Published in final edited form as:

J Diabetes Complications. 2019 August ; 33(8): 561–566. doi:10.1016/j.jdiacom.2019.05.002.

Targeting the cardiovascular system with sitagliptin improves diastolic cardiac function but does not improve cardiorespiratory fitness in adults with type 2 diabetes

Rebecca L. Scalzo, PhD^{1,3,5}, Deirdre Rafferty, MS², Irene Schauer, MD, PhD^{1,3,5}, Amy G. Huebschmann, MD, MS^{2,3}, Melanie Cree-Green, MD, PhD^{3,4}, Jane E.B. Reusch, MD^{1,3,5,*}, Judith G. Regensteiner, PhD^{2,3,*}

¹Divisions of Endocrinology, Department of Medicine, University of Colorado School of Medicine

²Divisions of General Internal Medicine, Department of Medicine, University of Colorado School of Medicine

³Divisions of Center for Women's Health Research; Department of Medicine, University of Colorado School of Medicine

⁴Division of Pediatric Endocrinology University of Colorado School of Medicine

⁵Rocky Mountain Regional Veterans Administration Medical Center

Abstract

Background.—People with type 2 diabetes mellitus (T2D) have preclinical cardiac and vascular dysfunction that predicts low cardiorespiratory fitness (CRF). CRF is a powerful predictor of cardiovascular mortality, a primary concern in T2D management. Glucagon-like peptide-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. We 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 100mg/day sitagliptin, 2mg/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 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 the need to incorporate aerobic exercise in the management of T2D to improve CRF and reduce the risk of premature cardiovascular mortality.

Corresponding author and person to who reprint requests should be addressed: Rebecca L. Scalzo, Ph.D., University of Colorado Anschutz Medical Campus, 12801 E 17th Ave, Aurora, CO 80045, Telephone: 303-724-3976, rebecca.scalzo@ucdenver.edu.

*Drs. Reusch and Regensteiner are co-senior authors.

www.clinicaltrials.gov identifier: NCT01364584

Clinical Trials Registration.—www.clinicaltrials.gov NCT01951339

Keywords

glucagon-like peptide-1; cardiovascular diseases; exercise; diabetes mellitus

1. Introduction

People with type 2 diabetes (T2D) have subclinical cardiac and vascular functional impairments. Cardiovascular function is a primary contributor to cardiorespiratory fitness, one of the strongest predictors of risk for premature death from all causes and 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.^{1,5}

Low cardiorespiratory fitness in people with T2D is related to disease-associated physiological barriers including insulin resistance,⁶ impaired vascular function which limits oxygen and nutrient rich blood flow to skeletal muscle,⁷ and impaired skeletal muscle mitochondrial function.⁸ Aerobic exercise training is one way to improve cardiorespiratory fitness, however, people with T2D are commonly sedentary. In addition to low cardiorespiratory fitness, people with T2D also have reduced submaximal exercise capacity during constant workloads accompanied by slowed oxygen uptake kinetics (VO₂ kinetics). Impairments in either cardiorespiratory fitness or submaximal responses to exercise may partly explain our previous findings that submaximal ambulatory activities require a greater relative effort for persons with T2D compared with controls.^{9,10} Pharmacological strategies that target the T2D-specific physiological barriers to exercise may potentially normalize the relative effort of physical activity and permit adaptation necessary to improve cardiorespiratory fitness and health outcomes.

Glucagon-like peptide-1 (GLP-1), an insulin secretagogue, improves glycemic control by lowering circulating glucose concentrations (both fasting and postprandial) and glycated hemoglobin (HbA1c).^{11,12} Independent of the impact on glucose control, GLP-1 may enhance oxygen delivery to skeletal muscle via augmentation of endothelial and cardiac function in T2D.^{11,13,14} Previous investigations of GLP-1 receptor agonists have demonstrated improvement of left ventricular systolic and diastolic function in humans, rodents, and canines.^{11,15–18} 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.^{19,20} In humans, treatment with GLP-1 receptor agonists recruit muscle microvasculature and lowers blood pressure in clinical trials.^{11,21} Thus, GLP-1 positively impacts two key contributors of oxygen delivery to skeletal muscle and potentially the cardiorespiratory fitness impairment observed in patients with T2D. 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 DPP4 inhibitor, would improve vascular function and hence possibly cardiorespiratory fitness in people with T2D.

