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Sitagliptin improves diastolic cardiac function but not cardiorespiratory fitness in adults with type 2 diabetes

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ABSTRACT

Background: People with type 2 diabetes mellitus (T2D) have preclinical cardiac and vascular dysfunction associated with low cardiorespiratory fitness (CRF). This is especially concerning because CRF is a powerful predictor of cardiovascular mortality, a primary issue in T2D management. Glucagon-like pepetide-1 (GLP-1) augments cardiovascular function and our previous data in rodents demonstrate that potentiating the GLP-1 signal with a dipeptidyl peptidase-4 (DPP4) inhibitor augments CRF. Lacking are pharmacological treatments which can target T2D-specific physiological barriers to exercise to potentially permit adaptations necessary to improve CRF and thereby health outcomes in people with T2D. We therefore hypothesized that administration of a DPP4-inhibitor (sitagliptin) would improve CRF in adults with T2D.

Methods and Results: Thirty-eight participants (64 ± 1 years; mean ± SE) with T2D were randomized in a double-blinded study to receive 100 mg/day sitagliptin, 2 mg/day glimepiride, or placebo for 3 months after baseline measurements. Fasting glucose decreased with both glimepiride and sitagliptin compared with placebo ($P = 0.002$). CRF did not change in any group (Placebo: Pre: 15.4 ± 0.9 vs. Post: 16.1 ± 1.1 ml/kg/min vs. Glimepiride: 18.5 ± 1.0 vs. 17.7 ± 1.2 ml/kg/min vs. Sitagliptin: 19.1 ± 1.2 vs. 18.3 ± 1.1 ml/kg/min; $P = 0.3$). Sitagliptin improved measures of cardiac diastolic function, however, measures of vascular function did not change with any treatment.

Conclusions: Three months of sitagliptin improved diastolic cardiac function, however, CRF did not change. These data suggest that targeting the physiological contributors to CRF with sitagliptin alone is not an adequate strategy to improve CRF in people with T2D.

Clinical trials registration: www.clinicaltrials.gov NCT01951339.

1. Introduction

People with type 2 diabetes (T2D) have subclinical cardiac and vascular functional impairments. These functional impairments are concerning because cardiovascular function is a primary contributor to cardiorespiratory fitness, one of the strongest predictors of risk for premature death from all causes as well as cardiovascular disease.[1,2] People with T2D have low cardiorespiratory fitness compared with age, sex, and activity matched controls[3,4] and there is a well-established T2D-associated increase in cardiovascular disease mortality.[1,2]

Low cardiorespiratory fitness in people with T2D is related to disease-associated physiological barriers to exercise including insulin resistance,[5] impaired vascular function which limits delivery of oxygen and nutrient rich blood flow to skeletal muscle,[6] and impaired skeletal muscle mitochondrial function.[7] Aerobic exercise training is one way to improve cardiorespiratory fitness, however, people with T2D are commonly sedentary.[8] In addition to low cardiorespiratory fitness, people with T2D also have reduced submaximal exercise capacity during constant workloads accompanied by slowed oxygen uptake kinetics (VO_2 kinetics).[9] Pharmacological strategies that target the T2D-specific physiological barriers to exercise may potentially permit the adaptations necessary to improve cardiorespiratory fitness and health outcomes in people with T2D.

Glucagon-like peptide-1 (GLP-1), an insulin secretagogue, lowers circulating glucose concentrations (both fasting and postprandial) and glycated hemoglobin (HbA1c).[10,11] Independent of the impact on glucose control, GLP-1 may enhance oxygen delivery to skeletal muscle

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via augmentation of endothelial and cardiac function in T2D.[10,12,13] Previous investigations of GLP-1 receptor agonists have demonstrated improvement of left ventricular systolic and diastolic function in humans, rodents, and canines.[10,14–17] Further, studies in rodents, both in vivo and ex vivo, suggest a direct effect of GLP-1 on endothelial function via endothelial nitric oxide synthase activation.[18,19] In humans, treatment with GLP-1 receptor agonists recruits muscle microvasculature, and it also lowers blood pressure in clinical trials.[10,20] Thus, GLP-1 positively impacts the cardiac and vascular systems in addition to improving skeletal muscle blood flow. These systems represent key physiological T2D-associated barriers to exercise and targeting them has the potential to improve cardiorespiratory fitness. One way to potentiate the endogenous GLP-1 signal is with a dipeptidyl peptidase-4 (DPP4) inhibitor as DPP4 degrades GLP-1 limiting the duration of action. We hypothesized that sitagliptin, a DDP4 inhibitor, would improve cardiorespiratory fitness in adults with T2D by improving cardiac and skeletal muscle function. To address this hypothesis, we measured cardiorespiratory fitness, cardiovascular function (the primary target of interest of GLP-1), and skeletal muscle oxidative phosphorylation (an endpoint impacted by changes in cardiovascular function that contributes to cardiorespiratory fitness) before and following three months of sitagliptin administration.

