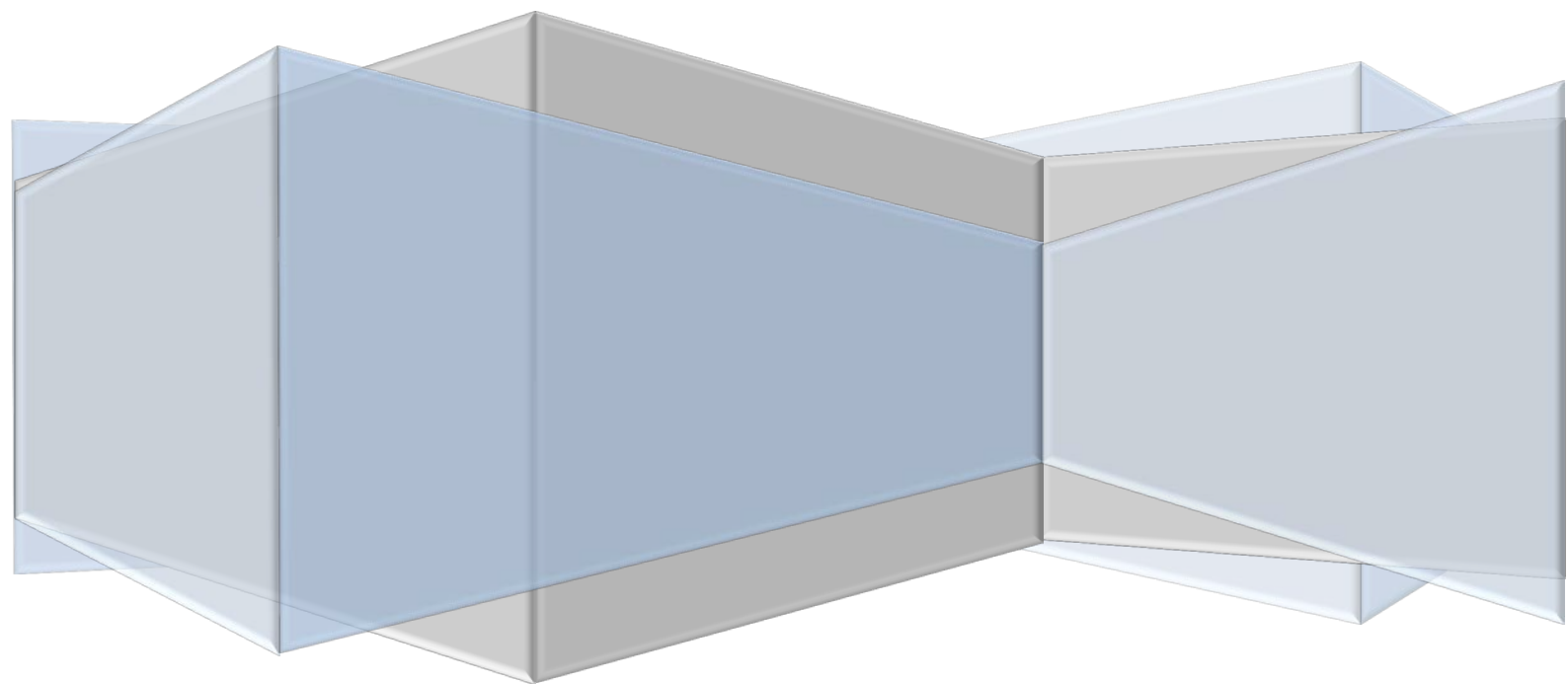# Low-volume interval training improves cardiovascular risk factors in type 2 diabetes

A randomized controlled trial

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Low-volume interval training improves cardiovascular risk factors in type 2 diabetes

NTNU, SPO3900 – thesis in exercise physiology
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Abstract

BACKGROUND: Type 2 diabetes (T2D) is predicted to affect about 500 million individuals by 2030, and is closely linked to cardiovascular disease. Exercise is considered a cornerstone in both the prevention and treatment of T2D, but despite the clear-cut evidence and well-established recommendations few patients with T2D exercise enough according to today's guidelines.

OBJECTIVES: To compare two different time-efficient high intensity exercise protocols in patients with T2D, and to investigate the effect on glycemic control and cardiovascular risk factors.

METHODS: Subjects with T2D were recruited and randomly assigned to either low-volume high intensity interval training (HIT) or extremely low-volume sprint interval training (SIT). Both groups exercised three days a week for 12 weeks. Changes in glycosylated hemoglobin (HbA$_{1c}$), aerobic capacity (VO$_{2peak}$), blood lipids, blood pressure and body composition were measured.

RESULTS: HIT and SIT combined reduced HbA$_{1c}$ significantly (-0.54 percentage points, p = 0.005) only in the patients with the poorest glycemic control at baseline. Both HIT and SIT improved VO$_{2peak}$, with no significant difference between groups. HIT, but not SIT, improved body fat percentage and visceral fat area. In hypertensive subjects blood pressure was reduced following HIT and SIT combined.

CONCLUSION: Time-efficient interval training of high intensity can improve glycemic control in type 2 diabetes-patients with poorly controlled hyperglycemia, but not in well-controlled subjects. Aerobic capacity, body composition and hypertension can be improved in type 2 diabetes following substantially less weekly time of training than currently recommended, given that intensity of training is high.

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Introduction

Diabetes mellitus affects at least 300 million adults worldwide [1, 2]. Nearly 95 % of these have type 2 diabetes (T2D), a metabolic disease characterized by chronically elevated blood glucose levels [3]. This makes T2D one of the most common chronic diseases, and the incidence is increasing even faster than expected only few years ago [4, 5]. A growing presence of obesity and a sedentary lifestyle are considered main factors responsible for the increase, and by 2030 7.7 % of the adult population will be affected, corresponding to a number of more than 500 million individuals

Abbreviations:

T2D = type 2 diabetes
HbA_{1c} = glycosylated hemoglobin
CVD = cardiovascular disease
ADA = American Diabetes Association
ACSM = American College of Sports Medicine
pp = percentage points
HIT = high intensity interval training
SIT = sprint interval training
CMT = continuous moderate training
VO_{2peak} = peak oxygen uptake
HR_{max} = maximum heart rate
HOMA-IR = homeostasis model assessment for insulin resistance
HDL = high-density lipoprotein cholesterol
LDL = low-density lipoprotein cholesterol
BMI = body mass index

[1, 2]. In addition, up to 50 % of all patients with T2D are undiagnosed [6, 7], because the classic symptoms are often not severe enough to be noticed at the early stages [3].

The hyperglycemia in T2D is a consequence of defects in insulin secretion, insulin action, or both [3]. These defects result from a combination of genetic predisposition, unhealthy diet and physical inactivity [8]. The American Diabetes Association (ADA) currently recommends the use of glycosylated hemoglobin (HbA_{1c}) values of 6.5 % or higher to diagnose diabetes. The HbA_{1c} value reflects average blood glucose levels over a 2- to 3-month period of time, and is widely used as the standard biomarker for the adequacy of glycemic control [3] .

Elevated HbA_{1c} is associated with increased risk of cardiovascular disease (CVD) [9, 10]. Thus, CVD often appears together with T2D. In fact, patients with T2D have 2-4 times higher risk of developing CVD than those without diabetes, independent from other conventional risk factors [11, 12], and CVD is accountable for about 70 % of all deaths in T2D [13]. The complications of T2D lead to substantially increased risk of hypertension and the development of heart failure. In addition, an increasing number of patients with CVD suffer from pre-states of diabetes [8].

Exercise is considered first-line treatment for T2D, together with medication and diet [14], and the evidence for a lowering effect of regular exercise on HbA_{1c} in T2D is compelling [15-22]. Regular aerobic exercise for 8 weeks or more consistently seems to lower HbA_{1c} about 0.6 percentage points (pp) in subjects with T2D [15, 21].

Numerous public health institutions worldwide, including a joint position statement from the American College of Sports Medicine (ACSM) and the ADA, recommends that individuals with T2D undertake at least 150 minutes of moderate to vigorous aerobic exercise at 40-75 % of individual peak oxygen uptake (VO_{2peak}) per week [23]. Umpierre et al. [24] concluded that there is an association between exercise volume and the amount of change in HbA_{1c}, with a significant HbA_{1c} reduction of 0.39 pp for each additional weekly aerobic exercise session. However, up to two thirds of patients with T2D attend no regular physical activity at all [25], and few achieve the recommended amount of weekly exercise [25-27]. Lack of time is often cited as a main reason for inactivity in T2D [28], and this highlights the need for less time-consuming exercise modalities that can yield similar or even greater health benefits.

The meta-analysis of Boulé et al. [16] found that higher intensity exercise could have additional benefits on cardiorespiratory fitness and HbA_{1c} in persons with T2D, with the only study investigating intensities above 75 % of VO_{2peak} [29] being the significantly most effective one. A few later studies have added to this knowledge, and recently Karstoft et al. [30] showed that repeated bouts of 3-minute walking intervals of an intensity of 70-85 % of VO_{2peak} had significantly greater effect on glycemic control and exercise capacity in T2D than a similar amount of continuous walking at a lower intensity. Furthermore, it has been speculated that intermittent exercise protocols of higher intensities than 75 % of VO_{2peak} (HIT) could be more effective in improving CVD risk factors in T2D than today's practice [31, 32]. The few available intervention studies that have compared HIT with continuous moderate training (CMT) in T2D show promising results on HbA_{1c}, blood lipids and/or body composition [33-35], but the protocols used in these studies did not take full advantage of the time-saving possibilities of HIT, and generally were as time-consuming as today's recommendations.

