA-PET study, the measured concentrations of glucose, FFA, and insulin during the study seemed to be lower than the fasting values reported in Table 1. Although we don't have any direct evidence to that, the most likely explanation is that the measurements of myocardial perfusion, and especially infusion of adenosine, shortly before the FTHA-PET study has caused those decreased concentrations either by direct actions of adenosine on metabolism or indirectly by altered hormonal milieu by adenosine. Therefore the FAU results do not reflect complete fasting state situation. Nevertheless, the measurements were performed similarly in the both groups and before and after the training, making it possible to make a conclusion that reduced FAU in patients with T2D and prediabetes may be at least partly restored by intensive SIT as well as by MICT in the most active muscles.

There are some limitations in this study. The study involved both male and female subjects, but the number of the subjects in both genders was so small that the possible gender differences in responses, as previously shown (Bagley *et al.*, 2016), could not be reliably addressed. In addition, this study was performed in subjects with T2D or prediabetes (IGT and/or IFG) and the results cannot therefore be directly applied to other populations. However, as the results paralleled pretty well our previous findings in healthy subjects, it may be expected that the observed phenomena could be more general. Considering diabetes status (T2D/prediabetes) the groups were slightly uneven, even if the difference between the groups was not statistically significant. Therefore gender and diabetes status were used as factors in the statistical analyses to remove any possible confounding effects. In the female subjects, the phase of the menstrual cycle or the incidence of menopause was not recorded or controlled during the study. Three of the ten female subjects were on menopausal hormone therapy. Thus the female population in this study was heterogeneous and that could have interfered with the results.

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There were no serious adverse reactions to SIT or MICT in the present study. The subjects went through a thorough physical examination by an experienced physician before the intervention and no serious adverse event occurred during the intervention. One of the participants in the SIT group got a migraine headache episode during the first exercise session. The subject's condition was carefully monitored and no serious consequences occurred.

Taken together, in individuals with T2D or prediabetes, already a short-term SIT or MICT training intervention leads to remarkably increased GU both in the thigh and upper arm muscles as well as increased FAU in the main working muscle QF. These findings further underscore the still underused possibilities that exercise training has to restore impaired skeletal muscle insulin-stimulated glucose uptake, insulin sensitivity, and fatty acid uptake even in a very short time frame in subjects with metabolic impairments.

PERSPECTIVE

In the present study, the pre-intervention QF insulin-stimulated GU was less than half of the values observed in the healthy middle-aged men in our previous study (Eskelinen *et al.*, 2015). Remarkably, after only two weeks of SIT it reached the same level as in the healthy subjects at the baseline (Eskelinen *et al.*, 2015). In the MICT group the increase was smaller and the post-training values did not quite reach the baseline level of the healthy subjects. However, most probably after a few more weeks of training they would have reached the same level. These findings emphasize the effectiveness of exercise training, especially high intensity exercise, in restoring impaired skeletal muscle glucose uptake that is one of the key disturbances in the subjects with metabolic disorders.

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Table 1. Subject characteristics and whole-body responses to the intervention in the SIT and MICT exercise groups.

	SIT		MICT		*p*		
	Pre	Post	Pre	Post	Group	Time	Group x Time
n	13	11	13	10			
men/women, *n*	9/4	7/4	7/6	6/4	0.69*		
DG, *n* (T2D) / *n* (IGT/IGF)	11/2	10/1	6/7	4/6	0.097 *		
Glucose lowering medication, *n*							
Metformin	7		4				
DPP-4 inhibitors (sitagliptin)	4		1				
Sulfonylurea (glimepiride)	1						
Other medication, *n*							
Antihypertensives	5		6				
Statins	4		3				
Affective medication			3				
Menopausal hormone therapy	1		2				
Age, yr	49 (47, 51)		49 (46, 51)		0.85†		

