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Effects of glucose-lowering agents on cardiorespiratory fitness

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Abstract

Exercise therapy is essential for the management of type 2 diabetes (T2D). However, patients with T2D show lower physical activity and reduced cardiorespiratory fitness than healthy individuals. It would be ideal for

clinicians to co-prescribe glucose-lowering agents that improve cardiorespiratory fitness or exercise capacity in conjunction with exercise therapy. Metformin does not improve cardiorespiratory fitness and may attenuate any beneficial effect of exercise in patients with T2D. In contrast, thiazolidinediones appear to improve cardiorespiratory fitness in patients with T2D. Although evidence is limited, sodium-glucose cotransporter 2 (SGLT2) inhibitors may improve cardiorespiratory fitness in patients with heart failure, and the effect of glucagon-like peptide-1 (GLP-1) receptor agonists on cardiorespiratory fitness is controversial. Recent clinical trials have shown that both SGLT2 inhibitors and GLP-1 receptor agonists exert a favorable effect on cardiovascular disease. It becomes more important to choose drugs that have beneficial effects on the cardiovascular system beyond glucose-lowering effects. Further studies are warranted to determine an ideal glucose-lowering agent combined with exercise therapy for the treatment of T2D.

Key words: Type 2 diabetes; Glucagon-like peptide 1 receptor agonist; Cardiorespiratory fitness; Exercise capacity; Metformin; Thiazolidinedione; Sodium-glucose cotransporter 2 inhibitors

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Core tip: What is the most effective combination of drugs and exercise for the treatment of type 2 diabetes? It has become increasingly important for clinicians to prescribe drugs that reduce cardiovascular disease and mortality in addition to their glucose-lowering effects. This review summarized the current literature investigating the effect of glucose-lowering agents on cardiorespiratory fitness. Thiazolidinediones, sodium-glucose cotransporter 2 inhibitors, and glucagon-like peptide-1 receptor agonists have the potential to improve cardiorespiratory fitness; however, further research will be needed to confirm.

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INTRODUCTION

More than 400 million people worldwide suffer from diabetes. Diabetes can lead to microvascular and macrovascular complications and increase the physical and psychological burden in patients^[1]. Nutrition and exercise therapy are essential for the management of diabetes, and patients with type 1 and 2 diabetes are recommended to engage in regular moderate-to-vigorous intensity aerobic exercise and resistance training^[2]. In addition, higher levels of physical activity are associated with reduced risk of breast cancer (14%), colon cancer (21%), ischemic heart disease (25%), and stroke (26%)^[3]. Exercise is a standard component of chronic disease prevention and management^[4]. However, patients with diabetes typically exhibit lower energy expenditure, physical activity duration^[5], skeletal muscle mass^[6], and cardiorespiratory fitness^[7], and it can be challenging to effectively and safely incorporate exercise therapy in diabetes patients also presenting with vascular complications and comorbidities. Combined diet and exercise therapy is effective against diabetes; however, in more severe cases, drugs are usually required to intensively improve glycemic control. There are currently nine different groups of glucose-lowering agents available: metformin, thiazolidinediones, sulfonylureas, glinides, α -glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and insulin. Of these, metformin^[8], SGLT2 inhibitors^[9,10], and a GLP-1 receptor agonists^[11] have beneficial effects on cardiovascular disease (CVD) as well as glycemic control, making these the drugs of choice for type 2 diabetes (T2D) treatment^[12].

Exercise is important in the primary and secondary prevention of CVD^[13] and, thus, should be an integral part of the strategy to reduce CVD risk. Individuals with low cardiorespiratory fitness (< 7.9 metabolic equivalent; MET) have a 1.70-fold and 1.56-fold increased risk of all-cause mortality and cardiovascular events, respectively, compared with those with high cardiorespiratory fitness (≥ 10.8 MET)^[14]. Ideally, clinicians should preferably prescribe drugs that improve cardiorespiratory fitness. However, the optimal combination of exercise and glucose-lowering agents remains unclear as the effects of glucose-lowering agents on exercise capacity/cardiorespiratory fitness are not well understood.