The aim of this study was to compare the effects of two different time-efficient high intensity exercise protocols on cardiovascular risk factors in patients with T2D. The main hypothesis was that low-volume high intensity interval training (HIT) would improve HbA_{1c} more than extremely low-volume sprint interval training (SIT). We also hypothesized that HIT was most effective in improving VO_{2peak}, insulin resistance (HOMA-IR), body composition, blood pressure and blood lipoprotein and triglyceride content.

A secondary aim was to gain knowledge about the minimum weekly amount of high intensity exercise needed to provide clinically relevant benefits for patients with T2D. To our knowledge no study has previously compared different high intensity protocols in this patient

group. We aimed to investigate training modalities that can potentially be both effective and outplay the lack of time-barrier often cited as the main reason for inactivity in T2D.

Background for HIT and SIT

A convincing amount of intervention studies and reviews show that HIT can yield greater improvements in aerobic capacity (VO_{2peak}) than CMT in both healthy [36-39] and diseased populations [40-45], at least when the total energy expenditure is similar in both groups. Most of the HIT protocols used in the mentioned trials [36, 39-43] consisted of 4x4-minute intervals at an intensity of approximately 90 % of maximum heart rate (HR_{max}) (85 % of VO_{2peak}) separated by 3-minute active rest periods at approximately 70 % of HR_{max} (60 % of VO_{2peak}). The rationale is that the rest periods make it possible to complete short work periods at a high intensity that challenges the heart's pumping ability [41]. In addition, exercise is completed in a shorter time-frame than CMT of similar energy expenditure, providing a time-efficient and highly effective alternative.

Lately, trials involving SIT have become increasingly popular. 4-6 30-second sprint intervals at all-out intensity was found more effective than isocaloric CMT in improving VO_{2peak} in healthy subjects [46]. In addition, SIT was found as effective as higher-volume CMT in improving VO_{2peak} [47] and peripheral vascular structure and function [48] in young, healthy subjects. These results suggest that significantly reducing the total exercise volume does not negatively affect exercise responses when the interval work periods are of maximum intensity. Total training time in the interval groups was 67 % lower than in the groups performing continuous moderate training [47, 48].

Kessler et al. [49] recently reviewed the effect of HIT and SIT on several CVD risk factors. A minimum of eight weeks of high intensity training was shown to promote superior improvements in aerobic fitness and similar improvements in some CVD risk factors compared to CMT. A minimum intervention period of 12 weeks was needed in order to improve fasting glucose levels, blood pressure and anthropometric measures, while eight weeks of HIT were sufficient to improve high-density lipoprotein cholesterol (HDL) in three out of ten studies. HIT was ineffective in improving total cholesterol, low-density lipoprotein cholesterol (LDL) and triglycerides.

A more focused review have evaluated the effects of HIT on CVD risk factors in patients with cardiometabolic disorders [44]. Only trials that matched HIT with CMT of the same total energy expenditure were included. Fasting blood glucose levels showed a tendency to

improve more following HIT than CMT, and VO_{2peak} increased significantly more following HIT than CMT. HIT and CMT were associated with similar improvements in blood pressure, body composition and blood lipids, and the meta-analysis concluded that further studies are needed to confirm any beneficial effect on insulin sensitivity or glucose transportation [44]. A similar review by Weston et al. [45] concluded that HIT was superior to CMT in improving CVD risk factors in patients with lifestyle-induced chronic diseases.

One study particularly relevant for T2D was done by Tjønna et al. [42] on patients with the metabolic syndrome. This condition is a clustering of cardiovascular risk factors, diagnosed from a combination of elevated waist circumference, elevated triglycerides, reduced HDL, elevated blood pressure, and elevated fasting glucose [50]. Most patients with T2D will have the metabolic syndrome by the proposed criteria [50]. Tjønna et al. showed 16 weeks of HIT to be more effective than a similar amount of CMT in improving VO_{2peak}, fasting blood glucose and insulin sensitivity in these patients. HDL increased significantly following HIT, but not CMT, while none of the other blood lipid variables changed significantly in either group. Blood pressure, waist circumference and body mass index (BMI) showed similar improvements in both groups. After the study, significantly more patients in the HIT than CMT group (46 % vs. 37 %) were no longer diagnosed with the metabolic syndrome, and the authors concluded that high intensity exercise was superior to moderate intensity exercise in reversing risk factors of the metabolic syndrome [42].

In line with these results, Earnest et al. [51] recently found six weeks of HIT more effective than eucaloric CMT for improving metabolic syndrome score in men at risk for insulin resistance. The conclusion from the study was that HIT appeared to have a more robust exercise effect on metabolic syndrome than CMT. In addition, insulin resistance was significantly improved following HIT both 24 and 72 hours after the last exercise sessions, whereas no change was seen following CMT. HIT also reduced body mass, body fat mass and waist circumference.

No study to our knowledge has compared SIT to CMT in subjects with increased CVD risk. However, just two weeks and six total sessions of 4-6 30-second sprint intervals has been shown to improve insulin action in both healthy [52, 53] and sedentary, overweight individuals [54]. A 2-week SIT intervention also decreased waist circumference and systolic blood pressure in overweight men [54], while four weeks of SIT were sufficient to improve VO_{2peak} and stroke volume during submaximal exercise in overweight/obese women [55].

While there is growing evidence for the benefits of high-intensity interval training in patients at high risk of T2D [42, 51], randomized controlled trials on time-efficient HIT and SIT in patients already diagnosed with T2D are lacking. A study by Terada et al. [34] found that HIT was feasible for subjects with T2D, while Backx et al. [33] showed that HIT can effectively decrease LDL, total cholesterol, HbA_{1c}, waist circumference and BMI in T2D-patients. However, the interventions in both studies [33, 34] included up to 300 minutes of weekly exercise, at least as time-consuming as the CMT it was compared to. This is double of the minimum recommendations of ADA and ACSM, and one can argue that these protocols were not suited to reduce the time-barrier often reported when patients with T2D explain their reasons for inactivity [28].

Mitranun et al. [35] recently showed that 10 weeks of HIT was more effective in improving VO_{2peak} than CMT of the same total energy expenditure and duration in older patients with T2D. The three weekly HIT exercise sessions consisted of 4-6 1-minute intervals at 80-85 % of VO_{2peak}, and total weekly training time in both groups was 90-120 minutes, considerably shorter than today's recommendation of minimum 150 minutes. HbA_{1c}, total cholesterol, HDL, LDL and systolic blood pressure only improved following HIT, whereas measures of body composition and insulin resistance changed similarly in both groups. The study shows that reduced total training time can yield improvement in CVD risk factors in T2D, especially if the intensity of exercise is high. However, we feel that the time-saving potential of HIT was not fully taken advantage of in the study, as the low-intensity breaks between each interval were as long as three minutes, and total training time matched that of CMT.

A pilot study recently showed that only two weeks with a total of six sessions of more time-efficient HIT reduced blood glucose significantly in individuals with T2D [56]. The training sessions consisted of 10 bouts of 1-minute intervals at 90 % of HR_{max}, each separated by 75 seconds at moderate intensity. Total training time was only 75 minutes per week, or half of the ADA and ACSM recommendations [23]. Bird and Hawley [57] suggested that such time-saving HIT protocols could be a vital alternative strategy to overcome the time-barrier and enable more people to gain the health benefits of exercise, and Hawley and Gibala [58, 59] have pointed out an urgent need to address this question in randomized controlled trials. In addition to its time-saving nature, HIT is associated with more joy than CMT [60], and increased enjoyment could be crucial for reducing inactivity in sedentary individuals [61]. Indeed, Wisløff et al. [41] reported that patients with heart failure found HIT more motivating than CMT, based on informal comments from different participants. Also, Babraj et al. [52]

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proposed that SIT can be used as a strategy to reduce metabolic risk factors in subjects who are not willing to part-take in more time-consuming traditional aerobic exercise regimes.

Methods

Design

Our study was a 12-week, single center, parallel-group randomized controlled trial conducted in Trondheim, Norway between August 2013 and January 2014. The study was approved by the regional ethical committee.

Participants

Subjects were recruited from a list of candidates that had volunteered, but eventually were not needed, in a previous intervention study by our research group. Additional recruitment was conducted through newspaper advertisement and websites, and through posters at local medical centers in Trondheim.

Patients were screened through an interview upon first meeting. To be considered for participation subjects had to be aged 20-65 years, diagnosed with T2D for less than 10 years, and able to exercise three times a week for twelve weeks. Subjects were excluded from the study if they were treated with insulin, or if they reported to achieve greater than the minimum exercise guidelines of 150 minutes per week prior to the start of the study.

