Can Time Efficient Exercise Improve Cardiometabolic Risk Factors in Type 2 Diabetes? A Pilot Study

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Abstract

Exercise is considered a cornerstone in the prevention and treatment of type 2 diabetes, but few individuals with type 2 diabetes exercise according to guidelines. We investigated the effect of two time efficient high intensity exercise interventions on exercise capacity, glycemic control and other cardiometabolic risk factors in patients with type 2 diabetes. Twenty-one individuals with type 2 diabetes were randomly assigned to low volume high intensity interval exercise (HIIE; 27 minutes/bout; 10x1-minute at 90 % of HR_{max}; n = 10) or extremely low volume sprint interval exercise (SIE; 10 minutes/bout; 2x20 seconds at maximum achievable intensity; n = 11) 3 days/week for 12 weeks. Aerobic exercise capacity (VO_{2peak}), glycosylated hemoglobin (HbA_{1c}), blood pressure and body composition were measured at baseline and post test. Both HIIE and SIE improved VO_{2peak} (3.3 $mL\cdot min^{-1}\cdot kg^{-1}$, 10.4 %), p < 0.01, and 1.4 $mL\cdot min^{-1}\cdot kg^{-1}$ (4.6 %), p = 0.03, respectively). Only HIIE reduced body fat percentage (4.5 %, p = 0.04) and two minute heart rate recovery (11.0 bpm, p = 0.02). Neither HIIE nor SIE improved HbA_{1c}. In conclusion, this study indicates that substantially lower exercise volumes than recommended in current guidelines can improve aerobic exercise capacity in individuals with type 2 diabetes. However, 12 weeks of time efficient high intensity exercise did not improve glycemic control, and interventions of longer duration should be investigated.

Key words: Low volume exercise, VO2peak, HbA1c, type 2 diabetes, cardiovascular risk.

Introduction

Type 2 diabetes is characterized by reduced aerobic exercise capacity (Wei et al., 1999) and poor glycemic control (Unwin et al., 2010). Both reduced aerobic exercise capacity and elevated glycosylated hemoglobin (HbA_{1c}) are associated with increased cardiovascular risk in type 2 diabetes (Emerging Risk Factors Collaboration et al., 2010; Wei et al., 2000; Zhang et al., 2012). Compared with healthy individuals, type 2 diabetics have a 2–4 times increased risk of developing cardiovascular disease (Emerging Risk Factors Collaboration et al., 2010), and more than 70 % of this patient population die of cardiovascular causes (Laakso, 2001).

Exercise training can improve aerobic exercise capacity (VO_{2peak}) (Boule et al., 2003) and glycemic control (Boule et al. 2001) in type 2 diabetes. The benefits of exercise training on overall mortality and cardiovascular risk exceed those explained by glucose lowering alone (Wei et al., 2000, Church et al., 2005). However, two out

of three individuals with type 2 diabetes do not exercise regularly (Thomas et al., 2004), and very few meet current exercise recommendations (Colberg et al., 2010). Lack of time is reported as one of the main reasons for the inactivity (Korkiakangas et al., 2009). This calls upon alternative exercise strategies that are less time consuming, yet effective to improve VO_{2peak}, glycemic control and other cardiometabolic risk factors.

In type 2 diabetes, high intensity interval exercise seems to be superior to continuous moderate exercise in improving aerobic exercise capacity and reducing several cardiovascular risk factors (Backx et al., 2011; Hollekim-Strand et al., 2014; Mitranun et al., 2014). Recent research indicates that low- and even extremely low volume intermittent high intensity exercise can be effective in improving glycemic control in type 2 diabetes (Little et al., 2011) as well as insulin sensitivity and VO_{2peak} in sedentary, healthy men (Metcalfe et al., 2012).

Thus, the aim of this pilot study was to investigate the effects of low volume high intensity interval exercise (HIIE; 10x1-minute intervals at 90 % of maximum heart rate (HR_{max})) and extremely low volume sprint interval exercise (SIE; 2x20-seconds intervals at maximum achievable intensity) on aerobic exercise capacity (VO_{2peak}), glycemic control (HbA_{1c}), insulin resistance (HOMA-IR), blood pressure and body composition in individuals with type 2 diabetes. The main hypothesis was that in type 2 diabetes individuals, time effective exercise of HIIE and SIE is effective in improving cardiometabolic risk factors, but HIIE more than SIE.