This review summarizes the current literature regarding the effects of glucose-lowering agents on cardio-

respiratory fitness in humans and aims to highlight the optimum drug selection in the treatment of patients with diabetes who engage in regular exercise.

METFORMIN AND CARDIORESPIRATORY FITNESS

Metformin is the most widely used oral glucose-lowering drug with known beneficial effects on macrovascular complications in T2D^[15]. While the mechanisms of action of metformin remain unclear, it is known to activate the cellular energy sensor, AMP-activated protein kinase (AMPK), suppress proinflammatory cytokine secretion, inhibit hepatic gluconeogenesis and lipogenesis, and stimulate GLP-1 secretion by modulating the gut microbiota^[16]. Metformin is a complex drug with multiple mechanisms of action. While it is the first-line medication recommended by the American Diabetes Association and the European Association of the Study of Diabetes^[17], clinicians usually also co-prescribe metformin with exercise therapy. It is important to understand whether metformin affects cardiorespiratory fitness/exercise capacity, and the interaction between metformin and exercise has been well studied^[18-25].

Johnson *et al*^[18] examined the acute effects of metformin on maximal oxygen consumption (VO_{2max}) during exercise. A cycle ergometer was used for graded maximal exercise tests. Participants cycled at 75–80 rpm with a resistance of 2.0 kp, which was increased by 0.5 kp every 3 min until volitional exhaustion. A single dose (1000 mg) of metformin increased mean VO_2 (2.9 ± 0.5 L/min vs 2.8 ± 0.5 L/min) during exercise but not VO_{2max} (4.00 ± 0.58 L/min vs 4.00 ± 0.66 L/min). Braun *et al*^[19] investigated the effect of metformin on aerobic capacity in healthy individuals. Peak aerobic capacity (VO_{2peak}) was measured 7–9 d after administration of either metformin or placebo. An incremental exercise test began using a cycle ergometer at 50–150 W or a treadmill at 6.4–9.6 km/h. The cycle resistance (+25–50 W) and treadmill grade (+2%) were increased every 2 min until exhaustion. The initial dose of metformin was 500 mg/d, which was increased every second day to a maximum of 2000 mg/d. Metformin treatment reduced VO_{2peak} (3.53 ± 0.29 L/min vs 3.63 ± 0.9 L/min for metformin and placebo, respectively; -2.7%), and there was no significant association between the decrease in VO_{2peak} and baseline cardiorespiratory fitness. Although the effect was physiologically subtle, short-term treatment with metformin had a negative effect on cardiorespiratory fitness. The same authors also examined the effect of metformin on fat oxidation during and after exercise^[20]. Fat oxidation, which was calculated from respiratory gas composition (volume of oxygen consumption (VO_2) and volume of carbon dioxide production (VCO_2)), was higher with metformin compared with placebo treatment during exercise but lower during recovery. In contrast, metformin increased carbohydrate