Other exclusion criteria included a history of overt cardiovascular disease, cardiac artery disease, moderate to severe valvular disease, atrial fibrillation or other severe arrhythmia, congenital heart disease, untreated hypertension of >140/90, left ventricular hypertrophy, retinopathy, neuropathy, micro- or macroalbuminuri, BMI >35, or a disease or disability making training difficult. Subjects who experienced ischemia at exercise electrocardiography performed during pre-testing were also excluded.

Following screening a total of 21 participants were found eligible for randomization. Each subject reviewed and signed a written informed consent approved by the regional ethical committee before taking part in the study. All the subjects were on antihyperglycemic medication, and were told not to change the dosage of medication throughout the intervention. The subjects were also encouraged not to change their food habits during the period, and were asked to fill out a habitual activity diary for each of the 12 weeks of exercise.

Initial assessment

Pre-testing took place within one week prior to the start of the training intervention. Blood samples were collected from the antecubital vein following 10 hours of overnight fasting. Blood glucose, HbA$_{1c}$, insulin C-peptide, total cholesterol, HDL, LDL, triglycerides and high sensitive c-reactive protein (hs-CRP) was analyzed using standard local procedures at St.

Olavs Hospital. To estimate β-cell function we used overall insulin resistance and the homeostasis assessment model (HOMA-IR).

Resting heart rate, systolic and diastolic blood pressure was measured with an automatic self-inflating oscillometric device (Criticare Comfort Cuff 506N, Criticare Systems Inc., Waukesha, Wisconsin, USA) with an 11 cm standard cuff. Three subsequent measurements were performed after five minutes of rest in a seated position, and the average value of the three measurements was calculated for each variable and used in later analysis.

Body height was measured by a wall mounted height scale. Waist circumference was measured with a measuring tape, using the average value from three subsequent measurements. Measures were taken in expiration, midway between the lower lateral costal margin and the iliac crest, with the subject standing. Other body composition measurements were made using InBody 720 (Biospace CO, Ltd, Seoul, Korea), and body weight, body mass index (BMI), muscle mass, body fat weight, body fat percentage, and visceral fat area were recorded.

Exercise test

Later the same day a treadmill (Woodway PPS 5, Woodway, Weil am Rheim, Germany) test to exhaustion was executed to obtain peak oxygen consumption (VO_{2peak}). Before measurements of VO_{2peak} the subjects were informed about the test, and instructed to exercise to their maximum limit. The test started on a treadmill with 3 % inclination, and the speed and inclination were individually adjusted for a 5-minute warm-up. Work economy was defined and recorded as the submaximal heart rate value obtained following three minutes of walking at an individually set pace and a treadmill inclination of 3 %.

After the warm-up period the subjects wore a mask for metabolic measurements using MasterScreen Spirometer (Jaeger Oxycon Pro, Jaeger GmbH & Co KG, Würzburg, Germany) or Metamax II (Cortex, Leipzig, Germany). The following VO_{2peak} test was performed using a ramp protocol where the speed was constant and the inclination increased with 2 % every minute until VO_{2peak} was reached. The mean of the three highest 10 second measurements in succession was used to determine VO_{2peak}. A subjective rating of perceived exertion (RPE; the Borg Scale) from 6 ("no feeling of exertion") to 20 ("very, very hard") was obtained immediately following the test.

Heart rate was continuously recorded with Polar RS 400 monitors (Polar Electro, Kempele, Finland) during the test to obtain maximum attainable heart rate. Maximum heart rate (HR_{max})

was determined from adding 5 beats to the peak HR-values obtained during the test. Heart rate recovery was recorded as the difference between peak heart rate and heart rate one minute (HRR_1) and two minutes (HRR_2) following exhaustion, with the subjects standing still on the treadmill between measurements.

Randomization

Following pre-testing the subjects (n = 21) were randomized into one of the following groups for a 12-week intervention period.

1. A 10x1-minute interval group (HIT, n = 10)
2. A 2x20-seconds interval group (SIT, n = 11)

Randomization was stratified by sex and completed by a computer program. Blinding of the participants was not done in this study, but blood samples were completed by personnel unaware of group allocation.

Exercise intervention

Both groups exercised three days a week for 12 weeks, for a total of 36 sessions, at the time of each participant's convenience. If a subject failed to show up for one session and was unable to compensate with an extra session the following week, an extra week of exercise was added to the intervention period. A compliance of at least 90 % (33 completed sessions at prescribed intensity) was considered acceptable.

All training sessions were performed on a treadmill, and all sessions were supervised by an instructor. Most of the training was performed at our test laboratory at St. Olavs Hospital in Trondheim, at the Department of Circulation and Medical Imaging. However, a few subjects (n = 2, one subject in each training group) performed some of the sessions at other venues due to long travel distances between their location and the test laboratory. The compliance and intensity of these sessions were the same as for the sessions at the hospital.

Exercise training intensity was determined based on the HR_{max}-values obtained from the maximal graded exercise test to exhaustion performed at pre-testing. During the intervention period Polar RS 400 heart rate monitors (Polar Electro, Kempele, Finland) were used at each exercise session to monitor heart rate and ensure the required exercise intensity was achieved and maintained.

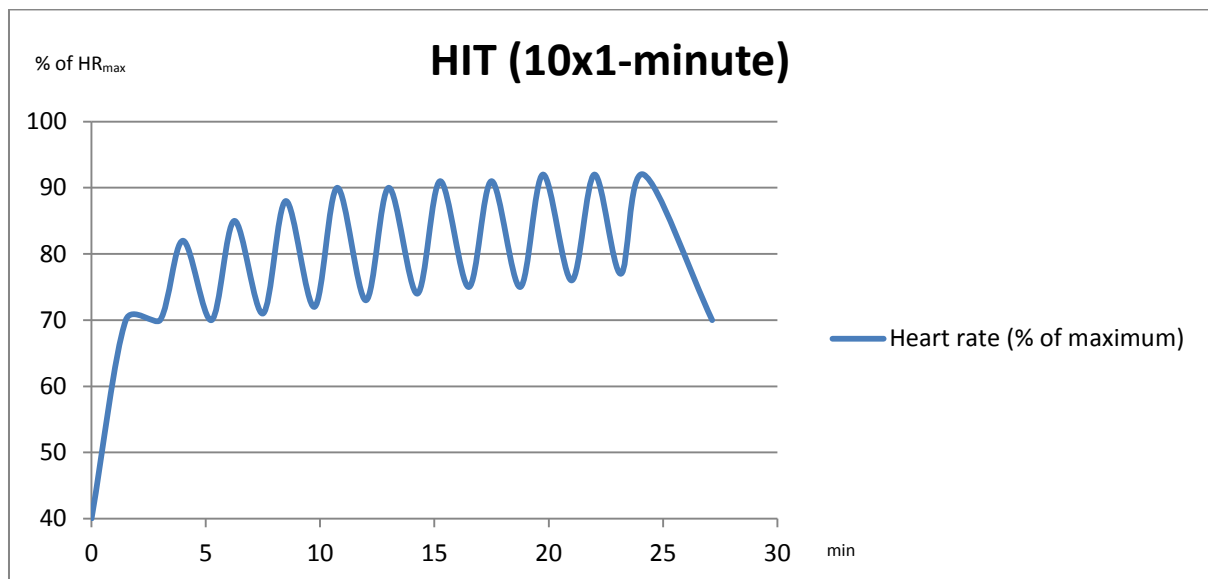1. HIT: Low-volume high intensity interval training (10x1-minute)

Figure 1: Theoretical outline of the HIT protocol. The figure describes heart rate (percentage of HR$_{max}$) at a given time (minutes).

The HIT exercise protocol is illustrated in figure 1. Exercise started with warming up for 3 minutes at 70 % of HR$_{max}$ before performing 10x1-minute intervals at approximately 90 % of HR$_{max}$, with 75 seconds of active recovery at approximately 70 % of HR$_{max}$ between each interval. The treadmill speed and inclination were held constant during all 10 intervals in each session, and the heart rate goal was supposed to be reached around the fourth interval. The session was concluded with a 3-minute cool-down at 70 % of individual HR$_{max}$. The protocol has previously been described by Little et al. [62].

As the subjects got fitter and/or more familiarized with treadmill exercise, the speed and/or inclination was adjusted to make sure the intensity matched their fitness level throughout the intervention period.

Training time per session in the HIT group was 27 minutes and 15 seconds, giving a total of 81 minutes and 45 seconds of exercise each week, with 30 minutes of the time spent at high intensity. This corresponded to a weekly training time of approximately half of the ADA and ASCM recommendations.

Picture 1: Participant performing 10x1-minute high-intensity interval training (HIT) on an elevated treadmill.