2. Materials and methods

2.1. Participants

Thirty-eight adults with T2D between the ages of 22 and 70 years were recruited through general advertising and local clinics for this trial (clinicaltrials.gov, NCT01951339). These individuals were screened and found not to have any clinically evident T2D-associated comorbidities such as cardiovascular disease. The Institutional Review Board of the University of Colorado School of Medicine (UCSOM) approved the experimental protocol, and the nature, purpose and risks of the study were explained before written informed consent was obtained from each participant.

Diagnosis of T2D was documented by chart review and presence of treatment for T2D. To make this investigation more generalizable to the patient population that is initiating a second-line medication for T2D, persons with T2D were included if their diabetes was treated by 1-2 g/day of metformin for at least 3 months and if they demonstrated glycemic control with a total HbA1c of <9% on therapy. All participants were sedentary (defined as exercising one hour per week or less) and inclusion in the study was only permitted if participants did not plan to alter their exercise or diet efforts during the study.

History, physical examination and laboratory testing confirmed the absence of comorbid conditions. Exclusion criteria included: use of GLP-1 receptor agonists or dipeptidyl peptidase 4 inhibitors, tobacco use within one year prior to study, evidence of acute liver disease, evidence of distal symmetrical neuropathy (by evaluation of symptoms [numbness, paresthesia] and signs [elicited by vibration, pinprick, light touch, ankle jerks]), autonomic dysfunction (>20 mmHg fall in upright blood pressure without a change in heart rate), proteinuria (urine protein >200 mg/dl) or kidney disease (creatinine ≥2 mg/dl), evidence of heart disease by history, echocardiography, or abnormal resting or exercise electrocardiogram (≥ 1 mm ST segment depression), angina, or other cardiac or pulmonary symptoms potentially limiting exercise performance and orthopedic conditions limiting exercise testing. Systolic blood pressure > 190 mmHg at rest or > 250 mmHg with exercise or diastolic pressure > 95 mmHg at rest or > 105 mmHg with exercise were also grounds for exclusion. All exclusions were made for reasons of participant safety or potential effects on exercise performance.

2.2. Study protocol

For each participant, all components of the study protocol were completed at the Vascular Research Laboratory at the UCSOM over a four-month period. During the first visit, a history and physical examination, a resting electrocardiogram and urinalysis were completed, as well as a venous blood draw for measuring several circulating metabolic factors. Sedentary lifestyle was confirmed with the Low-Level Physical Activity Recall survey (LoPAR).[21] Participants completed a graded cycle exercise test for habituation purposes and body composition was assessed via dual-energy x-ray absorptiometry (DEXA). During the second visit, in vivo skeletal muscle oxidative flux was determined via ^{31}phosphorus-Magnetic Resonance Spectroscopy (^{31}P-MRS). The final pre-randomization visit included echocardiography to determine cardiac function at rest, measurement of vascular function at rest, and finally a second graded cycle exercise test using a metabolic cart to determine peak oxygen uptake (VO_{2peak}). Additionally, participants completed three bouts of constant workload exercise for assessment of VO_2 kinetics. Following the conclusion of these visits, participants were randomized in a double blind design to receive either 2 mg/day glimepiride ($n = 14$) or sitagliptin 100 mg/day ($n = 13$) for three months. The entry procedures were repeated three months after treatment initiation. The referenced placebo control was a group of participants ($n = 11$) from a previous study conducted by our lab that used the same inclusion/exclusion criteria and experimental outcomes with the exception of ^{31}P-MRS.[22] Data from these participants were included to control for the effect of the anti-hyperglycemic properties of both glimepiride and sitagliptin.