Table 1 Effects of metformin on cardiorespiratory fitness in healthy individuals

Ref.	Study design	Subjects	Metformin dose and intervention	Results
Johnson <i>et al</i> ^[18] , 2008	Randomized, double-blind, placebo-controlled, crossover study	11 healthy and active men Age: 29.9 ± 3.7 yr Sex: All men BMI: 25.2 ± 2.8 kg/m ²	1000 mg/d Cycle ergometer at the mean intensity of 69 ± 5.5% of VO _{2max}	VO _{2max} →, ventilator threshold→, maximal heart rate→, time to fatigue→ Lactate↓, blood glucose concentrations↓
Braun <i>et al</i> ^[19] , 2008	Non-randomized, placebo-controlled study	18 healthy subjects Age: 27.9 ± 3.3 yr Sex: 11 men and 7 women BMI: 24.1 ± 3.6 kg/m ²	2000 mg/d Treadmill or cycle ergometer	VO _{2peak} ↓, peak heart rate↓, peak ventilation↓, peak respiratory exchange ratio↓, exercise duration↓ Rating of perceived exertion→
Malin <i>et al</i> ^[20] , 2010	Non-randomized, double-blind, counterbalanced crossover study	15 healthy and active subjects Age: 25 ± 4.4 yr Sex: 7 men and 8 women BMI: 22.8 ± 2.7 kg/m ²	2000 mg/d Cycle exercise at 5 submaximal cycle workloads	VO ₂ → During exercise: Fat oxidation↑ Postexercise: Fat oxidation↓
Learsi <i>et al</i> ^[21] , 2015	Randomized, placebo-controlled, counterbalanced study	10 healthy men Age: 23.5 ± 3.6 yr Sex: All men BMI: No description (height: 170.4 ± 4.8 cm, weight: 66.4 ± 6.5 kg)	500 mg/d Cycle ergometer: An incremental test, 6 submaximal workload test at 40%–90% VO _{2max} , 2 supramaximal tests at 110% VO _{2max}	VO ₂ →, maximal accumulated oxygen deficit→, lactate concentrations→ Time to exhaustion↑, VO ₂ recovery↑

BMI: Body mass index; VO₂: Oxygen consumption.

oxidation after exercise. Oxygen consumption was not different at rest or during exercise with metformin. Therefore, metformin may increase the rate of fat oxidation during exercise *via* activation of AMPK, but appears to have no effect on cardiorespiratory fitness. Learsi *et al*^[21] examined the effect of metformin on high-intensity, short-duration exercise on anaerobic capacity. Exercise tests comprised a maximal incremental test to evaluate VO_{2 max}, six workload tests with submaximal intensities (40%–90% of maximal power output), and two supramaximal intensity tests (110% of maximal power output). Participants took low-dose metformin (500 mg) or placebo prior to the supramaximal test. Time to exhaustion was improved with metformin (191 ± 33 s vs 167 ± 32 s for metformin and placebo, respectively), but VO₂ during the supramaximal test was not different between the groups. Maximum O₂ deficit and lactate concentrations did not differ between the groups. The authors concluded that metformin improves exercise performance by mediating the alactic anaerobic system. Table 1 summarizes the effects of metformin on cardiorespiratory fitness in healthy individuals. However, what is known about the interaction between metformin and cardiorespiratory fitness in patients with T2D or insulin resistance? A noteworthy study by Boulé *et al*^[22] investigated the interaction between metformin and exercise on the hormonal response to a standardized meal. The authors studied 10 patients with mild T2D who took metformin or placebo for 28 d, and measured exercise capacity, glucose, lactate, non-esterified fatty acids, insulin, and glucagon levels on the last two days. Resistance and aerobic exercise tests were conducted

using an isokinetic dynamometer and treadmill. After performing resistance exercise (leg extensions and flexions), the patients started three bouts of aerobic exercise comprising walking at 3.5 km/h with 0% gradient for 15 min, then increasing the speed and gradient until just below the ventilatory threshold, followed by walking at an intensity above the ventilator threshold for 5 min. The mean respiratory exchange ratio (0.96 ± 0.02 vs 0.98 ± 0.02) was lower, and the mean heart rate (124 ± 9 vs 118 ± 8 beats per min) was higher in the metformin group. Mean VO₂ was not affected. As expected, metformin improved glycemic response but glycemic response was attenuated in combination with exercise. In addition, glucagon levels were highest in the metformin plus exercise group. It is surprising that exercise has an opposing effect on the glucose-lowering effect of metformin. High-intensity exercise increases insulin counterregulatory hormones, such as epinephrine, norepinephrine, cortisol, and growth hormone, as well as glucagon, which may further deteriorate glucose response in T2D. Boulé *et al*^[23] also investigated the long-term effects of metformin on glycemic control and physical fitness in participants in the Diabetes Aerobic and Resistance Exercise trial^[26]. Subjects were randomly assigned to four groups, namely, aerobic exercise, resistance training, combined aerobic exercise and resistance training, and control. The exercise group performed progressive aerobic exercise, increasing to an intensity of 75% of maximum heart rate for 45 min. Resistance training included seven exercises: abdominal crunches, seated row, seated biceps curls, supine bench presses, leg presses,