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Height, cm	173 (168, 179)		172 (167, 176)		0.61†		
Weight, kg	88.9 (80.6, 97.2)	88.4 (80.1, 96.7)	91.5 (84.5, 98.6)	91.1 (84.0, 98.1)	0.62	0.083	0.95
BMI	30.5 (28.5, 32.5)	30.3 (28.4, 32.3)	31.0 (29.4, 32.7)	30.8 (29.2, 32.5)	0.69	0.070	0.83
Fat, %	34.8 (31.4, 38.5)	33.8 (30.5, 37.5)	33.8 (30.8, 36.9)	32.9 (30.0, 36.0)	0.67	**0.018**	0.87
FFM, kg	57.0 (51.8, 62.2)	57.6 (52.4, 62.8)	59.6 (55.0, 64.2)	59.8 (55.2, 64.5)	0.49	0.11	0.54
VO_{2peak}, $ml \cdot kg^{-1} \cdot min^{-1}$	25.7 (23.2, 28.2)	27.0 (24.6, 29.5)‡	27.0 (24.9, 29.2)	26.9 (24.6, 29.1)§	0.72	0.12	**0.050**‖
M-value, $\mu mol \cdot kg^{-1} \cdot min^{-1}$	20.6 (13.4, 27.7)	25.7 (18.4, 33.0)	15.7 (9.7, 21.6)	19.7 (13.6, 25.8)	0.24	**0.001**	0.66
HbA_{1c}, %	5.7 (5.4, 6.0)	5.5 (5.2, 5.8)	5.8 (5.5, 6.0)	5.6 (5.3, 5.9)	0.70	**0.002**	0.84
HbA_{1c}, mmol/mol	38.7 (35.5, 42.0)	36.9 (33.6, 40.2)	39.6 (36.9, 42.4)	37.6 (34.7, 40.5)	0.70	**0.001**	0.82
Hemoglobin g/l	145 (140, 150)	132 (127, 137)	144 (140, 148)	133 (128, 137)	0.92	**0.001**	0.52
Hematocrit, fraction	0.42 (0.41, 0.43)	0.39 (0.37, 0.40)	0.42 (0.41, 0.43)	0.39 (0.38, 40)	0.98	**0.001**	0.65
Fasting glucose, mmol/l	7.1 (6.5, 7.7)	7.0 (6.4, 7.6)	6.8 (6.3, 7.3)	7.0 (6.4, 7.5)	0.72	0.95	0.40
Fasting insulin, pmol/l	11.5 (7.8, 17.0)	11.6 (7.8, 17.2)	13.2 (9.5, 18.5)	13.5 (9.5, 19.0)	0.57	0.88	0.93
Fasting FFA, mmol/l	1.02 (0.85, 1.19)	1.03 (0.85, 1.21)	0.98 (0.84, 1.13)	0.90 (0.74, 1.07)	0.44	0.54	0.38
OGTT 2h glucose, mmol/l	10.4 (8.6, 12.3)	9.1 (7.2, 11.1)	10.5 (8.9, 12.1)	10.3 (8.6, 12.0)	0.60	0.089	0.21
OGTT 2h insulin, pmol/l	75.0 (50.3, 111.7)	71.1 (46.6, 108.4)	68.1 (48.1, 96.3)	62.9 (42.7, 92.5)	0.65	0.62	0.92
Glucose AUC in OGTT	1274 (1142, 1407)	1242 (1104, 1379)	1298 (1184, 1412)	1323 (1200, 1446)	0.53	0.90	0.41
Insulin AUC in OGTT	7162 (5264, 9746)	7109 (5181, 9756)	6871 (5273, 8954)	6748 (5106, 8920)	0.81	0.85	0.94

The results are presented as means (95% CI) for age and height. For all other parameters the results are presented as model-based means (95% CI). Group *p*-value indicates whether there is a level difference between the groups, time *p*-value displays the mean change between pre- and post-measurements and group x time *p*-value indicates whether the mean changes are different between groups. SIT, sprint interval training; MICT, moderate intensity continuous training; *n*, number of subjects; DG, diagnose group; T2D, type 2 diabetes; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; FFM, fat free mass; AUC, area under curve; * Fisher's exact test at baseline; † T-test; ‡ SIT time, p = 0.013; § MICT time, p = 0.75; ‖ exact p=0.0495. Significant differences are printed in boldface.

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Table 2. Plasma glucose, FFA and insulin concentrations during PET-scanning in the SIT and MICT exercise groups before and after the intervention.