2. <u>SIT: Extremely low-volume sprint interval training (2x20 seconds)</u>
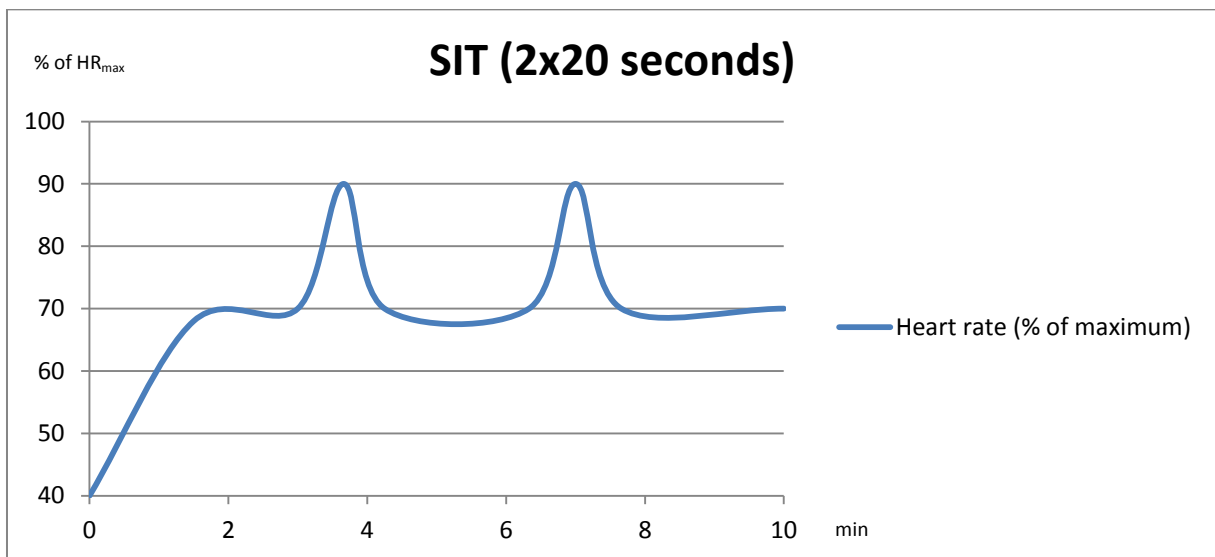

Figure 2: Theoretical outline of the SIT protocol. The figure describes heart rate (percentage of HR$_{max}$) at a given time (minutes). Note that the figure is only illustrative, as heart rate was controlled to achieve correct intensity at the low-intensity periods, but not during the all-out intervals at supramaximal intensity.

The SIT exercise protocol is illustrated in figure 2. Exercise started with warming up for 3 minutes at 70 % of HR_{max} before performing 2x20 seconds of maximum intensity intervals, with 3 minutes and 20 seconds of active recovery at 70 % of HR_{max} between each interval. Exercise was completed with 3 minutes cooling down at 70 % of HR_{max}. The treadmill was set to an inclination of 20 %, and the first few sessions were used to find the maximum speed the subjects could manage for exactly 20 seconds at this inclination. Speed was adjusted (i.e. increased) throughout the intervention period to make sure that the subjects exercised at an all-out intensity even as they got more fit or used to treadmill running. The same intensity protocol is previously described for stationary bicycle by Metcalfe et al. [63].

Training time per session in the SIT group was 10 minutes, giving a total of 30 minutes of exercise each week – one fifth of the ADA and ACSM recommendations. Exercise time at the supramaximal intensity level was 40 seconds per session and 2 minutes per week.

Picture 2: Participant performing supervised 2x20-second sprint interval training (SIT) on an elevated treadmill.

Post-testing
Post-testing was completed between 72 and 96 hours following the last exercise session to make sure acute effects of exercise were avoided. Procedures were equal to baseline testing, and the same measurements were done. Blood sampling was performed at the same time of

day (8.00 – 9.00 am.) for both baseline and post-test in order to avoid diurnal changes in the blood variables measures.

Outcomes

The primary outcome of this study was the effect of HIT and SIT on HbA_{1c}, within and between groups. Important secondary outcomes were the efficacy of HIT and SIT in improving insulin resistance, blood lipid measurements, anthropometry, VO_{2peak} and blood pressure.

Data analysis

Data was checked for normal distribution with quantile-quantile (Q-Q) plots. For normally distributed variables, within group improvement from baseline to post-test was identified by paired samples t-tests, while between group differences and changes were identified using independent samples t-tests. Where skewness from normal distribution was observed, non-parametric statistics were performed to find within group (Wilcoxon's Signed Rank Test) and between group changes (Mann-Whitney U Test). Simple Pearson product-moment correlation analyses were used to identify baseline correlations between variables and correlations of the change between variables from baseline to post-test.

All data analysis was carried out using a standard statistical software program (SPSS version 21.0; SPSS Inc, Chicago, Illinois, USA).

Results

Participants

Figure 3 shows the flow of the participants from baseline to post-test. A total of 18 subjects completed the training intervention as scheduled. Three subjects – two in the SIT group and one in the HIT group – dropped out during the intervention, leaving n = 9 (five men and four women) in both groups. One subject in each group reported calf pain related to the exercise as the reason for dropping out, whereas one subject in the

Figure 3: Flow chart of the study.

SIT group did not show up for a sufficient amount of training sessions each week and eventually dropped out with no further explanation.

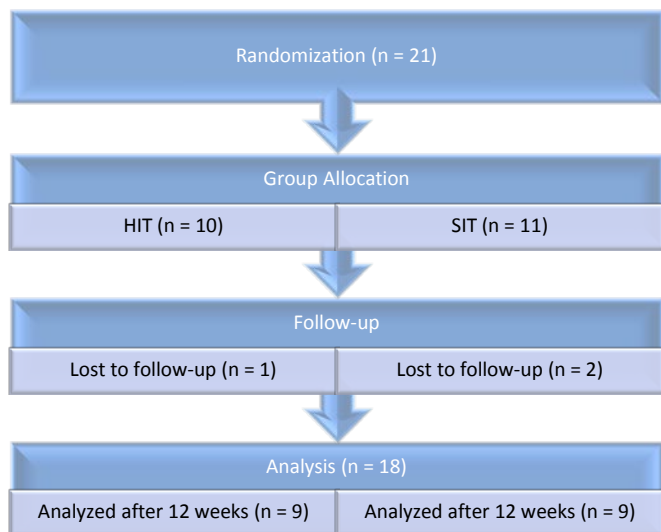All study participants reported that no change in drug dose or food intake was made throughout the intervention. The self-reported habitual activity was similar in both exercise groups, and did not change from week 1 to week 12 in any of the groups (data not shown).

Baseline characteristics

BASELINE CHARACTERISTICS

	HIT (n = 9)	SIT (n = 9)	p-value of the difference
Age (years)	56.5 ±6.5	49.6 ± 10.6	0.11
Years with T2D	4.2 ± 2.1	5.3 ± 2.5	0.32
HbA$_{1c}$ (%)	6.53 ± 0.96	7.87 ± 1.21	0.019
Height (cm)	168.7 ± 10.5	174.7 ± 12.4	0.29
BMI	26.3 ± 3.0	29.5 ± 3.9	0.06
Fat percentage	28.8 ± 6.7	31.4 ± 6.2	0.41
Systolic blood pressure (mmHg)	129.3 ± 16.3	135.3 ± 11.0	0.38
Diastolic blood pressure (mmHg)	76.8 ±7.2	84.44 ± 12.0	0.09

Table 1: Baseline data are presented as mean ± standard deviation. P-values show between group differences. HbA$_{1c}$ = glycosylated hemoglobin, BMI = body mas index.

There were significant baseline differences in HbA$_{1c}$ between the groups (p = 0.02). No other variable differed significantly between the groups at baseline. However, diastolic blood pressure as well as several anthropometric variables (i.e. weight, BMI, total fat weight, visceral fat area and waist circumference) showed a tendency to be higher in the SIT group than in the HIT group (p = 0.06-0.09, table 1).

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Blood analyses

HbA$_{1c}$ did not change in either group following the exercise intervention (Table 2). However, the 50 % subjects with the highest initial HbA$_{1c}$ values (>7.2 %, n = 9), regardless of exercise group, decreased their HbA$_{1c}$ value by a mean of -0.54 pp (-0.88, -0.21, p = 0.005) (Figure 2). The 50 % subjects with the lowest initial HbA$_{1c}$ values (<7.2 %, n = 9), showed no significant change from baseline to post-test, although there was a tendency of slightly worsened HbA$_{1c}$ in these subjects (0.19 pp [-0.05, 0.38], p = 0.055). The amount of change differed significantly between the "high" and "low" group (p-value of the difference = 0.001).