2. MATERIALS AND METHODS

2.1 Participants

Thirty-eight adults with uncomplicated T2D between the ages of 22 and 70 years were recruited through general advertising and local clinics for this trial ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01951339), NCT01951339). 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 1–2g/day of metformin for at least 3 months and if they demonstrated glycemic control with total HbA1C of less than 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 $\geq$ 2 mg/dl), evidence of heart disease by history, echocardiography, or abnormal resting or exercise electrocardiogram ($\geq$ 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).²² 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 ³¹phosphorus-Magnetic Resonance Spectroscopy (³¹P-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 ($\text{VO}_{2\text{peak}}$). 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 2mg/day glimepiride ($n = 14$) or sitagliptin 100mg/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.²³ Data from these participants was 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-hour fast for the measurement of glucose, insulin, HbA1C, and free fatty acid concentrations. Parameters were assayed according to previously reported methods.⁹ The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as $\text{HOMA-IR} = (\text{glucose (mg/dL)} \times \text{insulin } (\mu\text{U/mL}))/405$ (24).

2.4 ^{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.^{8,25}

The ^{31}P -MRS exercise protocol consisted of measurements during rest for 60 seconds, isometric plantar flexion exercise for 90 seconds at 70% maximal volitional contraction, and recovery for 5 min post-exercise. We selected a 90 second isometric exercise bout as this perturbation has been extensively modeled and utilized for assessing both aerobic and anaerobic processes.²⁶ 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 seconds 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^{27,28} utilizing AMARES (A Method of Accurate, Robust and Efficient Spectral fitting), a nonlinear least-square-fitting algorithm using previously built prior knowledge files.²⁹ 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.^{30,31} Calculations included the rates of oxidative phosphorylation (OxPhos) following exercise, creatine kinase reaction, initial PCr synthesis (VPcr), maximal mitochondrial function (Q_{max}) and anaerobic glycolysis (AnGly). ADP, PCr and Pi time constants were calculated via regression analyses with Sigmaplot (Systat Software, Inc, San Jose, CA, USA).

2.5 Graded Exercise Test

$\text{VO}_{2\text{peak}}$ was determined via graded exercise to exhaustion as previously described^{9,32} 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/minute increments (depending on age and sex) in order to allow each participant to reach maximum effort within 7–12 minutes. Peak VO_2 was confirmed by a respiratory exchange ratio (RER) greater than 1.1. During incremental exercise testing, the highest VO_2 and heart rate averaged over 20 seconds were defined as the maximum values.

2.6 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.^{4,9} During each transition, data were collected during two minutes of rest, then four minutes of pedaling with no resistance, and six minutes at 85% of anaerobic threshold. Transitions were separated by a minimum of 10 minutes of rest.

2.7 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.⁹ The data for each exercise transition were time interpolated to 1-second 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

2.8 Cardiac Echocardiography

Standard two dimensional and Doppler echocardiography³³ (GE Vivid 7 Dimension, Milwaukee, WI, USA) were performed using standard methods at rest by an ultrasonographer expert in these methods. A cardiologist blinded to the treatment allocation of the participants supervised the acquisition of these echocardiographic data, as well as performed all of the measurements and interpretation. Participants were examined in the left lateral decubitus position using standard parasternal, short-axis, 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. Circumferential and longitudinal strain were recorded as measures of systolic function while mitral valve E and A waves, and lateral and septal E wave (E') were assessments of diastolic function.

2.9 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.^{34,35} Measurements were made after a four-hour fast and prior to any other exercise testing performed in the same study visit.

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 $\pm$ 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 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%; $P = 0.6$).

3.3 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 ($P = 0.6$).

