Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes

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REGULAR EXERCISE IS AN EFFECTIVE strategy for the prevention and treatment of type 2 diabetes (T2D; 6). Most studies examining the therapeutic effects of exercise in T2D involve continuous, low- to moderate-intensity exercise such as walking, jogging, or cycling for ≥30 min/session (reviewed in Ref. 6). Although the optimal strategy has not been established, higher intensity exercise may be more effective for improving glycemic control in patients with T2D (2, 25). Recently revised guidelines from the American Diabetes Association advocate at least 150 min of moderate to vigorous exercise per week (6). High-intensity interval training (HIT), which involves repeated bursts of vigorous exercise interspersed with periods of rest, may be an attractive option to implement higher intensity exercise training in T2D. The utility of HIT for improving disease outcomes has yet to be established.

We (8, 14, 16) and others (1, 21) have shown that HIT elicits physiological remodeling comparable to moderate-intensity continuous training in healthy adults, despite a substantially lower time commitment and reduced total exercise volume. As little as six sessions of low-volume HIT over 2 wk increases skeletal muscle mitochondrial capacity (8), which may be of clinical relevance for T2D given that reduced content (22) or biogenesis (18) of mitochondria have been implicated in insulin resistance and T2D. Two weeks of low-volume HIT has also been shown to improve glucose tolerance (1) and enhance insulin sensitivity (21) in healthy adults. These findings are intriguing because they suggest that low-volume HIT may result in many of the same health benefits as traditional exercise training with substantially reduced exercise volume and time commitment. Low-volume HIT may, therefore, represent a potent, time-efficient exercise strategy to improve skeletal muscle metabolic control and glycemic regulation in patients with T2D.

The primary purpose of this pilot investigation was to examine the effects of low-volume HIT on glucose regulation and skeletal muscle mitochondrial capacity in individuals with T2D. On the basis of accumulating evidence indicating that postprandial hyperglycemia plays a predominant contributing role in diabetic complications (5), we used continuous glucose monitoring (CGM) to examine the effects of HIT on overall glycemic exposure and postprandial glucose fluctuations. We hypothesized that 2 wk of low-volume HIT would reduce hyperglycemia and increase mitochondrial capacity and GLUT4 content measured in skeletal muscle biopsy samples.

METHODS

Participants

Participants were recruited through local diabetes clinics, community diabetes information sessions, and poster advertisement. All participants were diagnosed with T2D at least 3 mo prior by a clinician according to standard criteria, including a fasting glucose ≥ 7.0 mmol/l and/or 2-h oral glucose tolerance test blood glucose concentration ≥ 11.1 mmol/l, were not taking insulin, and had no history of end-stage liver or kidney disease, neuropathy, retinopathy, hypertension that could not be controlled by standard medication, cardiovascular disease, or other contraindication to exercise. Eight individuals [mean age 62.5 ± 7.6 yr, body mass index 31.7 ± 5.8 kg/m², hemoglobin A1C (HbA1C) 6.9 ± 0.7% (range 6.4–8.5%)]
volunteered to participate in this study. Six participants were seden-
tary, which was defined as less than or equal to two exercise sessions
of 30 min/wk. Two participants reported engaging in ~30 min of
low-intensity walking exercise on 3–5 days/wk, in accordance with
guidelines provided from their diabetes care team. Six subjects were
taking blood glucose lowering medications but had HbA1C values
≤8.5% and were not on exogenous insulin therapy. Four patients were
-treated with metformin only, one patient with glitazide only, and one
patient with a combination of metformin, pioglitazone, sitagliptin, and
repaglinide. Due to the short duration of the intervention, participants
did not adjust their medications and were instructed to maintain their
typical dietary and activity patterns throughout. All participants pro-
vided written informed consent. The study protocol was approved by
the Hamilton Health Sciences/McMaster University Faculty of Health
Sciences Research Ethics Board.

Experimental Design

The experimental design consisted of 1) medical clearance and
familiarization, 2) baseline testing, 3) a 2-wk training intervention,
and 4) posttesting.

