EFFECTS OF POSTMEAL EXERCISE AND HYPOGLYCEMIC AGENTS ON POSTPRANDIAL GLUCOSE EXCURSIONS

by

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ABSTRACT

INTRODUCTION: Type 2 diabetes is a metabolic disease primarily characterized by hyperglycemia. Hypoglycemic agents are used clinically to reduce fasting and postprandial glucose. Metformin monotherapy is the first-line therapy, and once it is no longer adequate, additional hypoglycemic agents are implemented. Postmeal exercise has been shown to attenuate glycemic excursions, and may provide additional glucose-lowering benefit beyond that of hypoglycemic agents alone. **METHODS:** Study 1 employed a randomized crossover design in people on metformin monotherapy to assess the effects of postmeal walking (5 x 10 min bouts at 60% VO_2 max) after a standardized breakfast meal, using continuous glucose monitoring. Study 2 employed a repeated measures design to assess the effects of postmeal walking (3 x 10 min bouts at 50% VO_2 max) in people on add-on hypoglycemic agents after a standardized breakfast meal. **RESULTS:** In people on metformin monotherapy, postmeal exercise significantly reduced 2-hr peak ($p = 0.001$) and 2-hr AUC ($p = 0.006$), with the lowest peak observed with postmeal exercise and metformin combined ($p < 0.05$ vs. all other conditions: met/sed: 12 ± 3.4, met/ex: 9.7 ± 2.3, washout/sed: 13.3 ± 3.2, washout/ex: 11.1 ± 3.4 mmol/L). In people on add-on therapies, glucose was reduced during postmeal exercise, including peak

(drug only: 13.8 ± 3.7 mmol/L, drug and postmeal exercise: 9.9 ± 2.7 mmol/L; p = 0.02) and AUC (drug only: 500 ± 136 mmol/L x 40 min, drug and postmeal exercise: 357 ± 89 mmol/L x 40 min; p = 0.03). However, 2-hr peak and 2-hr AUC were not different between conditions.

DISCUSSION: Postmeal exercise added additional glucose-lowering benefit beyond medication alone in those on metformin monotherapy, as well as those on add-on therapies. A bigger glucose-lowering effect was observed in participants on metformin monotherapy.

CONCLUSION: Exercise during the postprandial phase may be important for optimizing glucose control in people on hypoglycemic agents.

INDEX WORDS: type 2 diabetes, continuous glucose monitoring, metformin, hypoglycemic agents, postprandial glucose excursions, diabetes treatment, postmeal exercise

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DEDICATION

To my most treasured:

My beautiful mom, Susan Erickson, for being my best role model and my best friend.

My late father, Robert Erickson, for all the fishing trips, basketball games, and bedtime stories.

My greatest teacher, Dr. Kevin McCully, for inspiring me to live a bold and authentic life.

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CHAPTER 1

INTRODUCTION

Type 2 diabetes is a metabolic disease primarily characterized by hyperglycemia. Long-term hyperglycemia has been linked to cardiovascular disease(2), which is the leading cause of mortality in people with type 2 diabetes. Improvements in glycemic control have been shown to reduce cardiovascular disease risk among people with type 2 diabetes(4); thus, type 2 diabetes treatment centers on achieving stable glycemic control.

The pathogenesis of type 2 diabetes begins with the development of insulin resistance in skeletal muscle and liver. The next step of disease progression involves decline and eventual failure of insulin secretion from pancreatic β cells(39). Each of these abnormalities in the skeletal muscle, liver, and pancreas contribute to the development of hyperglycemia. Treatment of type 2 diabetes involves attempts to correct these abnormalities leading to restoration of glycemic control. Treatments regimens are adjusted on an individual basis according to patient-specific characteristics and disease severity. Lifestyle modification, including diet and exercise, is the first recommended treatment. Failure to maintain glycemic control with lifestyle modification calls for implementation of pharmacologic agents that lower blood glucose(13). Exercise enhances insulin sensitivity leading to improvements in glycemic control(34). Currently, little is known about how exercise and hypoglycemic agents taken together influence blood glucose levels.

Postprandial glucose is gaining more recognition as a key glycemic target for health. Reducing postprandial glucose has been shown to improve overall glycemic control(60) as well

as lead to reductions in cardiovascular disease risk(56). For these reasons, the International Diabetes Federation (IDF) recently published guidelines for the management of postmeal glucose, recommending 160 mg/dL (9.0 mmol/L) 1-2 hours after meal ingestion as a target glucose value(12). Exercise during the postprandial period has been shown to acutely attenuate glucose excursions in people with type 2 diabetes(29), and is potentially an effective strategy for reducing hyperglycemia. Interestingly, the effects of combining postprandial exercise and hypoglycemic agents on glucose excursions after a meal are currently unknown.

During the initial signs of type 2 diabetes, lifestyle modification including weight loss through diet and exercise are recommended. If lifestyle modification is not sufficient for attaining glycemic control, then metformin monotherapy will be prescribed(13). Current research suggests that the combination of exercise and metformin on insulin sensitivity may be somewhat additive(90). However, other studies suggest that metformin has an inhibitory effect on the insulin-sensitizing effects of exercise(75, 102), indicating a need for further research on the combined effects of metformin and exercise on clinically meaningful glucose outcomes. For example, it is currently unknown how the combination postprandial exercise and metformin will affect glucose excursions after a meal.

Failure to achieve glucose control with metformin and exercise calls for more aggressive diabetes treatment. Most often, this involves implementation of additional hypoglycemic agents that further reduce hyperglycemia(13). There are several available hypoglycemic agents available for this purpose. For example, there are 9 different classes of "add-on" therapies approved by the Food and Drug Administration for treatment of type 2 diabetes(109). The American Diabetes Association (ADA) treatment algorithm(13), involves lifestyle modification in combination with pharmacological agents, even though very little is known about how these

add-on therapies interact with exercise. Thus, it is a need to better understand how postprandial exercise and add-on therapies in combination affect glucose excursions after a meal.

Statement of the Problem

Effective treatment of type 2 diabetes is complex as the pathogenesis involves multiple physiological systems, and is progressive in nature. Peak glucose excursions are predictive of macro- and microvascular damage. Thus, postprandial glucose excursions are a clinical target for the treatment of type 2 diabetes(12). A goal of diabetes treatment is to slow disease progression, beginning with lifestyle modification including diet and exercise, progressing to metformin treatment, then incorporating additional hypoglycemic agents, and finally use of exogenous insulin. While exercise has been shown to be an effective treatment, very little is known about the combined effects of exercise and pharmacological hypoglycemic agents. Specifically, it is unknown how metformin and postprandial exercise affect glucose excursions after a meal. Similarly, it is also unknown how add-on hypoglycemic agents and postprandial exercise affect glucose excursions after a meal. This is surprising because in real-world clinical settings, patients treated for type 2 diabetes are advised to improve their lifestyle by becoming more physically active and improve dietary habits, while at the same time they are prescribed hypoglycemic agents, including metformin and various add-on therapies.

Study 1

Specific Aim: **Examine the combined effects of postmeal exercise and metformin on peak postprandial glucose after a standardized breakfast meal**. Participants will have a prescription for metformin. The peak postprandial glucose excursion will be measured in 4

experimental conditions including (i) the combination of metformin and postmeal exercise, (ii) metformin only, (iii) postmeal exercise only, (iv) and a no treatment (no metformin and no exercise) control condition.

Hypothesis: The combination of metformin and postmeal exercise will result in the lowest peak postprandial glucose after a standardized breakfast meal, when compared to metformin treatment alone, exercise alone, and the untreated control condition.

Study 2

Specific Aim: **Examine the combined effects of postmeal exercise and add-on hypoglycemic agents after a standardized breakfast meal**. Participants will be people with type 2 diabetes being treated with hypoglycemic agents other than metformin monotherapy, but not requiring insulin. The peak postprandial glucose excursion will be measured in 2 experimental conditions including (i) add-on hypoglycemic agents only, versus (ii) the combination of postmeal exercise and add-on hypoglycemic agents.

Hypothesis: The combination of postmeal exercise and add-on hypoglycemic agents will result in lower peak postprandial glucose excursions after a standardized breakfast meal, when compared to add-on hypoglycemic agents alone.

Significance of Study

Improving glucose control is the number one strategy for reducing macrovascular and microvascular complications in type 2 diabetes. More effective treatments regimens are needed to improve glycemic control in all stages of disease severity. Postprandial glucose is a key target for improving glycemic control and reducing cardiovascular risk. Exercise during the

postprandial period is a potential strategy for managing glucose excursions. Importantly, postmeal exercise during treatment with hypoglycemic agents may offer even more benefit for lowering glucose excursions after a meal. Results of this study will contribute to our understanding of how postprandial exercise and hypoglycemic agents can be used in combination to lower postprandial glucose excursions in people with type 2 diabetes potentially improving diabetes care.

CHAPTER 2

REVIEW OF LITERATURE

Overview

Diabetes treatment aims to lower hyperglycemia by way of reducing or reversing the physiological defects that occur in the liver, skeletal muscle, and pancreas. Specifically, postprandial glucose is a key clinical target due to its role in the development of cardiovascular disease. Effective treatment requires use of multiple treatment modalities including weight loss through diet and exercise, hypoglycemic agents, and eventual insulin therapy. Exercise and metformin are recommended treatments during the initial stages of diagnosis. Interestingly, it is currently unknown how these treatments used in combination affect postprandial glucose excursions. Similarly, it is unknown how the combination of exercise and add-on hypoglycemic agents will affect postprandial glucose excursions.

Pathogenesis of Type 2 Diabetes

The etiology of type 2 diabetes traditionally focuses on defects in 3 organ systems including, the liver, skeletal muscle, and the pancreas. These defects each contribute to hyperglycemia. The natural history of type 2 diabetes begins with the development of insulin resistance in the liver and skeletal muscle. Liver insulin resistance manifests as increased hepatic glucose output into systemic circulation. Skeletal muscle insulin resistance manifests as reduced glucose uptake from circulation resulting in elevated levels of blood glucose. In

response to hyperglycemia, β cells of the pancreas compensate by increasing the secretion of insulin. Over time, however, the demands placed on the β cells to secrete insulin results in dysfunction and failure of these cells. The end result, as in severe type 2 diabetes, is dependency on exogenous insulin sources for proper metabolism and survival.

Insulin resistance is a key characteristic of type 2 diabetes. Hepatic insulin resistance leads to abnormal glucose responses in both fasted and postprandial states. During the fasted state, the liver over-secretes glucose into systemic circulation(101). During the postprandial state, glucose output remains abnormally high because the liver does not properly respond to insulin, which is the signal for glucose suppression during meal ingestion. Thus, the liver continuously secretes glucose into systemic circulation contributing to both fasting and postprandial hyperglycemia(101).

Skeletal muscle insulin resistance also contributes to hyperglycemia. One way in which glucose uptake from circulation occurs is through insulin-dependent pathways in skeletal muscle. Skeletal muscles can become resistant to insulin action through genetic predisposition as well as physical inactivity. In this case, glucose remains in circulation instead of being removed by skeletal muscle. Thus, skeletal muscle insulin resistance contributes to hyperglycemia in the insulin-stimulated, or postprandial, state(101).

Insulin resistance alone does not cause type 2 diabetes. It is the decline in function of pancreatic β cells that ultimately leads to the development of type 2 diabetes(39). The rate of progression of type 2 diabetes is determined by the rate of decline of pancreatic β cell function(39). Dysfunction of these cells begins as early as the prediabetic state(48). For example, one of the initial clinical signs of pancreatic β cell decline is impaired glucose

tolerance. By the time a diabetes diagnosis has been made, approximately 80% of β cell function is lost(39, 46).

There are several contributing factors to β cell dysfunction. The compensatory over-secretion for insulin during the presence of insulin sensitivity is thought to be a cause. Additional contributing factors to β cell dysfunction include elevated levels of circulating free fatty acids (FFA) and glucose, termed "lipotoxicity" and "glucotoxity" respectively(39). Experimental studies have shown that elevated levels of FFA leads to impaired insulin secretion in genetically predisposed individuals(65). Similarly, *in vitro* studies of isolated human islets have shown that chronic exposure to glucose leads to impaired insulin secretion(92). Thus, there are various contributing factors to β cell dysfunction including tissue insulin resistance, as well as sustained levels of elevated lipids and glucose.