3.5 $\text{VO}_{2\text{peak}}$ and VO_2 kinetics

The placebo group started with lower relative and absolute $\text{VO}_{2\text{peak}}$ compared with the treatment groups ($P = 0.04$ and $P = 0.01$ respectively; Table 2). $\text{VO}_{2\text{peak}}$ 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 ($P > 0.2$).

3.6 Cardiac Function

Table 3 contains echocardiography variables measured at baseline and following three months of placebo/glimepiride/sitagliptin administration. Baseline differences in mitral valve A wave and septal E:E' were present in the placebo group compared with glimepiride and sitagliptin groups ($P < 0.01$). Mitral valve E wave increased in all participants during the three month placebo/treatment time ($P = 0.02$) and mitral valve A wave decreased in participants treated with both glimepiride and sitagliptin compared with the participants that received placebo ($P = 0.006$). The mitral valve E:A ratio increased in all participants from baseline ($P = 0.02$). Mitral valve deceleration time was not affected by time or treatment group ($P > 0.09$). Septal E wave did not change in the placebo group, however, it decreased

in the glimepiride treated participants while increasing in the sitagliptin treated participants ($P = 0.05$). Septal E:E' increased from baseline ($P = 0.02$), however this change appears to be driven by the increases in the placebo and glimepiride groups as this measure decreased in the sitagliptin ($P = 0.1$ for the time $\times$ treatment interaction). Lateral E' and E:E' were not affected by time or treatment group ($P > 0.1$). Measures of systolic function: longitudinal strain and stroke volume were not affected by time or treatment ($P > 0.03$).

3.7 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 ($P > 0.2$).

3.8 In vivo Skeletal Muscle 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 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 cardiovascular function and thereby increase cardiorespiratory fitness. We used both a placebo control and a 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. Treatment with both sitagliptin and glimepiride decreased fasting glucose. The group that received glimepiride also demonstrated a lowering of the HbA1c, however, this effect was absent with administration of sitagliptin. 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 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.²⁰ While the effect with saxagliptin on exercise capacity was only present when it was administered in combination with exercise training, we felt in humans it was necessary to first identify the effect of the pharmacological agent with activities of daily living before adding exercise training to the model. We previously addressed this hypothesis using a GLP-1 receptor agonist, exenatide.²³ 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. 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 integrative physiology, and therefore cardiorespiratory fitness, in humans.

The concept of a pharmacological strategy to improve cardiorespiratory fitness is not novel.³⁶ We and others have successfully employed a peroxisome proliferator-activated receptor (PPAR) gamma agonist to improve cardiorespiratory fitness in people with T2D.^{37,38} 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^{39,40} and without a concomitant exercise training program.^{39,41} In addition to PPARs, targeting skeletal muscle energetics through AMPK activation⁴² and overexpression of PGC1 α and β ⁴³ has also resulted in increased exercise capacity in rodents. This current study, our previous report with a GLP-1 receptor agonist, and other work with the combination of a GLP-1 receptor liraglutide and exercise⁴⁴ suggest that targeting GLP-1 may not benefit the cardiovascular system adequately to impact cardiorespiratory fitness.

The biological differences in GLP-1 related pharmacological agents versus PPAR agonists might explain why one strategy has been successful and the other not. The impact of GLP-1 related agents with regard to improving cardiorespiratory fitness is limited to cardiac tissue and the vasculature.⁴⁵ Targeting these systems is important in the context of T2D because the diabetes-associated impairments in the cardiovascular system limit oxygenated blood flow to skeletal muscle thereby attenuating oxidative flux, and the diabetes-associated limitation in cardiovascular function has been shown to be related to lower cardiorespiratory fitness.^{6,46,47} Targeting GLP-1 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 target whole body insulin sensitivity, and therefore substrate availability, by acting on metabolically important tissues such as the liver, adipose tissue, and skeletal muscle.^{48,49} Additionally, PPAR agonists directly impact vascular function in response to insulin⁵⁰ augmenting substrate rich blood flow to skeletal muscle. In the context of promoting acute exercise capacity, PPAR agonists upregulate the transport of fatty acids for oxidative metabolism promoting a fuel partitioning pattern that may augment exercise capacity.⁴¹

