Physical exercise and non-insulin glucose-lowering therapies in the management of type 2 diabetes mellitus: A clinical review

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Abstract

In the UK the National Institute of Health and Care Excellence (NICE) advocates as a first line strategy the promotion of lifestyle programmes that attain the Chief Medical Officers recommended amount of physical activity in improving the health of people at risk of developing or already with type 2 diabetes. Many people may be prescribed pharmacological treatments to improve glucose management including both, oral and injectable therapies. NICE guidelines also support intensification of efforts to improve patient lifestyle along with these glucose-lowering therapies. However, there is a paucity of evidence in the available published literature examining the relation between glucose lowering therapies and exercise metabolism. This review examines the available research on potential interactions of oral and non-insulin injectable therapies with physical exercise or activity in people at risk or already with type 2 diabetes. The conclusions of this review may inform healthcare professionals of the need to monitor patients more closely in their adaptation to both pharmacological therapy and physical activity.

Keywords: Oral and non-insulin therapies, physical exercise, type 2 diabetes mellitus

Novelty statement:

- Independently, both lifestyle intervention programmes that encourage regular physical activity and glucose lowering oral or injectable therapies reduce the development of type 2 diabetes and improve glycaemia in those already with the condition.
- This review summarises and consolidates available research on the observed effects of each class of oral and non-insulin injectable diabetes medication in combination with acute or chronic physical activity in people at risk of developing, or already with type 2 diabetes.
- This review may help clinicians better understand the possible interactions of some oral and injectable diabetes medications with physical activity.

Introduction

Currently in the United Kingdom 4.5 million people live with diabetes, of which 90% have type 2 diabetes (T2DM) with an additional estimation of 1.1 million people that have undiagnosed diabetes (1). Furthermore, 4.75 million people are at increased risk of developing T2DM and 11.5 million people are classed as overweight or obese with central adiposity based on waist circumference data (2). The latest physical activity report estimates that around 39% of the UK population have low levels of activity (3), which is a modifiable risk factor for obesity and many chronic conditions including T2DM and cardiovascular diseases (4,5).

Increased physical activity is associated with a reduction in the risk of developing T2DM (6,7) and in people with T2DM, physical inactivity is associated with cardiovascular complications and mortality (8). In addition, physical activity improves physical exercise capacity, mental health and cardiovascular outcomes (9,10). In the United Kingdom, the National Institute of Health and Care Excellence (NICE) guidelines advocate positive lifestyle promotion for people at risk of developing or with T2DM (11). Lifestyle advice should always be offered for the management of T2DM, and if required oral or injectable glucose lowering therapies are recommended to improve blood glucose along with therapies to address other cardiovascular risk factors including hypertension and/or dyslipidaemia. A pragmatic approach to managing people with newly diagnosed T2DM is to simultaneously initiate pharmacotherapy by oral and injectable medications such as biguanides, sulfonylureas, thiazolidinediones (TZD), dipeptidyl peptidase-IV (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose-cotransporter-2 (SGLT-2) inhibitors along with lifestyle advice (12).

Healthcare professionals managing people with T2DM have an important role to encourage healthy behaviours including physical activity. However, there is evidence to suggest that healthcare professionals lack confidence in promoting and advising in relation to physical activity. This may be related to a number of factors such as medical or nursing education and training, knowledge and access to available resources, time constraints, patient-associated factors such as complications and willingness to engage in physical activity (13). Therefore, even though there is a strong evidence base to support physical activity in the management of T2DM and cardiovascular risk reduction, translation to clinical practice is often lacking (14). This review aims to examine the interaction between physical activity and commonly prescribed non-insulin glucose-lowering therapies. This review will not independently examine the efficacy of lifestyle programmes or of oral or injectable therapies on metabolic outcomes. Rather, this review will synopsise evidence to highlight issues pertaining to the management of people at risk of developing or already with T2DM adopting a physically active lifestyle whilst prescribed pharmacotherapy.