Table 2 Effects of metformin on cardiorespiratory fitness in patients with type 2 diabetes and metabolic syndrome

Ref.	Study design	Subjects	Metformin dose and intervention	Results
Boulé <i>et al</i> ^[22] , 2011	Randomized, placebo-controlled, crossover study	10 patients with type 2 diabetes Age: 58 ± 6 yr Sex: 8 men and 2 women BMI: 28.6 ± 5.3 kg/m ² HbA1c: 6.5 ± 0.6%	2000 mg/d Exercise mode: Treadmill at three different submaximal intensities Study duration: 22 wk	VO ₂ →, respiratory exchange ratio↓ Heart rate↑, lactate↑, rating of perceived exertion↑
Boulé <i>et al</i> ^[23] , 2013	Randomized controlled trial (Diabetes Aerobic and Resistance Exercise) trial	251 patients with type 2 diabetes (143 patients treated with metformin and 82 patients treated without metformin) Age: 54.9 ± 7.1 yr vs 53.1 ± 6.9 yr Sex (Men/Women): 100/43 vs 46/36 BMI: 33.3 ± 5.5 kg/m ² vs 33.3 ± 6.4 kg/m ² HbA1c: 7.78 ± 0.9% vs 7.47 ± 0.77%	Approximately 1600 mg/d Exercise mode: Aerobic training, resistance training, and combined aerobic and resistance training Study duration: 4 wk	VO _{2peak} →
Cadeddu <i>et al</i> ^[25] , 2014	Non-randomized, non-controlled trial	75 patients with insulin resistance Age: 46.2 ± 11 yr Sex: 35 men and 40 women BMI: 29.8 ± 4.1 kg/m ²	1000 mg/d 30–50 min of cycle exercise at the intensity of 60%–80% of the heart rate reserve Study duration: 12 wk	VO _{2peak} →
Paul <i>et al</i> ^[26] , 2017	Prospective observational study	15 patients with metabolic syndrome Age: No description Sex: No description BMI: No description (weight: 75.4 ± 12.08 kg)	1000 mg/d No intervention Study duration: 6 wk	VO _{2max} ↓

BMI: Body mass index; HbA1c: Hemoglobin A1c; VO₂: Oxygen consumption.

shoulder presses, and leg extensions. VO_{2peak} increased in the aerobic group by 0.16 L/min and in the combined exercise group by 0.11 L/min without metformin. However, VO_{2peak} did not change in any of the metformin groups. In the aerobic exercise group, HbA1c levels were reduced with metformin. In the combined exercise group, fasting glucose levels decreased with metformin. There were no significant differences in changes in HbA1c and glucose levels with or without metformin. The study concluded that metformin did not impair physical fitness or glycemic control when combined with exercise. The findings of this study are inconsistent with previous short-term studies that have shown that the addition of exercise to metformin showed a negative effect on cardiorespiratory fitness and glycemia. The authors speculated that difference in the characteristics of the study participants, such as duration of metformin treatment and glycemic control at baseline, may explain this discrepancy.