Moving forward, it is important how we frame the goals of research on exercise mimetics, and how we consider the impact of these agents on systems impacted by diabetes 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. Diabetes-specific physiological barriers to exercise such as insulin resistance,⁶ subclinical impairments in vascular function which limits oxygen and nutrient rich blood flow to skeletal muscle,⁷ and impaired skeletal muscle mitochondrial function⁸ make adoption of regular, progressive exercise difficult. The T2D associated physiological barriers to exercise result in lower maximal and submaximal exercise responses compared

with healthy individuals; this attenuation of maximal and submaximal exercise responses is coupled with a greater relative effort for persons with T2D when attempting to meet recommendations for exercise.^{9,10} If a medication can make it easier for a person to exercise, a major barrier to exercise will be removed and regular exercise may become more feasible for those with T2D. Accomplishing this objective could normalize the greater perceived exertion during submaximal exercise experienced by people with T2D, which might increase compliance to exercise prescriptions in this population, augment cardiorespiratory fitness, and ultimately lower premature mortality risk in people with T2D.

The purpose of this study was to determine the impact of sitagliptin on cardiorespiratory fitness in adults with T2D. The study design addressed this question, however, additional variables are of interest for future studies. Specifically, the impact of sitagliptin and other antihyperglycemic agents on the deterioration of cardiorespiratory fitness with age and T2D duration is an important consideration. Here we focused on the potential of sitagliptin to improve cardiorespiratory fitness; determining if a T2D treatment negatively impacts cardiorespiratory fitness is important when considering newly developed therapeutics. 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, targeting GLP-1 signaling in people with T2D modestly improves cardiac diastolic function. However, without the additional stress of exercise training, skeletal muscle oxidative flux does not change and cardiorespiratory does not improve. The combination of agents that target GLP-1 signaling with exercise training is warranted in future studies to permit cardiorespiratory improvements by lowering the T2D associated physiological barriers to exercise. The impact of antihyperglycemic agents on the deterioration of cardiorespiratory with age and DM duration is also needed.

ACKNOWLEDGEMENTS

JGR, JEER, AGH, DR, and IS conducted the study. DR collected data. RLS and MCG analyzed data. RLS wrote the manuscript. JEER and JGR 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 JEER 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.

We would like to thank the participants in the study who played such an important role. We thank Ian Leavitt, MS and Katie Rogers, MS (Department of Medicine, University of Colorado School of Medicine, Division of General Internal Medicine) for their role in helping to finalize the data analysis. Merck supported this investigator-initiated study. Other sources of funding for this study were provided by NIH-K23HL118133 (AGH), NIH-5T32HL007171 (RLS), VA Merit, Denver Research Institute, CCTSI-UL1RR025780 (JEER, JGR), ADA 1-12-CT-64 (JGR), the Center for Women's Health Research (JGR, JEER) and the Armstrong Foundation (JGR, JEER). Institution: NIH/NCATS Colorado CTSA UL1 TR002535, Research Magnet NIH 1S10OD018435.

REFERENCES:

1. Imboden MT, Harber MP, Whaley MH, Finch WH, Bishop DL, Kaminsky LA. Cardiorespiratory Fitness and Mortality in Healthy Men and Women. *J Am Coll Cardiol* 2018;72:2283–2292. [PubMed: 30384883]

2. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. *Ann Intern Med* 2000;132:605–611. [PubMed: 10766678]
3. Regensteiner JG, Bauer TA, Huebschmann AG, et al. Sex differences in the effects of type 2 diabetes on exercise performance. *Medicine & Science in Sports & Exercise* 2015;47:58–65. [PubMed: 24811327]
4. Bauer TA, Reusch JEB, Levi M, Regensteiner JG. Skeletal Muscle Deoxygenation After the Onset of Moderate Exercise Suggests Slowed Microvascular Blood Flow Kinetics in Type 2 Diabetes. *Diabetes Care* 2007;30:2880–2885. [PubMed: 17675540]
5. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN. Low Cardiorespiratory Fitness and Physical Inactivity as Predictors of Mortality in Men with Type 2 Diabetes. *Ann Intern Med* 2000;132:605. [PubMed: 10766678]
6. Nadeau KJ, Zeitler PS, Bauer TA, et al. Insulin Resistance in Adolescents with Type 2 Diabetes Is Associated with Impaired Exercise Capacity. *J. Clin. Endocrinol. Metab* 2009;94:3687–3695. [PubMed: 19584191]
7. Mason McClatchey P, Bauer TA, Regensteiner JG, Schauer IE, Huebschmann AG, Reusch JEB. Dissociation of local and global skeletal muscle oxygen transport metrics in type 2 diabetes. *J. Diabetes Complicat* 2017;31:1311–1317. [PubMed: 28571935]
8. Cree Green M, Scalzo RL, Harrall K, et al. Supplemental Oxygen Improves In Vivo Mitochondrial Oxidative Phosphorylation Flux in Sedentary Obese Adults With Type 2 Diabetes. *Diabetes* 2018;67:1369–1379. [PubMed: 29643061]
9. Regensteiner JG, Bauer TA, Reusch JE, et al. Abnormal oxygen uptake kinetic responses in women with type II diabetes mellitus. *J. Appl. Physiol* 1998;85:310–317. [PubMed: 9655791]
10. Huebschmann AG, Kohrt WM, Herlache L, et al. Type 2 diabetes exaggerates exercise effort and impairs exercise performance in older women. *BMJ Open Diabetes Res Care* 2015;3:e000124.
11. Mafong DD, Henry RR. The role of incretins in cardiovascular control. *Curr. Hypertens. Rep* 2009;11:18–22. [PubMed: 19146796]
12. Monami M, Marchionni N, Mannucci E. Glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized clinical trials. *European Journal of Endocrinology* 2009;160:909–917. [PubMed: 19318378]
13. Ceriello A, Davidson J, Hanefeld M, et al. Postprandial hyperglycaemia and cardiovascular complications of diabetes: an update. *Nutr Metab Cardiovasc Dis* 2006;16:453–456. [PubMed: 16934443]
14. Koska J, Sands M, Burciu C, et al. Exenatide Protects Against Glucose- and Lipid-Induced Endothelial Dysfunction: Evidence for Direct Vasodilation Effect of GLP-1 Receptor Agonists in Humans. *Diabetes* 2015;64:2624–2635. [PubMed: 25720388]
15. Luque M Glucagon-like peptide-1 (GLP-1) and glucose metabolism in human myocytes. *J. Endocrinol* 2002;173:465–473. [PubMed: 12065236]
16. Nikolaidis LA. Active metabolite of GLP-1 mediates myocardial glucose uptake and improves left ventricular performance in conscious dogs with dilated cardiomyopathy. *Am J Physiol Heart Circ Physiol* 2005;289:H2401–H2408. [PubMed: 16024574]
17. Sokos GG, Bolukoglu H, German J, et al. Effect of glucagon-like peptide-1 (GLP-1) on glycemic control and left ventricular function in patients undergoing coronary artery bypass grafting. *Am. J. Cardiol* 2007;100:824–829. [PubMed: 17719327]
18. Zhao T, Parikh P, Bhashyam S, et al. Direct effects of glucagon-like peptide-1 on myocardial contractility and glucose uptake in normal and postischemic isolated rat hearts. *J. Pharmacol. Exp. Ther* 2006;317:1106–1113. [PubMed: 16489128]
19. Nyström T The potential beneficial role of glucagon-like peptide-1 in endothelial dysfunction and heart failure associated with insulin resistance. *Horm. Metab. Res* 2008;40:593–606. [PubMed: 18792870]
20. Keller AC, Knaub LA, Miller MW, Birdsey N, Klemm DJ, Reusch JE. Saxagliptin restores vascular mitochondrial exercise response in diabetes. *J Cardiovasc Pharmacol* 2015;65:137–147. [PubMed: 25264749]