Methods

The authors undertook a detailed PubMed literature search for the following keywords: 'type 2 diabetes mellitus', 'T2DM', 'prediabetes', 'exercise', 'physical exercise', 'biguanides', 'metformin', 'sulfonylurea', 'sulphonylurea', 'glinides', 'thiazolidinediones', 'GLP-1 receptor agonist', 'DPP-4' and 'SGLT-2'. The literature search was conducted independently by all authors in December 2017. Disagreements were discussed by the two lead authors (MLE; DMW) and solved with total consistency. If necessary, a third author (RMB) was consulted. Further, reference lists of systematic reviews, reviews and included and excluded articles were manually screened for studies of relevance.

Biguanides

Biguanides are the first-line oral glucose lowering therapy and can be used in combination with other therapies to treat hyperglycaemia without consequent hypoglycaemia. The only prescribed biguanide is metformin, which reduces hepatic tissue gluconeogenesis via attenuation of 5' AMP-activated protein kinase (AMPK) (15). Similarly, skeletal muscle contraction activates AMPK, enhances non-oxidative glucose disposal, and improves insulin-stimulated glucose uptake by increased glucose transporter type 4 (GLUT-4) receptor activity

(16). Thus, in a possible synergistic relationship, metformin and physical exercise might improve insulin sensitivity and/or glycaemia (17). However, metformin has also been shown to act as a mitochondrial membrane complex I inhibitor (18) and could potentially alter exercise metabolism and/or exercise tolerance.

Glycaemia

Prediabetes

Several diabetes prevention programmes in China, USA, Finland and India detail separately the importance of metformin or lifestyle modification in reducing the development of T2DM (6,19–21). Few studies have researched the combined impact of both metformin and intensive lifestyle treatment in people at risk of developing diabetes.

Probably the largest exploration of the combined influence of metformin and intensive lifestyle intervention on progression to T2DM was reported in the Indian Diabetes Prevention Programme. In this 3-year study, 531 native Asian Indians with impaired glucose tolerance (age 46 ± 6 years, BMI 25.8 ± 3.5 $kg.m^{-2}$) were randomly allocated into a control group, lifestyle modification advice, metformin (~250 mg twice daily), or a combined lifestyle and metformin group. The primary outcome measure was diagnosis of T2DM after 3 years using World Health Organization criteria (fasting plasma glucose ≥7.0 mmol/l (126 mg/dl) or 2–h plasma glucose ≥ 11.1 mmol/l (200 mg/dl)). The relative risk reduction was 28.5% with lifestyle modification (95% CI 20.5-37.3, p = 0.018), 26.4% with metformin (95% CI 19.1-35.1, p = 0.029) and 28.2% with combined lifestyle and metformin (95% CI 20.3-37.0, p = 0.022), compared to the control group. Thus, although both lifestyle advice and metformin reduced the incidence of diabetes in Asian Indians with impaired glucose tolerance there was no added benefit from combining them. However, the participants background physical activity patterns were heterogenous; those who were involved in physical labour, walked or cycled for >30 min/day or were already performing exercises regularly were asked to continue whereas those who were sedentary or performed light physical activity were advised and regularly motivated to walk briskly for at least 30 minutes each day. This was assessed by self-reported weekly physical activity levels and despite monthly telephone calls, no objective measurements were applied to further assess any changes in levels of physical activity. Further, given the low metformin dose administered, it would have been insightful to explore the influence of metformin dose on different physical activity groups, especially given the high degree of insulin resistance in South East Asians. In

a follow-up analysis, the pattern of changes in insulin resistance and insulin to glucose ratio were reported as similar between individual intervention groups, though the data were collapsed and not individually reported in detail (22).

More intensive clinical research trials on smaller numbers of well-controlled participants at risk of developing T2DM report a similar finding (23). Primarily Caucasian participants were randomised equally to a control group, metformin-only (progressing from 500-2000 mg/day by week 4), supervised three times a week exercise-only (cycling at 70% of pre-training heart rate peak (HR_{peak}) for 45 minutes per session and resistance exercises performed at 70% of 1-repetition maximum) or a combined group. The addition of metformin to supervised exercise training in participants with low exercise capacity were not additive on insulin sensitivity, assessed by an euglycaemic-hyperinsulinaemic clamp technique. Indeed, there was a trend in the data of a 25-30% blunting of insulin sensitivity response but without changes in blood glucose concentrations in response to regular supervised exercise training when on metformin, compared to the control group. Other studies in the available literature described similar findings (24). Some researchers found alternate results where habitual metformin treatment (1307 ±220 mg/day) in eight people with T2DM and two people with impaired fasting glucose did not blunt the acute insulin-sensitising effects of 45 minutes of high-intensity interval cycle exercise (4 × 4 minute intervals at 90% of HR_{peak} interspersed with 3 minute active recovery at 70% HR_{peak}) (25).