There were no significant effects of training on any other blood variable measured in any of the exercise groups, and no between group differences (Table 2).
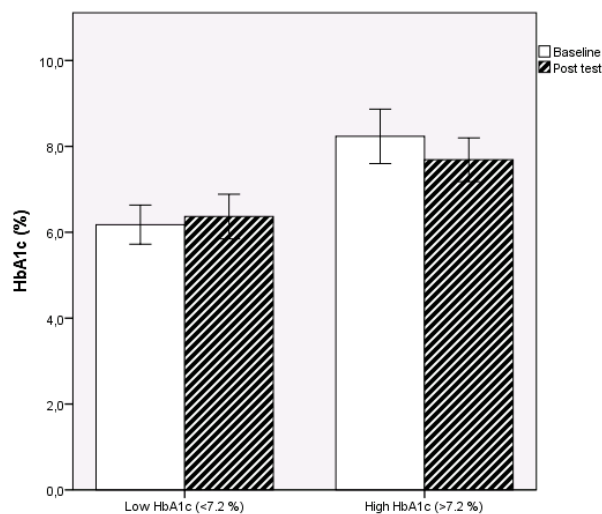

Figure 4 (above): Data represents mean change in glycosylated hemoglobin (HbA$_{1c}$) for the 50 % subjects with lowest and highest baseline levels of HbA$_{1c}$. n = 9 in both groups

BLOOD VARIABLES	Baseline HIT	Post HIT	Mean change	95 % CI	p-value	Baseline SIT	Post SIT	Mean change	95 % CI	p-value	p-value of difference
HbA$_{1c}$ (%)	6.53±0.96	6.47±0.75	-0.06±0.42	-0.38,0.27	0.70	7.87±1.21	7.57±0.80	-0.30±0.58	-0.75,0.15	0.21	0.33
HbA$_{1c}$ (mmol/mol)	48.00±10.56	47.22±8.18	-0.78±4.58	-4.30,2.74	0.62	62.44±13.41	59.22±8.80	-3.22±6.59	-8.29,1.24	0.16	0.38
Insulin resistance (HOMA)	2.04±0.45	1.81±0.41	-0.23±0.35	-0.50,0.05	0.08	2.42±0.79	2.34±0.66	-0.08±0.84	-0.72,0.58	0.79	0.61
Fasting glucose (mmol/L)	7.83±1.66	7.35±1.57	-0.48±0.70	-1.02,0.06	0.07	9.39±2.65	8.41±1.08	-0.98±1.94	-2.47,0.51	0.18	0.48
C-peptide (nmol/L)	0.81±0.21	0.73±0.19	-0.08±0.30	-0.18,0.03	0.13	0.89±0.25	0.91±0.26	0.02±0.30	-0.21,0.26	0.83	0.38
Total cholesterol (mmol/L)	4.51±0.90	4.54±1.07	0.03±0.52	-0.37,0.44	0.85	4.56±0.90	4.37±0.83	-0.19±0.79	-0.79,0.42	0.49	0.49
HDL-cholesterol (mmol/L)	1.26±0.26	1.33±0.31	0.07±0.09	-0.002,0.14	0.055	1.14±0.39	1.08±0.23	-0.06±0.22	-0.23,0.11	0.43	0.13
LDL-cholesterol (mmol/L)	2.60±0.84	2.66±1.04	0.06±0.64	-0.29,0.41	0.69	2.38±0.86 (n=8)	2.35±0.71	-0.03±0.64	-0.57,0.51	0.89	0.73
Triglycerides (mmol/L)	1.43±0.70	1.21±0.46	-0.22±0.36*	NA	0.10*	2.86±2.77	2.21±1.13	-0.65±1.96	NA	0.31*	0.93**
HDL/total cholesterol (%)	29.2±10.0	31.3±11.2	2.1±3.8	-0.8,5.1	0.14	26.5±11.5	25.6±7.4	-0.9±7.5	-6.7,4.8	0.71	0.30
hs-CRP (mg/L)	0.64±0.22 (n=8)	1.18±1.14	0.54±1.09*	NA	0.18*	1.82±1.86	1.70±1.57	-0.12±0.47	NA	0.91	0.24**

Table 2 (left): Baseline and post data are presented as mean ± standard deviation. Mean change is mean within group change ± standard deviation. 95 % confidence intervals (CI) and p-values of the change are shown in separate columns. Right column p-values show differences in changes between groups.

HbA$_{1c}$ = glycosylated hemoglobin, hs-CRP = high-sensitive c-reactive protein. n = 9 for all variables in both groups unless otherwise stated.

*Related-Samples Wilcoxon Signed Rank Test
**Independent-Samples Mann-Whitney U Test

Anthropometry

No effects of training were seen on anthropometric measures in the SIT group (Table 3). HIT reduced body fat percentage by 4.5 % (-1.3 pp [-2.6, -0.04], p = 0.044), and visceral fat area by 5.0 % (-5.3 cm^2 [-10.4, -0.3], p = 0.041). These effects on body composition were seen without any significant change in total body weight or BMI (Table 3). Despite no significant changes in the SIT group, neither body fat percentage nor visceral fat area changed significantly more following HIT than SIT from baseline to post-test (p-value of the difference = 0.10 and 0.56, respectively).

Mean reduced waist circumference did not reach statistical significance following HIT (-1.3 cm [-2.8, 0.3], p = 0.09). However, waist circumference changed differently between the two exercise groups (p-value of the difference = 0.046) (Table 3).

Maximal oxygen uptake and work economy

Both HIT and SIT improved VO$_{2peak}$, both in relative (mL/kg/min) and absolute values (L/min). Mean improvements in relative VO$_{2peak}$ was 10.4 % (3.3 mL/kg/min [1.6, 5.0], p = 0.002) following HIT and 4.3 % (1.4 mL/kg/min [0.1, 2.7], p = 0.034) following SIT. The between group difference of the improvements was almost significant (p-value of the difference = 0.056).

Both training modalities also improved work economy measured as heart rate at a given submaximal work load (Table 4), with no significant between group difference (p-value of the difference = 0.11). Only HIT improved heart rate recovery two minutes after the exercise test to exhaustion (11.0 bpm [2.4 – 19.6], p = 0.02), and the improvements were significantly different from SIT (Table 4, p of the difference = 0.025).

BODY COMPOSITION	Baseline HIT	Post HIT	Mean change	95 % CI	p-value	Baseline SIT	Post SIT	Mean change	95 % CI	p-value	p-value of difference
Height (cm)	168.7 ±10.5					174.7 ±12.4					
Weight (kg)	75.5 ±15.9	74.9 ±15.7	-0.6 ±1.5	-1.8, 0.5	0.24	91.4 ±20.3	91.5 ±21.3	0.1 ±	-1.6, 1.8	0.87	0.40
BMI (kg/m^2)	26.3 ±3.0	26.1 ±3.1	-0.2 ±0.5	-0.6, 0.2	0.27	29.5 ±3.9	29.5 ±3.9	0.0 ±	-5.3, 5.3	1	0.48
Fat percentage (%)	28.8 ±6.7	27.5 ±6.9	-1.3 ±1.6	-2.6, -0.04	0.04	31.4 ±6.2	31.5 ±5.4	0.04 ±	-1.2, 1.3	0.94	0.10
Total fat weight (kg)	21.6 ±6.0	20.5 ±6.5	-1.1 ±1.6	-2.3, 0.1	0.07	28.6 ±8.0	28.7 ±7.7	0.1 ±	-1.5, 1.7	0.85	0.18
Visceral fat area (cm^2)	106.1 ±21.6	100.8 ±22.5	-5.3 ±6.6	-10.4, -0.3	0.04	128.7 ±28.7	125.4 ±26.9	-3.3 ±	-9.5, 3.0	0.27	0.56
Waist circumference (cm)	93.8 ±8.2	92.5 ±7.8	-1.3 ±2.0	-2.8, 0.3	0.09	103.3 ±10.6	104.2 ±11.7	0.9 ±2.3	-0.8, 2.7	0.26	0.046
Skeletal muscle mass (kg)	30.0 ±7.7	30.3 ±7.6	0.3 ±0.7	-0.2, 0.8	0.18	35.2 ±9.4	35.1 ±9.4	-0.1 ±	-0.8, 0.5	0.68	0.23

Table 3 (left): Baseline and post data are presented as mean ± standard deviation. Mean change is mean within group change ± standard deviation. 95 % confidence intervals (CI) and p-values of the change are shown in separate columns. Right column p-values show differences in changes between groups.

BMI = body mass index. n = 9 for all variables in both groups

AEROBIC CAPACITY TEST

	Baseline HIT	Post HIT	Mean change	95 % CI	p-value	Baseline SIT	Post SIT	Mean change	95 % CI	p-value	p-value of difference
VO_{2peak} (mL/min/kg)	31.5±5.8	34.8±5.3	3.3±2.2	1.6, 5.0	0.002	32.0±9.5	33.4±8.9	1.4±1.6	0.1, 2.7	0.03	0.055
VO_{2max} (L/min)	2.41±0.75	2.64±0.76	0.23±0.2	0.07, 0.38	0.01	2.98±1.30	3.11±1.33	0.13±0.16	0.01, 0.26	0.04	0.29
Resting HR (bpm)	70.8±7.2	70.2±6.8	-0.6±3.4	-3.2, 2.1	0.64	73.4±11.6	71.6±10.0	-1.8±11.1	-10.3, 6.7	0.64	0.76
Maximum HR (bpm)	173.9±10.7	176.7±7.6	2.8±7.5	-2.9, 8.5	0.30	176.1±14.7	173.7±12.4	-2.4±5.0	-6.3, 1.4	0.18	0.10
1-minute HRR (bpm)	26.3±7.6	30.3±4.5	4.0±8.3	-2.4, 10.4	0.19	29.4±9.5	31.3±9.1	1.9±5.9	-2.6, 6.4	0.36	0.54
2-minute HRR (bpm)	46.6±13.1	57.6±11.1	11.0±11.1	2.4, 19.6	0.02	52.9±12.9	53.6±14.3	0.7±5.7	-3.7, 5.1	0.74	0.025
HR at submaximal load (bpm)	125.8±10.4	115.2±11.1	-10.6±11.1	-18.0, -3.1	0.01	125.8±10.8	121.6±10.9	-4.2±5.2	-8.2, -0.2	0.04	0.11
RPE	17.0±1.9	17.9±1.1	0.9±1.8	-0.5, 2.3	0.18	17.8±0.8	19.0±0.7	1.2±1.0	0.5, 2.0	0.005	0.64
RER	1.10±0.05	1.09±0.04	-0.007±0.05	-0.04, 0.03	0.68	1.13±0.04	1.14±0.04	0.010±0.02	-0.01, 0.03	0.26	0.37

Table 4 (left): Baseline and post data are presented as mean ± standard deviation. Mean change is mean within group change ± standard deviation. 95 % confidence intervals (CI) and p-values of the change are shown in separate columns. Right column p-values show differences in changes between groups.