21. Chai W, Zhang X, Barrett EJ, Liu Z. Glucagon-Like Peptide 1 Recruits Muscle Microvasculature and Improves Insulin's Metabolic Action in the Presence of Insulin Resistance. *Diabetes* 2014;63:2788–2799. [PubMed: 24658303]
22. Sallis JF, Haskell WL, Wood PD, et al. Physical activity assessment methodology in the Five-City Project. *Am. J. Epidemiol* 1985;121:91–106. [PubMed: 3964995]
23. Scalzo RL, Moreau KL, Ozemek C, et al. Exenatide improves diastolic function and attenuates arterial stiffness but does not alter exercise capacity in individuals with type 2 diabetes. *J. Diabetes Complicat* 2017;31:449–455. [PubMed: 27884660]
24. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–419. [PubMed: 3899825]
25. Cree Green M, Newcomer BR, Brown M, et al. Method for controlled mitochondrial perturbation during phosphorus MRS in children. *Medicine & Science in Sports & Exercise* 2014;46:2030–2036. [PubMed: 24576856]
26. Sirikul B, Hunter GR, Larson-Meyer DE, Desmond R, Newcomer BR. Relationship between metabolic function and skeletal muscle fatigue during a 90 s maximal isometric contraction. *Appl Physiol Nutr Metab* 2007;32:394–399. [PubMed: 17510673]
27. Klose U In vivo proton spectroscopy in presence of eddy currents. *Magn Reson Med* 1990;14:26–30. [PubMed: 2161984]
28. van den Boogaart A MRUI MANUAL V. 96.3. A user's guide to the Magnetic Resonance User Interface Software Package Delft Technical University Press, Delft; 1997.
29. Rico-Sanz J, Thomas EL, Jenkinson G, Mierisová S, Iles R, Bell JD. Diversity in levels of intracellular total creatine and triglycerides in human skeletal muscles observed by (1)H-MRS. *J. Appl. Physiol* 1999;87:2068–2072. [PubMed: 10601151]
30. Cree Green M, Gupta A, Coe GV, et al. Insulin resistance in type 2 diabetes youth relates to serum free fatty acids and muscle mitochondrial dysfunction. *J. Diabetes Complicat* 2017;31:141–148. [PubMed: 27839922]
31. Newcomer BR, Boska MD. Adenosine triphosphate production rates, metabolic economy calculations, pH, phosphomonoesters, phosphodiesteres, and force output during short-duration maximal isometric plantar flexion exercises and repeated maximal isometric plantar flexion exercises. *Muscle Nerve* 1997;20:336–346. [PubMed: 9052813]
32. Brandenburg SL, Reusch JE, Bauer TA, Jeffers BW, Hiatt WR, Regensteiner JG. Effects of exercise training on oxygen uptake kinetic responses in women with type 2 diabetes. *Diabetes Care* 1999;22:1640–1646. [PubMed: 10526728]
33. Henry WL, DeMaria A, Gramiak R, et al. Report of the American Society of Echocardiography Committee on Nomenclature and Standards in Two-dimensional Echocardiography. *Circulation* 1980;62:212–217. [PubMed: 7397962]
34. Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. *Hypertension* 2009;54:1328–1336. [PubMed: 19884567]
35. Wilkinson IB, Fuchs SA, Jansen IM, et al. Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *J. Hypertens* 1998;16:2079–2084. [PubMed: 9886900]
36. Goodyear LJ. The Exercise Pill — Too Good to Be True? | NEJM. *N. Engl. J. Med* 2008;359:1842–1844. [PubMed: 18946072]
37. Regensteiner JG, Bauer TA, Reusch JEB. Rosiglitazone improves exercise capacity in individuals with type 2 diabetes. *Diabetes Care* 2005;28:2877–2883. [PubMed: 16306548]
38. Kadoglou NPE, Iliadis F, Angelopoulou N, Perrea D, Liapis CD, Alevizos M. Beneficial effects of rosiglitazone on novel cardiovascular risk factors in patients with Type 2 diabetes mellitus. *Diabet. Med* 2008;25:333–340. [PubMed: 18307460]
39. Chen W, Gao R, Xie X, et al. A metabolomic study of the PPAR δ agonist GW501516 for enhancing running endurance in Kunming mice. *Scientific Reports* 2015;5:9884. [PubMed: 25943561]