Type 2 Diabetes

In a double-blind study comparing the glycaemic effects to 45 minutes of intermittent isometric one-legged exercise following 26 weeks of metformin (500 mg daily progressing to 1000 mg daily), rosiglitazone or placebo in T2DM, metformin increased the rate of skeletal muscle perfusion during exercise whilst on a euglycaemic-hyperinsulinaemic clamp, an effect possibly due to improvements in HbA_{1c} over the 26-week treatment. However, like the placebo group, participants receiving metformin did not display any improvement in whole body glucose uptake or whole-body insulin sensitivity after 26 weeks (26).

The glycaemic responses to 45 minutes cycling at 60% maximum oxygen uptake (VO_{2max}) have been described in people with T2DM who either abstained (3 days) from, or took their habitual metformin (1000-3000 mg/day) treatment, or in a BMI- and age-matched group without T2DM (27). Exercise-induced blood glucose concentrations were stable in people without T2DM but

decreased in people with T2DM when they had abstained from metformin treatment. Interestingly, there was a smaller decrease in blood glucose with exercise in the habitual metformin trial compared to when metformin was not taken. There was no influence of metformin on the exercise-induced increase in glucose rate of appearance and rate of disappearance, yet values were lower in the diabetes group compared to people without T2DM. However, notwithstanding this, after correcting for glucose mass action effects on glucose uptake, metabolic clearance rate was higher in diabetes participants when they took metformin compared to when they abstained from metformin. Similarly, people with T2DM treated with metformin (~2000 mg/day) exhibited a blunted reduction in blood glucose concentrations compared to the placebo arm during incremental cycle exercise to exhaustion. Following exercise, the rise in blood glucose with a post-exercise standardised lunch was lower in those taking metformin compared to those on placebo (17).

In a retrospective analysis, previously inactive people with T2DM who participated in 22 weeks of aerobic exercise training whilst on metformin (before training 1,603 ± 600 vs after training 1,654 ± 616 mg/day) improved their HbA_{1c} (−6.3 mmol/mol, 95% CI −11.5, −1.1; 0.57%, 95% CI −1.05, −0.10) more than those who performed training without metformin (−1.9 mmol/mol, 95% CI −8.5, 4.7; 0.17, 95% CI −0.78, 0.43). There was no influence of metformin on HbA_{1c} in those who performed only resistance exercise training three times a week. When participants performed both combined aerobic and resistance exercise training, metformin did not blunt the training-induced reduction in HbA_{1c}. Indeed, there was a greater reduction in fasting glucose seen in those participants who took metformin (−1.47 mmol/l vs −0.52 mmol/l). A caveat to the results of this study is that participants were not randomised to treatment groups and those receiving metformin had a significantly longer duration of diabetes (28).

Finally, the impact of metformin treatment on interstitial glucose concentrations of people with T2DM during brisk walking (50 minutes) has been examined. Participants who were habitually taking metformin completed four experimental conditions comprising of taking metformin: (i) in the morning and evening without exercise, (ii) in the morning and in the evening with exercise, (iii) in the evening only after walking, and (iv) in the morning only with walking. Glucose was measured for 72 hours using a continuous glucose monitoring system with standardised meals provided. The inclusion of walking to bi-daily metformin treatment increased mean 2-hour incremental post-prandial area under the curve but did not affect daily mean glucose or fasting glucose concentrations. A reduction in metformin dose by removal of morning or evening metformin did not alter the increase in postprandial glucose levels with walking nor affect mean glucose concentrations (29).

