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ORIGINAL ARTICLE

High-intensity aerobic interval training improves aerobic fitness and HbA1c among persons diagnosed with type 2 diabetes

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Abstract
Purpose It remains to be established how high-intensity aerobic interval training (HAIT) affects risk factors associated with type 2 diabetes (TD2). This study investigated effects of HAIT on maximal oxygen uptake (VO_{2max}), glycated Hemoglobin type A1C (HbA1c), insulin resistance (IR), fat oxidation (FatOx), body weight (BW), percent body fat (%BF), lactate threshold (LT), blood pressure (BP), and blood lipid profile (BLP) among persons with T2D. Results were compared to the effects after a moderate-intensity training (MIT) program.
Methods Thirty-eight individuals with T2D completed 12 weeks of supervised training. HAIT consisted of 4×4 min of walking or running uphill at 85–95% of maximal heart rate, and MIT consisted of continuous walking at 70–75% of maximal heart rate.
Results A 21% increase in VO_{2max} (from 25.6 to 30.9 ml kg^{-1} min^{-1}, $p<0.001$), and a reduction in HbA1c by −0.58% points (from 7.78 to 7.20%, $p<0.001$) was found in HAIT. BW and body mass index (BMI) was reduced by 1.9% ($p<0.01$). There was a tendency towards an improved FatOx at 60% VO_{2max} (14%, $p=0.065$). These improvements were significant different from MIT. Both HAIT and MIT increased velocity at LT, and reduced %BF, waist circumference, hip circumference, and BP, with no significant differences between the two groups. Correlations were found between change in VO_{2max} and change in HbA1c when the two intervention groups were combined ($R=-0.52$, $p<0.01$).
Conclusion HAIT is an effective exercise strategy to improve aerobic fitness and reduce risk factors associated with T2D.

Keywords Exercise intensity · Interval training · Maximal oxygen uptake · HbA1c · Fat oxidation

Abbreviations

%BF	Percent body fat
BG	Blood glucose
BMI	Body mass index
BP	Blood pressure
BLP	Blood lipid profile
BW	Body weight
CHO	Carbohydrate
CRF	Cardiorespiratory fitness
CV	Coefficient of variance
CVD	Cardiovascular disease
FatOx	Fat oxidation
GI	Glycemic index
HAIT	High-intensity aerobic interval training
HbA1c	Glycated hemoglobin type A1C
HOMA-IR	Homeostasis model of assessment for insulin resistance index
HR_{max}	Maximal heart rate
HR_{peak}	Peak heart rate

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KCAL	Kilo calories
KJ	Kilo joules
$[La^-]_b$	Blood lactate concentration
MIT	Moderate-intensity continuous training
POX	Protein oxidation
RER	Respiratory exchange ratio
T2D	Type 2 diabetes
TEI	Total energy intake
VCO_2	Volume of carbon dioxide
VO_2	Oxygen uptake
VO_{2max}	Maximal oxygen uptake

Introduction

Type 2 diabetes (T2D) is recognized as a cause of premature mortality, and is related to several severe medical conditions, such as cardiovascular disease (CVD), neuropathy, retinopathy, and kidney disease (American Diabetes Association 2016). Exercise is one of the cornerstones of both treatment and prevention of T2D (Carroll and Dudfield 2004; Colberg et al. 2010). A reduced cardiorespiratory fitness (CRF) expressed as a low maximal oxygen uptake (VO_{2max}) is related to a higher risk of developing CVD, obesity, and reduced glycemic control (McMurray et al. 1998; Bertoli et al. 2003; Solomon et al. 2015). Individuals with T2D have a reduced aerobic exercise capacity compared to healthy age-matched controls (Regensteiner et al. 1995; Kunitomi et al. 2000). Aerobic exercise has been well established as an intervention to improve aerobic capacity among persons with T2D (Boulé et al. 2003), and an increased VO_{2max} can thus be beneficial to reduce T2D-associated risk factors.

Aerobic exercise has traditionally been used and prescribed as an effective and suitable mode of exercise to prevent and treat T2D (Pedersen and Saltin 2006; Colberg et al. 2010). The American Diabetes Association (2016) recommends 150 min per week of moderate-intensity aerobic (50–70% HR_{max}) exercise spread over at least 3 days/week with no more than 2 consecutive days without exercise. In training interventions, moderate-intensity training (MIT) is typically referred to as an intensity between 70 and 85% of maximal heart rate (HR_{max}) (Tjønna et al. 2008), while high-intensity aerobic interval training (HAIT), most often refers to intensities between 85 and 95% HR_{max} (Helgerud et al. 2007). Previous research have shown that HAIT results in greater increases in VO_{2max} than aerobic exercise at lower intensities among healthy young individuals (Helgerud et al. 2007), patients with heart failure (Wisløff et al. 2007), individuals with metabolic syndrome (Tjønna et al. 2008), and persons with T2D (Hollekim-Strand et al. 2014). The increase in VO_{2max} after HAIT is typically 0.3–0.7% per training session in interventions with a duration of 8–12 weeks (Rognmo et al. 2004; Østerås et al. 2005; Helgerud et al. 2007; Hollekim-Strand et al. 2014; Wang et al. 2014; Støren et al. 2016). Although HAIT has been shown to give large improvements in VO_{2max} (Rognmo et al. 2004; Helgerud et al. 2011; Wisløff et al. 2007; Støren et al. 2016), few studies have explored the physiological adaptations after HAIT among T2D patients (Hollekim-Strand et al. 2014).

Over the last decade, there has been an increased focus on how different training modes affect physiological adaptations such as VO_{2max}, fat oxidation (FatOx), blood pressure (BP), blood lipid profile (BLP), anthropometrics, and glycated hemoglobin type A1c (HbA1c) (DiPietro et al. 2006; Kodama et al. 2007; Hansen et al. 2009; Segerstrøm et al. 2010; Hollekim-Strand et al. 2014; Revdal et al. 2016). Most of these studies have investigated the effects after moderate-intensity exercise. Several studies and reviews have also revealed positive results on one or more of these T2D-related risk factors after low-volume sprint intervals characterized by mainly anaerobic work (Gibala et al. 2012; Hawley and Gibala 2012; Terada et al. 2013; Revdal et al. 2016). The importance of training intensity is still debated, and reviews underpin the uncertainty about whether intensity and/or volume of exercise are most important to improve glycemic control and other variables related to T2D (Boulé et al. 2003; van Dijk and van Loon 2015).

The aim of this study was to investigate if HAIT is a more effective training strategy than moderate-intensity exercise to reduce important risk factors among individuals with T2D.

Methods

Participants

Thirty-eight sedentary overweight individuals (23 females, 15 males) diagnosed with T2D completed the 12 weeks training intervention. Average VO_{2max} values for men and women were 27.7 ± 7.3 and 24.4 ± 4.2 ml kg^{-1} min^{-1}, respectively. Subject characteristics in the two exercise groups are shown in Table 1.