Medical clearance and familiarization. Height and weight were
recorded, and a maximal exercise test on a recumbent cycle ergometer
(Corival, Lode BV, Groningen, The Netherlands) was performed with pre-
and postexercise 12-lead electrocardiogram (EKG) collection to
confirm the absence of any underlying contraindications to vigorous
exercise participation. The test started at 30 W and increased by 15
W/min until volitional exhaustion. Peak power output (Wmax) and
maximal heart rate (HRmax) were recorded. Following EKG clearance by
a study physician, participants completed one to two familiarization
sessions to become acquainted with low-volume HIT. These sessions
were also used to determine the interval power output that elicited ~90% HRmax.

Baseline testing. Prior to training, participants performed a 15-min
walking test to examine the cardiovascular response and ratings of
perceived exertion (RPE) during exercise. Speed was self-selected by
each participant during an initial 5-min warm-up. Heart rate was
measured by telemetry (Polar), and RPE was measured using the 0–10
continuous/interval scale.

At least 2 days after the walk test, participants reported to the
laboratory for CGM device insertion (CGMS iPro, Medtronic,
Northridge, CA). Participants were given a glucose meter (OneTouch
UltraMini, Lifescan, Milpitas, CA) with instructions for both calibra-
tion and capillary blood sampling and individualized control diets.
The following day served as a dietary control day for 24-h CGM data
collection. Subjects returned to the laboratory 2 days later for removal
of the CGM device and collection of a resting skeletal muscle biopsy
sample as we previously described (8). Briefly, muscle samples were
obtained under local anesthesia (1% Lidocaine) from the vastus
lateralis using a Bergstrom needle adapted with suction. Muscle
samples were quickly blotted to remove excess blood, sectioned into
several pieces, and placed in separate vials before snap freezing in
liquid nitrogen for subsequent analyses.

Training. Approximately 5 days after the muscle biopsy procedure,
subjects commenced training. The HIT protocol involved a total of six
supervised sessions over 2 wk (Monday, Wednesday, Friday each
week). Each session consisted of 10 × 60-s cycling intervals inter-
spersed with 60 s of recovery based on our recent work (14). Training
was performed on a cycle ergometer (LifeCycle C1 or R1, Life
Fitness, Schiller Park, IL) set in constant watt mode at a pedal cadence
of 80–100 revolutions/min. Individual workloads were selected to
elicit a heart rate of ~90% HRmax during the intervals. During
recovery, participants were allowed to rest or pedal slowly against a
resistance of 50 W. Each training session included a 3-min warm-up and
2-min cool-down at 50 W, for a total of 25 min. Therefore, the
training protocol involved a total of 30 min of high-intensity exercise
within a total time commitment of 75 min/wk, including warm-up,
cool-down, and the recovery interval between high-intensity efforts.

Posttesting. CGM data were collected for a 24-h period starting
~48 h after the final training session. Diet was controlled to be the
same as pretraining. Resting muscle biopsy samples were obtained
~72 h following the final training session. Approximately 2–4 days
after the biopsy, the walk test (performed at the same speed as
pretraining) and maximal exercise test were performed using the same
procedures as baseline testing. Perceived enjoyment of low-volume
HIT was assessed by asking participants how enjoyable they would
find engaging in 1) a single bout of HIT (10 × 1 min) and 2) HIT at
least 3 times/wk for the next 4 wk using a 9-point Likert scale ranging
from 1 (not enjoyable at all) to 9 (very enjoyable).

Continuous Glucose Monitoring

Average blood glucose concentration and area under the glucose
curve were calculated from CGM data for a 24-h period before and
after training. CGM data were also used to analyze the 3 h postpran-
dial areas under the glucose curve for breakfast, lunch, and dinner. On
CGM data collection days, participants consumed their habitual
breakfast but were provided with standardized snacks (e.g., almonds,
fruit, vegetables) based on their personal preferences and habits.
Lunch and dinner were standardized for all participants by providing
vouchers to a local sandwich restaurant. Subjects completed detailed
dietary logs to record the timing and quantity of all food consumed
during the pretraining day. For posttesting, these dietary logs, along
with all snacks and vouchers for lunch and dinner were provided with
instructions for diet replication under free-living conditions over the
24-h CGM data collection period. As per manufacturer’s recommen-
dations, capillary blood glucose samples were obtained at four points
during the day at a time when blood glucose would be expected to be
stable (i.e., upon awakening, before lunch, before dinner, and before
bed) and were automatically stored in the glucose meters provided to
participants. These four values were used during CGM downloading
to construct 24-h blood glucose curves based on interstitial glucose
recordings averaged every 5 min by the CGM device using the associated software algorithm (Solutions Software, Medtronic,
Northridge, CA). CGM data were exported and analyzed using Sigma-
Plot (Statsoft, Chicago, IL). Reproducibility of the CGM device in our
lab was verified in five volunteers who wore the monitor on two
occasions separated by 1 wk under identical dietary conditions. The
coefficient of variation for the 24 h blood glucose measurements was
2.8% (data not shown).