Two clinical studies have investigated metformin and cardiorespiratory fitness in individuals with insulin resistance and metabolic syndrome. Cadeddu *et al*^[25] investigated the effect of metformin, exercise alone, or a combination of metformin and exercise on exercise capacity. Study participants had impaired glucose tolerance and/or impaired fasting glucose and were allocated to one of the three groups. The exercise program comprised 30–50 min cycle ergometry with an intensity of 60%–80% of heart rate reserve based on the age of the subjects. After a 12-wk intervention, the exercise only group had improved VO_{2peak}, whereas

the metformin plus exercise therapy group did not. Moreover, metformin plus exercise therapy did not show an improved aerobic threshold compared with the exercise along group. The combination of metformin and exercise was not superior to exercise alone with regard to cardiorespiratory fitness. A recent study in India showed a negative effect of metformin on exercise capacity in patients with newly diagnosed metabolic syndrome^[25]. This study was a simple observational study to evaluate changes in VO₂, ventilatory anaerobic threshold, and other indicators of cardiorespiratory fitness in response to metformin treatment for 6 wk, and showed that VO_{2max} decreased from 1.10 ± 0.44 to 0.9 ± 0.39 L/min and ventilatory anaerobic threshold decreased by 1.5 mL/min per kilogram. However, these studies were non-randomized, non-controlled observational studies, and thus, the study design was suboptimal (Table 2).

Metformin improves energy metabolism in skeletal muscle and has a cardioprotective effect *via* AMPK activation^[27]. Metformin also inhibits mitochondrial respiratory-chain complex 1 and decreases ATP production^[27], which could potentially reduce oxygen consumption during exercise. In addition, metformin increases lactate concentrations and reduces the lactate threshold during exercise^[28]; however, lactate accumulation may have a protective effect on skeletal muscle rather than cause fatigue^[29]. Previous studies have suggested that the effect of metformin on cardiorespiratory fitness is clinically subtle. However, treatment with metformin does not appear to have a synergetic effect on cardiorespiratory

fitness in combination with exercise therapy.

THIAZOLIDINEDIONES AND CARDIORESPIRATORY FITNESS

The mechanism of action of thiazolidinediones is mediated by peroxisome proliferator-activated receptors (PPARs)^[30]. Thiazolidinediones exert an insulin-sensitizing effect by promoting fatty acid uptake and modulation of secretion of adipokines, such as interleukin-6, tumor necrosis factor- α , and adiponectin^[31]. PPAR- γ overactivation by thiazolidinediones increases body weight *via* fluid retention^[30] and stimulatory effect on adipogenesis and adipose tissue accumulation^[32]; thus, thiazolidinediones may be associated with increased cardiovascular risk in some patients. However, these drugs appear to improve cardiorespiratory fitness in patients with T2D.

In 2005, a randomized, double-blind, placebo-controlled study reported that rosiglitazone, a thiazolidinedione, improved exercise capacity *via* improvement in endothelial function in patients with T2D^[33]. Twenty patients were divided into rosiglitazone (4 mg/d) and placebo groups. After a 4-mo intervention, $\text{VO}_{2\text{ max}}$ increased from 1902 ± 603 mL/min (19.8 ± 5.3 mL/kg per minute) to 2074 ± 585 mL/min (21.2 ± 5.1 mL/kg per minute) in rosiglitazone-treated patients, but showed no improvement in controls. In addition, the change in $\text{VO}_{2\text{ max}}$ negatively correlated with changes in fasting insulin and homeostasis model assessment of insulin resistance (HOMA-IR) was positively correlated with insulin sensitivity, as measured by hyperinsulinemic-euglycemic clamp. Thiazolidinediones may improve $\text{VO}_{2\text{ max}}$ *via* multiple mechanisms. First, thiazolidinediones enhance gene transcription that promotes adipocyte differentiation and increases fatty acid transport, synthesis, and storage in the adipose tissue by binding to PPAR γ . This reduces ectopic fat accumulation in muscle and liver, and improves both cellular lipotoxicity and insulin sensitivity. Second, thiazolidinediones may also activate AMPK, which leads to increased fat oxidation and PPAR γ coactivator 1 α expression, regulating mitochondrial biogenesis^[34]. Mitochondrial dysfunction in patients with T2D is attenuated by thiazolidinediones^[35], which may result in an improvement in cardiorespiratory fitness.