Methods

Study participants

In this 12 week randomized exercise trial, individuals with type 2 diabetes were recruited through a local newspaper and advertising at the St. Olavs Hospital, Trondheim University Hospital, Norway. The study was conducted between August 2013 and January 2014.

Inclusion criteria were age 20–65 years, diagnosed with type 2 diabetes within the past 10 years with no use of insulin. Exclusion criteria were known cardiovascular disease or lung disease, untreated hypertension of 140/90 mmHg, orthopedic or neurological restrictions, severe obesity (BMI 35), pregnancy, inability to exercise, drug or alcohol abuse, and reluctance to sign the consent form. Subjects were not eligible if they were more physically active than recommended in current exercise guidelines, e.g. more than 150 min/week of exer-

cise at moderate intensity or greater (Colberg et al., 2010), assessed by a self-reported activity diary.

A total of 21 subjects were included. The unit of Applied Clinical Research at the Norwegian University of Science and Technology performed the randomization procedure. The protocol was approved by the Regional Committee for Medical and Health Research Ethics of Central Norway and was registered with the Clinical Trials Registry (ClinicalTrials.gov identifier: NCT02340260). Informed consent was obtained from all participants and all participants were insured.

Outcome measures

The primary outcome measure was glycosylated hemoglobin (HbA_{1c}). Secondary outcome measures were aerobic exercise capacity, measured as peak oxygen uptake (VO_{2peak}), blood glucose, insulin resistance (HOMA-IR), blood pressure and body composition.

Exercise training protocols

The HIIE protocol was described in detail previously (Little et al., 2011). Participants performed 3 minutes warm up at 70 % of HR_{max} (determined from the exercise capacity test, methodology described later), 10x1-minute intervals of fast uphill walking or running at approximately 90 % of HR_{max} with 75 seconds of active recovery between each interval, and 3 minutes cool down. Heart rate was continuously monitored by an experienced exercise physiologist throughout the intervention period, and treadmill speed and/or inclination was successively adjusted throughout the exercise intervention to make sure heart rate levels were met.

The SIE protocol was adapted to treadmill from a protocol previously described for stationary bicycle (Metcalfe et al., 2012). Participants performed 3 minutes warm up at 70 % of HR_{max}, 2x20-seconds sprint intervals at maximum achievable intensity, with approximately 3 minutes active recovery between intervals at an intensity of 70 % of HR_{max}, and subsequently 3 minutes cool down. The treadmill was set to 20 % incline and the first one or two sessions were used to find maximum achievable running speed. Speed was successively adjusted to ensure the intensity was according to the protocol throughout the intervention period.

Both groups exercised 3 times a week throughout the 12 week intervention. Exercise times per session in the HIIE and SIE group were 27 minutes and 10 minutes, respectively. It was not the aim of this trial to compare two isocaloric exercise protocols, but rather two protocols with different potential to reduce the time-burden associated with exercise in type 2 diabetes. Thus, the exercise protocols were not matched for energy expenditure.

Clinical and laboratory examinations

All measurements were performed at baseline and after completion of the 12 weeks of exercise. Post test measurements were made between 48 and 72 hours after the last exercise bout, in order to reduce the acute effects of the final exercise session.

Peak oxygen uptake

Exercise capacity (VO_{2peak}) was measured during walking on a treadmill (Woodway PPS 5, Woodway, Weil am Rheim, Germany) by indirect calorimetry as previously described (Rognmo et al. 2004) using MasterScreen Spirometer (Jaeger Oxycon Pro, Jaeger GmbH & Co KG, Würzburg, Germany). However, due to unexpected technical problems with the Jaeger device during the final days of pre-testing, VO_{2peak} in some of the patients (n = 4 [HIIE; n = 2, SIE; n = 2]) were measured using Metamax II (Cortex, Leipzig, Germany). These patients (n = 4) were also tested with Metamax II after completion of the exercise intervention, in order to prevent the measuring method to inflict on the results. 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.

During the test, heart rate was continuously recorded using Polar RS 400 monitors (Polar Electro, Kempele, Finland) to obtain maximum attainable heart rate. HR_{max} was determined by adding five beats to peak heart rate obtained during the test, as few subjects reach their true HR_{max} during a test of VO_{2peak} (Ingjer 1991). This calculation of HR_{max} is also routinely used in our research group to make sure that the HR obtained during exercise sessions is not lower than intended. Heart rate recovery was calculated as the difference between peak heart rate and heart rate one minute and two minutes following exhaustion, with the subjects standing still on the treadmill between measurements.