Muscle Analyses

Citrate synthase enzyme activity. One piece of muscle (~20 mg)
was homogenized using a glass tissue grinder (Kimble/Kontes
885300–0002) in 10 volumes of buffer containing (in mM) 70
sucrose, 220 mannitol, 10 HEPES (pH 7.4) supplemented with pro-
tease inhibitors (Complete Mini, Roche Applied Science, Laval, PQ,
Canada) and used to determine the maximal activity of citrate syn-
thase (CS) as we previously described (8, 16). Protein concentration of homog-
ennate was measured by the Bradford assay (Pierce, Rockford, IL), and enzyme activity is ex-
pressed as millimoles per kilogram of protein per hour wet weight.

Western blotting. A second piece of muscle (~30 mg) was homog-
enized in RIPA buffer for Western blot analyses using techniques
described previously (8, 16). Briefly, protein concentration of homog-
ennates were determined as above and equal amounts of protein (5–20
µg) were prepared in 4× Laemmli’s buffer and heated to 95°C before
being separated by 10–12.5% SDS-PAGE and electrotransferred to
nitrocellulose membranes. Ponceau S staining was performed follow-
ing transfer to visualize equal loading and transfer. Following 1 h
blocking in 5% fat-free milk Tris-buffered saline 0.1% Tween 20
(TBS-T), membranes were incubated in primary antibodies overnight
at 4°C or at room temperature for 2 h in 3% fat-free milk TBS-T or

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Following training (P/H9251-Tubulin (Cell Signaling Technology, #2125), which did not change (NIH) was used to quantify the optical density of protein bands. Imaging System (Alpha Innotech, San Leandro, CA). ImageJ software for the following proteins of interest were used: NDUFA9 (Mitosciences, MS111), Complex II 70 kDa subunit (Mitosciences, MS204), Complex I Core 2 protein (Mitosciences, MS304), cytochrome c oxidase (COX) subunit II (MitoSciences, MS405), COX subunit IV (Mitosciences, MS408), ATP synthase α-subunit (Mitosciences, MS507), CS (kind gift from Dr. Brian Robinson, The Hospital for Sick Children, Toronto, Canada), mitofusin (Mfn) 2 subunit IV (Mitosciences, MS408), ATP synthase α-subunit also increased, but did not reach statistical significance (P = 0.06–0.12; Fig. 3A).

Statistical Analyses

All data were analyzed using paired Student’s t-tests with significance set at P ≤ 0.05 (Sigma Stat v3.10). Values are means ± SD in the text and on figures.

RESULTS

Descriptive Characteristics of Training

All participants completed all prescribed intervals during training with no complications. Interval intensity averaged across all intervals for all subjects corresponded to 95 ± 14% of Wmax, elicited 88 ± 3% HRmax, and RPE was 6.4 ± 1.3 (0–10 scale). The response to each interval averaged across all six training sessions for all subjects is depicted in Fig. 1. Training had no effect on body mass (pre: 93 ± 19 kg vs. post: 92 ± 18 kg, P = 0.28). On average, perceived enjoyment of HIT was rated high by this group of participants (single session, 8.1 ± 1.0; 3 times/wk, 7.9 ± 1.0).

Continuous Glucose Monitoring

Average blood glucose concentration over 24 h was reduced from 7.6 ± 1.0 to 6.6 ± 0.7 mmol/l after training (Fig. 2A, P = 0.01). Area under the 24-h blood glucose curve was also lower following HIT (pre: 11,066 ± 1,703 vs. post: 9,572 ± 995 mmol·l⁻¹·day⁻¹, P = 0.02). The sum of the 3-h postprandial area under the glucose curves for breakfast, lunch, and dinner was significantly lower postraining (pre: 965 ± 483 vs. post: 679 ± 437 mmol·l⁻¹·h⁻¹, P = 0.01). Pre- and postraining 24-h blood glucose curves for a representative subject are shown in Fig. 2B.