In summary, insulin resistance in the liver and skeletal muscle contribute to the development of hyperglycemia. A detrimental consequence of hyperglycemia is compensatory overuse and failure of pancreatic β cells, which is the central cause of type 2 diabetes. Additional contributing factors of β cell dysfunction include elevated levels of lipids and glucose in circulation. Consequently, a destructive positive feed-forward loop exists, in which hyperglycemia leads to β cell dysfunction, resulting in further continuous and sustained hyperglycemia.

Complications of Elevated Postprandial Glucose

High glucose concentrations play a central role in the development of diabetes-related complications. The link between hyperglycemia and cardiovascular disease is well supported by multiple lines of evidence (2, 26, 28). As a result, diabetes treatment centers on improving glycemic control. The gold standard for assessing glycemic control is hemoglobin A_{1C} (HbA_{1C}),

which is an index of long-term glycemic control representative of 3 months. Fasting glucose and postprandial glucose contribute to HbA_{1C}, and their relative contributions vary by disease severity(85). Postprandial glucose is gaining more recognition as a key clinical target due to recent evidence linking postprandial glucose excursions and cardiovascular disease. The following section will review epidemiological, biological, experimental, and interventional evidence supporting this link.

Epidemiological: Data from epidemiological studies indicate that postprandial glucose is predictive of cardiovascular disease. For example, the Honolulu Heart Program showed that glucose measured 1-hour (hr) into the postprandial phase predicts coronary heart disease(43). Similarly, the Helsinki Policemen studies showed that 2-hr glucose predicts all-cause mortality and coronary heart disease mortality(19), and the Rancho Bernardo Study showed that 2-hr postload hyperglycemia more than doubles the risk for fatal cardiovascular and heart disease(20). Some studies indicate that postprandial glucose may be a better predictor than fasting glucose; results of the DECODE study showed that OGTT was a better predictor than fasting glucose for identifying those with impaired glucose tolerance(5). Additionally, some studies show that postprandial glucose is actually a better cardiovascular disease predictor than HbA_{1C}, such as the Framingham Offspring Study(80), Hoorn Study(37), and Islington Diabetes Survey(63). Thus, epidemiological evidence supports a strong association between postprandial glucose and cardiovascular disease risk.

Biological: There is biological evidence supporting the association between postprandial glucose and diabetic vascular complications. Acute hyperglycemia has been implicated in the development of microvascular complications, including nephropathy(104), retinopathy(53), and

neuropathy(115). Acute hyperglycemia has also been associated with markers of atherosclerosis such as abnormal carotid intima-media thickness(44, 107).

There is also mechanistic evidence identifying oxidative stress as the link between hyperglycemia and atherosclerosis(25). For example, elevated levels of circulating glucose promote the excessive production of free radicals by the mitochondria, such as superoxide(94). Excessive production of free radicals results in cellular dysfunction, particularity endothelial cell dysfunction(91). Overall, there is biological evidence supporting the link between elevated glucose contributing to reduced vascular function.

Experimental: The causal relationship between postprandial glucose and the development of cardiovascular disease is supported by evidence from experimental studies in humans. Laboratory-based studies have shown that acute glycemic increases are detrimental to the vascular tree causing hemodynamic changes and endothelial dysfunction, and these changes are reversed by antioxidant administration. For example, acute hyperglycemia (270 mg/dL or 15 mmol/L) was shown to increase blood pressure, heart rate, and circulating catecholamines, and these changes were reversed by infusion of the antioxidant glutathione, suggesting the role of a glutathione-sensitive pathway(77). A study similar in design showed reversal of hyperglycemia-induced increases in blood pressure, heart rate, and circulating catecholamines after infusion of L-arginine, a nitric oxide donor, suggesting that glycemic-induced endothelial dysfunction is due, in part, to reduced nitric oxide availability. Another study showed that acute glucose loading in diabetic and non-diabetic groups led to reductions in endothelial function, and the magnitude of endothelial dysfunction was proportional to glucose load-induced increases in reactive oxygen species(66). Similarly, acute experimental oscillations of glucose have been shown to induce endothelial dysfunction and increase oxidative stress to a higher degree than

continuous, elevated glucose conditions(27). The acute nature of the glucose load used in these experimental human studies points to the role of postprandial glucose as a contributor to the development of cardiovascular disease. Reversal of hemodynamic changes via antioxidant administration suggests that oxidative stress is a mechanism underlying the development of hyperglycemia-induced endothelial dysfunction.

Interventional: Studies involving treatment interventions also have contributed to our understanding of the link between postprandial glucose and cardiovascular disease. Pharmacological agents specifically targeting and reducing postprandial glucose excursions have led to reductions in cardiovascular disease risk factors. The STOP-NIDDM trial implemented acarbose, an α-glucosidase inhibitor, which slows carbohydrate absorption and reduces peak postprandial glucose in individuals with impaired glucose tolerance after a treatment period of 12 months. Results of this study showed a 36% risk reduction in diabetes progression(32), a 34% risk reduction in incidence of hypertension and 49% risk reduction in cardiovascular events(33). Additionally, acarbose was shown to slow the progression of carotid intima-media thickness in a subset of participants(57). These trials indicate that treatment of postprandial glucose leads to reduced cardiovascular disease risk.

Similar findings have been reported when insulin-secretagogues were administered to patients with type 2 diabetes. Insulin-secretagogues stimulate meal-related insulin secretion causing a reduction in postprandial glucose. Treatment with the insulin-secretagogue, glyburide, resulted in reduced peak glucose, as well as carotid intima-media thickness regression in 18% of participants. Treatment with another insulin-secretagogue, repaglinide, resulted in an average reduced peak glucose, as well as carotid intima-media thickness regression in 52% of

participants(45). Results of these trials suggest that treatment of postprandial glucose will reduce cardiovascular disease risk in those with type 2 diabetes.

Due to the growing body of evidence supporting the link between postprandial glucose and cardiovascular disease, the International Diabetes Federation (IDF) published guidelines for the management of postmeal glucose in 2014. Specifically, the target glucose value 1-2 hours after meal ingestion is 160 mg/dL (9.0 mmol/L)(12). Recommendations for treatment of postprandial glucose include pharmacologic and non-pharmacological strategies(12). Interestingly, exercise was not part of the IDF recommendation.

Current Treatments for Type 2 Diabetes

As mentioned previously, type 2 diabetes treatment centers on management of blood glucose. The American Diabetes Association (ADA) recommends that treatment strategies should aim to achieve an HbA_{1C} value < 6.5%. Specifically, the ADA recommends constant manipulation of treatment regimens until this goal is achieved, which has proven to be difficult in real world settings due to the complexity and progressive nature of type 2 diabetes. The ADA has published a treatment algorithm, which flows through different tiers of treatment regimens driven by HbA_{1C} values(13). The foundation of treatment involves titration of hypoglycemic agents along with continued lifestyle modification. This is considered a 'tiered' treatment approach, and it involves routine assessments of glycemic control (every 3-6 months).

During the initial clinical signs of type 2 diabetes, such as fasting glucose $\geq$ 126 mg/dL or 2-hr postprandial glucose $\geq$ 200 mg/dL, the first step of treatment is a recommendation for lifestyle modification including increasing physical activity levels and diet modification, as well as metformin treatment. Once the combination of lifestyle modification and metformin is unable

to adequately control glucose, as assessed by HbA_{1C}, then additional hypoglycemic agents will be added to the treatment regimen.

Postprandial Exercise in Type 2 Diabetes

Exercise during the postprandial period may be a novel approach for reducing postprandial glucose responses. Exercise has been shown to be important for both prevention and treatment of type 2 diabetes, and the ADA and American College of Sports Medicine have developed exercise guidelines for people with type 2 diabetes(34). However, these guidelines are not specific to postprandial glucose, and they do not mention exercise timing in relation to meal ingestion. This highlights a need for more research related to postprandial exercise and its effects on diabetes-related outcomes.

Exercise acutely increases glucose uptake in skeletal muscles, and importantly, this occurs through an insulin-independent process(95, 99) and therefore is applicable to type 2 diabetes. Muscle contraction serves as a signal for GLUT-4 receptor translocation on skeletal muscle plasma membrane(52). GLUT-4 receptors are responsible for removing glucose from circulation and into skeletal muscle. This effect occurs after just a single bout of exercise, meaning the glucose-lowering effects can be realized immediately(52). Furthermore, the acute nature of this response indicates that long-term training adaptations are not needed for beneficial effects on blood glucose to occur. Exercise during the postprandial period is advantageous for glycemic control, as glucose values are highest after a meal.

Postprandial exercise has been shown to be safe(49) and effective in people with type 2 diabetes(29). Exercising after a meal is more advantageous for glucose homeostasis when compared to exercising before a meal in those with type 2 diabetes(58). This is because exercise

during the fasted state leads to low glucose values triggering the "counter-regulatory" hormonal response, resulting in increased blood glucose. The counter-regulatory hormonal response is the release of hormones into circulation, such as glucagon, catecholamines (epinephrine and norepinephrine), cortisol, and growth hormone in order to offset decreases in blood glucose during exercise(93). The counter-regulatory effect has been demonstrated experimentally after maximal cycling exercise in men with type 2 diabetes(68), 45 minutes of moderate cycling (~60% VO_2max) in people with metabolic syndrome(41), and after 20 minutes of self-paced walking in people with type 2 diabetes(35). Exercise during the postprandial phase may be less susceptible to the counter-regulatory hormonal response as blood glucose levels will be higher than during the fasted state.

The glucose-lowering effects of exercise have been reported after just 15 minutes of walking in participants with impaired glucose tolerance(42). The optimal timing for postprandial exercise has been suggested to be 30 minutes after the start of a meal(58). This is because peak postmeal glucose values typically occur within 90 minutes(36), and initiating exercise during this time window will blunt peak glucose excursions protecting the endothelial wall from pro-atherogenic glucose concentrations.

Low to moderate intensity exercise during the postprandial period may be optimal for glucose homeostasis. A comparison of moderate and high intensity exercise bouts equal in caloric expenditure showed more effective glycemic control after moderate intensity exercise. This may be due to the counter-regulatory hormonal response that occurred during high intensity exercise (i.e. increased epinephrine and norepinephrine)(71). A second comparison of low and high intensity exercise bouts equal in caloric expenditure showed larger reductions in hyperglycemia after low intensity exercise measured with continuous glucose monitoring(76).

While high intensity exercise still offers benefit, low to moderate exercise may be most appropriate as it is less susceptible to triggering the counter-regulatory hormonal response.

In summary, exercise during the postprandial period may be a potentially unique strategy for targeting postmeal glucose excursions in people with type 2 diabetes and improving the health of people with type 2 diabetes. Exercising 30 minutes after a meal is likely to blunt the peak glucose response and protect the vessel wall from pro-atherogenic glycemic concentrations. Low to moderate intensity exercise may be more advantageous than high intensity exercise, as it is less prone to counter-regulatory hormonal responses on glucose homeostasis. Furthermore, as glycemic excursions are highest in the morning(84), applying postprandial exercise to the breakfast meal may offer the most benefit.

Metformin- The First Line Pharmacotherapy

According to the ADA treatment algorithm, if lifestyle modification is not effective for improving glycemic control, then metformin treatment is recommended. Metformin is an oral dimethylbiguanide used to lower blood glucose in type 2 diabetes(15). On average, metformin reduces the HbA_{1C} endpoint by 1-2%(17). Metformin can be administered as monotherapy or in combination with add-on therapies(17). In 2009, approximately 42 million prescriptions of metformin were given in the U.S.(6). Metformin is a clinical favorite because it is effective, inexpensive, safe, and well tolerated by patients(16). Metformin works primarily by 1) decreasing hepatic glucose output and 2) increasing peripheral glucose uptake(16). Its full mechanism of action is still being examined.

Exercise and Metformin in Combination

In real-world situations, recommendations for increased physical activity and metformin prescriptions often go hand-in-hand(87). This has led to a growing interest in better understanding the interactive effects of exercise and metformin. There are only 2 studies examining the interaction of metformin and exercise on postprandial blood glucose in people with type 2 diabetes. One study showed that the combination of exercise and metformin was more effective than exercise alone for lowering plasma glucose concentrations during exercise initiated 3 hours after a standardized breakfast meal in a group of 10 participants with type 2 diabetes(23). A second study showed no differences in 2-hr postprandial glucose concentrations after an acute bout of high-intensity interval training with or without metformin treatment in 10 patients with insulin resistance(90). It is important to note that in the second study, exercise was performed in the fasted state. This has important implications for interpreting blood glucose data, as exercise during fasted states has weaker effects on lowering blood glucose when compared to exercise during fed states(96) possibly due to counter-regulatory hormonal signaling to increase hepatic glucose output. Thus, it is possible that the effect of exercise, as well as the combination of exercise and metformin might be more effective during the postprandial phase.