Biochemical measurements

Blood samples were collected in the fasted state (10 hours). HbA_{1c} was analyzed from EDTA tubes using an automated immunological method (Cobas Integra 400, Roche Diagnostics, Mannheim, Germany), serum blood glucose was analyzed using an enzymathic method (Modular P., Roche Diagnostics, Mannheim, Germany), and insulin c-peptide was analyzed by immonulogical methology (DPC Immulite 2000, Siemens, Erlangen, Germany), using standard procedures at St. Olavs Hospital, Trondheim University hospital. Overall insulin resistance was calculated using the homeostasis assessment model (HOMA-IR).

Resting heart rate and blood pressure

Blood pressure was measured in sitting position using a Criticare Comfort Cuff 506N (Criticare Systems Inc., Wisconsin, USA). After 5 minutes rest, the mean systolic and diastolic blood pressure of three subsequent measurements was noted and used in later analysis.

Body composition

Waist circumference was measured in expiration, midway between the lower lateral costal margin and the iliac crest, with the subject standing. The average value of three subsequent measurements was collected for analysis. Body weight, BMI, muscle mass and fat percentage were recorded using bioimpedance (InBody 720, Biospace CO, Ltd, Seoul, Korea) in the fasted state (10 hours).

Statistical methods

Normal distribution of the data was verified by a Kolmogorov-Smirnov test. The student t-tests were used to analyze between group differences at baseline and within group mean absolute changes in physiological, anthropometrical and biochemical variables during the 12-weeks intervention period. A p-value of 0.05 was considered statistically significant. Because of significant between group differences at baseline in the main outcome variable, ANCOVA with baseline HbA$_{1c}$ as a covariate was used to analyze between group changes from baseline to post test. Results are given as mean ± standard deviation (SD) in text and tables, and as mean (SEM) in figures unless stated otherwise. All data analysis was carried out using SPSS version 21.0 (SPSS Inc, Chicago, Illinois, USA).

Results

Baseline characteristics and compliance
Participants in the SIE group had higher HbA1c levels at baseline compared to the HIIE group (p = 0.02; Table 1). No significant differences at baseline were seen for other demographic or clinical characteristics (Table 1).

A total of 18 subjects (SIE, n = 9; HIIE, n = 9) completed the exercise intervention as scheduled. Three subjects (SIE, n = 2; HIIE, n = 1) dropped out during the intervention period. One subject in each group dropped out due to exercise related calf pain, whereas one subject in the SIE group dropped out without reporting any reason. The HIIE and SIE group performed 96.0 % and 95.4 % of the scheduled exercise sessions at target heart rate, respectively.

Most of the participants (n = 15) used oral antihyperglycemic medication, and the remaining participants (n = 3) were treated with diet only (Table 1). All participants complied with their medical treatment regimen and did not change the medication during the 12 week intervention period.

Peak oxygen uptake
Mean improvements in relative VO$_2$peak were 3.3

mL·min^{-1}·kg^{-1} (10.4 %, p < 0.01) and 1.4 mL·min^{-1}·kg^{-1} (4.3 %, p = 0.03) following HIIE and SIE, respectively (Table 2; Figure 1). The between group difference of the improvements were tending towards being significant (p = 0.052). Only HIIE improved heart rate recovery two minutes after the exercise test to exhaustion (11.0 bpm, p = 0.02), and the improvements were almost significantly different from SIE (p = 0.052; Table 2).

Table 1. Baseline characteristics. Data represents mean and (standard deviation) unless otherwise noted.

	HIIE (n=9)	SIE (n=9)
Age (years)	56.5 (6.5)	49.6 (10.6)
Female/male (n)	4/5	4/5
Diabetes duration (years)	4.2 (2.1)	5.3 (2.5)
HbA$_{1c}$ (%)	6.53 (.96)	7.87 (1.21)*
BMI (kg·m^{-2})	26.3 (3.0)	29.5 (3.9)
Fat percentage	28.8 (6.7)	31.4 (6.2)
Systolic blood pressure (mmHg)	129.3 (16.3)	135.3 (11.0)
Diastolic blood pressure (mmHg)	76.8 (7.2)	84.44 (12.0)
Glucose-lowering medication (n)	7	8
Antihypertensive medication (n)	2	4

* p < 0.05 between-group difference. HbA$_{1c}$ = glycosylated hemoglobin, BMI = body mass index.