Eligible volunteers for study participation were individuals diagnosed with T2D, aged between 20 and 70 years, and no medical contra-indications for testing and training. The exclusion criteria were medical contradictions to physical testing and exercise according to the ACSM guidelines, sickness for a minimum of 2 consecutive weeks the last month prior to testing, illness during the last week prior to physical testing, diseases or injuries lasting more than 1 week during the 12 weeks intervention period, change in diet habits, and less than 75% of the training sessions

Table 1 Subject characteristics

	MIT ($N=19$)	HAIT ($N=19$)	p value
Diagnosis (years)	6 ± 5	9 ± 7	0.073
Age (years)	59 ± 10	59 ± 11	0.745
Height (cm)	170 ± 6	172 ± 6	0.146
BW (kg)	89.1 ± 15.6	95.0 ± 15.3	0.250
BMI (kg m^{-2})	31.1 ± 4.5	32.0 ± 4.7	0.564
BF (%)	33.2 ± 7.6	33.1 ± 7.6	0.962
VO_{2max} (ml kg^{-1} min^{-1})	25.8 ± 5.5	25.6 ± 6.2	0.934
VO_{2max} (L min^{-1})	2.29 ± 0.61	2.39 ± 0.55	0.571
HbA1c (%)	6.84 ± 0.88	7.78 ± 1.39	0.020*
HOMA2-IR##	1.83 ± 0.73	1.76 ± 0.94	0.825
FatOx (g min^{-1})	0.341 ± 0.083	0.368 ± 0.095	0.371
SystBP (mmHg)	160 ± 20	160 ± 22	0.984
DiastBP (mmHg)	86 ± 12	87 ± 9	0.621
Triglycerides (mmol L^{-1})	1.58 ± 0.78	1.66 ± 0.78	0.822
HDL (mmol L^{-1})	1.24 ± 0.38	1.09 ± 0.34	0.611
LDL (mmol L^{-1})	3.05 ± 0.64	2.98 ± 0.72	0.777

Values are mean ± standard deviation

MIT moderate training intensity group, *HAIT* high-intensity aerobic interval training group, *BW* body weight, *BF* body fat percentage, *BMI* body mass index, *VO_{2max}* maximal oxygen consumption, *HbA1c* glycated hemoglobin type A1C, *HOMA2-IR* homeostatic model assessment of insulin resistance, *FatOx* fat oxidation, *Syst. BP* systolic blood pressure, *Diast. BP* diastolic blood pressure, *HDL* high-density lipoproteins, *LDL* low-density lipoproteins, *HOMA-IR* The homeostatic model assessment of quantifying insulin resistance

*Significant difference between MIT and HAIT, $p<0.05$

Table 2 Exercise per week in minutes before and during the 12 weeks intervention

	MIT		HAIT	
	Before ($N=19$)	During ($N=19$)	Before ($N=19$)	During ($N=19$)
Easy	63 ± 50	41 ± 34**	55 ± 80	61 ± 47
Mod	48 ± 32	243 ± 62**	54 ± 59	110 ± 39**§§
High	3 ± 6	2 ± 3	3 ± 6	29 ± 5**§§
Total	113 ± 54	286 ± 78**	112 ± 109	200 ± 72**§§

Values are given in minutes per week and are presented as mean ± standard deviation

MIT moderate intensive training group, *HAIT* high-intensity aerobic interval training group, *Before* mean training volume per week the last month before intervention start, *During* mean training volume per week during intervention, *Easy* minutes per week of training at an intensity below 70% HR_{max}, *Mod* minutes per week of training at an intensity between 70 and 85% HR_{max}, *High* minutes per week of training above 85% HR_{max}, *Total* total of minutes per week of aerobic exercise

**$p<0.01$ different from pre-value. §§$p<0.01$ different from change in MIT

completed during the intervention period. HbA1c data were excluded if the participants had to change their medication during the intervention period. Three from MIT and three from HAIT changed their blood sugar medications during the intervention period. One person in each group reduced on insulin, and one in each group reduced on biguanides in the middle of the intervention to prevent hypoglycemia. In addition, one person in each group had recently added one type of biguanides approximately 2 weeks before intervention start. These HbA1c results were excluded from the analysis as shown in Table 5. However, the physician and the project group did not consider these changes in medication to be extensive enough to be a potential bias on other selected variables such as VO_{2max}, BW, or BP. The changes in blood sugar medication among these six individuals were also very similar between the two groups, and biguanides have been found to be BW neutral (Inzucchi et al. 2012). It was further checked whether or not the six persons with changed medication expressed a pattern of adaptations to the intervention which differed from the other subjects. No such differences were found. It was thus decided to keep these participants in the analyses regarding all other variables than HbA1c.

The participants were recruited from the local community through regional newspaper advertisement, local medical offices and hospitals, local rehabilitation centers, and information folders at public places. The study is a non-randomized study, as the two different training interventions started at two different time points with 5 months in between. However, the participants did not know which training protocol they were recruited to before volunteering. The specific training intensity was given after the subjects volunteered to the study. Thorough oral and written information about the purpose and possible risks of the intervention were given to the subjects before they volunteered to participate. The two groups were matched in age and physical activity level (Table 2).

Forty-nine volunteered for the study and 43 were included (Fig. 1). The subjects underwent medical examination by a physician including an electrocardiogram examination prior to inclusion. All participants refrained from exercise for at least 24 h before blood samples were taken. All the participants were Norwegians with Scandinavian origin, except from two individuals who were of African origin (one in HAIT and one in MIT). A medical consult with the same physician was performed during both assessment days. The subjects gave a written informed consent to participate in the study. The Regional Committees for Medical Research Ethics—South East Norway approved the study (2010/3016), and all the procedures undertaken in the study is in accordance with the principles outlined in the Declaration of Helsinki. The study is registered in the clinical trial registry ISRCTN.