Some studies have investigated the interactive effects of metformin and exercise on skeletal muscle insulin sensitivity, although the results are mixed. One acute study showed an attenuation of exercise-induced insulin sensitivity after metformin treatment in people with type 2 diabetes(102). The exercise bout used in this study involved 30 minutes of cycling at 65% VO_2 peak followed by 10 minutes of cycling at 85% VO_2 peak(102). Similar findings were reported after 12 weeks of exercise training in a group of participants with prediabetes. Results

suggest that metformin blunted training-induced adaptations in skeletal muscle insulin sensitivity(75).

A laboratory-based study reported contradictory results, suggesting that chronic metformin usage actually enhanced the insulin-sensitizing effects of an acute exercise bout. The exercise bout used in this study consisted of 45 minutes of high-intensity interval training(90). Differences in results of these studies could be attributed to metformin dosage, duration of usage, as well as baseline differences in insulin-sensitivity among control and disease groups. Additional evidence comes from a retrospective analysis of an exercise training trial in people with type 2 diabetes(103). While insulin sensitivity was not assessed in this study, results from this trial indicate that metformin users did not have smaller reductions in HbA_{1C} when compared to non-metformin users(22). In summary, the combined effects of metformin and exercise are not fully characterized due to differences in study outcomes, ranging from acute measures of insulin sensitivity to indices of long-term glycemic control (HbA_{1C}). Currently, studies investigating the combined effects of metformin and exercise on postprandial glucose excursions are lacking. Better characterization of the combined effects of metformin and exercise could potentially lead to more efficacious treatment strategies for individuals with type 2 diabetes.

Role of Hypoglycemic Agents

The ADA recommends a tiered approach to treatment, also known as the ADA treatment algorithm(13). The first tier involves metformin monotherapy plus lifestyle modification. The second tier involves dual-therapy with an additional hypoglycemic agent plus lifestyle modification. The third tier involves three-drug combination therapy with a second hypoglycemic agent plus lifestyle modification, and the fourth tier involves insulin therapy.

Patients move through these tiers if they are unable to maintain an HbA_{1C} value of less than 7.0%, and a key treatment goal is slowing the progression through treatment tiers(13).

Metformin is the drug of choice for the first treatment tier. However, the second and third treatment tiers are not standardized. There are currently 9 FDA-approved classes of oral hypoglycemic agents(109) and several injectable agents appropriate for this tier. The ADA treatment algorithm emphasizes 4 classes to be used in combination with metformin, and they include sulfonylureas, thiazolidinediones (TZD), dipeptidyl peptidase 4 inhibitors (DPP-4 Is), and glucagon-like peptide-1 (GLP-1) receptor agonists. Interestingly, some drug classes have specifically been named in the IDF Guideline for Management of Postmeal Glucose due to their ability to target and reduce postprandial glucose. They include α-glucosidase inhibitors, DPP-4 inhibitors, glinides, GLP-1 derivatives, short-acting sulphonylureas, and insulin regimens(12). The appropriate "add-on" therapy should be guided by factors including tolerability, side effects, cost, effects on weight, comorbidities, hypoglycemia, and future glycemic goals(13).

Physiological mechanisms of action vary among drug classes, and will be briefly described here. **Sulfonylureas** are popular in the clinic and their main mechanism of action is increasing endogenous insulin secretion by binding to sulfonylurea receptors on pancreatic β cells. Therefore, patients must have functioning β cells to receive benefit(111). Interestingly, however, their HbA_{1C} lowering effects are not sustained long-term, with most benefit occurring during the initial 2 years of treatment(39). **Biguanides**, such as metformin, reduce hepatic glucose output and enhance glucose uptake in the periphery by increasing insulin sensitivity(16). **α-Glucosidase inhibitors**, such as acarbose, lower postprandial glucose excursions by reducing the rate of glucose reabsorption in the small intestine(7). **Meglitinides** are nonsulfonylurea secretagogues, meaning they stimulate pancreatic β cell insulin secretion(8). The two most

common meglitinides used clinically are nateglinide and repaglinide(109). **TZDs** are also popular in the clinic and they work by activating nuclear transcription factor peroxisome proliferator-activated receptor-γ (PPAR-γ), which leads to insulin-dependent glucose disposal resulting in increased hepatic and skeletal muscle insulin sensitivity(9, 38). TZD's are also used clinically to increase insulin sensitivity in skeletal muscle to a greater extent than metformin(82). **DPP-4 inhibitors** work by promoting insulin secretion from pancreatic β cells, decreasing glucagon concentrations, and reducing hepatic glucose production leading to lowered fasting and postprandial glucose(18, 40, 55). **GLP-1** are incretins, and a common example is prescribed in the U.S. is exenatide(14). GLP-1 works by suppressing abnormal levels of glucagon, slowing gastric emptying, and suppressing appetite(110). **Bile acid sequestrants**, such as colesevelam, have been approved for hypoglycemic use, although the mechanism of action in unclear(109). **Dopamine receptor agonists** have been shown to improve glucose control and this may be through increased insulin sensitivity without affecting insulin levels(1). **Sodium-glucose cotransporter 2 inhibitors** (SGLT-Is) reduce glucose primarily by acting on the kidney. Specifically, SGLT-Is reduce glucose reabsorption in the proximal tubes leading to greater urinary glucose excretion(10). Examples include dapagliflozin, canagliflozen, and empagliflozin(109). The appropriate drug used for treatment depends on individual characteristics. These agents are clinically implemented due to their hypoglycemic effects such as reducing postprandial glucose response. These drugs are summarized in Table 1.

Table 2.1

Drug Class	ADA Algorithm (13)	IDF Postmeal Guideline (12)	Postprandial Glucose Reduction (Ref)
Sulfonylureas	Yes	Yes (short-acting)	14% (106)
Biguanides (metformin)	Yes (Tier 1)	No	(15, 114)
α-glucosidase Inhibitors	No	Yes	19% (67)
Meglitinides	No	Yes	19% (106)
TZD	Yes	No	20% (50)
DPP4-I	Yes	Yes	23% (73)
GLP-1	Yes	Yes	6% (47)
Bile Acid Sequestrants	No	No	15% (79)
Dopamine Receptor Agonists	No	No	43% (51)
SGLT2-I	No	No	55% (64)

Current Needs in Diabetes Treatment

Treatment for type 2 diabetes is difficult due to the complexity of the underlying pathophysiology. A wide array of treatment regimens can be used to treat the pathophysiological abnormalities, with diet, physical activity, and hypoglycemic agents being the foundation. The Centers for Disease Control and Prevention reports that among adults with diagnosed diabetes, 56.9% use oral medications, 14% use insulin, 14.7% use both, and 14.4% use neither(11). This indicates that 71.6% of diagnosed patients used hypoglycemic agents. Thus, understanding how exercise interacts with hypoglycemic agents is a relevant consideration for diabetes treatment.

While several hypoglycemic agents are currently available for the treatment of type 2 diabetes, blood glucose control remains a challenging issue. In the long-term, single drug treatment is often inadequate for maintaining glycemic control. Findings from United Kingdom Prospective Diabetes Study (UKPDS) show that after 3 years of monotherapy (with either metformin or sulfonylureas) only 50% of participants attained HbA_{1C} below 7%. After 9 years of monotherapy, only 25% of participants attained HbA_{1C} below 7%(112). Reports from an Australian cohort provide some insight into diabetes medication prescription trends. Monotherapy (either metformin or sulfonylurea) treatment was sustained for approximately 3-4

years before dual-therapy was initiated(89). These findings show that monotherapy is often inadequate indicating the need for additional treatment modalities. It is possible that postprandial exercise may have a role in addressing this need.

Interestingly, the ADA treatment algorithm has been criticized for lacking a foundation in pathophysiology(39). For example, ADA treatment goals are primarily based on controlling HbA_{1C}, rather than actually treating the underlying cause of abnormal glucose control(13). However, an approach that treats the underlying cause of abnormal glucose homeostasis may be more effective for β cell preservation and long-term glycemic stability. A pathophysiologic-based approach has been proposed(39), however, this approach has not been adopted by the medical community. Therefore, the optimal treatment strategy remains an on-going debate. This highlights the need for further research into pathophysiology-oriented therapeutic strategies. Postprandial exercise in combination with hypoglycemic agents could potentially be an effective strategy for management of blood glucose.

Currently, there is a lack of evidence of how exercise and hypoglycemic agents might work in combination. Although postprandial exercise has been shown to be an effective means of reducing blood glucose levels following a meal, no studies to date have examined the combined effect of postprandial exercise and hypoglycemic agents other than metformin on postmeal glucose excursions. Moreover, postprandial exercise will likely be an effective strategy for lowering glucose during all stages of disease progression, as insulin is not required for muscle contraction-induced glucose uptake into skeletal muscle. Thus, it is possible that patients with severe type 2 diabetes who have dysfunctional β cells could benefit from this treatment approach.

Summary

Postprandial glucose has been linked to the development of cardiovascular disease and is a key clinical target, as highlighted by the 2014 IDF Guideline for Management of Postmeal Glucose(12). Postprandial exercise may be a unique way to attenuate peak postmeal glucose excursions. Exercise is advantageous for type 2 diabetes since contraction-induced glucose uptake occurs through insulin-independent mechanisms. It is plausible that postprandial exercise would offer benefit when used in combination with hypoglycemic agents; however, this has never been tested.

The study of hypoglycemic agents and postprandial glucose in combination as a potential therapeutic strategy is important because the treatment of type 2 diabetes is difficult and complex. Type 2 diabetes is progressive in nature, so the ADA recommends a tiered approach to treatment. In order to comprehensively examine exercise as a potential treatment modality, it is necessary to investigate across multiple treatment tiers (13). The proposed research will investigate the initial two treatment tiers, which are 1) metformin plus lifestyle modification (study 1) and 2) dual therapy plus lifestyle modification in a laboratory-based setting (study 2). These studies will, in part, address the need for research aimed at improving treatment strategies for people with type 2 diabetes.

CHAPTER 3

POSTMEAL EXERICSE REDUCES PEAK POSTPRANDIAL GLUCOSE EXCURSIONS IN PEOPLE ON METFORMIN MONOTHERAPY[1]

[1]Erickson, M.L., Little J.P., Gay J.L., McCully K.K, Jenkins N.T. Submitted to *Diabetologia*, 7/1/2016

ABSTRACT

AIMS/HYPOTHESIS: Type 2 diabetes is characterized by elevations in fasting and postprandial glucose. Metformin is used clinically to reduce fasting glucose with minimal effects on postprandial glucose. Postmeal exercise reduces postprandial glucose and may offer additional glucose-lowering benefit beyond metformin therapy alone. It is currently unknown how postmeal exercise and metformin monotherapy used in combination will affect postprandial glucose. We examined the independent and combined effects of postmeal exercise and metformin monotherapy on postprandial glucose. **METHODS:** A randomized-crossover design was used to assess the influence of postmeal exercise on postprandial glucose in 10 people treated with metformin monotherapy (57 ± 10 yrs, HbA_{1C} = 6.3 ± 0.6%). Testing occurred both during metformin treatment and during a metformin washout period. Peak postprandial glucose within a 2-hr time window and 2-hr total area under the curve was assessed after a standardized breakfast meal, using continuous glucose monitoring. Postmeal exercise consisted of 5 x 10-min bouts of treadmill walking at 60% VO_2 max. **RESULTS:** Postmeal exercise significantly reduced 2-hr peak (p = 0.001) and 2-hr AUC (p = 0.006), with the lowest peak observed with postmeal exercise and metformin combined ($p < 0.05$ vs. all other conditions: met/sed: 12 ± 3.4, met/ex: 9.7 ± 2.3, washout/sed: 13.3 ± 3.2, washout/ex: 11.1 ± 3.4 mmol/L).