Another randomized controlled study investigating the effect of rosiglitazone on cardiorespiratory fitness in patients with T2D was conducted in Greece^[36]. Seventy patients (28 men and 42 women) with T2D were randomly assigned to a rosiglitazone (8 mg/d) treatment group or a control group. Rosiglitazone treatment for 6 mo increased $\text{VO}_{2\text{ peak}}$ from 24.47 ± 3.98 to 26.39 ± 4.04 mL/kg per minute. Changes in adiponectin, HOMA-IR, and HbA1c levels were independent predictors of incremental increase in $\text{VO}_{2\text{ peak}}$. Rosiglitazone, a PPAR γ activator, may improve cardiorespiratory fitness *via*

upregulation of adiponectin. Recently, Yokota *et al*^[37] showed that pioglitazone improves cardiorespiratory fitness in Japanese patients with metabolic syndrome. Fourteen male patients with metabolic syndrome received 15 mg/d of pioglitazone for four months. Pioglitazone increased $\text{VO}_{2\text{ peak}}$ from 25.1 ± 4.9 to 27.2 ± 3.9 mL/kg per minute, and the anaerobic threshold from 12.7 ± 1.9 to 13.6 ± 0.6 mL/kg per minute. Pioglitazone also decreased the intramyocellular lipid content in resting calf muscle by 26%, with no concurrent change in the cross-sectional area of the muscle. There was an inverse correlation between the increase in anaerobic threshold and the decrease in intramyocellular lipid content. These data suggest that pioglitazone improves cardiorespiratory fitness *via* skeletal muscle fatty acid metabolism. In addition, pioglitazone decreased muscle phosphocreatinine loss during exercise, suggesting that altered mitochondrial function contributes to the improvement in skeletal muscle energy metabolism. Taken together, these studies indicate that thiazolidinediones have a beneficial effect on cardiorespiratory fitness in patients with T2D and metabolic syndrome (Table 3).

INCRETIN-RELATED DRUGS AND CARDIORESPIRATORY FITNESS

GLP-1 is secreted by the intestine and has multiple physiological effects, including brain neuroprotection, suppressing appetite, cardiovascular protection, improving cardiac function, slowing gastric emptying, decreasing glucose production in the liver, increasing glucose uptake in adipose tissue and skeletal muscle, stimulating insulin secretion, suppressing glucagon secretion, promoting pancreatic β -cell proliferation, and inhibiting pancreatic β -cell apoptosis^[38]. Secretion and function of GLP-1 is severely diminished in patients with T2D, and GLP-1 receptor agonists effectively improve diabetes and obesity *via* pleiotropic effects. Additionally, there could be an interaction between exercise and GLP-1 in patients with T2D^[39]. The effect of GLP-1 receptor agonists on exercise capacity/cardiorespiratory fitness remains controversial. Lepore *et al*^[40] investigated whether albiglutide, a long-acting GLP-1 receptor agonist, improved cardiac function and exercise performance in patients with chronic heart failure. Eighty-one patients participated in this multicenter, randomized, placebo-controlled study, and received either 30 mg of albiglutide or placebo for 12 wk. The albiglutide group showed improved $\text{VO}_{2\text{ peak}}$ (from 16.2 ± 0.9 to 17.1 ± 1 mL/kg per minute), an increase of 1.5 mL/min per kilogram compared with the placebo group. However, no significant improvement in cardiac function, 6-min walk test, myocardial glucose, and oxygen use was observed. The authors stated that the improvement in cardiorespiratory fitness may have been mediated by a physiological effect rather

Table 3 Effects of thiazolidinediones on cardiorespiratory fitness in patients with type 2 diabetes and metabolic syndrome