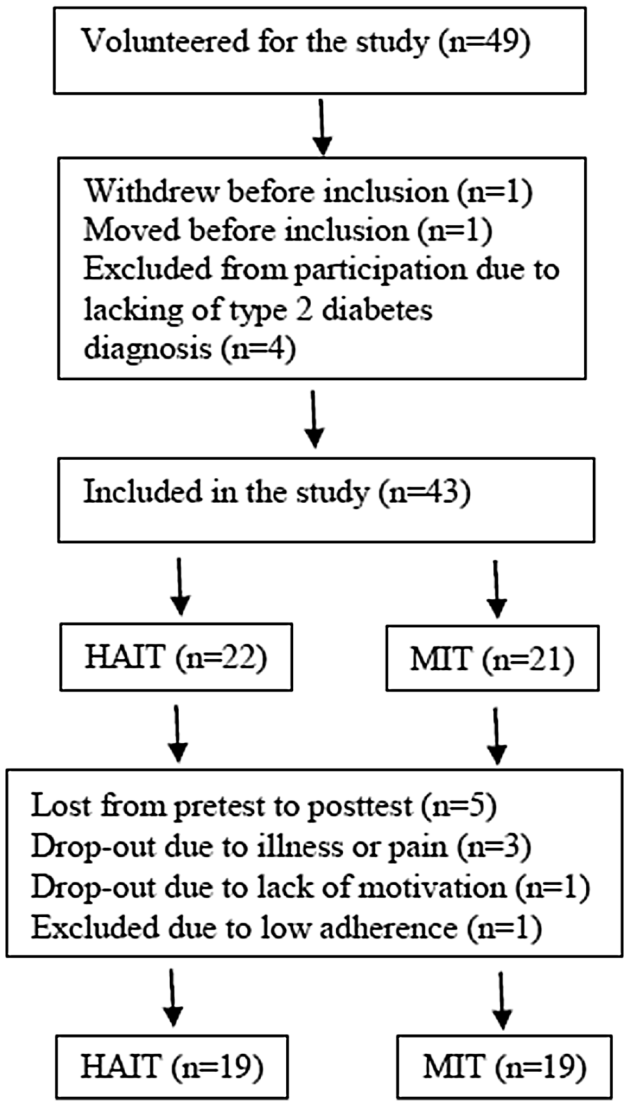

Fig. 1 Flowchart of study participation

Training protocol

The HAIT group conducted high-intensity aerobic interval training of 4×4 min at an intensity between 85–95% HR_{peak}. The MIT group conducted continuously moderate work at 70–75% HR_{peak}. All exercise sessions were supervised and carried out as walking or running in an outdoor environment. Both HAIT and MIT trained three times per week, and all training sessions were monitored. The HAIT and MIT training protocols were matched for total work, and the equations made to calculate $\%HR_{peak}$ to $\%VO_{2max}$ are based on the formula:

$\%HR_{peak} = 0.6463 \times \%VO_{2\,max} + 37.182$ (Swain et al. 1994).

The matching of energy cost during exercise was calculated using the participants' mean VO_{2max} values. Mean VO_{2max} was 2.34 L min^{-1}. The HAIT session started with ~15 min warm up at ~52% VO_{2max} (70% HR_{peak}), followed by 4×4 min at ~82% VO_{2max} (90% HR_{peak}) with 3-min recovery between intervals at ~52% VO_{2max}, and ~12 min cool down at ~52% VO_{2max}. This amounts 36 min at 52% VO_{2max} and 16 min at 82% VO_{2max}. 82% VO_{2max} would imply a mean O_2 expenditure of 1.92 L min^{-1}, a RER of ~0.88, and an energy cost of ~4.89 kcal L^{-1} O_2 consumption (McArdle et al. 2010). 52% VO_{2max} means an average O_2 expenditure of 1.22 L min^{-1}, an RER of ~0.80, and an energy cost of ~4.80 kcal L^{-1} O_2 consumption. The equation would therefore be 1.92 L × 4.89 kcal L^{-1} × 16 min = 150 kcal, and 1.22 L × 4.80 kcal L^{-1} × 36 m in = 211 kcal. This means 361 kcal for each HAIT session lasting ~52 min. The MIT training consisted of continuous work at ~56% VO_{2max} (73% HR_{peak}, RER ~0.83, 4.84 kcal L^{-1} O_2 consumption). To find the same energy cost as for HAIT, the duration was calculated as *x* min × 0.5 6 × 2.34 L × 4.84 kcal L^{-1} O_2 consumption = 361 kcal, giving an *x* of ~57 min. The MIT group exercised for ~60 min, since a few minutes were added in order to gradually reach steady-state heart rate representing 70–75% HR_{peak} and to ensure that energy cost in HAIT did not exceed the energy cost in MIT. The training protocol is similar to other studies (Helgerud et al. 2007; Tjønna et al. 2008).

Before the training started, all subjects learned how to use a polar heart rate monitor to ensure the right training intensity. They were also given thorough instructions about how to register duration, average heart rate, and time in their specific individual intensity zones of either 85–95% HR_{peak} or 70–75% HR_{peak}.

Anthropometric measurements

Height measurements were collected using a wall-mounted measuring tape. Body weight was measured on a Tefal Sensitive Computer scale (Pp 6010, France) that was calibrated before the test period. The participants' heights were measured with a wall-mounted measuring tape. Their body weights were measured on a Tefal Sensitive Computer scale (Pp 6010, France) that was calibrated before the test period. %BF was calculated based on five-site skinfolds (triceps, chest, abdomen, suprailiac, and thigh) with a Harpenden skinfold caliper (Saehan Medical Skinfold Caliper, SH5020, Korea). Waist and hip circumferences were measured using a measuring tape. Waist circumference was measured between iliac crest and the lowest rib, while hip measurements were taken at the widest point around the hip. The same experienced investigator made all the anthropometric measurements at all time points to avoid different individual measuring techniques. BMI was calculated as weight in kilograms divided by height in squared meters (kg m^{-2}).

Blood pressure

The same physician performed the BP measurements during the medical consult on both pre- and post-test days. BP was measured manually using stethoscope and a blood pressure cuff (Welcyallyn SK, Germany and Tycos 2006z, USA). The subject was sitting still for 5 min before measurement.

Physical testing procedures

The testing procedures were equal at each time point and consisted of 2 consecutive test days. The participants were not allowed to do any strenuous physical activity the last 2 days prior to testing. All food and fluid intake the 2 days before and during the test days were thoroughly monitored using a 1 g accurate food scale in addition to recording in food registration forms.

Only water was allowed the last 2 h before test-start. At day 1, anthropometric measurements, lactate threshold (LT), work economy (WE), and VO_{2max} were measured. In addition, the participants were interviewed and answered questionnaires about physical activity habits (IPAQ questionnaire), vitality (Subjective Vitality Scale), and depression (Beck Depression Inventory—II). At day 2, a FatOx test was completed at 60% VO_{2max}. All physical tests were carried out using a Woodway PPS 55 sport (Waukesha, Germany) treadmill calibrated for inclination and speed. Heart rate was registered continuously during all physical tests using a Polar rs100 (Polar Kempele, Finland).