CONCLUSION/INTERPRETATION: Postmeal exercise and metformin in combination resulted in the lowest peak postprandial glucose compared to either treatment modality alone. Timing exercise to the postprandial phase may be important for optimizing glucose control during metformin monotherapy.

Introduction

Type 2 diabetes is a progressive disease primarily characterized by hyperglycemia(2). Long-term hyperglycemia has been associated with the development of macrovascular and microvascular dysfunction, which leads to severe medical consequences including cardiovascular disease, nephropathy, retinopathy, and neuropathy(2). Metformin monotherapy is used clinically to reduce hyperglycemia(15). However, metformin monotherapy is often insufficient for long-term glycemic control due to progressive beta cell decline, and eventually additional treatments are needed to achieve further glucose reduction(112). Exercise during the postprandial phase, or postmeal exercise, has been shown to lower postprandial glucose excursions(29), and may offer additional glucose-lowering benefit beyond metformin monotherapy alone. The glucose-lowering effect of exercise is an insulin-independent process that occurs after just a single bout(95, 99). As such, the benefits of exercise on blood glucose are immediate and long-term training adaptations are not necessary for favorable effects to occur(52).

Given that exercise and metformin are first-line treatments for type 2 diabetes(31), it is important to understand how these two treatment modalities interact. Some studies suggest that when used in combination, the effects of exercise and metformin may interfere with each other(23, 75, 86). For example, findings from a previous study in individuals with prediabetes showed that the combination of endurance training and 12 weeks of metformin treatment resulted in attenuated improvements in skeletal muscle insulin sensitivity compared to combined training and placebo treatment(75). Other studies in individuals with type 2 diabetes have shown that adding exercise to metformin treatment does not lead to additional glucose-lowering benefit(23, 86). It is important to note that in these studies exercise was not performed during the postprandial phase. This may be an important consideration for interpretation of these

findings, as the independent and combined effects of postmeal exercise and metformin on postprandial glucose have not been examined previously.

Historically, studies of exercise and diabetes that focus on insulin sensitivity as an outcome have relied on methods such as oral and intravenous glucose tolerance tests, and hyperglycemic-euglycemic clamps. Recently, continuous glucose monitoring (CGM) has gained popularity as an alternative(105). The advantage of CGM is that it samples continuously, allowing for characterization of minute-by-minute glucose fluctuations over the course of several days. In comparison to venous blood draw and capillary assessment, CGM is more feasible and convenient for multi-day glucose assessment in real-word settings, and can be used to evaluate the magnitude and time course of postprandial glucose excursions allowing for measurements of peak glucose, area under the glucose curve (AUC), and indices of glycemic variability(69).

It is currently unknown how postmeal exercise during metformin treatment affects peak postprandial glucose. Postprandial glucose excursions are highest in the morning(84, 97) suggesting that the breakfast meal might be the most beneficial time for assessment of the effects of postmeal exercise. The purpose of this study was to examine the independent and combined effects of post-breakfast exercise and metformin monotherapy on peak postprandial glucose. It was hypothesized that the combination of post-breakfast exercise and metformin monotherapy would result in the lowest peak postprandial glucose, when compared to metformin monotherapy alone, post-breakfast exercise alone, and a metformin washout, non-exercise control condition.

Methods

Participants

Ten participants were recruited for this study through newspaper and e-mail advertisements distributed to the local community. Participants were screened for eligibility based on the following inclusion criteria: between 18-75 years of age, prescribed to metformin monotherapy, on a self-reported stable dosing regimen for at least 3 months prior to testing, and an $HbA_{1C} < 10\%$. Participants were excluded from the study if they were on additional hypoglycemic agents, had an $HbA_{1C} \geq 10\%$, or had physician-diagnosed cardiovascular disease. Eight participants had a diagnosis of type 2 diabetes, 1 participant had a diagnosis of prediabetes, and 1 participant was being treated for diabetes prevention. Participants did not deviate from personal medical treatment plans and took their metformin at physician-prescribed times during study protocols. Eight participants took metformin at breakfast and dinner, 1 participant took metformin at lunch and dinner, and one participant took metformin only at dinner. This study was approved by the Western Institutional Review Board. All participants provided written informed consent prior to study participation.

Study Design

This study used a randomized crossover design to evaluate both a metformin condition and a metformin washout condition (Fig 1A). The metformin washout condition involved stopping metformin treatment 48 hours prior to, and during, the continuous glucose monitoring (CGM) protocol. Each metformin and metformin washout condition consisted of one CGM protocol involving a CGM insertion visit, a sedentary day, an exercise day, and CGM removal visit (Fig 1B). The exercise day was always performed last to avoid potential residual effects of

exercise on the subsequent day(34). Participants took all other medications per usual during study protocols, with the exception of acetaminophen which was avoided due to possible interference with CGM sensor performance(21). One week separated the start of the metformin condition and the metformin washout condition. Data from each CGM protocol was therefore analyzed between 4 conditions for each participant, which included the following: metformin/sedentary, metformin/exercise, metformin washout/sedentary, and metformin washout/exercise.

Procedures

Baseline Testing: Initial assessments included height, weight, HbA_{1C}, age, current clinical diagnoses and duration, and current medication usage. A dual x-ray absorptiometry scan (GE Lunar, Fairfield CT, USA) was used to measure body composition. Submaximal exercise testing was performed for estimation of maximal oxygen uptake, in which participants walked on a treadmill at a constant speed (2-3 mph). Percent grade of the treadmill was increased by 1% every 2 minutes until 85% of age-predicted maximum heart rate was reached. Maximal oxygen consumption was calculated using the American College of Sports Medicine metabolic equation for walking(3). Heart rate was monitored with a Polar Heart Rate Monitor and ratings of perceived exertion were assessed during each exercise stage.

Continuous Glucose Monitoring Protocol

This study used the iPro®2 Professional Continuous Glucose Monitor (CGM) (Medtronic, Northridge CA, USA), which provides average glucose values every 5 minutes. As

mentioned previously, participants completed two CGM sessions, one during metformin treatment and the other during metformin washout.

Standardized Meals: A total of 7 standardized meals were provided during each CGM protocol. This included 1 initialization dinner before starting the protocol, as well as breakfast, lunch, and dinner meals for the following two study days. Participants were assigned to daily meal plans based on their daily energy requirements, which were calculated using Mifflin equations(81). For assignment of daily meal plans, daily energy expenditure for each participant was rounded up to nearest 250 kcal increment, as done previously(88). Possible meal plans for daily energy needs ranged from 1750, 2000, 2250, 2500, 2750, and 3000 kcals. Total daily kcals were distributed equally among 3 meals per day, meaning that one third of daily kcals was given at each breakfast, lunch, and dinner meal. The macronutrient profile was the identical across all meals, consisting of 65% carbohydrate, 25% fat, and 10% protein, as done previously(74). Participants documented time of meal consumption in logbooks.

Prior to Day 1 of the CGM protocol, participants reported to the lab for insertion of the CGM device. During this visit, participants received capillary glucose measurement supplies (glucometers, glucose strips, lancets, sharps container) and were shown how to measure their capillary glucose and record values in a logbook. Participants were also provided with a standardized dinner meal for consumption on the night prior to morning testing.

On Day 1, participants reported to the lab in a fasted state and consumed a standardized breakfast meal consisting of waffles, syrup, and chocolate milk equivalent to one third of their individual daily energy needs. After meal consumption, participants remained seated in the lab for the duration of the postprandial phase (3 hours). Next, participants left the lab with standardized lunch and dinner meals to eat later that day. On Day 2, participants reported to the

lab in the fasted state for an identical standardized breakfast meal given at the same clock time as the previous sedentary condition. Exactly 30 minutes after the first bite of the breakfast meal, participants completed an exercise bout consisting of 5 x 10-min bouts at 60% of estimated maximal oxygen uptake, with 3-min rest periods between intervals. This interval protocol was chosen after pilot testing, and adopted as a strategy to produce a sufficient exercise stimulus that was tolerable to deconditioned participants. After completion of exercise, participants remained seated in the lab for the duration of the 3-hour postprandial phase. Next, participants left the lab with identical standardized lunch and dinner meals as the previous sedentary day and consumed meals at identical clock times. On the following day, participants returned to the lab for removal of the CGM device.

CGM Analysis

CGM data were uploaded to http://ipro.medtronic.com. Raw CGM data were exported, plotted, and analyzed in Excel. CGM data were calibrated with capillary glucose values taken over the course of the day. The main glycemic variables of interest were peak glucose within a 2-hr time window during the postprandial phase of the breakfast meal, and 2-hr total area under the glucose curve using the trapezoidal method. Peak glucose within a 3-hr time window, and 3-hr total area under the glucose curve after the breakfast meal were also analyzed. The 2-hr increment was chosen because it is consistent with clinical end-points, while the 3-hr increment was incorporated for a more comprehensive assessment of the postprandial response. Glucose spikes from meals were calculated as the difference between peak postprandial glucose and pre-meal glucose. Pre-meal glucose was determined by averaging 15 minutes of glucose data prior to meal consumption, as done previously(74).

Postprandial glucose excursions during lunch and dinner meals were analyzed for sustained glucose-lowering effects of post-breakfast exercise. Outcomes included peak glucose during the postprandial phase within a 2-hr time window, as well as 2-hr total area under the glucose curve. Glycemic variability indices including time averages, standard deviations (SD), and mean amplitude of glycemic excursions (MAGE) were calculated with the EasyGV Version 8.8.2.R2 Excel Macro from University of Oxford (2010-2014)(59). The 24-hr timespan was defined as midnight to midnight, and the 12-hr timespan was defined as 12 hours after initiation of the exercise bout.

Statistical Analysis

Descriptive data are presented as means ± standard deviations. Hypothesis testing for determination of within-subject effects of postmeal exercise and metformin treatment on primary outcomes (2-hr peak and 2-hr AUC), as well as additional glucose outcomes, was done using repeated measures ANOVA (2 x 2). Hypothesis testing for additivity between treatment conditions was done by using t-tests, in which additivity was defined as the combination of postmeal exercise and metformin treatment resulting in a lower glucose value than either treatment used alone. SPSS v22 was used to perform statistical analysis procedures. Significance was accepted at $p < 0.05$.

Results

Participant characteristics are shown in Table 1. The average HbA_{1C} value was 6.3 ± 0.6% (45 ± 6.7 mmol/mol), so participants were well-controlled according to ADA criteria(31). All participants completed all experimental protocols. Due to mobility limitations, one

participant completed cycling exercise, which was performed on a cycle ergometer at the same relative intensity based on heart rate. (Lode Excalibur Sport 2000; Lode BV, Groningen, The Netherlands).

Postmeal exercise effect: Representative CGM data from one individual during the breakfast postprandial phase for all four conditions are shown in Fig 2A. Postmeal exercise reduced average peak glucose within the 2-hr postprandial phase after the breakfast meal (Fig 2B, exercise main effect $p < 0.001$), with the lowest peak observed during the combination of postmeal exercise and metformin. A significant glucose-lowering effect of exercise occurred within the metformin conditions ($p < 0.001$) and within the metformin washout conditions ($p = 0.045$). In addition, the combination of postmeal exercise and metformin was lower than the postmeal exercise only condition, suggesting additivity between metformin and postmeal exercise. Similar reductions were seen for peak glucose within the 3-hr postprandial phase (exercise main effect $p = 0.001$; data not shown), with a significant glucose-lowering effect of exercise occurring within the metformin conditions ($p = 0.003$). The interaction effects of postmeal exercise and metformin were not statistically significant for 2-hr peak ($p = 0.545$) or 3-hr peak ($p = 0.590$).

Postmeal exercise reduced 2-hr AUC (Fig 2C, exercise main effect $p = 0.006$) after the breakfast meal, with the lowest AUC observed during the combination of postmeal exercise and metformin. A significant glucose-lowering effect of exercise occurred within the metformin conditions ($p = 0.001$). Consistent results were observed for 3-hr AUC (exercise main effect $p = 0.036$; data not shown). The interaction effects of postmeal exercise and metformin were not statistically significant for 2-hr AUC ($p = 0.360$) or 3-hr AUC ($p = 0.597$).

Postmeal exercise reduced glucose spike after the breakfast meal (Fig 2D, exercise main effect $p < 0.001$), with the lowest spike observed during the combination of postmeal exercise and metformin. A significant glucose-lowering effect of exercise occurred within the metformin conditions ($p = 0.012$) and the metformin washout conditions ($p = 0.015$). The interaction effect of postmeal exercise and metformin was not statistically significant for the breakfast spike ($p = 0.919$).