Biochemical measurements, blood pressure and body composition
Neither HbA1c, fasting blood glucose nor HOMA-IR changed in either group following the exercise intervention (Table 2). There were strong negative correlations between baseline HbA1c (%) and changes in HbA1c after 12 weeks, reaching statistical significance in the SIE group only (HIIE; r = -0.66, p = 0.052, SIE; r = -0.88, p < 0.01).

SIE decreased diastolic blood pressure by 5.7 mmHg (p = 0.04; Table 2). However, this was not significantly different from HIIE (p = 0.59). Only HIIE reduced body fat percentage by 4.5 % (p = 0.04). The change was not significantly different from SIE (p = 0.07). There was no change in BMI, waist circumference or skeletal muscle mass in either group.

Table 2. Changes in cardiometabolic risk factors. Data represents mean and (standard deviation).

	HIIE (n=9)			SIE (n=9)			HIIE vs. SIE
	Baseline	12 weeks	Change	Baseline	12 weeks	Change	p interaction[†]
VO$_{2peak}$ (mL·min^{-1}·kg^{-1})	31.5 (5.8)	34.8 (5.3)	3.3 (2.2)**	32.0 (9.5)	33.4 (8.9)	1.4 (1.6)*	.052
VO$_{2peak}$ (L·min^{-1})	2.41 (.75)	2.64 (.76)	.23 (.2)**	2.98 (1.30)	3.11 (1.33)	.13 (.16)*	.30
2-minute HRR (bpm)	46.6 (13.1)	57.6 (11.1)	11.0 (11.1)**	52.9 (12.9)	53.6 (14.3)	.7 (5.7)	.052
HbA$_{1c}$ (%)	6.53 (0.96)	6.47 (0.75)	-.06 (.42)	7.87 (1.21)	7.57 (0.80)	-.30 (.58)	.23
HbA$_{1c}$ (mmol·mol^{-1})	48.0 (10.6)	47.2 (8.2)	-.8 (4.6)	62.4 (13.4)	59.2 (8.8)	-3.2 (6.6)	.20
HOMA-IR	2.04 (.45)	1.81 (.41)	-.23 (.35)	2.42 (.79)	2.34 (0.66)	-.08 (.84)	.14
Glucose$_{Fast}$ (mmol·mol^{-1})	7.83 (1.66)	7.35 (1.57)	-.48 (.70)	9.39 (2.65)	8.41 (1.08)	-.98 (1.94)	.47
Weight (kg)	75.5 (15.9)	74.9 (15.7)	-.6 (1.5)	91.4 (20.3)	91.5 (21.3)	.1 (2.2)	.40
BMI (kg·m^{-2})	26.3 (3.0)	26.1 (3.1)	-.2 (.5)	29.5 (3.9)	29.5 (3.9)	.0 (.7)	.51
Fat percentage	28.8 (6.7)	27.5 (6.9)	-1.3 (1.6)*	31.4 (6.2)	31.5 (5.4)	.04 (1.6)	.07
Waist$_{Circum}$ (cm)	93.8 (8.2)	92.5 (7.8)	-1.3 (2.0)	103.3 (10.6)	104.2 (11.7)	.9 (2.3)	.11
SMS (kg)	30.0 (7.7)	30.3 (7.6)	.3 (.7)	35.2 (9.4)	35.1 (9.4)	-.1 (.8)	.32
SBP (mmHg)	129.3 (16.3)	126.3 (14.6)	-3.0 (5.5)	135.3 (11.0)	130.7 (10.6)	-4.6 (10.7)	.99
DBP (mmHg)	76.8 (7.2)	75.9 (8.9)	-.9 (5.3)	85.4 (12.0)	79.7 (7.7)	-5.7 (7.3)*	.59