The first test consisted of three or four submaximal workloads each lasting 5 min. The velocity during the first warm up period corresponded to ~60% VO_{2max}. The tests were conducted at an incline of 3%. This incline was set to maintain a normal walking speed during all periods. Blood lactate ($[La^-]_b$) was measured after each period using a Lactate Pro Analyzer (Arcray Inc). The speed was increased at each period, until the subjects elicited an intensity above LT defined as the warm up $[La^-]_b$ value +2.3 mmol L^{-1}. If the LT was not reached during the third period, a fourth period was completed. An incremental VO_{2max} was performed where the test started at an incline of 3–4%, and at a speed between 3 and 6 km h^{-1} according to each individual's physical fitness. The incline was increased with 1% and/or the speed was increased by 0.5 km h^{-1} every 30 s depending on the individual VO_2 curve and the subjective evaluation of the test leader. The test ended at voluntary exhaustion, and verbal encouragement was given towards the end of the test. The criteria used to determine if VO_{2max} was accomplished were flattening of the VO_2 curve, RER ≥1.05, HR_{peak} ≥95% of expected HR_{max}, and concentration of blood lactate above 8 mmol L^{-1}. These criteria have been used in earlier studies (Støren et al. 2008; Sunde et al. 2010; Helgerud et al. 2010). The average of the two highest continuous VO_2 measurements was set as VO_{2max}, and the highest heart rate at the end of the VO_{2max} test was recorded as peak heart rate (HR_{peak}).

Measurements of insulin resistance

The homeostasis model of assessment for insulin resistance index (HOMA-IR) was used to assess IR. The IR was calculated by the Oxford University HOMA2-IR online calculator (http://www.dtu.ox.ac.uk/homacalculator/, accessed June 7, 2015), based on measurements from c-peptide and fasting blood glucose as described in Wallace et al. (2004). HOMA-IR is the reciprocal of HOMA %S, where HOMA %S (insulin sensitivity) represents values of 100% in normal adults. The validity and accuracy of measuring IR by HOMA-IR has been evaluated several times and has a high correlation with the glucose clamp test (Matthews et al. 1985; Okita et al. 2013).

FatOx calculations

The fat oxidation tests were performed at approximately the same time during the day (±3 h). The FatOx test was a 10-min protocol where VO_2 and VCO_2 were used to calculate respiration exchange ratio (RER) values. Values were measured every 20 s. FatOx was calculated from the average RER values between 4 and 8 min, using the a formula from Frayn (1983): FatOx (g min^{-1}) = ($VO_2 \times 1.67$) − ($VCO_2 \times 1.67$) × 0.307 × (POX), where POX (g min^{-1}) is the protein oxidation rate, assumed to be (KJ min^{-1}) × (0.12 g J)/17.74 KJ. The 10-min duration of the FatOx test is in line with Bordenave et al.'s (2007) who recommended a work duration of longer than 3 min to ensure a stable level gas exchange when using indirect calorimetry to assess FatOx during exercise.

The FatOx test was performed at the relative workload of 60% VO_{2max}. VO_{2max} and the 5 min submaximal workloads were used to establish the linear regression for VO_{2max} and velocity (Helgerud et al. 2010). This linear regression was used to determine the velocity at 60% VO_{2max}. The calculation of the specific individual velocity representing 60% VO_{2max} is based on the physiological principle that oxygen consumption is linearly related to the work intensity (Støren et al. 2008; Sunde et al. 2010; Helgerud et al. 2010). Sunde et al. (2010) showed that the linearity from this regression averaged an $R^2 = 0.992 \pm 0.005$, $p < 0.0001$.

Ergo spirometry equipment

Sensor Medics Vmax Spectra (Sensor Medics 229, Yorba Linda, California, USA) was used during all physical tests. Gas exchange was measured with 20 s intervals. The

flow sensor was calibrated against a 3.0 L syringe (Hans Rudolph, Kansas City, MO, USA). O_2 and CO_2 sensors were calibrated against known gases (26% O_2 and 16% O_2) before each test. According to the manufacturer, the Sensor Medics Vmax Spectra has a VO_{2max} accuracy within a range of ±3%. However, test-to-test variations in our laboratory have shown to be less than ±1%.

Diet registrations

The participants agreed to continue with their habitual diets through the participation period, but were encouraged to increase energy intake equivalent to the energy expended during exercise. They registered their diets 2 days prior to testing, during both test days (Table 3), and also during 3 consecutive days in the middle of the 12 weeks intervention, to achieve an extra control of habitual diet patterns. To ensure accurate diet registration, all food was weighed on a 1-g accurate food scale (Wilfa, KW-4, Hagan, Norway) and recorded in food registration forms.

Use of medications

A physician examined the use of medications in both groups (Table 4), which were similar between the two groups.

Statistics

Experimental data are presented as mean ± standard deviation, as well as delta values (Δ) and coefficient of variance (CV) in percent. A Pearson bivariate correlational test was used to determine possible relationships between baseline values and between changes in the physiological variables from baseline to post-test. Paired student *t* test was performed to discover differences between baseline and post-test within each intervention group. Independent t tests were used to discover significant differences in changes between the two exercise groups. The Shapiro–Wilk test and normal *Q*–*Q* plot were used to test for normality. The HbA1c values were not normally distributed. Therefore, non-parametric tests were used when analyzing the HbA1c data. A Wilcoxon signed rank test was used to assess pre- to post-changes within each group, and a Mann–Whitney *U* test was used to explore between-group differences in changes. Due to a significant difference in pre-HbA1c levels between the two groups, a post hoc analysis was conducted. In the post hoc analysis, the HbA1c data were corrected for skewness (1.7 ± 0.4), which normalized the distribution and excluded the two extreme outliers in the HAIT group. An independent *t* test was then used to explore whether the differences in HbA1c adaptations between the groups were caused by these outliers. The results from this analysis are only presented within the "Results" section, and not in the main result table.

In all tests, significance was accepted at $p < 0.05$. Analyses were performed using Statistical Package for the IBM SPSS (version 22; IBM Corp., Armonk, NY, USA).

Table 4 Use of medications

Medication	*N*, HAIT	*N*, MIT
Biguanides (metformin or glucophage)	12	9
Sulfonylurea medications	6	3
DPP-4 inhibitors	2	2
GLP-1 analog	2	0
Pioglitazone	1	0
Insulin	3	2
Hypertension	10	10
Cholesterol	9	12

HAIT high-intensity aerobic interval training, *MIT* moderate-intensity training

Table 3 Diet registrations at pre- and post-tests

	MIT (*N* = 17)				HAIT (*N* = 18)			
	Pre	Post	Δ	CV (%)	Pre	Post	Δ	CV (%)
TEI (Kcal)	2166 ± 445	2040 ± 420	−126 ± 254	8.6	1989 ± 390	1925 ± 417	−65 ± 326	11.8
CHO(g)	215 ± 71	206 ± 72	−9 ± 49	16.5	195 ± 56	182 ± 56	−14 ± 46	17.2
Fat (g)	100 ± 26	92 ± 24	−8 ± 18	13.3	92 ± 26	92 ± 29	0 ± 23	17.7
Prot (g)	101 ± 23	91 ± 19 #	−10 ± 18	13.3	92 ± 23	93 ± 23	1 ± 21	16.1
%CHO	38.7 ± 6.5	39.9 ± 6.9	1.3 ± 6.1	11	39.0 ± 7.3	37.4 ± 8.5	−1.6 ± 6.9	12.8
%Fat	42.0 ± 7.3	41.8 ± 7.0	−0.2 ± 5.5	9.3	42.1 ± 7.7	43.0 ± 7.6	0.9 ± 7.8	12.8
%Prot	19.4 ± 4.0	18.4 ± 3.4	1.0 ± 3.1	11.6	19.3 ± 3.9	20.0 ± 3.2	0.7 ± 5.0	18.0