	SIT		MICT		*p*		
	Pre	Post	Pre	Post	Group	Time	Group x Time
Glucose (FTHA), mmol/l	6.1 (5.6, 6.7)	5.9 (5.3, 6.5)	6.0 (5.5, 6.4)	5.9 (5.4, 6.4)	0.80	0.095	0.47
Glucose (FDG), mmol/l	4.8 (4.7, 4.9)	4.9 (4.7, 5.1)	4.9 (4.8, 5.1)	5.0 (4.8, 5.1)	0.15	0.33	0.73
FFA (FTHA), mmol/l	0.83 (0.72, 0.93)	0.80 (0.68, 0.92)	0.83 (0.74, 0.92)	0.80 (0.70, 0.90)	0.99	0.27	0.94
FFA (FDG) mmol/l	0.09 (0.06, 0.11)	0.07 (0.05, 0.10)	0.09 (0.06, 0.11)	0.08 (0.05, 0.10)	0.93	0.13	0.90
Insulin (FTHA), pmol/l	10.8 (6.9, 14.6)	8.3 (4.3, 12.2)	10.4 (7.2, 13.5)	8.6 (5.3, 11.9)	0.99	**0.002**	0.54
Insulin (FDG), pmol/l	88.9 (80.3, 97.4)	90.4 (80.9, 99.8)	86 (78.8, 93.2)	85.8 (77.7, 94.0)	0.46	0.84	0.80

The results are presented as model-based means (95% CI). Group *p*-value indicates whether there is a level difference between the groups, time *p*-value displays the mean change between pre- and post-measurements and group x time *p*-value indicates whether the mean changes are different between groups. PET, positron emission tomography; SIT, sprint interval training; MICT, moderate intensity continuous training; FTHA, 14(R,S)-[18F]fluoro-6-thia-heptadecanoic acid study; FDG, 2-deoxy-2-(18F)fluoro-D-glucose study; FFA, plasma free fatty acid concentration. The FTHA study was conducted in the fasting state and the FDG study was conducted under hyperinsulinemic euglycemic clamp. Significant differences are printed in boldface.

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Figure legends

Fig. 1. Skeletal muscle insulin-stimulated glucose uptake (A, B, C, D) and free fatty acid uptake in the fasting state (E, F, G, H) in thigh- (A, B, E, F) and upper arm (C, D, G, H) muscles. Open dots show the results of the SIT group and black dots the results of the MICT group before and after the intervention presented as model-based means with 95% confidence interval. Group p-value indicates whether there is a level difference between the groups, time p-value displays the mean change between pre- and post-measurements and group x time p-value indicates whether the mean changes are different between groups. GU, glucose uptake; FAU, fatty acid uptake; QF, quadriceps femoris; Ham, hamstrings; Bic, biceps brachii; Tri, triceps brachii.

Fig. 2. Skeletal muscle insulin-stimulated glucose uptake (A, B, C, D) and free fatty acid uptake in the fasting state (E, F G, H) in the four heads of the quadriceps femoris. Open dots show the results of the SIT group and black dots the results of the MICT group before and after the intervention presented as model-based means with 95% confidence interval. Group p-value indicates whether there is a level difference between the groups, time p-value displays the mean change between pre- and post-measurements and group x time p-value indicates whether the mean changes are different between groups. * SIT $p<0.001$ for the time effect, MICT $p=0.015$ for the time effect, pre-intervention difference between groups $p=0.31$, postintervention difference between groups $p=0.016$. GU, glucose uptake; FAU, fatty acid uptake; RF, rectus femoris; VL, vastus lateralis; VM, vastus medialis; VI, vastus intermedius.