Lipid metabolism

Obesity, insulin resistance and T2DM are intimately associated with derangements in lipid metabolism. Increased levels of fatty acids inhibit insulin-stimulated glucose transport and/or glucose breakdown on skeletal muscle. Dysregulation in skeletal muscle fatty acid metabolism involves increased fatty acid transport, reduced fatty acid oxidation and an accumulation of reactive lipid species like diacylglycerols and ceramides. It is a common finding that acute moderate intensity exercise elevates whole body lipid utilisation, along with increasing use of hepatic and skeletal muscle triglyceride pools. Chronic physical training increases lipid combustion capacity compared to the untrained state and enhances the use of non-esterified fatty acids (NEFA), lowers circulating lipids (LDL-cholesterol, triglycerides) and raises HDL-cholesterol (30). Reducing ectopic lipids such as NEFA and increasing HDL improve insulin signalling, decreases the risk of developing and the progression of T2DM and exerts a beneficial effect on cardiovascular disease risk (31).

Metformin reduces lipid storage in human skeletal muscle (32,33) and aids improvement in whole body lipid turnover, promoting fatty acid oxidation. In rats, 8 weeks of metformin treatment reduced hyperglycaemia, and skeletal muscle FAT/CD36 transporter abundance, ceramide and diacylglyceride content (34). In humans, chronic metformin treatment has also been shown to reduce plasma triglycerides and/or total and LDL-cholesterol concentrations (35,36) though plasma free fatty acids (FFA) were unchanged. However, research studies have demonstrated no change on FFA turnover or oxidation but chronic metformin treatment has been shown to improve body weight (26).

Thus, the combined effect of both metformin and regular exercise might increase fatty acid metabolism more than either effect alone. Indeed, in a combined lifestyle modification with metformin participants demonstrated a significantly greater reduction in total cholesterol, LDL- and increase in HDL-cholesterol compared to lifestyle modification alone (37,38). In the Indian Diabetes Prevention trial, the proportions of participants with elevated LDL-cholesterol decreased in all active treatment groups but not in the control group. Increased weight loss from pre-trial values was evident in participant groups with lifestyle modification plus metformin (39). Combined treatments may also be beneficial in increasing insulin sensitivity (40) and in treatment motivation. Interestingly there is some evidence of elevated lipid oxidation during submaximal walking in people with T2DM on metformin (evidenced by a lower respiratory

exchange ratio) compared to walking alone (17) with similar findings in people without T2DM (41).

Exercise Tolerance

There is limited evidence of metformin influencing exercise tolerance. Increased exercise-induced lactate concentrations have been shown in some studies when participants were taking metformin (17,24). However, this was not shown at rest (35). Elevated heart rate (17) with higher self-reported ratings of perceived exertion to exercise have been also recorded (17,24). This may have implications on exercise tolerance in people at risk of developing T2DM and those already with the condition.

Metformin and Physical Activity: In people at risk of developing T2DM, addition of metformin to a lifestyle modification programme or supervised exercise training did not alter long-term alterations in glycaemia more than metformin only or physical training alone nor impact on numbers progressing to T2DM.

In an acute exercise setting, metformin can reduce the decline in blood glucose in people with T2DM but the glycaemic effects of metformin whilst performing exercise, in people at risk or with T2DM appear transient and minor. Longer-term combined treatments seem equivalent to both training or metformin alone. In some studies, metformin can alter the participants' perceived exertion to acute exercise which might impact exercise tolerance.

Sulfonylureas

Sulfonylureas are an established oral glucose lowering therapy and continue to be used in the clinical practice for the management of people with T2DM (12). They act to depolarise the pancreatic β-cell by binding ATP-sensitive potassium channels and inducing insulin release. Though there is debate regarding cardiovascular safety, sulfonylureas remain the most common second-line oral hypoglycaemic agent prescribed in people with T2DM (11,12). Common side-effects of sulfonylureas include weight gain and hypoglycaemia, particularly in the older adult (42).