Ref.	Study design	Subjects	Thiazolidinedione dose	Results
Regensteiner <i>et al</i> ^[33] , 2005	Randomized controlled trial	20 patients with type 2 diabetes (10 patients received rosiglitazone and 10 patients received a placebo) Age: 55 ± 7 yr vs 56 ± 1 yr Sex (Men/Women): 5/5 vs 5/5 BMI: 32.2 ± 5.6 kg/m ² vs 30.4 ± 5.8 kg/m ² HbA1c: 7.2 ± 1.1% vs 7.2 ± 1.0%	Rosiglitazone, 4 mg/d	VO ₂ ↑, insulin sensitivity↑, endothelial function↑
Kadoglou <i>et al</i> ^[36] , 2008	Randomized controlled trial	70 patients with type 2 diabetes (35 patients received rosiglitazone and 35 patients received a placebo) Age: 63.8 ± 7.3 yr vs 66.7 ± 9.6 yr Sex (Men/Women): 14/21 vs 16/19 BMI: 29.5 ± 3.8 kg/m ² vs 29.9 ± 4.3 kg/m ² HbA1c: 8.2 ± 1.2% vs 8 ± 0.8%	Rosiglitazone, 8 mg/d	VO _{2peak} ↑, duration of the exercise test↑, oxygen pulse↑ Insulin resistance↓, diastolic blood pressure↓
Yokota <i>et al</i> ^[37] , 2017	Before-after study	14 patients with metabolic syndrome Age: 52 ± 11 yr Sex: All men BMI: 26.6 ± 3.3 kg/m ² HbA1c: 5.7 ± 0.6%	Pioglitazone, 15 mg/d	VO _{2peak} ↑, anaerobic threshold↑ Intramyocellular lipid content↓, muscle phosphocreatinine loss during exercise↓

BMI: Body mass index; HbA1c: Hemoglobin A1c; VO₂: Oxygen consumption.

than cardiac function due to the administration of albiglutide. Scalzo *et al*^[41] investigated the effect of exenatide on functional exercise capacity in patients with T2D after 3-mo treatment of 10 µg twice-daily exenatide. Exenatide did not improve VO_{2peak} or endothelial function, but diastolic cardiac function and arterial stiffness improved.

The controversial results from these studies may be attributed to patient characteristics. One study was conducted using patients with chronic heart failure (without diabetes) and the other used patients with mild T2D (without heart failure). Although the underlying mechanisms are unknown, the baseline cardiac function may have influenced the change in cardiorespiratory fitness due to the GLP-1 receptor agonist treatment.

A randomized, placebo-controlled, double-blind, parallel group, phase IV trial which aims at examining the effect of liraglutide on physical performance in patients with T2D is currently underway^[42], with promising results.

To the best of our knowledge, to date, no human studies have reported the effect of DPP-4 inhibitors on exercise capacity/cardiorespiratory fitness. However, one animal study suggested that exercise capacity and mitochondrial biogenesis in skeletal muscle are improved by the administration of a DPP-4 inhibitor in mice with heart failure^[43]. DPP-4 inhibitors may also have the potential to improve exercise capacity/cardiorespiratory fitness in humans.

SGLT2 INHIBITORS AND CARDIORESPIRATORY FITNESS

SGLT2 inhibitors decrease glucose reabsorption at the proximal renal tubules, which increases urinary glucose excretion and improves glycemic control. SGLT2

inhibitors also exert various metabolic effects, including weight loss, insulin sensitivity improvement, blood pressure lowering, renal hemodynamic modulation, and reduction in albuminuria, which leads to cardiovascular and renal protection^[44]. Treatment using empagliflozin resulted in a 35% risk reduction in hospitalization for heart failure compared with placebo^[9], suggesting that SGLT2 inhibitors also have an effect on cardiorespiratory fitness in patients with T2D.