VO$_{2peak}$ = peak oxygen uptake; HRR = heart rate recovery; HbA$_{1c}$ = glycosylated hemoglobin; HOMA-IR = homeostatic model assessment of insulin resistance; Glucose$_{Fast}$ = Fasting glucose; BMI = Body mass index; Waist$_{Circum}$ = Waist circumference; SMS = Skeletal muscle mass; SBP = Systolic blood pressure; DBP = Diastolic blood pressure.
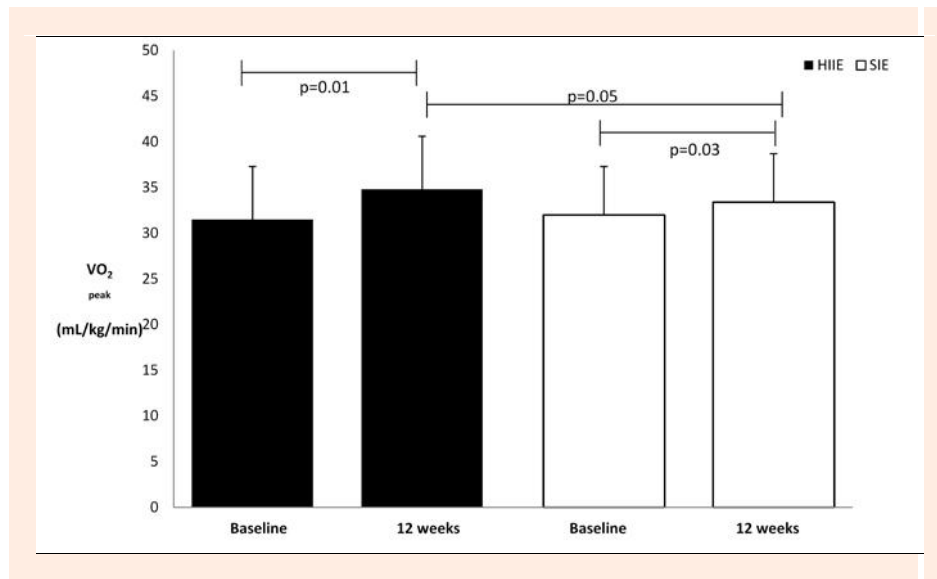* p < 0.05 and ** p < 0.01 within-group difference. † p value: difference in mean change between groups

Figure 1. Changes in VO$_{2peak}$. Data represents mean change in relative VO$_{2peak}$ from baseline to post test. HIIE = high intensity interval exercise; SIE = sprint interval exercise; VO$_{2peak}$ = peak oxygen uptake.

Discussion

This pilot study shows improved aerobic exercise capacity in individuals with type 2 diabetes following exercise durations of 81 and 30 minutes/week, respectively. The high intensity, time efficient exercise performed in this study could be implemented to reduce the time barrier associated with exercise in these individuals. However, the small amount of weekly exercise was not enough to yield improvements in glycemic control, which might have been achieved by a longer duration of the intervention. The strong negative correlations between baseline values of HbA$_{1c}$ and changes in HbA$_{1c}$ after 12 weeks could possibly indicate a more positive effect of the exercise intervention in patients with higher HbA$_{1c}$. However, this might also be a consequence of the regression to the mean phenomenon, and requires further investigation in future trials.

Mean VO$_{2peak}$ at baseline in our study was lower than age-matched reference values from a general population (Aspenes et al., 2011). Subjects with type 2 diabetes frequently have lower aerobic capacity than healthy subjects of similar age and body mass, and aerobic exercise capacity in these individuals is primarily determined by exercise habits (Wei et al., 1999). Our results add to the growing body of evidence that high intensity interval exercise is effective in improving exercise capacity in individuals with type 2 diabetes, and is the first to show that sprint interval exercise improves VO$_{2peak}$ in this patient group.

The 3.3 mL·min^{-1}·kg^{-1} improvements in VO$_{2peak}$ after HIIE in the present study are in line with the findings in the metaanalysis of Boulé et al. (2003). The results also support Mitranun et al. (2014), who found that high intensity intermittent exercise improved exercise capacity in type 2 diabetes patients even if total exercise time was reduced to half of the recommendations. Improving VO$_{2peak}$ could be crucial, as low aerobic capacity is a powerful and independent predictor of long-term cardiac

mortality in type 2 diabetes (Church et al., 2005; Wei et al., 2000). Furthermore, every 3.5 mL·min^{-1}·kg^{-1} increase in aerobic exercise capacity confers a 12% improvement in survival in men referred for exercise testing (Myers et al., 2002).

Our study is the first to show improved VO$_{2peak}$ following SIE in type 2 diabetes individuals, although the improvements were smaller than previously seen following SIE in healthy subjects (Metcalfe et al., 2012). The clear trend towards greater improvements following HIIE than SIE in our study may be due to the difference in influence of stroke volume during exercise between groups (Zhou et al., 2001) and thus cardiac adaptation to exercise. This is also indicated by the improvement in heart rate recovery in the HIIE group compared to the SIE group. Decreased heart rate recovery is associated with increased risk of cardiovascular disease and all-cause death among patients with type 2 diabetes, and a higher fitness level derived from exercise training may positively affect autonomic function and heart rate recovery in patients with diabetes (Cheng et al., 2003).