Glycaemic interactions of physical exercise and sulfonylureas

At the onset of exercise, there is a temporary mismatch between glucose uptake by the working musculature and release from hepatic glycogen stores that affects blood glucose (43). In particular for continuous low-intensity exercise, people treated with sulfonylureas may be at a higher risk of exercise-induced hypoglycaemia especially if initial blood glucose concentrations are low at the onset of exercise (44). The combination of glibenclamide and exercise increases the risk of hypoglycaemia by 33% compared to glibenclamide alone and by 83% compared to exercise alone (45). Greater circulating insulin concentrations were found when participants performed a 60-min ergometer cycle exercise at 57 ± 3% of VO_{2max} after taking 7 mg of glibenclamide. Furthermore, the rate of reduction in blood glucose was faster and the glucose appearance rate in the circulation lower during exercise combined with glibenclamide compared with exercise alone (46). In another study, the administration of 3 mg of glimepiride or 10 mg of glibenclamide one hour prior to moderate intensity (heart rate-120 bpm) cycle exercise resulted in a lower three-hour blood glucose area under the curve in 167 people with T2DM compared to those who did not exercise with similar results for both medications. Also, exercise was associated with a decrease in C-peptide and insulin area under the curve in the glimepiride group, but the same effect was not found with glibenclamide treatment indicating a suppression in endogenous insulin release with glibencamide (47). The above studies suggest vigilance in monitoring glycaemic responses during exercise for people with T2DM on glibenclamide.

Lipids

Sulfonylureas may impact on cardiovascular disease risk by influencing body mass, blood pressure and lipid metabolism (48). Contrary to metformin users, sulfonylurea users usually experience some weight gain (3-5 kg) and an increased blood pressure during a 12-month period (12). A recent meta-analysis concluded that the effect of sulfonylureas on lipids is small, however a statistically significant increase in FFA and triglycerides but decrease in HDL and LDL was detected (49). However, no evidence exists on the impact of both exercise and sulfonylureas on lipid metabolism over each treatment alone.

Exercise Metabolism and Tolerance:

We found no direct evidence of altered exercise tolerance resulting from sulfonylurea therapy, though the indirect impact of hypoglycaemia would be factor.

Sulfonylurea and physical activity: Sulfonylureas should be taken with caution around acute exercise, since the combined influence of both can rapidly decrease blood glucose levels and lead to hypoglycaemia.

Glinides

Similar to sulfonylureas, glinides work by binding to pancreatic β-cell ATP-sensitive K^+-channels to induce insulin secretion. Results from the placebo cohort of the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study revealed small but significant associations between increases in accelerometer-recorded physical activity levels and a reduction in oral glucose tolerance test (OGTT) 2-h glucose values. This relationship was lost in participants taking both nateglinide and valsartan, though it is difficult to ascribe the observed effect to either of the two medications in this study and how both of them interacted with exercise (50).

Glinides and Physical Activity : There is no evidence to detail the impact of glinides on physical exercise and metabolic outcomes.

Thiazolidinediones

Glucose and Lipids

Currently, pioglitazone is the only TZD licensed for use. Troglitazone was withdrawn following individual cases of liver injury and failure of therapy and rosiglitazone was withdrawn due to an association with increased cardiovascular events (51). Generally, TZDs activate peroxisome-proliferator-activated receptor gamma (PPAR-γ) (51). and increase fuel use thus, reducing FFA concentration in plasma and excessive accumulation in the liver, enhancing hepatic and skeletal muscle insulin sensitivity (12). There are a limited number of studies measuring the effect of pioglitazone in combination with exercise in relation to glycaemic control. The Insulin

Resistance Intervention After Stroke (IRIS III) study included 1298 people with T2DM who were prescribed their normal diabetes treatment along with pioglitazone for 20 weeks. Participants were stratified according to level of exercise ('never', 'sometimes' or 'regularly'). Glycaemic control, blood pressure and lipid levels improved with increasing self-rated levels of exercise. The impact of exercise on insulin resistance was positively correlated to the exercise level, however pioglitazone treatment is recommended independent from the exercise level of the study participants (52). In another study, people that were newly diagnosed or had diet-treated T2DM were randomised to rosiglitazone (4 mg, twice a day), metformin (1g, twice a day) or placebo. Those on rosiglitazone experienced increased insulin responsiveness in resting skeletal muscle (38% increase) and a doubling of glucose uptake during one-legged exercise using 10% maximum force (26).

Exercise Metabolism and Tolerance

A small trial of 24 participants found that after 24 weeks, people with T2DM receiving pioglitazone had significantly increased cardiac stroke volume and ejection fraction (53). Although no longer prescribed, rosiglitazone (4 mg per day for four months) was associated with an improved peak rate of oxygen consumption (VO_{2peak}) compared to placebo in individuals with previously sedentary lifestyles (54). Interestingly, the change in VO_{2peak} was correlated with improved insulin sensitivity (54).