To date, two pilot studies have investigated whether empagliflozin improves cardiorespiratory fitness in patients with T2D with heart failure. Núñez *et al*^[45] showed that short-term (4 wk) empagliflozin treatment increased VO_{2peak} by 1.21 mL/kg per minute (11.1%) from baseline. Conversely, Carbone *et al*^[46] showed that empagliflozin treatment for 4 wk did not significantly improve VO_{2peak} (14.5 mL/kg vs 15.8 mL/kg per minute). Intriguingly, patients concomitantly treated with loop diuretics demonstrated improved VO_{2peak} (+0.9 mL/kg per minute), whereas those without loop diuretics demonstrated a decrease in VO_{2peak} (−0.9 mL/kg per minute). Indeed, all patients in the study by Núñez *et al*^[45] received loop diuretics. The authors hypothesized that empagliflozin acts on the proximal renal tubules by interacting with sodium/hydrogen exchangers, thereby increasing sodium delivery at the distal renal tubules and enhancing the effect of loop diuretics^[47,48]. Carbone *et al*^[46] also speculated that empagliflozin improves cardiorespiratory fitness in patients concomitantly treated with loop diuretics by reducing the activity of the rennin-angiotensin-aldosterone system. Empagliflozin may exert cardiovascular and renal benefits *via* changes in myocardial and renal energy metabolism. Empagliflozin increases ketone oxidation instead of fat and glucose oxidation, which can improve cardiac and renal work efficiency^[49]. Taken together, these studies suggest that SGLT2 inhibitors improve cardiorespiratory

Table 4 Effects of sodium–glucose cotransporter 2 inhibitors on cardiorespiratory fitness in patients with type 2 diabetes

Ref.	Study design	Subjects	SGLT2 inhibitors dose	Results
Núñez <i>et al</i> ^[45] , 2017	Before-after study	19 patients with type 2 diabetes and heart failure Age (median): 72 yr Sex: 14 men and 5 women BMI: 30.6 ± 5.5 kg/m ² HbA1c: No description	Empagliflozin, 10 mg/d	VO _{2peak} ↑, ventilatory efficiency during exercise↑, 6-minute walking distance↑, ↓ antigen carbohydrate 125
Carbone <i>et al</i> ^[46] , 2018	Before-after study	15 patients with type 2 diabetes and heart failure Age (median): 60 yr Sex: 7 men and 8 women BMI (median): 34 kg/m ² HbA1c (median): 7.8%	Empagliflozin, 10 mg/d	VO _{2peak} ↑ in patients using loop diuretics VO _{2peak} ↓ in patients without loop diuretics

SGLT2: Sodium–glucose cotransporter 2; BMI: Body mass index; HbA1c: Hemoglobin A1c; VO₂: Oxygen consumption.

Table 5 Effect of glucose-lowering agents on cardiorespiratory fitness

Glucose-lowering agents	Cardiorespiratory fitness
Metformin	→ or ↓
Thiazolidinediones	↑
DPP-4 inhibitors	Unknown (↑ in mice with heart failure)
GLP-1 receptor agonists	↑ in patients with heart failure → in patients with type 2 diabetes
SGLT2 inhibitors	↑ in patients treated with loop diuretics

DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide-1; SGLT2: Sodium–glucose cotransporter 2.

fitness in patients with T2D with heart failure (Table 4).

CONCLUSION

Metformin does not improve cardiorespiratory fitness and may attenuate a beneficial effect of exercise on cardiorespiratory fitness in patients with T2D. In contrast, thiazolidinediones appear to improve cardiorespiratory fitness in patients with T2D. The effect of GLP-1 receptor agonists on cardiorespiratory fitness remains controversial and is not fully understood. Notably, SGLT2 inhibitors may improve cardiorespiratory fitness in patients with heart failure by modulating cardiac energy metabolism or *via* a synergetic effect with loop diuretics. Unfortunately, no human studies have examined the effect of DPP-4 inhibitors, sulfonylureas, glinides, or α -glucosidase inhibitors on cardiorespiratory fitness (Table 5). This review cannot recommend the optimal combination of exercise and glucose-lowering agents with regard to cardiorespiratory fitness in patients with T2D; however, thiazolidinediones, GLP-1 receptor agonists, and SGLT2 inhibitors have the potential to improve both glycemic control and cardiorespiratory fitness without interfering with exercise therapy. Further studies are warranted to demonstrate the clinical benefits of glucose-lowering agents for cardiorespiratory fitness, and to elucidate the underlying mechanisms of action.

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