Adaptations in Skeletal Muscle

The maximal activity of CS was elevated following training (Fig. 3A, P = 0.04). Training also increased skeletal muscle mitochondrial protein content as evidenced by changes in Complex II 70 kDa subunit (P = 0.03), Complex III Core 2 protein (P = 0.04), and COX subunit IV (P = 0.02) measured by Western blotting (Fig. 3B). The protein content of CS (~57%; data not shown), NDUFA9, COX subunit II (~53%; data not shown), and ATP synthase α-subunit also increased, but did not reach statistical significance (P = 0.06–0.12; Fig. 3B).

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The protein content of Mfn2 was elevated following training (~71%, P = 0.02; Fig. 4), as was total GLUT4 protein (~369%, P = 0.003; Fig. 5).

**Functional Exercise Performance**

Maximal workload achieved on the ramp cycling test was increased by ~10% following training (pre: 111 ± 36 vs. post: 124 ± 37 W, P = 0.03). Training reduced heart rate (pre: 73 ± 7 vs. post: 66 ± 6%HRmax, P < 0.001) and RPE (pre: 2.4 ± 0.7 vs. post: 1.3 ± 1.2, P = 0.01) during the walk test.
DISCUSSION

The present study demonstrates that low-volume HIT can rapidly reduce hyperglycemia and increase skeletal muscle oxidative capacity in patients with T2D. These improvements were realized despite a small total volume of exercise that consisted of six training sessions over 2 wk. The training protocol involved a total of only 30 min of high-intensity exercise and a total time commitment of only 75 min/wk. This is much lower than current physical activity guidelines for T2D that recommend a total of 150 min of moderate to vigorous intensity exercise each week (6). Given that the majority of individuals with and without T2D does not accumulate sufficient exercise to achieve health benefits (6) and the most common cited barrier to regular exercise is lack of time (26), our results suggest that low-volume HIT may be a viable, time-efficient strategy to improve health in patients with T2D.

Low-Volume HIT and Glycemic Control

Glycemic control is an important aspect of T2D treatment and is an independent risk factor for the development of diabetic complications (24, 27). We used CGM to assess the effects of short-term low-volume HIT on overall glycemic exposure and postprandial glucose responses. CGM provides information about direction, magnitude, and frequency of blood glucose excursions and may provide a sensitive means to detect acute changes in blood glucose throughout the day (15). Although exercise is regarded as an effective strategy to improve glycemic control (2, 6, 25), there are limited data regarding the effect of exercise training on glucose control using CGM. Studies using CGM technology in patients with T2D have reported that acute resistance exercise reduces the prevalence of hyperglycemia (19) and acute endurance exercise reduces 24-h average blood glucose concentration (17). In the only training study conducted to date, Cauza et al. (4) reported a greater reduction in 24-h average blood glucose concentration following 4 mo of resistance training compared with endurance-type training in individuals with T2D, but interpretations on the effects of exercise are potentially limited by significant changes in body composition and an apparent lack of dietary control.

To our knowledge, this is the first study to examine the effects of HIT on glycemic regulation using CGM. Average blood glucose concentration and area under the glucose curve measured under standardized dietary conditions from ~48 to 72 h after the final training session were significantly lower than pretraining, indicating that short-term, low-volume HIT improved glycemic control, particularly glycemic excursions after meals. Although reducing fasting hyperglycemia is a significant aspect of T2D treatment, increasing evidence suggests lowering postprandial hyperglycemia is as important, if not more important, for achieving targeted HbA1C levels (27). Additionally, elevated postmeal blood glucose excursions have been implicated in the development and progression of T2D related comorbidities such as cardiovascular disease (5, 27). Following HIT, the sum of the postprandial areas under the glucose curve for breakfast, lunch, and dinner was significantly lower than pretraining, highlighting the potency of HIT to lower postmeal glucose excursions. These findings demonstrate that low-volume HIT may be an effective strategy for improving glycemic regulation in individuals with T2D and suggest that CGM may be a sensitive technique to measure the effects of exercise on glucose control.