Thiazolidinediones and Physical Activity : While evidence in this area is limited, published findings to date suggest that in combination with exercise, some TZDs might improve exercise capacity and reduce cardiovascular disease risk.

Incretin-based therapies

Incretins are gut-derived post-prandial hormones secreted by the distal jejunum and ileum, which stimulates insulin release from the β-cells, inhibits glucagon release from the α-cells, delays gastric emptying and increases early satiety. This endogenous response is impaired in T2DM. The two classes of approved therapies which potentiate the incretin effect are GLP-1RA and DPP-4 inhibitors. GLP-1RAs potentiate the incretin effect directly, whilst DPP-4

inhibitors prevent incretin hormone degradation (12). Few studies have examined these therapies in conjunction with physical exercise.

GLP-1 Receptor agonists

Glycaemia

In a sample of overweight participants with T2DM and suboptimal glycaemic control, liraglutide in combination with a 16-week exercise training programme (consisting of cycling and resistance exercises) demonstrated greater reductions in fasting plasma glucose compared to a placebo and training arm (-3.4 ± 2.3 vs -0.3 ± 2.6 mmol.L^{-1}, $p<0.05$), and HbA_{1c} (2.0% ± 1.2% vs. 0.3% ± 0.9%, $p<0.05$) (55). Liraglutide in combination with exercise training also improved body mass and blood pressure compared to a placebo and exercise training group although similar changes in estimated percent body fat, VO_{2peak} and quality of life markers were noted between the groups in response to exercise training (55).

Cardiovascular alterations and exercise tolerance

Cardiovascular function may be impaired in people with T2DM and increases the likelihood of cardiovascular disease. Although dependent on characteristics such as exercise duration, intensity and length of training, exercise has been shown to improve several factors involved in cardiovascular function in T2DM (56). In a double-blind, placebo-controlled study, liraglutide treatment for 12 weeks did not improve left ventricular ejection fraction during dobutamine stress echocardiography in people with stable coronary heart disease. Furthermore, no changes were observed in systolic function and/or exercise performance in a graded exercise test (56). Twelve weeks of exenatide treatment was associated with improved diastolic function and arterial stiffness, but not endothelial function in a double-blind study of 23 people with uncomplicated T2DM randomised to receive exenatide or placebo. Participants performed graded exercise tests before and after treatment but neither VO_{2peak} nor VO_2 kinetics changed as a result of exenatide treatment (58). Interestingly, a combination of cycling and resistance exercise training (3 times a week for 60 mins per session for 16 weeks) with liraglutide or placebo did not alter left ventricle or atrial dimensions, systolic measurements or heart rate in people with T2DM. However, liraglutide blunted the improvement in diastolic function with training as evidenced by a lack of change in early diastolic mitral annular tissue velocity and

the ratio of early and atrial mitral annular myocardial tissue velocities, which estimate the relative contribution of the passive left ventricular filling to the active contribution. Therefore, currently, despite the observed benefits on glycaemia, the impact of liraglutide on cardiovascular changes with regular physical exercise is complex and demands further investigation.

GLP-1RA and Physical Activity: Combined, there appear to be some positive effects on glycaemia and exercise capacity with some impact of GLP-1RA on cardiovascular indices.

Dipeptidyl peptidase-4 inhibitors

Within this literature review, we found no human studies that assessed the combined impact of DPP-4 inhibitors and exercise on metabolic outcomes. Prediabetic mice who undertook swimming exercise or were given DPP-4 inhibitors over 8 weeks both independently showed significant improvements in body weight, fasting and random plasma glucose plus improved glucose tolerance and insulin sensitivity compared with mice that did not exercise or receive DPP-4 intervention (59). Thus, human trials that explore DPP-4 inhibitor treatment and exercise training are warranted.

DPP-4 inhibitors and Physical Activity: There is no evidence for an influence of DPP-4 inhibitors on physical activity in humans.