2.3. Blood collection and preparation

Blood was drawn from participants after a 12-h fast for the measurement of glucose, insulin, HbA1C, and free fatty acid concentrations. Parameters were assayed according to previously reported methods.[23] The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as HOMA-IR = (glucose (mg/dL) x insulin (μU/mL))/405.[24]

2.4. Graded exercise test

VO_{2peak} was determined via graded exercise to exhaustion as previously described[9,23] using a stationary cycle ergometer (Lode Bike, Groningen, The Netherlands) and a metabolic cart (Medgraphics Ultima CPX, Medical Graphics Corp., St. Paul, MN, USA). After the start of exercise, the work rate was increased in 10–20 watt/min increments (depending on age and sex) to allow each participant to reach maximum effort within 7–12 min. Peak VO_2 was confirmed by a respiratory exchange ratio (RER) >1.1. During incremental exercise testing, the highest VO_2 and heart rate averaged over 20 s were defined as the maximum values.

2.5. Constant work rate (CWR) exercise testing

Participants performed three identical exercise transitions from rest to constant work rate (CWR) exercise (85% of anaerobic threshold) on a cycle ergometer as previously described.[4,23] During each transition, data were collected during two minutes of rest, then during four minutes of pedaling with no resistance, and then for six minutes at 85% of anaerobic threshold. Transitions were separated by a minimum of 10 min of rest.

2.6. VO_2 kinetic methods

Gas exchange and heart rate data for kinetic analysis were processed using a software program developed in our laboratory as previously described.[23] The data for each exercise transition were time interpolated to 1-s intervals. The three CWR exercise transitions were

time-aligned and averaged to provide a single, averaged exercise response for each subject.

Oxygen uptake kinetic responses were evaluated using a 2-component exponential model allowing individual components of the VO_2 kinetic response to be evaluated as previously reported.[4]

2.7. Cardiac echocardiography

Standard two dimensional and Doppler echocardiography[25] (GE Vivid 7 Dimension, Milwaukee, WI, USA) were performed using standard methods at rest by an ultrasonographer expert in these methods and under supervision of echocardiographers. Participants were examined in the left lateral decubitus position using standard parasternal and apical views. All recordings and measurements were obtained by the same observer according to the recommendations of the American Society of Echocardiography and were performed at the same time of day for each subject to avoid the possible influence of circadian rhythm on left ventricular diastolic function. Global longitudinal strain (measure of left ventricular wall deformation during systole) was recorded as a measure of systolic function. Mitral valve E and A waves (early and late left ventricular filling velocities), and lateral and septal E' (left ventricular wall relaxation velocity), were the measures used to provide an assessment of diastolic function.

2.8. Arterial stiffness

Arterial stiffness was assessed via measurement of pulse-wave velocity and augmentation index (SphygmaCor CP system, AtCor Medical, Itasca, IL, USA) according to methods previously described.[26,27] Measurements were made after a four-hour fast and prior to any other exercise testing performed in the same study visit.

2.9. 31-P MRS exercise protocol

Strength testing was done on a custom-built MR-compatible plantar flexion device with force measurement capability as previously described.[7,28]

The ^{31}P-MRS exercise protocol consisted of measurements during rest for 60 s, isometric plantar flexion exercise for 90 s at 70% maximal volitional contraction, and recovery for 5 min post-exercise. We selected a 90 s isometric exercise bout as this perturbation has been extensively modeled and utilized for assessing both aerobic and anaerobic processes.[29] Force was monitored continuously throughout the exercise, with verbal feedback to help keep the force measurements within the target goal. The average force applied was recorded in kg. All participants were able to complete the exercise for 90 s at or near their personal target force of 70% maximal volitional contraction.

Spectroscopy Analysis:

Peak positions and areas of interest [phosphocreatine (PCr), inorganic free phosphate (Pi), β-ATP(3 peaks), α-ATP(2 peaks), γ-ATP (2 peaks), and phosphomonoester] were determined by time domain fitting using jMRUi[30,31] utilizing AMARES (A Method of Accurate, Robust and Efficient Spectral fitting), a nonlinear least-square-fitting algorithm using previously built prior knowledge files.[32] All exercise spectra were corrected for saturation using the fully relaxed spectra for that day. The jMRUi data was used to calculate the following metabolic variables as previously described.[33] Calculations included the rates of oxidative phosphorylation (OxPhos) following exercise, creatine kinase reaction, initial PCr synthesis (VPcr), maximal mitochondrial function (Qmax) and anaerobic glycolysis (AnGly). ADP, PCr and Pi time constants were calculated via regression analyses with Sigmaplot (Systat Software, Inc., San Jose, CA, USA).