VO_{2peak} = peak oxygen uptake, HR = heart rate, HRR = heart rate recovery, RPE = rating of perceived exertion, RER = respiratory exchange ratio. n = 9 for all variables in both groups

Blood pressure

SIT decreased diastolic blood pressure by -5.8 mmHg (-11.4, -0.2, p = 0.044). No other significant blood pressure changes were seen in any of the training groups (Table 5), and no between group differences of the change existed.

In both groups combined, diastolic (-8.7 mmHg [-14.5, -2.8], p = 0.013) as well as systolic (-8.4 mmHg [-14.8, -2.1], p = 0.016) blood pressure decreased in the patients with hypertension (>135 systolic [n = 9] and/or >85 diastolic [n = 6]) at baseline, but not in the patients with normal blood pressure at the start of the intervention (systolic; n = 9, 0.9 mmHg [3.3, 5.0], p = 0.63, diastolic; n = 12, -0.3 mmHg [-4.3, 3.6], p = 0.86). Both systolic (p-value of the difference = 0.013) and diastolic (p-value of the difference = 0.015) blood pressure changed significantly more in the hypertensive than normotensive patients.

Table 5 (right): Baseline and post data are presented as mean ± standard deviation. Mean change is mean within group change ± standard deviation. 95 % confidence intervals (CI) and p-values of the change are shown in separate columns. Right column p-values show differences in changes between groups.

BP = blood pressure. n = 9 for all variables in both groups.

BLOOD PRESSURE

	Baseline HIT	Post HIT	Mean change	95 % CI	p-value	Baseline SIT	Post SIT	Mean change	95 % CI	p-value	p-value of difference
Systolic BP (mmHg)	129.3±16.3	126.3±14.6	-3.0±5.5	-7.2, 1.2	0.14	135.3±11.0	130.7±10.6	-4.6±10.7	-12.8, 3.7	0.24	0.70
Diastolic BP (mmHg)	76.8±7.2	76.4±8.9	-0.4±6.2	-5.2, 4.3	0.84	85.4±12.0	79.6±7.7	-5.8±7.3	-11.4, -0.2	0.04	0.11

CORRELATION TABLE

	HbA1c Baseline	HbA1c Change	HOMA-IR Baseline	HOMA-IR Change	BMI Baseline	BMI Change	Visceral fat area Baseline	Visceral fat area Change
HOMA-IR	0.40 (p = 0.10)	0.37 (p = 0.14)						
BMI	0.41 (p = 0.09)	0.12 (p = 0.64)	0.59 (p = 0.01)*	0.15 (p = 0.56)				
Visceral fat area	0.46 (p = 0.053)	0.41 (p = 0.09)	0.71 (p = 0.001)*	0.30 (p = 0.23)	0.87 (p < 0.001)*	0.61 (p = 0.008)*		
Total cholesterol	0.08 (p = 0.76)	0.55 (p = 0.02)*	-0.03 (p = 0.89)	0.47 (p = 0.052)	-0.18 (p = 0.47)	0.02 (p = 0.93)	-0.24 (p = 0.34)	0.43 (p = 0.08)
LDL	-0.08 (p = 0.76)	0.54 (p = 0.03)*	-0.20 (p = 0.45)	0.32 (p = 0.20)	-0.27 (p = 0.29)	0.04 (p = 0.88)	0.16 (p = 0.53)	0.32 (p = 0.21)
HDL	-0.30 (p = 0.23)	-0.20 (p = 0.42)	-0.44 (p = 0.07)	-0.69 (p = 0.001)*	-0.37 (p = 0.13)	-0.29 (p = 0.25)	-0.28 (p = 0.26)	-0.12 (p = 0.63)
Triglycerides	0.37 (p = 0.13)	0.53 (p = 0.02)*	0.51 (p = 0.03)*	0.59 (p = 0.01)*	0.23 (p = 0.36)	0.01 (p = 0.96)	-0.28 (p = 0.27)	0.41 (p = 0.09)
VO2peak	-0.45 (p = 0.06)	-0.07 (p = 0.78)	-0.39 (p = 0.11)	0.04 (p = 0.87)	0.09 (p = 0.71)	-0.24 (p = 0.71)	-0.24 (p = 0.33)	-0.58 (p = 0.01)*

	Total cholesterol Baseline	Total cholesterol Change	LDL Baseline	LDL Change	HDL Baseline	HDL Change	Triglycerides Baseline	Triglycerides Change
LDL	0.93 (p < 0.001)*	0.94 (p < 0.001)*						
HDL	-0.21 (p = 0.41)	-0.27 (p = 0.28)	-0.18 (p = 0.48)	-0.23 (p = 0.38)				
Triglycerides	0.30 (p = 0.22)	0.46 (p = 0.054)	0.12 (p = 0.64)	0.40 (p = 0.11)	-0.69 (p = 0.002)*	-0.44 (p = 0.07)		
VO2peak	0.23 (p = 0.37)	0.11 (p = 0.67)	0.16 (p = 0.53)	0.12 (p = 0.66)	0.09 (p = 0.73)	0.04 (p = 0.89)	0.04 (p = 0.88)	-0.07 (p = 0.79)

Correlations

Correlations between selected variables are summed up in table 6. At baseline HbA1c correlated positively with insulin resistance (HOMA), BMI, visceral fat area and triglycerides and negatively with VO2peak, even though none of the correlations were strong enough to reach statistical significance (Table 6). There was a strong positive correlation between HOMA-IR and visceral fat area at baseline ($r = 0.71$, $p = 0.001$).

Changes in HbA1c and HOMA-IR from baseline to post-test were significantly associated with changes in blood lipids (Table 6). The positive correlation between changes in HbA1c and visceral fat mass was not significant ($r = 0.41$, $p = 0.09$).

Table 6: Pearson product-moment correlations are presented as r-values at baseline and r-values of the change from baseline to post-test. Exact p-values are reported, and significant correlations (p < 0.05) are flagged (*)

HbA1c = glycosylated hemoglobin, HOMA-IR = homeostasis model assessment of insulin resistance, BMI = body mass index, LDL = low-density lipoprotein cholesterol, HDL = high-density lipoprotein cholesterol, VO2peak = peak oxygen uptake

Discussion

The main finding from this study was that HbA_{1c} only improved following HIT and SIT in the T2D-patients with the poorest glycemic control at baseline. In well-controlled subjects, neither 10x1-minute intervals at 90 % of HR_{max} (HIT) nor 2x20-second sprint intervals at supramaximal intensity (SIT) improved long-term glycemic control. Consequently, HIT did not improve HbA_{1c} more than SIT as hypothesized. Both groups improved VO_{2peak}, with no significant difference between HIT and SIT. Contrary to SIT, HIT also reduced body fat percentage and visceral fat area. HIT and SIT combined reduced both systolic and diastolic blood pressure in hypertensive, but not normotensive, patients.

HbA_{1c}

HIT and SIT combined improved HbA_{1c} in the 50 % subjects with the poorest long-term glycemic control in this study, and the -0.54 pp reduction is comparable to improvements seen in earlier training studies and meta-analyses [15-22]. A reduction by such magnitude is considered clinically significant, compares well to the reductions achieved by common glucose-lowering medication [10, 64], and could lead to substantially reduced risk of macrovascular and microvascular complications and all-cause mortality [9, 10].

However, when including all subjects no changes in HbA_{1c} were seen in any of the exercise groups in this study. This is in line with the results of Terada et al. [34], who found no effect on HbA_{1c} following 12 weeks of HIT. In contrast, Mitranun et al. [35] recently found significant improvements in HbA_{1c} following a HIT protocol similar to the one in our study and the Terada-study. 10 weeks and 30 sessions of 4-6 1-minute intervals at 80-85 % of VO_{2peak} improved long-term glycemic control, as opposed to isocaloric CMT. The reason for the discrepancy between our results and the results of Mitranun et al. is unclear, but could be due to the relatively higher initial HbA_{1c} values (7.6 ± 0.2 %) in the HIT group in that study, compared to both our (6.5 ± 1.0 %) study and the Terada-study (6.6 ± 0.6 %). This suggestion is supported by a recent systematic review [21], and is strengthened by the significant exercise effect on HbA_{1c} seen in the present study when evaluating subjects with baseline levels higher than 7.2 %, regardless of exercise group. Umpierre et al. [24] have suggested that exercise volume is more important than exercise intensity for improving HbA_{1c} in patients with T2D, and it could be argued that the volume of exercise needs to be higher than in the present study to be effective in improving HbA_{1c} in subjects with relatively well-controlled T2D.