Sustained glucose-lowering effects of exercise on subsequent lunch and dinner meals were not observed. Peak glucose within the 2-hr postprandial phase and 2-hr AUC were not affected at lunch (exercise main effect $p = 0.376$; $p = 0.811$, respectively) or dinner meals (exercise main effect $p = 0.292$; $p = 0.140$, respectively), shown in Table 2.

Metformin effect: Metformin treatment significantly reduced 24-hr average glucose (drug main effect $p = 0.031$) and 12-hr average glucose (drug main effect $p = 0.009$). Metformin treatment reduced lunch postprandial glucose excursions (drug main effect 2-hr peak: $p = 0.002$; 2-hr AUC: $p = 0.001$). A glucose-lowering effect of metformin was observed within the postmeal exercise conditions for 2-hr ($p = 0.043$) and 3-hr peak ($p = 0.045$) during the lunch meal. A glucose-lowering effect of metformin was not observed on glucose excursions at breakfast (drug main effect 2-hr peak: $p = 0.082$; 2-hr AUC: $p = 0.131$) or dinner meals (drug main effect 2-hr peak: $p = 0.134$; 2-hr AUC: $p = 0.240$). Breakfast postprandial glucose excursions were re-analyzed after removal of data from two participants who were not prescribed to take metformin at the breakfast meal, and a significant glucose-lowering effect was observed for 2-hr peak ($p = 0.037$).

Glycemic Variability: 24 hr and 12 hr MAGE was significantly reduced by postmeal exercise and metformin treatment (Table 2). 24 hr and 12 hr standard deviation was significantly

reduced by postmeal exercise and 12 hr standard deviation was reduced by metformin treatment (Table 2).

Discussion

The primary finding of this study was a significant glucose-lowering effect of postmeal exercise on breakfast postprandial glucose excursions in people being treated with metformin monotherapy. This was observed during both the presence (-21% peak reduction) and absence (-18% peak reduction) of metformin treatment. The magnitude of exercise-induced postprandial glucose reductions were comparable to that of hypoglycemic agents traditionally used for reducing postprandial glucose, such as sulfonylureas (-14%)(106), thiazolidinediones (-20%)(50), and dipeptidyl peptidase-4 inhibitors (-23%)(73). Our findings are similar to previous exercise studies, which have reported glucose reductions with postmeal exercise compared to sedentary conditions (ranging from 20-50%)(61, 96), as well as glucose reductions with postmeal exercise compared to exercise not timed to the postprandial phase (ranging from 17% - 50%)(35, 41, 42). Overall, these findings support the combination of postmeal exercise and metformin as more effective in lowering postprandial glucose than either treatment alone.

We did not observe a significant interaction effect of postmeal exercise and metformin treatment on the breakfast postprandial glucose responses including peak (2-hr and 3-hr) and AUC (2-hr and 3-hr). In our study, metformin did not negatively impact the glucose-lowering effects of postmeal exercise, as glucose reductions similar in magnitude occurred in both metformin treatment and metformin washout conditions. This finding is in contrast to previous studies, which reported slight increases in postprandial glucose after adding exercise to metformin treatment(23, 86). In the previous studies, exercise bouts were not timed to the

postprandial phase; rather, exercise occurred prior to the standardized meal in which the postprandial phase was assessed. Taken together, these findings support the potential importance of timing exercise after a breakfast meal in people being treated with metformin monotherapy. An advantage to exercising while glucose values are high (i.e., during the postprandial phase) is a reduced susceptibility to glucose counter-regulation, which may contribute to increases in blood glucose(93).

Although this study was not designed to characterize the glucose-lowering effects of metformin over the course of a day, the effects of metformin on postprandial glucose were consistent with the time course of action of the drug. Specifically, metformin had a significant glucose-lowering effect on lunch postprandial glucose responses, as well as 24-hr (-9.3% reduction) and 12-hr (-11.4% reduction) average glucose values. Breakfast peak postprandial glucose responses approached significance ($p = 0.08$), and dinner peak postprandial glucose responses were not reduced by metformin. Breakfast peak postprandial glucose responses reached significance after removal of 2 participants who did not take metformin at breakfast ($p = 0.001$). It is possible that the metformin effect was strongest at lunch and absent at dinner because metformin reaches peak plasma concentrations 1-2 hours post-ingestion(16), and eight of 10 participants took their metformin at the breakfast meal. Metformin is recommended to be taken with meals, however, the delayed action suggests that the strongest glucose-lowering effect may be observed on the subsequent meal. Taken together, these results suggest that optimizing glucose control with postmeal exercise and metformin treatment may involve appropriately timing these two treatment modalities.

Post-breakfast exercise did not reduce postprandial glucose responses to subsequent lunch and dinner meals, nor did it lower average glucose values (12-hr and 24-hr). These

findings are consistent with previous studies that also reported a lack of effect on subsequent meals after exercise(41, 70, 71). However, some studies have reported reduced postprandial glucose responses to subsequent meals(74). Differences in findings may be related to varying amounts of exercise-induced changes in glycogen depletion, which is thought to be a contributor to glucose homeostasis(62, 98, 116). It is possible that the exercise protocol employed in this study (which was sufficient to acutely lower postprandial glucose) was not of sufficient intensity or duration to cause substantial glycogen depletion and/or sustained improvements in insulin sensitivity throughout the 24 hours following exercise. Our results highlight the potential for further studies on exercise timing and its impact on glucose fluctuations occurring after exercise.

The main glycemic variables assessed in this study were peak glucose within a 2-hr time window, 2-hr glucose AUC, and glucose spike (difference between peak postprandial glucose and pre-meal glucose). These outcomes are consistent with previous studies using CGM. We also analyzed peak within a 3-hr time window and 3-hr AUC glucose values, and these outcomes supported our conclusions. Glycemic variability (acute changes in glucose peaks and nadirs) has been suggested as a possible clinical target for the treatment of diabetes(83). Glucose fluctuations have been proposed to activate oxidative stress, a mechanism underlying the vascular complications of diabetes(83). In this study, both postmeal exercise and metformin treatment reduced indices of glycemic variability, including MAGE and SD. Thus, it is possible that postmeal exercise and metformin could attenuate oxidative stress and thereby reduce the severity of diabetic vascular complications. This hypothesis warrants testing in future studies.

There are several possible mechanisms responsible for the glucose-lowering effects seen in this study. For example, exercise acutely increases glucose uptake through skeletal muscle contraction via an insulin-independent process(95, 99). Skeletal muscle contraction serves as a

signal for GLUT-4 receptor translocation on the skeletal muscle plasma membrane(52), which is responsible for facilitating glucose uptake. In addition, metformin treatment reduces hepatic glucose output(16), so it is possible that the combination of postmeal exercise and metformin targets hyperglycemia by promoting both an increase in skeletal muscle glucose uptake and a reduction in hepatic glucose production. Indeed, data from the current study showed that the combined use of postmeal exercise and metformin resulted in the lowest postprandial glucose response when compared to either treatment used alone.

Our study is not without limitations that warrant mention. Participant recruitment for this study was primarily based on having a prescription to metformin monotherapy, not necessarily disease status. Overall, eight of 10 participants had physician-diagnosed type 2 diabetes and analysis of study outcomes did not differ after removal of participants without this diagnosis. Participants adhered to their physicians' recommendation for metformin dose timing during study protocols. This approach was taken to avoid the potential impact of changing of medication timing within participants, and to enhance translatability of results to varied treatment regimens seen in real-world settings. Nevertheless, a prospective trial of metformin treatment in people with newly diagnosed type 2 diabetes with a strictly controlled dosing regimen would be informative. Additionally, this study applied postmeal exercise to the breakfast meal only. This meal was selected because morning postprandial glucose excursions are the highest(84, 97) and potentially most amenable to a glucose-lowering effect of exercise. However, the effects of exercise after lunch and/or dinner should be addressed in future studies. Insulin measurements would have provided a more comprehensive physiological assessment of exercise effects, however, techniques for frequent sampling in real-world settings are currently unavailable.

In conclusion, we found that post-breakfast exercise reduced postprandial glucose responses, both in the presence and absence of metformin monotherapy. In contrast to previous exercise and metformin studies, the combination of metformin and exercise was more beneficial for glucose reduction than metformin alone or exercise alone. Post-breakfast exercise did not have sustained glucose-lowering effects later in the day or on subsequent meals. Our study is unique in that we evaluated the immediate glucose-lowering effect of exercise intentionally timed to the postprandial phase. The use of CGM allowed us to comprehensively assess the postprandial glucose excursions through measurements of absolute glucose peak, AUCs, and glucose spike from meals. Future research is required to understand the underlying mechanisms, but the additive effects of postmeal exercise and metformin likely involve alterations in skeletal muscle glucose uptake, peripheral insulin sensitivity, and/or hepatic glucose output. Overall, our results indicate that the combination of postmeal exercise and metformin provide the greatest glucose-lowering benefit over either treatment modality alone. These findings suggest that exercise during the postprandial phase may be key to optimizing glucose control during metformin monotherapy.

Table 3.1

Participant Characteristics

Characteristic	Values
Sex (M/F)	2/8
Age (years)	57 ± 10
Height (cm)	166.1 ± 9.8
Weight (kg)	94 ± 20
BMI (kg/m^2)	33.8 ± 4.7
HbA_{1C} % (mmol/mol)	6.3 ± 0.6 (45 ± 6.7)
Estimated VO_2 peak ($ml/kg/min^{-1}$)	24.7 ± 6.4
Fasting Glucose (mmol/L)	6.8 ± 1.8
Tissue Fat (%)	45.6 ± 6.9
Fat Tissue (kg)	43.8 ± 15.2
Lean Tissue (kg)	49.7 ± 12.9
Metformin Duration (yrs)	7.9 ± 8.2
Other Medications (n)	
Antihypertensive	7
Lipid Lowering (statins)	4
Blood Thinners (aspirin)	5
Thyroid	4
Other	5

Data are presented as means ± SD (n = 10).

Table 3.2

CGM Variables

	Metformin/ Sedentary	Metformin/ Exercise	Washout/ Sedentary	Washout/ Exercise	Metformin Effect	Exercise Effect
24 hr avg	7.6 ± 2.0	7.4 ± 1.8	7.9 ± 2.0	8.3 ± 2.2	p = 0.031	p = 0.311
12 hr avg	7.9 ± 2.1	7.8 ± 1.8	8.6 ± 2.0	8.7 ± 2.3	p = 0.009	p = 0.652
2 hr $Peak_{Lunch}$	9.0 ± 2.3	9.0 ± 2.3	11.0 ± 3.0	11.5 ± 3.2	p = 0.011	p = 0.220
2 hr AUC_{Lunch}	960 ± 249	944 ± 268	1123 ± 266	1156 ± 329	p = 0.001	p = 0.811
$spike_{Lunch}$	3.0 ± 2.0	3.0 ± 1.5	4.7 ± 2.3	5.3 ± 2.1	p = 0.004	p = 0.587
2 hr $Peak_{Dinner}$	9.4 ± 2.0	10.1 ± 2.4	10.6 ± 2.8	10.7 ± 3.0	p = 0.240	p = 0.096
2 hr AUC_{Dinner}	993 ± 233	1081 ± 244	1121 ± 301	1178 ± 332	p = 0.094	p = 0.140
$spike_{Dinner}$	2.8 ± 1.5	3.0 ± 1.4	3.2 ± 1.6	2.6 ± 1.8	p = 0.968	p = 0.680
12 hr MAGE	4.1 ± 2.1	3.5 ± 1.2	5.8 ± 1.7	4.3 ± 1.4	p = 0.018	p = 0.040
24 hr MAGE	4.1 ± 1.0	3.5 ± 1.1	5.2 ± 1.7	4.2 ± 0.8	p = 0.030	p = 0.023
12 hr SD	1.9 ± 0.6	1.4 ± 0.3	2.2 ± 0.6	1.9 ± 0.6	p = 0.019	p < 0.001
24 hr SD	1.7 ± 0.4	1.4 ± 0.5	2.0 ± 0.6	1.7 ± 0.5	p = 0.055	p = 0.021

Data are presented as means ± SD (n = 10) unless otherwise specified. Values are reported in mmol/L. P-values indicate main effects from 2 x 2 ANOVA.