2.10. Statistical analysis

Repeated measures analysis of variance was used to determine the influence of time and treatment (placebo, glimepiride, and sitagliptin) using Graphpad Prism version 6 (San Diego, CA, USA). Pairwise comparisons were performed using the Tukey test when there was a significant effect of treatment or a time by treatment interaction. The level of statistical significance was set at $P < 0.05$. Data are expressed as mean ± standard error.

3. Results

3.1. Participants

T2D was confirmed in all participants during the enrollment screening procedures. Baseline physical characteristics and circulating metabolic factors obtained from research participants are presented in Table 1. There were no baseline (i.e. pre-treatment) differences between the three groups. Pharmacological management of the participants in this study aligned with usual care for T2D and was similar between groups; all participants were prescribed metformin. Participants randomized to the glimepiride and sitagliptin groups tolerated the treatment well, with no drop-outs. Medication adherence did not vary by treatment group (glimepiride: 89% vs. sitagliptin: 87%; $P = 0.6$).

3.2. Circulating metabolic factors

Circulating metabolic factors at baseline and following three months of treatment are presented in Table 1. Fasting blood glucose concentration significantly decreased following three months of both glimepiride and sitagliptin with no change in the placebo group ($P = 0.002$). There was no change in circulating insulin in any group ($P = 0.9$). Treatment with glimepiride resulted in a significant decrease in HbA1c, which was not seen in the sitagliptin or the placebo groups ($P = 0.013$). HOMA-IR did not change in any of the groups ($P = 0.6$)

Table 1
Participant characteristics at baseline and post-treatment.

	Placebo ($n = 11$)		Glimepiride ($n = 14$)		Sitagliptin ($n = 13$)	
	Baseline	Post-treatment	Baseline	Post-treatment	Baseline	Post-treatment
Age	64 ± 1	–	57 ± 3	–	59 ± 2	–
Sex (m/f)	5/7	–	8/6	–	6/7	–
Body mass (kg)	87.9 ± 3.3	88.0 ± 3.2	100.8 ± 3.5	101.2 ± 3.6	92.9 ± 4.2	94.9 ± 4.3
Body Mass Index (kg/m^2)	31.3 ± 1.2	31.4 ± 1.1	33.6 ± 1.4	33.6 ± 1.6	32.3 ± 1.0	32.9 ± 1.0
Fasting glucose (mg/dl)	127.9 ± 8.0	153.5 ± 4.7	157.6 ± 9.6	137.4 ± 8.7‡	160.8 ± 12.0	146.5 ± 10.8‡
Fasting insulin (μU/ml)	34.6 ± 6.4	28.2 ± 4.7	22.1 ± 3.1	26.1 ± 3.6	22.7 ± 3.6	24.4 ± 4.0
HbA1c (%)	7.2 ± 0.4	7.0 ± 0.4	7.8 ± 0.2	6.9 ± 0.2‡	7.6 ± 0.3	7.6 ± 0.5
HOMA-IR	11.3 ± 2.3	10.5 ± 1.9	8.7 ± 1.6	9.0 ± 1.5	9.4 ± 3.1	8.4 ± 1.6

Data are mean ± standard error.
‡ $P < 0.01$ significant interaction of treatment and time.

Table 2
Measures of maximal and submaximal exercise capacity at baseline and post-treatment.

	Placebo		Glimepiride		Sitagliptin	
	Baseline	Post-treatment	Baseline	Post-treatment	Baseline	Post-treatment
VO_{2peak} (ml/kg/min)	15.4 ± 0.9[†]	16.1 ± 1.1[†]	19.6 ± 1.3	19.1 ± 1.3	19.8 ± 1.2	19.1 ± 1.2
VO_{2peak} (ml/min)	1362 ± 95[†]	1419 ± 119[†]	1953 ± 113	1881 ± 151	1893 ± 138	1849 ± 135
RER_{peak}	1.21 ± 0.03	1.25 ± 0.04	1.20 ± 0.02	1.24 ± 0.03	1.21 ± 0.02	1.20 ± 0.02
Peak heart rate (bpm)	133 ± 5	137 ± 5	149 ± 5	142 ± 6	148 ± 6	146 ± 7
VO_2 kinetics τ (*sec*)	65.3 ± 6.0	67.2 ± 2.7	54.2 ± 7.3	54.6 ± 4.3	56.2 ± 5.0	67.5 ± 8.0

Data are mean ± standard error. Peak oxygen consumption: VO_{2peak}. Respiratory exchange ratio: RER. Beats per minute: bpm.
[†] $P < 0.04$ main effect of group.