Sodium-glucose-cotransporters-2 (SGLT-2) inhibitors

The SGLT-2 inhibitors prevent the re-uptake of glucose within the proximal convoluted tubule of the kidney, thereby increasing urinary glucose excretion. The reduced renal glucose re-absorption caused by SGLT-2 inhibitors results in the passage of greater volumes of urine by osmosis, with patients producing up to 470 ml more urine per day (60). However, blood flow to kidneys of ~1.0 litre per minute is remarkably stable during exercise, representing approximately 20-25% of the cardiac output at rest, and due to sympathetic nerve-induced renal vasoconstriction 3-5 % of total blood volume during exercise (61). During exercise, water loss occurs, with exhaled moist breath and sweat contributing to the 1-1.5 litres per hour loss in

temperate environments (62). Dehydration is a concern but perhaps more serious, and potentially exacerbated by dehydration is the condition of euglycaemic diabetic ketoacidosis, arising because of ketone formation due to a decreased insulin-to-glucagon ratio in participants using SGLT-2 inhibitors (63). Sub-maximal sustained exercise, especially in the unfed condition, may also lead to increased lipid use and consequent ketone body formation. Studies directly investigating the potential for accentuated ketone body formation and hydration status on SGLT-2 inhibitor treatment are warranted.

SGLT-2 inhibitors are considered cardio-protective, with their use associated with reduced body weight, blood pressure, uric acid levels and endothelial oxidative stress (64). Moreover, SGLT-2 inhibitors affect lipid levels also, with canagliflozin increasing HDL and LDL levels, and reducing serum triglycerides (65). Though, physical exercise improves cardiovascular and respiratory systems we found no published studies directly assessing the combined effect of SGLT-2 inhibitors and exercise. Such research is needed as the combined use of SGLT-2 inhibitors and exercise may confer greater glycaemic or cardiovascular benefits but at a potential expense of increased potential for diabetic ketoacidosis or renal function impairment.

SGLT-2 inhibitors and Physical Activity: No human studies have yet investigated the effects of SGLT-2 drugs combined with exercise.

Future directions

Many gaps exist in the published literature relating to our understanding of the impact of different oral and non-insulin injectable therapies (as monotherapy and in combination), in individuals wishing to improve their lifestyle by incorporating physical activity (Table 1). Future areas of investigation should explore

- risk of potential hypoglycaemic episodes in acute exercise in people taking sulfonylureas.
- long-term studies to investigate the effects of GLP-1RA combined with exercise on cardiovascular indices.
- studies investigating SGLT-2 inhibitors interaction with exercise and potential ketone formation in people with T2DM might be warranted to avoid diabetic ketoacidosis.

Conclusion

Though the current incidence and future growth patterns of T2DM are disappointing, the healthcare professional has two first-line treatments to improve patient outcomes i.e. pharmacotherapy and promotion of positive lifestyle behaviours. To date there is limited understanding of the interactions between oral/injectable agents in people at risk or already living with T2DM that are also encouraged to engage in physical activity. The current review advocates physical exercise for people at risk of developing- or already with T2DM whilst using drug monotherapy with some caveats. Healthcare professionals should promote physical activity but be vigilant in monitoring patients and be prepared to make prudent adjustments to medications or physical activities if adverse events are experienced.

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671 Table 1: Combination effect of Drug class + exercise

Drug + Exercise	Glycaemic Control	Exercise Tolerance	C
Biguanides *Pre-Diabetes*	Insulin sensitivity ↑↑; Glucose ↔	HR ↔	
T2DM	HbA_{1c} ↓; glucose ↔	VO_2 ↑↑; HR ↑↑; Lactate ↑↑	
Sulfonylureas	Hypoglycaemia ↑↑; Glucose ↓	VO_2 ↔; HR ↔; Lactate ↔	
Glinides	Glucose ↓	(↔)	
Thiazolidinediones	HbA_{1c} ↓	HR ↓; VO_2 ↑	
GLP-1 Receptor Agonists	HbA_{1c} ↓; Fasting glucose ↓	VO_2 ↑; HR ↑	
DPP-4 inhibitors	Glucose (↓)	(↔)	
SGLT-2 inhibitors	HbA_{1c} (↓); Glucose (↓)	HR (↔)	

672 *↑: increase, ↑↑: strong increase, ↓: decrease, ↓↓: strong decrease, ↔: ambiguous results. BMI: Body Mass Index, BP*
673 *Free Fat Mass, HR: Heart Rate, T2DM: Type 2 Diabetes Mellitus, VO_2: oxygen uptake. Brackets indicate a relative lack of e*