Values are mean ± standard deviation, delta values (Δ), and coefficient of variance (CV) in per cent

Kcal kilo calories, *g* gram, *TEI* total energy intake, *CHO* carbohydrate, *Prot* protein. #$p < 0.05$ different from pre-values

Results

Results are presented in Table 5. The HAIT group increased their relative VO_{2max} by 21% (25.6 to 30.9 ml kg^{-1} min^{-1}; $p<0.001$) in ml kg^{-1} min^{-1} and absolute VO_{2max} by 19% (2.39 ± 0.55 to 2.84 ± 0.66 L min^{-1}; $p<0.001$), respectively. There was no change in VO_{2max} in MIT. Velocity at lactate threshold improved in both groups (HAIT; from 5.5 ± 1.0 to 6.2 ± 1.2 km h^{-1}, $p<0.001$, MIT; from 5.7 ± 0.4 to 6.1 ± 0.6 km h^{-1}, $p<0.001$). LT expressed as % VO_{2max} did not change in either of the groups from pre- to post-measurements, and there was no difference in change between the groups.

A significant improvement was found in HbA1c in HAIT compared to MIT ($p < 0.01$), with a 0.58% reduction in HbA1c (from 7.78 to 7.20%, $p < 0.001$) in HAIT, while no change was found in MIT (Fig. 2). A post hoc analysis of HbA1c corrected for skewness still revealed significant difference in change between HAIT and MIT ($p<0.01$) with a significant reduction of 0.47% (from 7.36 to 6.89%, $p<0.01$) in HAIT, and no reduction in MIT ($p=0.804$).

Significant correlations were found between change in absolute VO_{2max} and change in HbA1c when the two intervention groups were combined (L min^{-1}; $R = -0.524$, $p<0.01$, SEE = 0.44), see Fig. 3.

There were no within-group changes or between-group differences in change in HOMA-IR. There was a tendency towards an improved FatOx at 60% VO_{2max} (from 0.368 to 0.420 g min^{-1}) in HAIT ($p=0.065$). No change was found in MIT. While the changes from pre- to

Table 5 Physiological adaptations after 12 weeks of exercise

	Moderate ($N=19$)				HAIT ($N=19$)			
	Pre	Post	ΔPost–pre	CV (%)	Pre	Post	ΔPost–pre	CV (%)
Anthropometrics								
BW (kg)	89.1 ± 15.6	88.6 ± 15.4	−0.5 ± 1.5	1.2	95.0 ± 15.3	93.3 ± 15.1	−1.7 ± 1.8**§	1.4
BMI (kg m^{-2})	31.1 ± 4.5	31.2 ± 4.1	0.1 ± 1.4	3.1	32.0 ± 4.7	31.4 ± 4.7	−0.6 ± 0.6**§	1.8
BF (%)	33.2 ± 7.6	31.4 ± 7.3	−1.8 ± 0.9**	1.9	33.1 ± 7.6	30.4 ± 7.6	−2.7 ± 2.3**	5.2
Waist (cm)	108 ± 11	106 ± 12	−2 ± 1.6**	1.1	110 ± 11	108 ± 10	−2 ± 3**	1.7
Hip (cm)	108 ± 11	107 ± 11	−1 ± 1.8**	1.2	107 ± 9	106 ± 9	−1 ± 2**	1.5
HbA1c and physical tests								
HbA1c (%)#	6.84 ± 0.88	6.83 ± 0.84	−0.02 ± 0.30	3.1	7.78 ± 1.39	7.19 ± 1.10	−0.59 ± 0.55**§§	5.2
HOMA-IR##	1.83 ± 0.73	1.79 ± 0.77	−0.04 ± 0.50	19.7	1.75 ± 0.94	1.91 ± 1.00	0.16 ± 0.42	55.4
VO_{2max} (L min^{-1})	2.29 ± 0.61	2.25 ± 0.58	−0.04 ± 0.16	4.9	2.39 ± 0.55	2.84 ± 0.66	0.45 ± 0.22**§§	5.9
VO_{2max} (mL kg^{-1} min^{-1})	25.8 ± 5.5	25.6 ± 5.4	−0.2 ± 1.7	4.7	25.6 ± 6.2	30.9 ± 7.8	5.3 ± 2.6**§§	6.6
FatOx (g·min^{-1})	0.341 ± 0.083	0.312 ± 0.087	−0.034 ± 0.105	22.5	0.368 ± 0.01	0.420 ± 0.131	0.053 ± 0.117§	21.1
RER FatOx (VCO_2/VO_2)	0.81 ± 0.04	0.82 ± 0.05	0.01 ± 0.04	3.6	0.80 ± 0.03	0.81 ± 0.05	0.01 ± 0.05	4.2
VO_2FatOx	1.37 ± 0.58	1.27 ± 0.51	−0.10 ± 0.17*	8.8	1.31 ± 0.26	1.61 ± 0.54	0.30 ± 0.38**§§	18.2
Velocity FatOx (km h^{-1})	3.9 ± 1.4	3.9 ± 1.4	–	4.7	3.9 ± 1.2	4.8 ± 1.5	0.9 ± 0.5**§§	7.3
LT (%VO_{2max})	77.5 ± 11.1	80.2 ± 9.3	2.7 ± 8.5	7.6	78.7 ± 10.2	77.6 ± 9.1	−1.1 ± 7.9	7.6
LT at 3% incline (km h^{-1})	5.7 ± 0.4	6.1 ± 0.6	0.4 ± 0.4**	4.3	5.5 ± 1.0	6.2 ± 1.2	0.7 ± 0.6**	9.9
Blood pressure and blood lipids								
Syst. BP (mmHg)	160 ± 20	148 ± 26	−12 ± 21*	9.8	160 ± 22	154 ± 18	−6 ± 17	7.1
Diast. BP (mmHg)	86 ± 12	78 ± 11	−8 ± 12*	10.3	87 ± 9	81 ± 8	−6 ± 8**	6.9
Trigl. (mmol L^{-1})	1.58 ± 0.78	1.37 ± 0.81	−0.21 ± 0.40*	19.3	1.68 ± 0.78	1.53 ± 0.81	−0.15 ± 0.50	21.8
Chol. (mmol L^{-1})	4.73 ± 0.75	4.75 ± 0.82	0.02 ± 0.58	8.7	4.43 ± 0.89	4.29 ± 0.72	−0.14 ± 0.61	9.9
HDL (mmol L^{-1})	1.24 ± 0.38	1.33 ± 0.38	0.09 ± 0.16*	8.6	1.08 ± 0.33	1.11 ± 0.31	0.03 ± 0.14	9.0
LDL (mmol L^{-1})	3.05 ± 0.64	2.98 ± 0.71	−0.07 ± 0.52	12.1	2.95 ± 0.76	2.77 ± 0.60	−0.17 ± 0.47	11.5