3.3. VO_{2peak} and VO_2 kinetics

The placebo group started with lower relative and absolute VO_{2peak} compared with the treatment groups ($P = 0.04$ and $P = 0.01$ respectively; Table 2). VO_2peak did not change in response to placebo or either treatment ($P = 0.3$). Similarly, VO_2 kinetics were not altered by treatment ($P = 0.3$). Peak heart rate and RER were not different at baseline between the groups and neither variable changed with treatment in the three groups ($P > 0.2$).

3.4. Cardiac function

Table 3 contains echocardiography variables measured at baseline and following three months of placebo/glimepiride/sitagliptin administration. A baseline difference in septal E:E' was present in the placebo group compared with glimepiride and sitagliptin groups ($P < 0.01$). The mitral valve E:A ratio increased in participants treated with both glimepiride and sitagliptin compared with the participants that received placebo ($P = 0.02$) representing greater early filling velocity relative to late filling velocity, an indication of greater ventricular relaxation in diastole. Septal E' wave velocity did not change in the placebo group, however, it decreased in the glimepiride treated participants while increasing in the sitagliptin treated participants ($P = 0.05$) denoting slowed relaxation with glimepiride treatment compared with sitagliptin. Septal E:E' increased from baseline ($P = 0.02$) representing increased filling velocity relative to septal wall relaxation (i.e. ventricular stiffness during diastole). This change in septal E:E', however, appears to be driven by the increases in the E:E' for the placebo and glimepiride groups as this measure decreased in the sitagliptin group ($P = 0.1$ for the time x treatment interaction). Lateral E' and E:E' were not affected by time or treatment group ($P > 0.1$). Global longitudinal strain (a measure of systolic function) was not affected by time or treatment ($P > 0.3$).

3.5. Vascular function

There were no baseline differences between the groups or changes with treatment in the measures of vascular function (Table 4): pulse wave velocity ($P > 0.2$) and augmentation index ($P > 0.2$).

3.6. In vivo skeletal muscle oxidative flux

Skeletal muscle oxidative flux is a determinant of cardiorespiratory fitness and impaired in people with T2D.[7] This measure was included in the current study because of the potential impact of GLP-1 on the cardiovascular system and the downstream augmentation of delivery of oxygenated blood to muscle, which increases oxidative flux. There were no baseline differences between the groups or changes with treatment in the measures of in vivo skeletal muscle oxidative flux (Table 5): PCr Time Constant ($P > 0.4$), VPCr ($P > 0.4$), Qmax ($P > 0.4$), ADP Time Constant ($P > 0.09$), and OxPhos ($P > 0.1$). There was a significant increase in the force all participants exerted during the isometric exercise from baseline to post-intervention ($P = 0.019$).

4. Discussion

The purpose of this study was to determine if potentiating endogenous GLP-1 signaling with a DPP4 inhibitor, sitagliptin, would improve cardiorespiratory fitness through augmentation of cardiovascular function and skeletal muscle oxidative flux. We used both a placebo control and an active sulfonylurea medication control, glimepiride, which also augments insulin secretion, to determine if any effect observed with sitagliptin was the result of GLP-1 signaling or rather the improvement in glycemia. A key measure of diastolic cardiac function (septal E:E') improved in the sitagliptin treatment group while a secondary measure of diastolic cardiac function (mitral valve E:A) improved with both sitagliptin and glimepiride treatment. Neither sitagliptin nor glimepiride administration improved cardiorespiratory fitness.

We found that treatment with both sitagliptin and glimepiride decreased fasting glucose. However, while the group that received glimepiride demonstrated a lowering of the HbA1c, this effect was absent with administration of sitagliptin. Adherence was carefully assessed and did not differ between groups. Although it cannot be determined why HbA1c did not decrease in the sitagliptin group, it is possible that the absence of HbA1c change in this group was because participants in this study already had relatively well-controlled T2D.

We have previously shown that potentiating GLP-1 signaling with the DPP4 inhibitor saxagliptin improves vascular function and augments the response to exercise training in a rodent model.[19] While

Table 3
Echocardiography measurements at rest at baseline and post-treatment.