The importance of improving long-term glycemic control in T2D-patients with higher HbA_{1c} is pointed out by the fact that these patients have an increased relative risk of 4.2 of dying

from ischemic heart disease, substantially higher than patients with lower HbA_{1c} [65]. Lowering HbA_{1c} in T2D is also found to decrease the absolute risk of developing coronary heart disease within 10 years by 5-17 %, as well as decreasing all-cause mortality within the same time frame by 6-15 % [66]. The effect seen in the patients with the poorest long-term glycemic control in our study, could suggest that both HIT and SIT potentially have their place in an exercise regime for patients with T2D, but further studies are needed to confirm this effect.

Insulin resistance

The homeostasis model assessment (HOMA-IR) is widely used for assessing insulin resistance in patients with T2D, and correlates well with the more expensive and time-consuming glycemic clamp technique [67, 68]. Even though the results did not reach statistical significance, our study shows a non-significant improvement in insulin resistance in the HIT group and no change following SIT (Table 2). The tendency of an improvement following HIT seems to be mainly related to decreased fasting plasma glucose concentrations, but also to a lesser degree decreased C-peptide concentrations.

The role of exercise in preventing and treating insulin resistance through improvements in insulin sensitivity is well documented in subjects with T2D [69-72], but to our knowledge the study of Mitranun et al. [35] is the only one to previously investigate HOMA-IR response to high intensity interval training in this patient group. They found that HOMA-IR decreased significantly by -0.6 following HIT, similar to the decreases following isocaloric CMT. The improvements are greater than in our study (-0.23), and the differences can possibly be explained by the higher baseline HOMA-IR values in the Mitranun-study. The potential for improved insulin resistance following HIT is also shown by Earnest et al. [51], who found that six weeks of HIT at 90-95 % of VO_{2peak} is effective in improving HOMA-IR in pre-diabetic men at risk for insulin resistance, whereas isocaloric CMT did not affect insulin resistance in this population.

Reduced insulin resistance following exercise in T2D could result from adaptations that increase insulin action in skeletal muscle. Defects in insulin-mediated glucose-uptake in T2D have been tracked to defects in the function and distribution of the GLUT-4 protein in skeletal muscle cells [73, 74]. GLUT-4 is responsible for the insulin-regulated transport of glucose into muscle cells [75, 76], and a training-induced increase in GLUT-4 content is frequently seen following regular aerobic exercise in T2D [77-79]. Another possible explanation for improved insulin resistance following exercise is increased mitochondrial content in skeletal

muscle. Muscle oxidative capacity is a significant predictor of insulin sensitivity [80], and patients with T2D are reported to have reduced mitochondrial capacity [81]. HIT has been shown to increase skeletal muscle mitochondrial content together with reduced hyperglycemia in patients with T2D [56]. However, it is unclear whether skeletal muscle adaptations were responsible for the trend of improved HOMA-IR following HIT in our study, as neither GLUT-4 nor mitochondrial content were measured.

No study to our knowledge has previously investigated HOMA-IR following SIT. However, three weekly sessions of 4-6 30-second sprints have been shown to increase insulin sensitivity in healthy adults [52, 53] and in obese men [54], without changes in circulating fasting plasma glucose or insulin concentrations. Even lower-volume SIT, equal to the weekly amount of exercise in the present study, is shown to improve insulin sensitivity in men, but not in women [63]. Direct measures of insulin sensitivity were not done in our study – however, 12 weeks of low-volume SIT did not improve insulin resistance (HOMA) or fasting plasma glucose concentration in patients with T2D.

Blood lipids

Our results suggest that HIT, but not SIT, could be effective in improving lipid profile in patients with T2D, even though the beneficial effects did not reach statistical significance. The 5.3 % improvements in HDL (0.07 mmol/L [-0.002, 0.14], p = 0.055) are smaller than those seen by Mitranun et al. [35], whereas the 15.4 % (-0.22 mmol/L, p = 0.10) reduction in triglyceride content following HIT is in line with the results from that study. However, two other intervention studies found that HIT was ineffective in altering HDL and triglycerides in T2D [33, 34]. Also, our study does not support the significant effect of HIT on lowering LDL and total cholesterol seen by Mitranun et al. [35] and following higher-volume HIT [33].

The mechanisms to explain any favorable effects on lipid profile following exercise are not fully understood. However, low levels of HDL and high levels of triglycerides are likely related to both insulin resistance and an increased amount of visceral fat [82], and in the present study HOMA-IR was strongly correlated to both visceral fat area, triglycerides and HDL at baseline (table 6). In addition, changes in HOMA-IR were negatively correlated with changes in HDL (r = -0,69, p = 0.001) and positively correlated with changes in triglycerides (r = 0.59, p = 0.01), indicating an association between altered lipid profiles and insulin resistance. The correlations between changes in visceral fat area and HDL (r = -0.12, p = 0.63) and visceral fat area and triglycerides (r = 0.41, p = 0.09) were not significant.

Patients with T2D generally have high triglyceride levels compared with the general population, often in combination with low levels of HDL [83, 84]. The levels of LDL and total cholesterol do not differ significantly from the general population [83]. Low values of HDL and high values of LDL, total cholesterol and triglycerides are associated with increased CVD risk [85], and every 0.1 mmol/L decrease in HDL is associated with a 2-3 % increased risk of coronary heart disease [86]. It is difficult to conclude on certain health benefits from the small and non-significant improvements in blood lipids following HIT in our study, especially when considering the inconsistent results from earlier studies [33-35]. However, given the low HDL and high triglyceride values often seen in patients with T2D, any improvements could prove beneficial. Small increases in HDL and decreases in triglycerides are previously seen in T2D following regular non-interval based exercise [17-20, 22], and the promising results following HIT in the present study should be further investigated in later studies.

Our study is the first to date to evaluate lipid profiles following SIT in T2D, and possibly the first to do so in any population or patient group. No changes were seen in any of the blood lipid variables following the sprint interval intervention, and from our results it does not seem likely that a small weekly amount of SIT is sufficient to alter lipid profile in patients with T2D.

Anthropometry

Despite no reduction in BMI or total body weight, HIT did reduce body fat percentage and visceral fat area significantly, and tended to reduce total fat weight and waist circumference (Table 3). None of these effects were seen following SIT. Interestingly, the SIT group tended to have a higher mean total body weight, BMI, fat weight and visceral fat area than the HIT group at baseline (p-value of the difference = 0.05-0.09 for all variables), and one could argue that the room for improvement was greater in the SIT group. Even so, improvements were seen in the HIT group only, and at post-test the HIT group had significantly lower waist circumference (p-value of the difference = 0.03), and total fat weight (p-value of the difference = 0.03) than the SIT group.

In patients predisposed to T2D high levels of visceral fat lead to elevated levels of free fatty acids in blood plasma, which could lead to impaired insulin secretion [87]. This might explain the strong positive correlation between visceral fat area and HOMA-IR (r = 0.71, p = 0.001) seen at baseline in our study. Increased triglyceride synthesis in skeletal muscle during and after acute exercise prevents fatty acid-induced insulin resistance [88], and offers a possible

explanation for a combined reduction in insulin resistance and abdominal fat. However, in our study the correlation between the reduction in visceral fat area and HOMA-IR failed to reach statistical significance (r = 0.30, p = 0.22).

The results from HIT in our study are in line with the results of Mitranun et al. [35] and Terada et al. [34], who also found that HIT was effective in reducing fat percentage and visceral fat in T2D without significant reductions in BMI or body weight. Similar results have been seen following continuous moderate training of higher volume [19, 29, 89, 90]. Our results show that HIT can potentially give the same benefits with reduced weekly exercise time. Reducing visceral fat area and waist circumference could be especially important in this patient group, as intra-abdominal fat is a greater risk factor for T2D than overall adiposity [91, 92]. Over 50 % of patients with T2D are obese (BMI >30.0) [93], and even those who are not may have an increased amount of intra-abdominal fat [3]. Decreasing waist circumference in T2D is associated with a reduction in HbA_{1c} as well as reduced risk of developing CVD. [94].

Possible mechanisms underlying the abdominal fat loss following HIT have previously been discussed by Boutcher [95]. Only a few sessions of high intensity interval training is enough to increase whole body and skeletal muscle capacity for fatty acid oxidation [96, 97]. Increased fat oxidation both during and after HIT could result from inhibited anaerobic glycogenolysis, meaning that ATP is predominantly resynthesized from intramuscular triglycerides [98]. Postexercise fat metabolism could also be influenced by the catecholamines generated by HIT and/or the need to remove lactate and H^+ and resynthesize glycogen [95].

However, our results clearly indicate that even at high intensity a certain volume of exercise is needed to reduce abdominal fat and improve other anthropometric variables in T2D. Whyte et al. [54] has previously shown that waist circumference was reduced in overweight men following only two weeks of SIT, but this does not seem to be true in patients with T2D. It is likely that the total weekly energy expenditure from exercise was too low to cause an effect on body weight and body composition in the SIT group in our study.