The current study indicates that substantially lowering exercise volume from today's recommendations hampers the beneficial effects on HbA$_{1c}$. In contrast, Mitranun et al. (2013) recently found improved HbA$_{1c}$ following a weekly 90–120 minutes of high intensity interval exercise for 12 weeks in type 2 diabetes patients. The discrepancy between results can possibly be related to the comparably higher baseline HbA$_{1c}$-values reported in the Mitranun et al.'s study (2014). This notion is supported by informal subgroup observations from our study, indicating reduced HbA$_{1c}$ following exercise in individuals with baseline values above 7 % (data not shown). A treatment target HbA$_{1c}$ value of 7 % is regarded as cardiovascular disease prevention in type 2 diabetes (American Diabetes Association, 2014). The potential of low volume high intensity exercise to improve HbA$_{1c}$ in subjects with poor glycemic control should be investigated in future studies. Furthermore, we cannot rule out that an exercise

period of 12 weeks is too short to change the metabolism and reduce HbA_{1c} in a group of type 2 diabetes patients with relatively well-controlled hyperglycemia.

More than 50 % of patients with type 2 diabetes are obese (Daousi et al., 2006). The HIIE group significantly reduced body fat percentage, which is in line with earlier studies on type 2 diabetes and high intensity interval exercise (Mitranun et al., 2014; Hollekim-Strand et al. 2014; Terada et al., 2013). There was also a trend to reduced waist circumference in the HIIE group following exercise. Fat percentage and waist circumference are probably better indicators for the effectiveness of the intervention than changes in BMI, which did not change in either group after 12 weeks of exercise, indicating that the total energy expenditure of the interventions was too small to induce changes in body weight (Ballor and Keesey, 1991). High intensity intermittent endurance exercise can increase skeletal muscle mass in overweight patients with type 2 diabetes, which can explain a reduction in fat percentage and abdominal fat despite no change in body weight (Boudou et al., 2003). Although the increased amount of muscle mass following HIIE in this study was not significant, it seems likely that HIIE initiated favorable overall changes in body composition. SIE, however, was not effective in improving body composition.

Strengths and limitations

The strengths of the present study include the well-defined exercise interventions and closely supervised exercise sessions. A main limitation is the small sample size. There were several trends of improvement, especially in the HIIE group, and it is possible that these results would have reached significance if the group size had been larger. The study also lacks a sedentary control group, preventing firm conclusions about the pre-post effect of the exercise interventions.

All subjects were asked to fill out a habitual activity diary throughout the study, but adherence was low and the incomplete information was not suited for statistical analysis. Also, we have no information on dietary habits. These variables could possibly differ between the two intervention groups and confound our results. However, before the study all participants reported to be less physically active than 150 minutes/week, and were instructed not to change their activity or diet during the study period.

A lack of a dynamic measure of insulin resistance (e.g. glycemic clamp or oral glucose tolerance test) is another limitation. The study is also limited by the use of clinic blood pressure measurements, as 24-hour recordings of ambulatory blood pressure currently are considered the gold standard. The accuracy of bioimpedance in measurements of body composition can also be questioned. However, the validity of the Inbody720 has been documented in several studies (Ling et al., 2011). The present study is the first study to investigate SIE on a treadmill, which makes the all-out nature of the sprint intervals slightly different than in previous studies performed on a stationary bicycle.

Conclusion

In conclusion, this pilot study indicates that substantially lower exercise volumes than recommended in current guidelines can improve aerobic exercise capacity and heart rate recovery in individuals with type 2 diabetes. However, 12 weeks of time efficient high intensity exercise did not improve glycemic control, and interventions of longer duration should be investigated.

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Key points

- Low volume high-intensity interval exercise can improve peak oxygen uptake in previously sedentary individuals with type 2 diabetes
- The weekly exercise volumes in the two intervention groups of 81 and 30 minutes, respectively, is substantially lower than recommended in current exercise guidelines and could reduce the time-barrier associated with exercise among patients with type 2 diabetes.
- However, 12 weeks of structured, supervised low-volume exercise did not improve glycemic control, indicating a need for exercise volumes or longer intervention period.

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