	Placebo		Glimepiride		Sitagliptin	
	Baseline	Post-treatment	Baseline	Post-treatment	Baseline	Post-treatment
Longitudinal strain	−19.3 ± 0.7	−18.5 ± 0.8	−18.2 ± 0.9	−18.4 ± 0.6	−18.2 ± 0.5	−18.8 ± 0.6
MV E:A wave velocity	0.83 ± 0.06	0.82 ± 0.06[*]	0.87 ± 0.07	1.1 ± 0.08[*]	0.91 ± 0.08	1.1 ± 0.11[*]
Septal E'	0.07 ± 0.00	0.07 ± 0.1	0.08 ± 0.01	0.07 ± 0.1[‡]	0.08 ± 0.01	0.09 ± 0.01[‡]
Septal E:E'	10.4 ± 0.8[†]	12.6 ± 1.4[†,*]	8.0 ± 0.7	9.7 ± 0.7[*]	8.1 ± 0.7	7.7 ± 0.5[*]
Lateral E'	0.09 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.10 ± 0.01	0.10 ± 0.01
Lateral E:E'	8.5 ± 0.7	9.4 ± 0.9	7.6 ± 1.0	8.4 ± 1.2	8.1 ± 0.7	6.7 ± 0.6

Data are Mean ± Standard Error. Mitral Valve: MV
[*] $P = 0.02$ Different from baseline.
[‡] $P < 0.05$ Significant interaction of treatment and time.
[†] $P < 0.01$ different from glimepiride and sitagliptin at both time points.

Table 4
Measures of vascular function at baseline and post-treatment.

	Placebo		Glimepiride		Sitagliptin	
	Baseline	Post-treatment	Baseline	Post-treatment	Baseline	Post-treatment
Pulse wave velocity (m/s)	10.5 ± 0.8	11.5 ± 1.1	10.1 ± 1.0	9.8 ± 0.9	11.6 ± 1.1	11.8 ± 1.1
Augmentation index$_{75}$	27.5 ± 2.8	23.8 ± 3.7	22.7 ± 2.0	21.0 ± 2.7	25.2 ± 3.5	23.9 ± 3.0

Data are mean ± standard error.

the effect of saxagliptin on exercise capacity was only present when it was administered in combination with exercise training in rodents, we felt in humans it was necessary to first identify the effect of the pharmacological agent alone before adding exercise training to the study design. We previously addressed this hypothesis using a GLP-1 receptor agonist, exenatide.[22] In adults with T2D, exenatide improved several indices of cardiovascular function as compared with placebo, however, cardiorespiratory fitness did not improve in those participants. One potential explanation for absence of an effect on cardiorespiratory fitness was that endogenous GLP-1 signaling is timed with meals while exenatide administration agonizes GLP-1 receptors continuously, potentially causing receptor down regulation and impaired signaling. In the current study, use of a DPP4 inhibitor, sitagliptin, allowed us to investigate if the endogenous secretion of GLP-1 was necessary to improve cardiorespiratory fitness. The data from the current study, however, do not support the hypothesis that sitagliptin alone is enough to alter cardiorespiratory fitness in humans.

The concept of a pharmacological strategy to improve cardiorespiratory fitness is not novel.[34] We and others have successfully employed a peroxisome proliferator-activated receptor (PPAR) gamma agonist to improve cardiorespiratory fitness in people with T2D.[35,36] These studies provided proof of concept that addressing the physiological barriers to exercise in people with T2D with pharmacology could improve cardiorespiratory fitness. Similarly PPAR delta administration to rodents increases running capacity with[37,38] and without a concomitant exercise training program.[37,39] In addition to PPARs, targeting skeletal muscle energetics through AMPK activation[40] and overexpression of PGC1α and β[41] has also resulted in increased exercise capacity in rodents. The current study, our previous report with a GLP-1 receptor agonist,[22] and other research utilizing the combination of a GLP-1 receptor liraglutide and exercise[42] suggest that targeting GLP-1 may not benefit the cardiovascular system adequately to impact cardiorespiratory fitness.