#N MIT = 16, N HAIT= 16; Reduced N in HbA1c due to change in medications during intervention period. ##N MIT = 16, N HAIT = 14; Reduced N in IR due to change in medications during intervention period and two missing c peptid values in HAIT. Values are mean ± standard deviation. Moderate, moderate training intensity group

HAIT high intensity aerobic interval training group, *BW* body weight, *BMI* body mass index, *BF* body fat percentage, *Waist* waist circumference, *Hip* hip circumference, *VO2max* maximal oxygen consumption, *mL* milliliters, *L* liters, *HbA1c* glycated hemoglobin type A1C, *FatOx* fat oxidation, *RER* respiratory exchange ratio, *Syst. BP* systolic blood pressure, *Diast. BP* diastolic blood pressure, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *La-* lactate, *Mmo* L^{-1} millimoles per litre, *HR* heart rate

*$p < 0.05$ different from pre value. **$p < 0.01$ different from pre value. §$p < 0.05$ different from change in MIT. §§ $p < 0.01$ different from change in MIT.

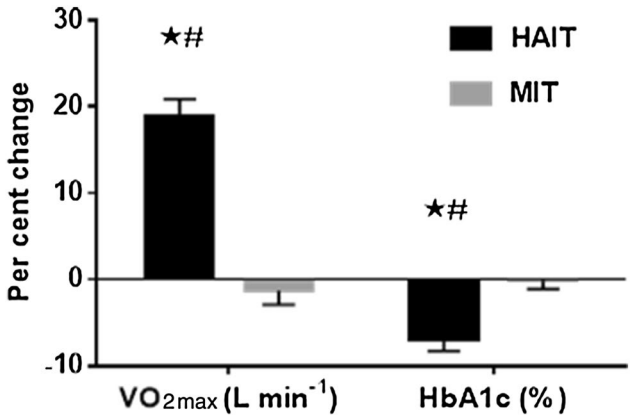

Fig. 2 Changes in VO_{2max} and HbA1c from pre- to post-intervention

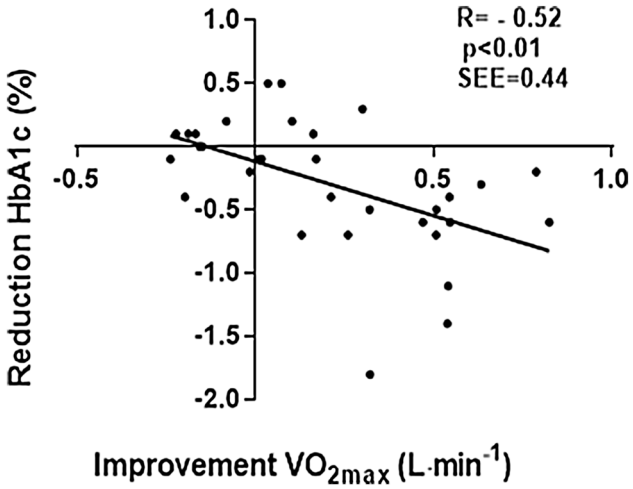

Fig. 3 Correlation between VO_{2max} and HbA1c changes ($n = 32$)

post-test within each exercise group were not significant, an independent *t* test revealed a significant difference in change between HAIT and MIT ($p < 0.05$).

In HAIT, reductions were found in BW (95.0 ± 15.3 to 93.3 ± 15.1 kg; $p < 0.01$), BMI (32.0 ± 4.7 to 31.4 ± 4.7 kg; $p < 0.01$), %BF (33.1 ± 7.6 to 30.4 ± 7.6 kg; $p < 0.001$), waist circumference (110 ± 11 to 108 ± 10 cm; $p < 0.01$), and hip circumference (107 ± 9 to 106 ± 9 cm; $p < 0.01$). In MIT, there were no changes in BW or BMI, but waist circumference (108 ± 11 to 106 ± 12 kg; $p < 0.001$), hip circumference (108 ± 11 to 107 ± 11 kg; $p < 0.01$), and %BF (33.2 ± 7.6 to 31.4 ± 7.3 kg; $p < 0.001$) were all reduced. Only the changes in BW and BMI were significant different between HAIT and MIT ($p < 0.05$), with the greatest improvement in HAIT (−1.7 versus −0.6 kg, respectively). The changes in BP and BLP were not significantly different between the groups.

Discussion

The main findings in this study were increased VO_{2max} and decreased HbA1c in HAIT compared with MIT. The changes in BW, BMI, and FatOx were also significantly different from MIT.

Maximal oxygen uptake and lactate threshold

The 21% (ml kg^{-1} min^{-1})—and 19% (L min^{-1}) increase in VO_{2max} after HAIT, imply an average increase of 0.7% per training session, which is somewhat higher than the results from other studies with different adult populations (Rognmo et al. 2004; Østerås et al. 2005; Hollekim-Strand et al. 2014; Wang et al. 2014; Støren et al. 2016). To our knowledge, very few studies have investigated the importance of exercise intensity among T2D, using a HAIT protocol. However, a pilot study by Hollekim-Strand et al. (2014) found an increase of 13 and 11% in relative and absolute VO_{2max} in ml kg^{-1} min^{-1} and L min^{-1}, respectively, after 12 weeks of exercise with a similar training protocol. The larger improvements in the present study could be due to the lower baseline values. Hansen et al. (2009) also investigated the clinical benefits of continuous exercise at either low-to-moderate (50% VO_{peak}) intensity or at moderate-to-high (75% VO_{peak}) intensity among T2D patients. Improvements of 8% (50% VO_{peak}) and 16% (75% VO_{peak}) were found in VO_{2max} after 8 weeks of exercise (Hansen et al. 2009). The intensity at 50% and 75% VO_{peak} corresponds to 69% and 85% HR_{max}, respectively (Swain et al. 1994). This is slightly lower than the two different intensity levels in the present study, and may explain the difference in improvements.

A low pre-VO_{2max} level might influence the exercise response since persons with lower CRF have a greater potential to improve their physical fitness (Støren et al. 2016). It has been hypothesized that the lower baseline VO_{2max} level found among T2D may be caused by higher BG levels, low capillary density, reduced oxygen delivery capacity, increased blood viscosity, and presence of vascular and neuropathic complications typically found in T2D (Reusch et al. 2013). The positive effects of HAIT on improving VO_{2max} in the present study are also shown in studies with different subject characteristics, such as young healthy (Helgerud et al. 2007), old healthy sedentary (Østerås et al. 2005), and different patient populations (Rognmo et al. 2004; Wisløff et al. 2007; Helgerud et al. 2011). These compliant results reveal the great potential of HAIT to be an effective strategy to improve cardiovascular health in all age groups (Støren et al. 2016), counteracting the metabolic disturbances accompanied with T2D (Fletcher et al. 2002; Hawley and Zierath 2008).