The mechanisms mediating the improvement in glycemic control following HIT remain to be determined. Training had no effect on body mass, and, while not assessed directly, it is unlikely that such a short exercise intervention would lead to any substantial changes in body composition. Therefore, it is tempting to speculate that adaptations in skeletal muscle were involved. Since reduced mitochondrial capacity in skeletal muscle has been reported in insulin resistance and T2D (22) and muscle oxidative capacity has been shown to be a significant predictor of insulin sensitivity (3), it is possible that the rapid increase in skeletal muscle mitochondrial content following low-volume HIT may be a contributing factor related to reduced insulin resistance and improved glycemic control. However, the notion that mitochondrial deficiency mediates insulin resistance has been questioned recently (12), indicating that other adaptations in skeletal muscle may be more important. The training-induced increase in GLUT4 protein content likely plays a role in improving glucose regulation. Studies in rodents indicate that the exercise-induced increase in GLUT4 protein is directly related to the increase in muscle glucose uptake at any given insulin concentration (20). Thus, even in the face of insulin resistance, an increase in skeletal muscle GLUT4 could facilitate greater muscle glucose uptake and contribute to improved glycemic regulation. In addition to skeletal muscle adaptations, training-induced alterations in hepatic glucose output cannot be ruled out. The effect of exercise training on hepatic insulin resistance in T2D has not been directly assessed in humans, although there is evidence to suggest that endurance exercise training improves hepatic insulin signaling and glycemic control in rodents (10).

We did not directly assess the effects of training on insulin sensitivity using hyperinsulinemic-euglycemic clamps and therefore cannot conclude whether low-volume HIT improves muscle insulin sensitivity. CGM assesses exposure to hyperglycemia as well as glycemic excursions throughout the day. Exposure to hyperglycemia over time may be a better indicator of diabetic complications than insulin sensitivity per se (5) and therefore CGM may provide greater insight into the clinical benefits of exercise training. Changes in HbA1C are commonly used to assess the effectiveness of glucose-lowering interventions in T2D but due to the short duration of the current study was not measured.

Low-Volume HIT and Skeletal Muscle Mitochondrial Adaptations

Individuals with insulin resistance and T2D have been shown to have reduced mitochondrial content (22), impaired in vivo mitochondrial function (23), and/or reduced markers of mitochondrial biogenesis (18) in skeletal muscle. These findings have led to the hypothesis that reduced mitochondrial capacity or impaired regulation of mitochondrial biogenesis in skeletal muscle may play a role in the pathogenesis of T2D (18, 22, 23). Although it is currently unclear whether skeletal muscle mitochondrial impairment causes insulin resistance (12), interventions that increase muscle mitochondrial content may be effective for the treatment and prevention of T2D (9, 13). Given the potency of low-volume HIT to induce mitochondrial biogenesis in young, healthy subjects (8, 16), we hypothesized that HIT might also increase mitochondrial capacity in skeletal muscle of individuals with T2D. Low-volume HIT was a potent stimulus to increase mitochondrial capacity.
in the current study, as evidenced by increased enzyme activity of CS as well as elevated protein content of several subunits from complexes in the electron transport chain.

Another novel observation in the present study was that low-volume HIT increased the protein content of Mfn2. The primary role of Mfn2 is in mitochondrial fusion, although it also appears to regulate the expression of electron transport chain subunits and influence mitochondrial bioenergetic capacity (28). Our findings provide evidence that elevated Mfn2 may be involved in regulating the increase in mitochondrial capacity following low-volume HIT. A role for Mfn2 in the pathogenesis of T2D is supported by studies reporting reduced Mfn2 expression in skeletal muscle of patients with T2D (11), suggesting that alterations in mitochondrial fusion/fission may contribute to mitochondrial impairment. Whether a training-induced increase in muscle Mfn2 is linked to improved metabolic health is unknown. Further studies are needed to clarify the role of mitochondrial dynamics and examine the effects of exercise and other interventions on Mfn2 skeletal muscle.

Conclusions

Two weeks of low-volume HIT, involving only 30 min of vigorous exercise within a total time commitment of 75 min/wk, lowered 24-h average blood glucose concentration, reduced postmeal blood glucose excursions, and increased markers of skeletal muscle mitochondrial capacity in individuals with T2D. The total weekly training time commitment in the present study was 50% lower than recently revised guidelines that call for 150 min of moderate to vigorous exercise per week. While longer-term comparative studies are clearly warranted, our findings indicate that low-volume HIT may represent a time-efficient exercise strategy for the treatment of T2D. Future research is needed to examine the long-term influence of HIT and to comprehensively examine how this type of training compares to traditional therapeutic exercise strategies.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


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