Importantly, aerobic exercise training engages an integrated response of the cardiovascular system, the skeletal muscle, and fuel metabolism. The biological differences in GLP-1 related pharmacological agents versus PPAR agonists might explain why one strategy has been successful in humans and the other not, in terms of increasing cardiorespiratory fitness. People with T2D have subclinical impairments in cardiovascular function that contribute to lower cardiorespiratory fitness.[5,43,44] We have demonstrated that cardiovascular delivery and distribution of oxygenated blood flow to skeletal muscle limits oxidative flux in T2D. As such, both the cardiovascular system and skeletal muscle may need to be targeted to improve cardiorespiratory fitness.[6,7] GLP-1 agents target the cardiac tissue and the vasculature.[45] GLP-1 administration alone, however, does not provide a perturbation of skeletal muscle metabolism to alter substrate uptake and use, two key factors for increasing aerobic exercise performance. In contrast, PPAR agonists augment whole body insulin sensitivity, and therefore substrate availability, by acting on metabolically important tissues such as the liver, adipose tissue, and skeletal muscle.[46,47] Additionally, PPAR agonists directly impact vascular function in response to insulin[48] augmenting substrate rich blood flow to skeletal muscle. In the context of promoting acute exercise capacity, PPAR agonists up regulate the transport of fatty acids for oxidative metabolism promoting a fuel partitioning pattern that may augment exercise capacity.[39]

Table 5
Measures of in vivo skeletal muscle oxidative flux at baseline and post-treatment.

	Glimepiride ($n = 8$)		Sitagliptin ($n = 7$)	
	Baseline	Post-treatment	Baseline	Post-treatment
Mean force (kg)	26.5 ± 2.3	29.2 ± 2.3†	27.5 ± 1.8	30.7 ± 2.7†
PCr time constant (seconds)	30.9 ± 3.9	29.6 ± 3.6	34.1 ± 7.3	26.6 ± 2.9
VPCr (mmol/s)	0.17 ± 0.03	0.20 ± 0.06	0.12 ± 0.03	0.17 ± 0.03
Qmax (mmol/s)	0.44 ± 0.07	0.45 ± 0.09	0.36 ± 0.07	0.50 ± 0.09
ADP time constant (seconds)	24.5 ± 3.5	21.2 ± 2.9	28.0 ± 5.3	19.4 ± 1.1
OxPhos (mmol/L/s)	0.11 ± 0.02	0.16 ± 0.04	0.09 ± 0.03	0.15 ± 0.05

Data are Mean ± Standard Error.
† $P < 0.01$ different from baseline.

Moving forward, it is important to consider how we frame the goals of research on exercise mimetics, and how we interpret the impact of these agents on systems impacted by T2D in the context of integrative physiology. The limited success of pharmacological exercise mimetics in human trials demonstrates the need to focus on interventions that also include participation in a progressive aerobic exercise training program to increase cardiorespiratory fitness. Therefore, future studies should focus on pharmacological and exercise training combination trials.

The purpose of this study was to determine the impact of sitagliptin on cardiorespiratory fitness in adults with T2D. Determining how a T2D treatment impacts cardiorespiratory fitness is important when considering newly developed therapeutics, as contemporary literature is focused on the potential negative interactions of other antihyperglycemic agents and cardiorespiratory fitness.[49,50] The current study design addressed this question related to sitagliptin and cardiorespiratory fitness, however, additional variables are of interest for future studies. Glimepiride was administered at a submaximal dose (2 mg/day, maximum is 8 mg/day). This dose was chosen to reduce the risk for hypoglycemia in participants because their baseline HbA1c values were <9%. While this dose of glimepiride resulted in significant improvement in HbA1c, it is possible that additional effects on the measurements of the study could have been observed with a greater dose. Additionally, the current investigation was not powered to determine sex-specific responses to sitagliptin. Consideration of sex-specific responses in future experimental designs could provide valuable insight regarding sitagliptin treatment.

In summary, the purpose of this study was to investigate whether targeting GLP-1 signaling in people with T2D would improve cardiorespiratory fitness by augmenting cardiovascular function and skeletal muscle oxidative flux. While sitagliptin administration improved cardiac diastolic function, neither cardiorespiratory fitness nor muscle oxidative capacity improved. We hypothesize that without the additional stress of exercise training, skeletal muscle oxidative flux does not change and cardiorespiratory fitness does not improve. The combination of agents that target GLP-1 signaling with aerobic exercise training is warranted in future studies to permit cardiorespiratory improvements by lowering the T2D associated physiological barriers to exercise.

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initiated the project and edited the manuscript. All authors contributed to the revision of the manuscript for important intellectual content and approved the final version of the manuscript for publication. JGR and JEBR are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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