40. Manio MCC, Inoue K, Fujitani M, Matsumura S, Fushiki T. Combined pharmacological activation of AMPK and PPAR δ potentiates the effects of exercise in trained mice. *Physiol Rep* 2016;4.
41. Fan W, Waizenegger W, Lin CS, et al. PPAR δ Promotes Running Endurance by Preserving Glucose. *Cell Metab* 2017;25:1186–1193.e4. [PubMed: 28467934]
42. Marcinko K, Bujak AL, Lally JSV, et al. The AMPK activator R419 improves exercise capacity and skeletal muscle insulin sensitivity in obese mice. *Mol Metab* 2015;4:643–651. [PubMed: 26413470]
43. Tadaishi M, Miura S, Kai Y, Kano Y, Oishi Y, Ezaki O. Skeletal muscle-specific expression of PGC-1 α -b, an exercise-responsive isoform, increases exercise capacity and peak oxygen uptake. *PLoS ONE* 2011;6:e28290. [PubMed: 22174785]
44. Mensberg P, Nyby S, Jørgensen PG, et al. Near-normalization of glycaemic control with glucagon-like peptide-1 receptor agonist treatment combined with exercise in patients with type 2 diabetes. *Diabetes Obes Metab* 2016;19:172–180. [PubMed: 27717126]
45. Drucker DJ. The Ascending GLP-1 Road From Clinical Safety to Reduction of Cardiovascular Complications. *Diabetes* 2018;67:1710–1719. [PubMed: 30135132]
46. Regensteiner JG, Bauer TA, Reusch JEB, et al. Cardiac Dysfunction during Exercise in Uncomplicated Type 2 Diabetes. *Medicine & Science in Sports & Exercise* 2009;41:977–984. [PubMed: 19346991]
47. Bjornstad P, Truong U, Dorosz JL, et al. Cardiopulmonary Dysfunction and Adiponectin in Adolescents With Type 2 Diabetes. *J Am Heart Assoc* 2016;5:e002804. [PubMed: 26994128]
48. Loviscach M, Rehman N, Carter L, et al. Distribution of peroxisome proliferator-activated receptors (PPARs) in human skeletal muscle and adipose tissue: relation to insulin action. *Diabetologia* 2000;43:304–311. [PubMed: 10768091]
49. Kersten S, Stienstra R. The role and regulation of the peroxisome proliferator activated receptor alpha in human liver. *Biochimie* 2017;136:75–84. [PubMed: 28077274]
50. Zhang Y, Zhan R-X, Chen J-Q, et al. Pharmacological activation of PPAR gamma ameliorates vascular endothelial insulin resistance via a non-canonical PPAR gamma-dependent nuclear factor-kappa B trans-repression pathway. *European Journal of Pharmacology* 2015;754:41–51. [PubMed: 25687252]

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

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
Stroke Volume (mL/beat)	81.0 ± 6.1	80.7 ± 6.2	72.7 ± 6.1	77.8 ± 6.7	58.2 ± 5.5	64.6 ± 11.9
MV E Wave Velocity	0.74 ± 0.06	0.78 ± 0.06 [*]	0.59 ± 0.03	0.66 ± 0.04 [*]	0.59 ± 0.05	0.65 ± 0.05 [*]
MV A Wave Velocity	0.85 ± 0.04 [†]	0.91 ± 0.04 [†]	0.93 ± 0.07	0.67 ± 0.05 [‡]	0.95 ± 0.05	0.61 ± 0.03 [‡]
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 [*]
MV Deceleration Time (msec)	283 ± 13	240 ± 15	220 ± 18	222 ± 16	215 ± 18	207 ± 16
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/sec)	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.

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/sec)	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.