The lack of VO_{2max} improvement in MIT in the present study was somewhat surprising. MIT was expected to increase VO_{2max}, although not to the same extent as HAIT. The effectiveness of MIT to increase VO_{2max} among T2D is still inconclusive. Hollekim-Strand et al. (2014) failed to discover changes in VO_{2max} after moderate exercise, while others have revealed positive effects (Hansen et al. 2009; Giannopoulou et al. 2005). It should be noted that baseline VO_{2max} in both Hansen et al. (2009) and Giannopoulou et al. (2005) were lower compared to the present study. In Hollekim-Strand et al. (2014), only relative VO_{2max} increased when measured as ml kg^{-1} min^{-1} and not when measured as L min^{-1}, thus suggesting a weight reduction effect.

The velocity at LT increased in both groups although not significantly different between groups. The lack of change in LT expressed as % VO_{2max} in both groups supports the findings from other studies among more well-trained individuals, which have revealed minor or no effects on this variable after aerobic exercise (Helgerud et al. 2007; Støren et al. 2014).

HbA1c

The 0.58% point reduction in HbA1c in HAIT (from 7.78 ± 1.39 to 7.19 ± 1.10%) represents 8% improvement. This implies an important reduction in risk of CVD, as earlier studies have shown a 15–20% reduction in CVD events when HbA1c is reduced by 1% point (Stratton et al. 2000; Selvin et al. 2004). For HAIT, this would mean a risk reduction of approximately 8–10% after only 12 weeks of exercise. Although few studies have investigated the effects of HAIT and HbA1c among T2D, Hollekim-Strand et al. (2014) also found a similar positive effect on HbA1c after 12 weeks of HAIT. A reduction in HbA1c was observed (7.0 ± 1.2 to 6.6 ± 0.9%) as a result of HAIT. The greater effect in the present study may be due to higher baseline HbA1c levels (7.78 ± 1.39 vs 7.0 ± 1.2%). Similar to our study, Hollekim-Strand et al. (2014) found no changes in HOMA-IR.

There was no change in HbA1c in MIT. The lack of VO_{2max} improvement in MIT may have influenced the lack of HbA1c improvements since the present study showed a relationship between improvement in VO_{2max} and reduction in HbA1c ($R = -0.52$, $p < 0.01$) meaning that approximately 25% of the reductions in HbA1c could be related to increased VO_{2max}. However, since SEE was 0.44 L min^{-1}, a quite high increase in VO_{2max} is needed to predict reductions in HbA1c. It may of course not be causality between the improvements in VO_{2max} and HbA1c. However, our study's results are consistent with a meta-analysis conducted by Boulé et al. (2003) which concluded that exercise intensity was a better predictor of weighted mean difference in HbA1c than exercise volume.

Similar to the results in MIT in the present study, Hollekim-Strand et al. (2014) found no changes in either VO_{max} or HbA1c after moderate exercise in T2D. The lower baseline HbA1c in MIT compared to HAIT in our study is also one plausible explanation behind the HbA1c results. It could be expected that higher pre-HbA1c values would lead to a greater decrease in HbA1c (Krook et al. 2003). In contrast, Revdal et al. (2016) examined the physiological adaptations comparing high-intensity short-interval training (HIIE; 27 min per bout; 10 min at 90% of HR_{max}) and extremely low-volume sprint interval exercise (SIE; 10 min per bout; 2 × 20 s at maximum achievable intensity). None of the groups found a significant change in HbA1c, despite a significant difference in baseline HbA1c (pre-values were 6.53 ± 0.96 versus 7.87 ± 1.21 in HIIE and SIE, respectively) and improvement in CRF (HIIE 10%; SIE 4.3%). Hollekim-Strand et al. (2014) also had baseline levels of HbA1c below 7.0%. In contrary to MIT in our study, Hansen et al. (2009) found improved HbA1c levels in T2D after both low- to moderate-intensity (69% HR_{max}) and moderate- to high-intensity (85% HR_{max}) continuous exercise. After 8 weeks, HbA1c were reduced by 0.1% points from 7.4 ± 0.3 to 7.3 ± 0.3% in LI and by 0.2% points from 7.1 ± 0.2 to 6.9 ± 0.2 in HI. Unlike MIT in our study, 69% HR_{max} in Hansen et al. (2009) improved VO_{2max}, and the training effects accompanying improvements in VO_{2max} might have influenced their HbA1c results.

Due to the significant difference in pre-HbA1c levels between the two groups in the present study, a post hoc analysis was conducted where the HbA1c data were corrected for skewness (1.7 ± 0.4%). This correction normalized the distribution and excluded the two outliers in the HAIT group. After the correction for skewness, there was no significant difference between MIT and HAIT baseline HbA1c values. The post hoc analysis still revealed a significant difference in improvement between HAIT and MIT ($p < 0.01$) with a significant reduction of 0.47% (from 7.36 to 6.89%, $p < 0.01$) in HAIT, and no reduction in MIT ($p = 0.804$). The "corrected" reduction of 0.47% in HAIT is similar to the reduction found in Hollekim-Strand et al. (2014).

The National Health and Nutrition Examination Survey showed that only 37% of persons diagnosed with T2D achieved the treatment goal of <7% HbA1c (Saydah et al. 2004). A recent study from Norway (Mouland 2014) revealed that 55% achieved the treatment goal of <7% HbA1c. The −0.58% points reduction in HbA1c in HAIT after only 12 weeks of exercise in the present study is very similar to the effects found after long-term (>12 weeks) medication (drug or insulin) treatment only (0.6–0.8% points) (UKPDS 1998). This indicates the potential of

HAIT to be an effective additive or even a substitute treatment to medication to reduce T2D risk factors, highlighting the potential of HAIT to reduce the use of medications.