Figure Legends

Figure 3.1: Panel A: Randomized crossover design, in which the randomized factor was metformin and metformin washout conditions. Panel B: Individual CGM session protocol.

Figure 3.2: Panel A: Individual representative CGM data displaying all 4 experimental conditions during the breakfast postprandial period. Each data point represents a raw CGM measurement. Time 0 indicates first bite of the breakfast meal. Postmeal exercise began 30 minutes into postprandial period. Panel B: Average peak glucose within a 2-hr time window after the breakfast meal. Panel C: Average 2-hr total glucose area under the curve after the breakfast meal. Panel D: Average glucose spike (difference between peak postprandial glucose and pre-meal glucose) after the breakfast meal. Data are represented as means and standard deviations. * indicates $p \leq 0.05$. Open bars represent washout/sed, thin lined bars represent met/sed, thick lined bars represent washout/ex, and closed bars represent met/ex.

Figure 3.1

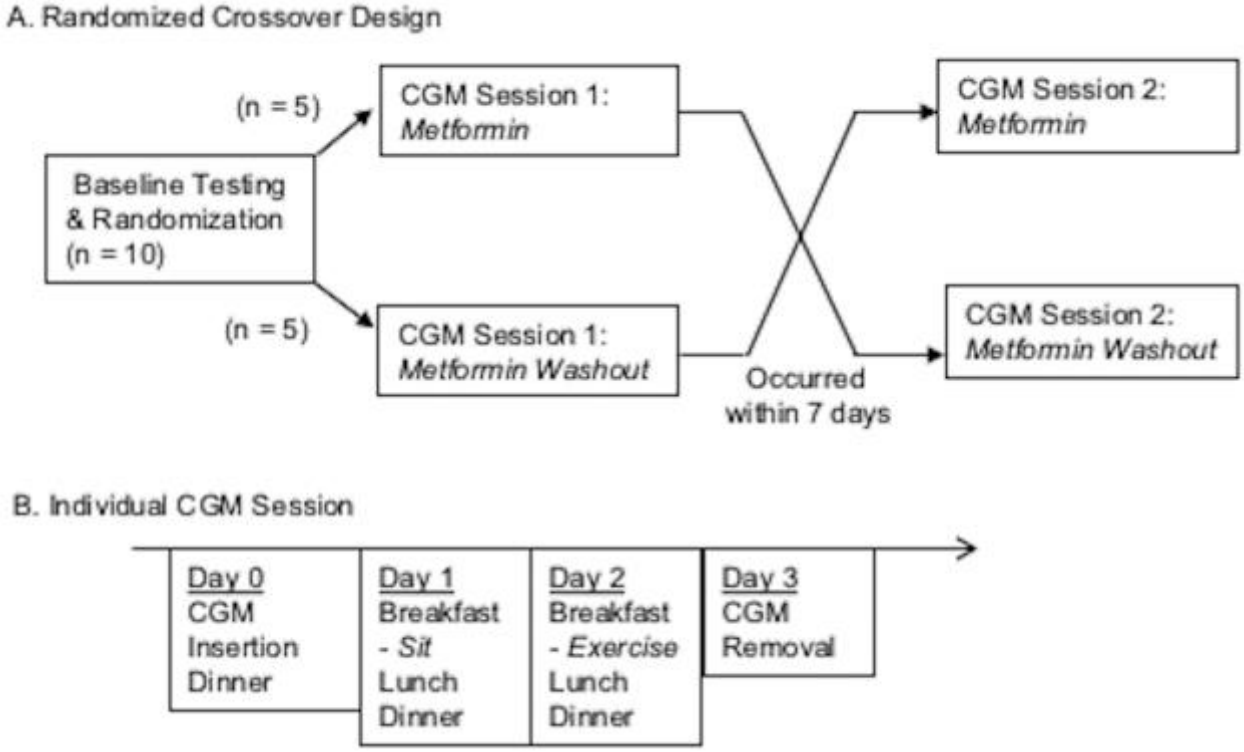
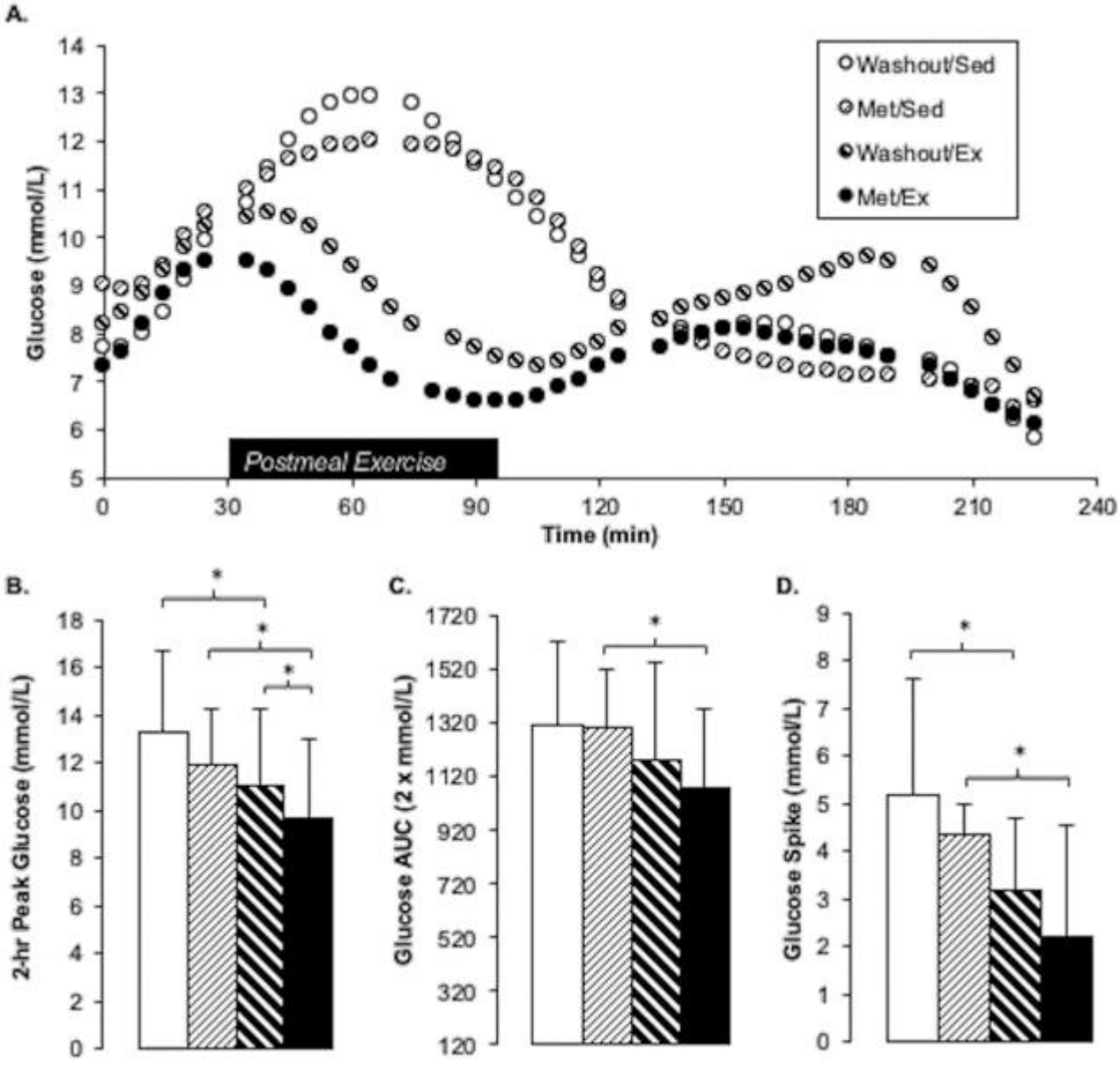

A. Randomized Crossover Design
(n = 5)
CGM Session 1:
Metformin
Baseline Testing
& Randomization
(n = 10)
(n = 5)
CGM Session 1:
Metformin Washout
CGM Session 2:
Metformin
CGM Session 2:
Metformin Washout
Occurred
within 7 days
B. Individual CGM Session
Day 0
CGM
Insertion
Dinner
Day 1
Breakfast
- Sit
Lunch
Dinner
Day 2
Breakfast
- Exercise
Lunch
Dinner
Day 3
CGM
Removal

Figure 3.2


A.
Glucose (mmol/L)
Time (min)
Washout/Sed
Met/Sed
Washout/Ex
Met/Ex
Postmeal Exercise
B.
2-hr Peak Glucose (mmol/L)
C.
Glucose AUC (2 x mmol/L)
D.
Glucose Spike (mmol/L)

CHAPTER 4

EFFECTS OF POSTMEAL EXERCISE ON POSTPRANDIAL GLUCOSE EXCURSIONS IN PEOPLE WITH TYPE 2 DIABETES TREATED WITH ADD-ON HYPOGLYCEMIC AGENTS[1]

[1]Erickson, M.L., Little J.P., Gay J.L., McCully K.K, Jenkins N.T. Submitted to *Diabetes Research and Clinical Practice*.

ABSTRACT

AIMS: Type 2 diabetes treatment primarily focuses on reducing hyperglycemia, including postprandial glucose excursions. Hypoglycemic agents are used clinically to lower fasting and postprandial glucose. Metformin is the first-line therapy; however, if metformin is inadequate then 'add-on' hypoglycemic agents are implemented. Postmeal exercise has been shown to lower postprandial glucose. The aim of this study was to assess if postmeal exercise provides additional glucose-lowering benefit, beyond medication alone, in those on add-on hypoglycemic agents. **METHODS**: Postprandial glucose excursions in eight participants with type 2 diabetes (Age: 60 ± 10.7, HbA1C: 7.9 ± 2.3) being treated with add-on hypoglycemic agents were assessed during both drug-treated sedentary and drug-treated postmeal exercise conditions. Continuous glucose monitoring was used to assess peak and total area under the glucose curve (AUC) during exercise, as well as peak within a 2-hr time window and 2-hr AUC after a standardized breakfast meal. Postmeal exercise consisted of 3 x 10-min intervals of treadmill walking at 50% maximal oxygen uptake. **RESULTS**: Glucose was reduced during postmeal exercise, including peak (drug only: 13.8 ± 3.7, drug/exercise: 9.9 ± 2.7 mmol/L; $p = 0.02$) and AUC (drug only: 500 ± 136, drug/exercise: 357 ± 89 mmol/L x 40 min; $p = 0.03$). However, 2-hr peak and 2-hr AUC were not different between conditions, nor was glucose reduced during subsequent lunch and dinner meals. **DISCUSSION**: Post-breakfast exercise lowered glucose during the exercise bout; however, this effect was not sustained throughout the day or even the duration of the breakfast postprandial period.

Introduction

Type 2 diabetes is a metabolic disease characterized by defects in insulin action and/or insulin secretion, which ultimately contribute to hyperglycemia(39). Hyperglycemia has been associated with the development of macrovascular and microvascular disease(2). Thus, treatment of type 2 diabetes centers on regaining glycemic control(13). Clinical glucose targets include both fasting and postprandial components of hyperglycemia(13).

Pharmacologic therapies that reduce hyperglycemia are currently the foundation of type 2 diabetes treatment(13). Metformin is an oral biguanide used to reduce fasting glucose and is the first-line therapy(15). However, metformin is typically inadequate for long-term glycemic control likely due to the progressive nature of the disease(112). When this occurs, additional hypoglycemic agents, termed "add-on" therapies, are implemented into treatment regimens. There are a variety of drug classes that are used as add-on therapies, such as sulphonylureas, dipeptidyl peptidase-4 inhibitors (DPP-4 Is), and glucagon-like peptide-1 (GLP-1) receptor agonists(109). Currently, the American Diabetes Association does not prioritize these drug classes for treatment. Instead, selection of the appropriate add-on therapies depends on several factors including cost, tolerability, side-effects, and co-morbidities(13).

Exercise is also a cornerstone of type 2 diabetes treatment due to improvements in skeletal muscle insulin sensitivity that occur after an exercise bout(34). Exercise may have added benefits if it is appropriately timed in the post-meal period(30). Exercising during the postprandial period has been shown to cause acute reductions in postprandial glucose(35, 41, 42, 61, 70). As a result, postmeal exercise is gaining interest as a potential glucose-lowering method for people with type 2 diabetes(30). Postmeal exercise exploits the non-insulin dependent process of glucose uptake that occurs during skeletal muscle contraction. Thus, postmeal

exercise may be an effective approach for lowering glucose during all stages of disease progression, including those with severe type 2 diabetes who have dysfunctional insulin secretion.