Aerobic capacity

As hypothesized, both HIT and SIT improved peak aerobic capacity, but the difference in improvement between the groups marginally failed to reach significance (p-value of the difference = 0.056). Subjects with T2D frequently have lower aerobic capacity than healthy subjects of similar age and body mass [99, 100], and improving VO_{2peak} could be crucial, as

low aerobic capacity is a powerful and independent predictor of long-term cardiac mortality in this patient group [101].

The 10.4 % increase in VO_{2peak} following HIT in the present study is highly comparable to the results from the metaanalysis by Boulé et al. [16], who found an 11.8 % increase following at least 8 weeks of structured, continuous aerobic exercise equivalent to the ADA and ACSM recommendations. An improvement of this size could be sufficient to reduce the risk of cardiac mortality from T2D [101, 102]. Our results clearly indicate that the same benefits can be reached with high intensity training even if total training time is reduced to half of the recommendations. This is supported by the findings of Mitranun et al. [35], who showed that HIT is more effective than isocaloric CMT in improving VO_{2peak} in patients with T2D.

7 – 12 % increases in VO_{2peak} following only a few weeks of SIT is previously seen in healthy [46, 47, 63], and overweight subjects [54, 55], but our study is the first to extend these findings to subjects with T2D. Despite the longer duration of the intervention in our study, the subjects only increased their VO_{2peak} by 4.3 %. This could be explained by the fact that the weekly amount of SIT was even lower than in most of the earlier studies. However, Metcalfe et al. [63] found a 12 % increase following a similar protocol to ours, and one can not rule out that the rate of improvement is different in healthy subjects compared to patients with T2D.

Despite the substantially higher volume of high-intensity exercise in the HIT group, HIT did not improve VO_{2peak} significantly more than SIT. The findings are similar to Tjønna et al. [103], who found that low-volume HIT was as effective as high-volume HIT in improving VO_{2peak} in overweight men. The results from our study could indicate that the extremely high intensity of all-out supramaximal exercise makes up for the smaller total volume of exercise in the SIT group. However, these findings should be interpreted with caution and challenged in later studies, as there was a clear trend of greater improvements following HIT than SIT.

From the existing literature it could be speculated that HIT and SIT affect different factors to increase VO_{2peak}. Wisløff et al. [41] showed that a combination of central (i.e. increased stroke volume of the heart) and peripheral adaptations (i.e. enhanced mitochondrial function through increased skeletal muscle oxidative capacity) was responsible for improvements in VO_{2peak} following high intensity aerobic intervals in heart failure patients. Sprint interval training has been shown to improve mitochondrial function [96, 104] and to increase VO_{2peak} [47, 54, 55, 63] without change in the stroke volume [105]. According to Gibala et al. [106], it could be that SIT severely stresses cellular and peripheral vasculature, while the brief exercise bouts are insufficient to stress the heart. Thus, a certain volume of high-intensity training is

possibly needed in order to improve central functions associated with VO_{2peak}, a speculation supported by Gibala and McGee [107]. Mitochondrial function is generally reduced in individuals with T2D [81, 108, 109], and could be an important predictor of insulin sensitivity [80]. HIT has been shown to improve mitochondrial function in obese men with T2D [56], and although no direct measures of mitochondrial function were done in the present study it seems possible that similar adaptations occur following SIT in T2D.

Both groups improved work economy at a fixed absolute submaximal intensity, with no between group differences. The improvements likely result from the increased aerobic capacity as well as improved mechanical and neuromuscular skills following the intervention. At the start of the study, many of the subjects were unaccustomed to walking on a treadmill, and 36 sessions of practicing that skill probably contributed to the improvement.

Heart rate recovery two minutes after the treadmill test to exhaustion improved following HIT only, and significantly more than following SIT. No effect was seen on 1-minute HRR in any of the exercise groups. Decreased HRR is associated with increased risk of CVD and all-cause death among patients with T2D, and a higher fitness level derived from exercise training may positively affect autonomic function and HRR in patients with diabetes [110]. It is unclear why HIT improved 2-minute HRR more than SIT in the present study, but we could speculate that it is related to the trend of greater improvements in VO_{2peak} in the HIT group.

Blood pressure

Decreased systolic blood pressure is previously seen following SIT in overweight men [54], but to our knowledge ours is the first study to show decreased diastolic blood pressure in any patient group following SIT. It is difficult to say why diastolic blood pressure was reduced following SIT only, but there was a tendency of higher baseline values in the SIT group than in the HIT group ($p = 0.09$), so the room for improvement was possibly larger.

Previously, HIT has improved systolic, but not diastolic blood pressure in T2D [35]. It is unclear why similar effects on systolic blood pressure were not seen in our study, but earlier studies and metaanalyses show conflicting results on the effect of exercise on blood pressure in T2D [17, 19, 20, 22].

Raised blood pressure of >135 mmHg systolic and/or >85 mmHg diastolic is far more common in patients with T2D than in the general population [111]. However, in our study about half of the subjects were normotensive at baseline, with blood pressure levels approximately equal to the recommended levels of 120 mmHg systolic and or 80 mmHg

diastolic. One could argue that these subjects already had optimal blood pressure, and as one might expect did not improve systolic or diastolic blood pressure following the exercise intervention. Interestingly, in the subjects with systolic blood pressure above 135 mmHg (n = 9) and in the subjects with diastolic blood pressure above 85 mmHg (n = 6) at baseline, the combined decrease following HIT and SIT was ≈ 8.5 mmHg for both systolic and diastolic blood pressure. These reduction levels compare well to the reductions seen in an earlier study on HIT in hypertensive patients without T2D [112].

The mechanisms for the blood pressure lowering effect of exercise are complex and not fully understood. Blood pressure in the aorta is regulated by several mechanisms, and the most rapid to change are peripheral resistance and stroke volume. Decreased sympathetic tone is most likely involved in training-induced blood pressure reduction [113]. However, blood volume, viscosity of the blood and the elasticity of the large arteries can also be changed. Physical activity on a regular basis can increase the production of NO and enhance perfusion and flow in the peripheral vascular system [114].

The risk of fatal and non-fatal diabetes-related complications are higher in hypertensive than normotensive patients with T2D, even when adjusted for other risk factors associated with hypertension [115]. Few exercise studies have been conducted on patients with T2D and raised, untreated blood pressure, but lowering blood pressure by 2.1/0.9 mmHg is shown to reduce the risk of major cardiovascular events in T2D by approximately 10 % [116]. From our results it seems possible that low-volume interval training could positively affect blood pressure in hypertensive patients with T2D, as opposed to normotensive patients. This effect should be further investigated in later studies, but reductions by the magnitude indicated in this study could potentially reduce CVD risk substantially in these patients.

It should be noted that blood pressure measurements performed at a clinic can be imprecise and inconsistent for a number of reasons. The main concerns are that clinic measurements lead to an overestimation of blood pressure because of the white-coat effect [117], and that it can potentially mask hypertension due to uncalibrated devices or inaccurate and inconsistent placement of the cuff [118-120]. Recording of 24-hour ambulatory blood pressure is currently considered the gold standard. Research show a significant difference between 24-hour and clinic measurements [121], and that daytime ambulatory blood pressure is more effective at predicting mortality than clinic blood pressure [122]. Ideally, 24-hour measurement would have been performed for more accurate results, but economical and practical considerations made that difficult in the current study.

Limitations

It is possible that the relatively small sample size in this study prevented more significant improvements within group and masked significant between group changes on some variables. There were several trends of improvement, especially in the HIT group, and it is possible that these results would have reached significance if the group size had been somewhat larger. Given the small sample sizes, particularly large between-group changes from baseline to post-test would perhaps be required to show outcomes of statistical significance.

When interpreting findings from the present study, the tendency of baseline differences in some of the characteristics should be taken into consideration. These differences included significant between group differences in the primary outcome variable, HbA_{1c}, at baseline. There was also large individual variability in some of the changes.

Another limitation is the use of clinic blood pressure measurements in our study. 24-hour recordings could possibly have yielded different results, as one can not rule out that the white-coat effect or measuring inaccuracy played a role. However, the same cuff and equipment were used for all measurements, and every blood pressure was taken and interpreted by the same investigator, which should reduce the risk of random bias.

Ours is the first study to investigate SIT on a treadmill, which makes the all-out nature of the sprint intervals slightly different than in previous studies performed on a stationary bicycle. On a bicycle the subjects are able to go all-out from the first second of each high-intensity interval, and power decreases as fatigue sets in towards the end of each interval. In our treadmill protocol the intensity was kept constant during the entire high-intensity interval. However, both training methods allow for the subjects to be totally exhausted at the end of each interval, and it seems unlikely that the effects should be very different from each other.

Conclusion

In type 2 diabetes-patients with poor glycemic control, a small amount of weekly exercise could be enough to yield improvements in glycosylated hemoglobin and several cardiovascular risk factors associated with the disease. Our results add to the growing body of evidence that high intensity interval training is effective in improving aerobic capacity in a number of patient groups, and is the first to show that sprint interval training improves VO_{2peak} in type 2 diabetes. Both exercise protocols in this study are the most time-efficient yet to be investigated in type 2 diabetes, and could be implemented to reduce the time-barrier associated with exercise in these patients. However, it seems likely that a larger volume of total exercise is necessary to gain optimal results on glycemic control and cardiovascular risk.

Acknowledgments

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