Fat oxidation

There was a tendency towards an improved FatOx in HAIT in the present study ($p = 0.065$). A longer duration of the exercise intervention might have led to a significant improvement. Although the changes from pre- to post-test within each exercise group were not significant, an independent *t* test revealed a significant difference in change between HAIT and MIT ($p < 0.05$). Energy status and nutrition composition can have profound effects on metabolism and therefore act as a potential confounding factor on "exercise effects" (Støa et al. 2016). A strict control of energy status and nutrition composition was therefore emphasized to ensure a high internal validity. Although both groups reduced their BW during the 12 weeks of exercise, the BW reductions were only minor (−1.7 versus −0.6 kg in HAIT and MIT, respectively), and nutrition composition were not changed from to pre- to post-test. The results in the present study are thus most likely not biased by the participants' diets. It has been suggested that individuals with T2D should exercise at lower intensities closer to FatMax (Suk et al. 2015) since FatOx during the FatMax intensity has been suggested to be twofold greater than at any other exercise intensity (Sahlin et al. 2008). Although exercising at an intensity closer to FatMax (~56% VO_{2max}), MIT did not improve FatOx after 12 weeks of exercise. Generally, FatOx effects after exercise are influenced by the responses in muscle oxidative capacity by the adaptations in mitochondrial density, and mitochondrial enzyme content and activity, and oxygen delivery to muscle (Melanson et al. 2009). As described in Achten and Jeukendrup (2004), it is also suggested that aerobic exercise increases the gene expression and protein content of several FA transporters, which may improve the uptake and delivery of FA to mitochondria. Other studies with training protocols of typical high-intensity, shorter duration, and more sprint-like intervals have revealed positive effects on these factors as thoroughly summarized in other studies (Gibala and McGee 2008; Bird and Hawley 2012). Although mitochondrial measurements were not conducted in the present study, these factors have likely influenced the FatOx adaptations.

Anthropometrics

Both HAIT and MIT led to positive adaptations in body composition. The small reduction in BW (−1.7 versus −0.6 kg in HAIT and MIT, respectively), and also the relatively minor changes in BMI, %BF, waist circumference, and hip circumference, was expected since the intervention did not include a diet restriction program. The improvements in body composition in both groups are similar to other exercise interventions with no diet restrictions (Giannopoulou et al. 2005; Hollekim-Strand et al. 2014), which is in accordance with the well-known importance of a combination of exercise and diet to obtain an effective loss of fat mass (Wing 2002). Although minor changes, the body composition adaptations found in the present study are still of great importance in a longer perspective to increase glucose control among T2D, since a reduction in fat mass is associated by improved insulin sensitivity (Racette et al. 2006), and any increase in muscle mass itself will lead to increased blood glucose uptake without changing the muscle's intrinsic ability to react to insulin. It may be noteworthy to mention that despite the instruction to the participants to increase their caloric intake after the training sessions to match the increase in energy expenditure, both groups had a slight but not significant decrease in caloric intake of about 2–5%. This could be due to a change in appetite, but appetite was not measured in the present study.

There may be a possible link between the improvements in VO_{2max}, FatOx, HbA1c, and body composition. The improvements in VO_{2max} could be due to an increased ability to utilize oxygen in the exercising muscles (Helgerud et al. 2007). Since an increased FatOx may rely on an increased O_2 supply (Nordby et al. 2006), the improvements in VO_{2max} may partly explain the tendency towards an increased FatOx in HAIT, in addition to the peripheral musculature adaptations. On the other hand, the actual training sessions during HAIT reveal higher RER values than MIT training sessions. This means a higher stimulation of muscle glycogenolysis and glucose uptake (Romijn et al. 1993). Adaptations to this stress may partly explain the lowering of HbA1c in HAIT. An improved VO_{2max} also improves the ability of energy production at any given submaximal intensity (McArdle et al. 2010). These improvements taken together may thus explain the reduced %BF.

Blood pressure

The decreases in systolic BP and diastolic BP (−12 and −7 mmHg, respectively) in MIT and diastolic BP (−6 mmHg) in HAIT in the present study are similar to the results in Cornelissen and Smart (2013). Although there seems to be an agreement on the effectiveness of exercise to reduce BP among healthy individuals (Pescatello et al. 2004), the effectiveness of aerobic exercise to reduce systolic and diastolic BP among T2D is still debated as exercise interventions show contradictive results (Dobrosielski 2012; Cornelissen and Smart 2013; Colberg et al. 2010). In the 2010 joint position statement from the American College of Sports Medicine (ACSM)/American Diabetes Association (ADA), the authors conclude that exercise may lead

to a reduction in systolic BP, while decreases in diastolic BP are less common among T2D (Colberg et al. 2010). The positive adaptations in diastolic BP in both MIT and HAIT could partly be due to the high baseline BP levels in the present study.

Blood lipids

Improvements in BLP were only found in MIT, where triglycerides decreased (from 1.58 ± 0.78 to 1.37 ± 0.81 mmol L^{-1}, $p < 0.05$) and HDL increased (from 1.24 ± 0.38 to 1.33 ± 0.38 mmol L^{-1}, $p < 0.05$). However, the changes in BLP were not significantly different between the groups. The improvements in both triglyceride level and HDL are still of importance due to the BLP associations with CVD (Wilson et al. 1998). The increase in HDL in MIT is of clinical relevance since every 0.026 mmol L^{-1} increase in HDL is associated with 2–3% reduction in risk of CVD (Maron 2000). None of the groups changed their LDL level although both groups had LDL levels above the recommended 2.5 mmol L^{-1} treatment goal among persons with T2D (Daniel 2011). This finding is in accordance with other studies (Trejo-Gutierrez and Fletcher 2007) and may be due to the lack of diet restrictions.

Practical implications

In the present study, we demonstrated that HAIT is an effective exercise strategy to improve cardiovascular risk factors. The public health message remains to focus on "increasing physical activity." However, the present study demonstrated an additional effect on CRF and HbA1c with higher aerobic intensity. CRF is an independent prognostic marker for death among persons with T2D (Wei et al. 2000), and should thus be taken into consideration when designing exercise prescriptions and establishing physical activity guidelines. The ~20% increase in VO_{2max} would also imply ~20% increase in energy expenditure during exercise at a given exercise intensity (%VO_{2max}). This implies a beneficial consequence of HAIT in a weight reduction perspective.

Two out of three individuals with T2D do not exercise regularly (Thomas et al. 2004), and "lack of time" is one of the most common explanations for inactivity (Stutts 2002). These are the arguments behind the increased investigation on alternative training models that are less time consuming, yet effective to improve cardiovascular health among T2D. The training protocol in the present study can be accomplished in ~30–40 min three times per week. Different exercise methods (such as walking, running, bicycling, cross-country skiing, and rowing) can be used in this training protocol as long as it involves large muscle mass to give optimal stress on the cardiovascular system. Intervals may advantageously be conducted in hills or with treadmill inclination, since this makes it easier to obtain the right intensity zone, and is also less stressful on the joints. The training response to HAIT seems not to be affected by age (Støren et al. 2016). With increasing age however, individuals may have different physical restrictions. Therefore, a personalized training regime should be developed to each individual based on potential physically restrictions, personal experiences with different training methods, and practical feasibility.

Conclusion

High-intensity aerobic interval training (85–95% HR_{max}) is an effective strategy to improve important risk factors associated with T2D, and more effective than moderate continuous exercise in improving VO_{2max} and lowering HbA1c.

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Compliance with ethical standards

Conflict of interest There is no conflict of interest.

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