Since hypoglycemic agents and exercise are prescribed together for patients with type 2 diabetes, recent attention has been given to the interactive effects of these two treatment modalities(75, 90, 102). Some data suggest that the combination of metformin monotherapy and exercise may not always lead to additive glucose-lowering effects(23, 86). On the other hand, some studies show that exercise and sulphonylurea treatment have additive effects(54, 72, 78, 100), although these studies did not time exercise to the postprandial phase. To our knowledge, the effects of postmeal exercise during treatment with add-on hypoglycemic agents has not been tested.

It is currently unknown how the combination of postmeal exercise and treatment with add-on hypoglycemic agents will affect postprandial glucose in people with type 2 diabetes. The main objective of this study was to determine if postmeal exercise lowers peak postprandial glucose within a 2-hr time window of the postprandial breakfast phase in people with type 2 diabetes being treated with add-on hypoglycemic agents. It was hypothesized that the combination of postmeal exercise and add-on hypoglycemic agents would result in a lower peak postprandial glucose response compared to treatment with add-on hypoglycemic agents alone. We also tested the lasting effects of post-breakfast exercise on the subsequent glycemic responses to standardized lunch and dinner meals later in the day.

Materials and Methods

Participants

Eight participants were recruited for this study from the local community using website postings and newspaper advertisements. Participants had to be between the ages of 18-75 years of age, and were recruited based on their diabetes medication regimen defined as being treated with more than just metformin monotherapy, but not on insulin. Participants were excluded from this study if they had severe diabetes-related complications including nephropathy, renal or liver disease. During study protocols, participants did not deviate from their physician prescribed treatment regimens. This study was approved by the Western Institutional Review Board. All participants provided written informed consent prior to study participation.

Study Design

This study used a repeated measures design to assess the effects of postmeal exercise on peak postprandial glucose excursions in people with type 2 diabetes being treated with add-on hypoglycemic agents, but not on insulin. Participants completed a continuous glucose monitoring protocol consisting of one sedentary day and one postmeal exercise day. To avoid potential residual effects of the exercise, the sedentary day was always conducted prior to the postmeal exercise day.

Study Procedures

Baseline Testing: Height, weight, HbA_{1C}, age, current clinical diagnoses, medication usage, and body composition via dual x-ray absorptiometry scan (GE Lunar, Fairfield CT, USA) were collected at the initial visit. In addition, submaximal exercise testing on a treadmill was

conducted to estimate maximal oxygen consumption. The purpose of this test was to determine the appropriate parameters of treadmill walking (speed/grade) needed to achieve an exercise bout of 50% maximal oxygen uptake. For this submaximal exercise testing protocol, walking speed was held constant and percent grade was increased by 1% every 2 minutes until 85% of age-predicted maximum heart rate was reached. During each exercise stage, heart rate (Polar Heart Rate Monitor) and ratings of perceived exertion were assessed. American College of Sports Medicine metabolic equation for walking was used for calculating maximal oxygen consumption(3).

Continuous Glucose Monitoring Protocol

This study used the iPro®2 Professional Continuous Glucose Monitor (CGM) (Medtronic, Northridge CA, USA), which provides average glucose values every 5 minutes. Each CGM protocol consisted of an insertion visit, a sedentary day, a postmeal exercise day, and a removal visit (Fig 1). During CGM protocols, participants did not deviate from their physicians' recommendation for medication dosing and timing. Acetaminophen was avoided due to possible interference with sensor performance(21).

Standardized Meals: Participants were assigned to daily meal plans based on their daily energy requirements calculated using Mifflin equations(81). For assignment of daily meal plans, daily energy expenditure was rounded up to nearest 250 kcal increment, as done previously(88). Possible meal plans for daily energy needs ranged from 1750, 2000, 2250, 2500, 2750, and 3000 kcals. Total daily kcals were distributed equally among 3 meals per day, meaning that one third of daily kcals was given at each breakfast, lunch, and dinner meal. The macronutrient profile

was the identical across all meals, consisting of 65% carbohydrate, 25% fat, and 10% protein, as done previously(74). Participants documented the time of meal consumption in logbooks.

On Day 0 of the CGM protocol, participants reported to the lab for insertion of the CGM device. Participants were shown how to measure their capillary glucose used for CGM calibration and record values in a logbook. Participants were provided with capillary glucose measurement supplies (glucometers, glucose strips, lancets, sharps container), as well as a standardized dinner meal for consumption on the night prior to morning testing. Day 1 consisted of the sedentary day, in which participants reported to the lab in a fasted state. Participants consumed a standardized breakfast meal consisting of waffles, syrup, and chocolate milk equivalent to one third of their daily energy needs. After meal consumption, participants remained seated in the lab for a 3-hr postprandial phase. Next, participants left the lab with standardized lunch and dinner meals to eat later that day. Day 2 consisted of the postmeal exercise day, in which participants reported to the lab in the fasted state. Participants consumed an identical standardized breakfast meal given at the same clock time as the previous sedentary condition. Exactly 30 minutes after the first bite, participants completed an exercise bout consisting of 3 x 10-min bouts at 50% of estimated maximal oxygen uptake, with 3-min rest periods between intervals. The interval protocol was chosen to be tolerable to participants unaccustomed to exercise, while still providing a sufficient exercise stimulus. After the exercise bout, participants remained seated in the lab for the duration of the 3-hour postprandial phase. Next, participants left the lab with identical standardized lunch and dinner meals as the previous sedentary day and consumed meals at identical clock times. On the following day, participants returned to the lab for removal of the CGM device.

CGM Analysis

The primary glycemic variables of interest included peak glucose within a 2-hr time window during the postprandial phase of the breakfast meal, as well as 2-hr total area under the glucose curve (AUC) using the trapezoidal method. Peak glucose during the time of the exercise bout, and total AUC during the time of the exercise bout were also calculated. CGM data were uploaded to http://ipro.medtronic.com. Raw CGM data were exported, plotted, and analyzed in Microsoft Excel 2016. CGM data were calibrated with capillary glucose values taken over the course of the day.

To assess the effects of postmeal exercise throughout the duration of the breakfast postprandial period, point-by-point differences between average CGM values of drug-treated sedentary versus drug-treated postmeal exercise conditions were assessed, spanning from min 0-180.

Individual responses of the postmeal exercise effect were calculated as the delta between drug-treated sedentary and drug-treated postmeal exercise conditions for outcomes including peak within a 2-hr window and 2-hr AUC. A positive value indicates a glucose-lowering effect of exercise. In addition, assessment of sustained glucose-lowering effects of the post-breakfast exercise bout on subsequent lunch and dinner meals were examined by analyzing glucose peak within a 2-hr window, and 2-hr area under the glucose curve.

Secondary glycemic variables included glucose spike and total AUC, as well as indices of glycemic variability. Glucose spikes from meals were calculated as the difference between peak postprandial glucose and pre-meal glucose. Pre-meal glucose was determined by averaging 15 minutes of glucose data prior to meal consumption, as done previously(74). Glycemic variability indices including time averages, standard deviations, and mean amplitude of glycemic

excursions (MAGE) were calculated with the EasyGV Version 8.8.2.R2 Excel Macro from University of Oxford (2010-2014)(59). The 12-hr timespan defined as 12 hours after initiation of the exercise bout and the 24-hr timespan defined as midnight to midnight.

Statistical Analysis

Descriptive data are presented as means ± standard deviations. When data were non-normally distributed, median and interquartile range were reported. Hypothesis testing was done by determining differences between drug-treated sedentary and drug-treated post-meal exercise conditions on primary glycemic outcomes (2-hr peak and 2-hr AUC) during the breakfast postprandial period using Student's paired t-test.

Additional analyses of glucose during the breakfast postprandial phase were performed on outcomes including peak glucose during the time of the exercise bout, as well as total AUC during exercise. Differences were determined using Student's paired t-test. As an exploratory analysis, the effects of postmeal exercise and time throughout the duration of the breakfast postprandial period was assessed using a two-way (condition x time) repeated measures ANOVA, in which the time variable was each 5-minute CGM data point collected during the breakfast postprandial period (spanning from min 0-180). Post-hoc analysis (Student's paired t-test) was used to assess differences between drug-treated sedentary versus drug-treated postmeal exercise conditions at specific time points.

Differences in secondary glycemic variables including glucose spike and indices of glycemic variability were determined using Student's paired t-test. When data were non-normally distributed, Wilcoxon signed ranks Test was used to determine differences. SPSS v22 was used to perform statistical tests. Significance was accepted at $p < 0.05$.

Results

Participant characteristics and add-on hypoglycemic agent regimens are shown in Table 1. BMI was non-normally distributed (median, IQR: 32 kg/m^2, 27.4 - 36.4). All participants had physician-diagnosed type 2 diabetes. No participants were being treated with insulin. Six participants were being treated with anti-hypertensives and four participants were being treated with lipid-lowering medications. All participants successfully completed all study protocols, with the exception of one participant who opted out of the DXA scan. Average CGM values for drug-treated sedentary and drug-treated postmeal exercise conditions during the postprandial breakfast period are shown in Fig 2A.

Glucose-lowering effects on postprandial glucose: Significant differences were not observed on 2-hr peak (Fig 2B) or on 2-hr AUC (Table 2) during the breakfast meal. Individual variability of postmeal exercise effects on 2-hr peak and 2-hr AUC are shown in Fig 3.

Glucose-lowering effects during exercise: Differences between drug-treated sedentary and drug-treated postmeal exercise conditions were detected on peak glucose during the time of the exercise bout ($p = 0.02$; Fig 2B), as well as on AUC during the time of the exercise bout (drug only: 500.3 ± 136.4 mmol/L x 40 min, drug and exercise: 356.5 ± 88.7 mmol/L x 40 min; $p = 0.03$).

Glucose-lowering effects throughout the duration of the breakfast postprandial phase: The two-way repeated measures ANOVA showed a significant effect of time (time main effect: $p < 0.000$), but not exercise (exercise main effect $p = 0.01$). The interaction term was significant ($p < 0.000$). Follow-up post-hoc analyses of breakfast postprandial period showed that differences between drug-treated sedentary and drug-treated exercise conditions occurred from 40-100 minutes within the postprandial period (Fig 2A).

Sustained glucose-lowering effects on subsequent lunch and dinner meals were not observed (Table 2). Indices of glycemic variability did not differ among drug-treated sedentary and drug-treated postmeal exercise conditions (Table 2).

Discussion

Contrary to our hypothesis, the glucose-lowering effects of exercise were not observed on glucose peak within a 2-hr time window, or 2-hr AUC during the breakfast postprandial period. However, consistent reductions in CGM glucose values were observed during the exercise bout. In addition, glucose peak during the time of exercise, as well as AUC during the time of exercise were reduced. Taken together, these results suggest that postmeal exercise lowers glucose during the time of exercise, but this effect did not persist throughout the duration of the breakfast postprandial period or to the subsequent meals.

There are several possible explanations for the lack of significant effect on postprandial outcomes (2-hr peak and 2-hr AUC) observed in this study. Significant glucose reductions were observed during the time of the exercise bout, but these reductions were not sustained throughout the duration of the entire breakfast postprandial period. This suggests that the influence of postmeal exercise on postprandial glucose outcomes primarily occurred during the time of the exercise bout, but the glucose-lowering effect diminished upon cessation of exercise. Moreover, variability in glucose responses during the post-exercise phase could have also contributed to the weakened effect of exercise on postprandial outcomes.

Our findings are generally consistent with previous studies investigating the combination of exercise and add-on hypoglycemic agents. For example, people taking sulphonylureas experience a glucose-lowering effect during the time of the exercise bout (54, 72, 78, 100),

similar to our current observations. One study showed that 60 minutes of cycling in the post-absorptive state at 57% VO_2 max resulted in a higher rate of plasma glucose reduction during sulfonylurea treatment compared to sulfonylurea treatment alone(72). Similar findings were also reported during 60 minutes of cycling in the fasted state at 75% age-predicted max heart rate(54). It is important to note that these studies did not time exercise to the postprandial phase. Our study adds to the current literature by investigating the effects of a practical form of exercise (moderate intensity walking) performed during the postprandial period.