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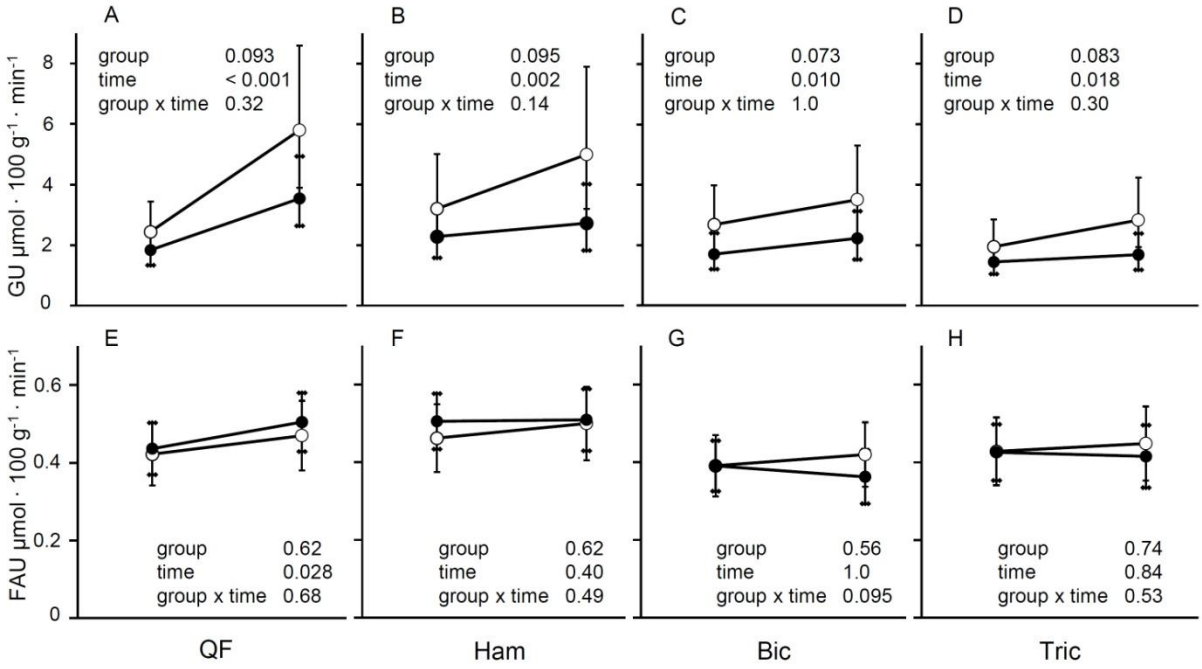

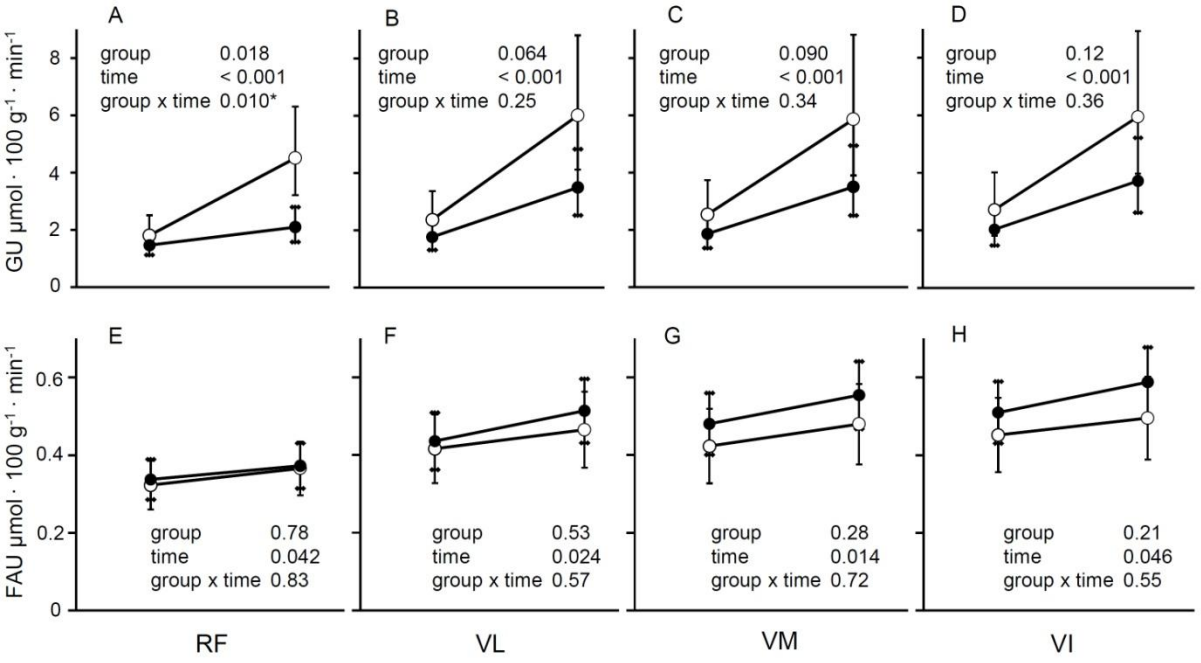

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