Variability among individual responses to exercise-induced glucose changes has been consistently reported across diabetes studies (24, 78, 108, 113). In the current study, there was variability in individual responses to exercise-induced glucose effects. Serial glucose measurements made with CGM (every 5 minutes) allowed for precise analysis of glucose changes throughout the postprandial period revealing that major source of variability occurred during the post-exercise phase, and not during the time of the exercise bout. A possible explanation for the variability observed during the post-exercise phase could be related to differences in disease severity among participants. For example, insulin has been shown to increase during the post-exercise phase in people with type 2 diabetes being treated with hypoglycemic agents(72). The degree to which insulin secretion occurs will likely depend on the state of pancreatic beta cell function as well as differences in liver glucose output. Therefore, the interplay between disease severity and drug treatment may have contributed to the heterogeneity in responses.

The exercise dose used in this study may not have been sufficient to blunt the severe hyperglycemic responses observed in our participants. That is, the ability of an exercise bout to attenuate postprandial hyperglycemia may be related to the duration and magnitude of the

hyperglycemic response. While shorter exercise bouts (15 min) have been shown to reduce 24-hr average glucose in people with impaired glucose tolerance(42), those who experience severe hyperglycemia may require a larger dose in comparison. Previous studies investigating the combined use of exercise and sulfonylureas in people with type 2 diabetes have used exercise bouts ranging from 60-90 minutes in duration(54, 72, 78, 100). This study adds to current literature by applying a shorter dose of exercise to a group of participants with increased disease severity.

There are several gaps in the literature that this study was designed to address. First, the group of participants investigated in this study is particularly novel. They were required to be on add-on hypoglycemic agents, meaning those on metformin monotherapy were excluded. It was our intention to recruit and study participants with increased disease severity and avoid those with newly onset diabetes. In addition, previous studies of exercise and sulphonylureas have used medication naïve participants, while our approach of including participants on stable medication regimens avoided possible complications of introducing a new medication, as well as increases external validity. Second, this is one of the first studies to apply postmeal exercise to people with type 2 diabetes being treated with add-on hypoglycemic agents, as the majority of postmeal exercise studies using moderate intensity have focused on healthy populations or those with type 1 diabetes. Third, this study used a shorter duration of exercise (3 x 10 min), while previous studies have used longer bouts of continuous exercise (60-90 min). The interval approach used in this study was chosen to be more tolerable to those unaccustomed to exercise.

There are some limitations of this study that warrant mention. Participants were on hypoglycemic agents in various drug classes, which may have contributed to the variability observed in this study. However, our small sample size precluded analysis of whether the effects

of exercise on postprandial glucose varied among participants on different classes of hypoglycemic agents. Future studies are needed to determine the influence of specific drug classes (e.g., sulphonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, etc.) on the glucose-lowering effects of postmeal exercise. Medication timing was not standardized. Instead, participants adhered to their personal prescription plans which enhances external validity of the study. Measurements of insulin and additional hormonal responses would have aided in interpretation of findings. Finally, we excluded individuals on exogenous insulin, so it is unclear how postmeal exercise would affect participants on insulin regimens.

Postmeal exercise has been shown previously to reduce postprandial glucose excursions, but the combined effects of postmeal exercise and add-on hypoglycemic agents have not been documented. This is one of the first studies to apply postmeal exercise to people with type 2 diabetes being treated with add-on hypoglycemic agents. Findings from the current study indicate that exercising during the postprandial period leads to reductions in glucose, however, this effect did not persist throughout the day, or even throughout the duration of the postprandial period. Although speculative, it is possible that the exercise dose may need to be tailored according to the duration and magnitude of the hyperglycemic response for optimal results. Therefore, the influence of postmeal exercise may differ across the hyperglycemia continuum. More research is needed to determine the optimal exercise strategy for targeting postprandial glucose excursions in people with advanced type 2 diabetes being treated with add-on hypoglycemic agents.

Table 4.1

Participant Characteristics

Characteristic	Values
Sex (M/F)	5/3
Age (years)	60 ± 10.7
Height (cm)	167.8 ± 6
Weight (kg)	94.2 ± 23.5
BMI (kg/m^2)	33.8 ± 10.3
HbA_{1C} (%)	7.9 ± 2.3 (63 mmol/mol)
Estimated VO_2 peak ($ml/kg/min^{-1}$)	26.7 ± 8.6
Fasting Glucose (mmol/L)	7.9 ± 1.9
Tissue Fat (%)	41.9 ± 10.3
Fat Tissue (kg)	41.2 ± 19.2
Lean Tissue (kg)	53.7 ± 7.2
Hypoglycemic Agents (n)	
Metformin + sulfonylurea	4
Metformin + GLP-1	1
Metformin + sulfonylurea + GLP-1	1
Metformin + DPP4-I	1
DPP4-I	1

Data are presented as means ± SD (n = 8)

Table 4.2

CGM Variables

	Sedentary	Exercise	P-value
2 hr $AUC_{Breakfast}$	1473 ± 328	1206 ± 329	p = 0.10
$spike_{Breakfast}$	7.5 ± 4.3	5.2 ± 4.1	p = 0.13
2 hr AUC_{Lunch}	1065.6 ± 226	1265.7 ± 398	p = 0.93
$spike_{Lunch}$	4.0 ± 4.6	7.2 ± 5.1	p = 0.10
2 hr AUC_{Dinner}	1266 ± 398	1060 ± 200	p = 0.40
$spike_{Dinner}$	7.2 ± 5.1	4.6 ± 5.0	p = 0.16
12 hr avg	9.7 ± 2.2	9.0 ± 2.4	p = 0.41
24 hr avg	8.6 ± 1.8	8.5 ± 2.4	p = 0.89[#]
12 hr MAGE	7.1 ± 4.8	7.1 ± 4.9	p = 1.00
24 hr MAGE	7.0 ± 4.7	6.2 ± 3.9	p = 0.25
12 hr SD	2.7 ± 1.6	2.5 ± 1.4	p = 0.47
24 hr SD	2.9 ± 1.8	2.4 ± 1.4	p = 0.16

Data are presented as means ± SD (n = 8) unless otherwise specified. Values are reported in mmol/L. P-values indicate significance from Student's paired t-test. [#] indicates p-value determined from Wilcoxon signed rank test when data were non-normally distributed. AUC: area under the glucose curve; spike: difference between peak postprandial glucose and pre-meal glucose; MAGE: mean amplitude of glycemic excursion.

Figure Legends

Figure 4.1: CGM protocol.

Figure 4.2: Panel A: Average CGM data for drug-treated sedentary and drug-treated exercise conditions during the breakfast postprandial period. Time 0 represents the time of first bite. Post-breakfast exercise began 30 minutes after first bite. * indicates $p \leq 0.05$ (significance between drug-treated sedentary and drug-treated exercise conditions using Student's paired t-tests). Panel B: Average peak glucose within the exercise time window, as well as peak glucose within the 2-hr time window during the breakfast postprandial period, as well as during the subsequent lunch and dinner meals. Data are represented as means and standard deviations.

Figure 4.3: Panel A: Individual responses of the exercise effect on peak glucose within a 2-hr time window after the breakfast meal. Positive values represent a glucose lowering-effect of exercise. Panel B: Individual responses of the exercise effect on 2-hr area under the glucose curve after the breakfast meal. Met: metformin; DPP4-I: dipeptidyl peptidase 4-inhibitor; Sulf: sulfonylurea; GLP-1: glucagon-like peptide-1 agonist.

Figure 4. 1

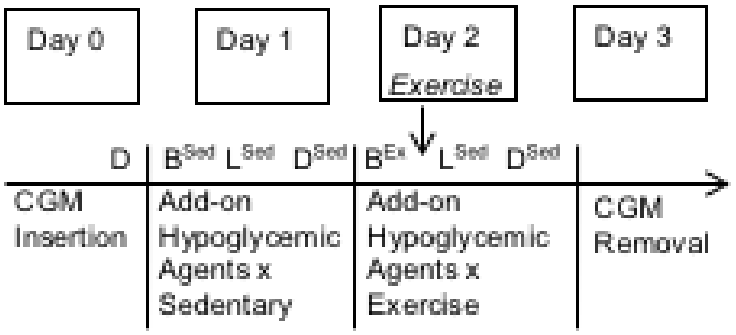

Day 0
Day 1
Day 2
Exercise
Day 3
D
B^Sed L^Sed D^Sed
B^Ex L^Sed D^Sed
CGM Insertion
Add-on Hypoglycemic Agents x Sedentary
Add-on Hypoglycemic Agents x Exercise
CGM Removal

Figure 4.2

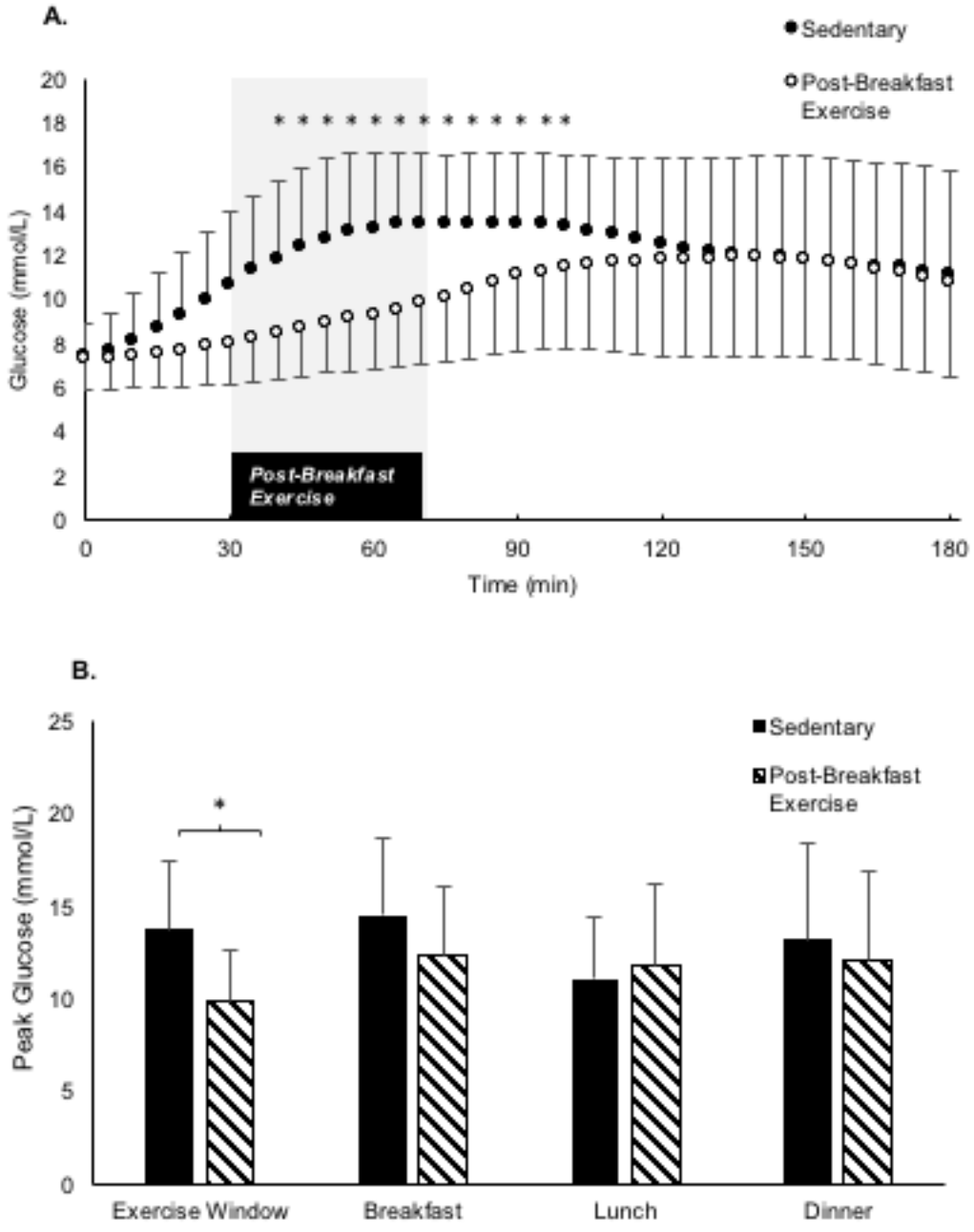
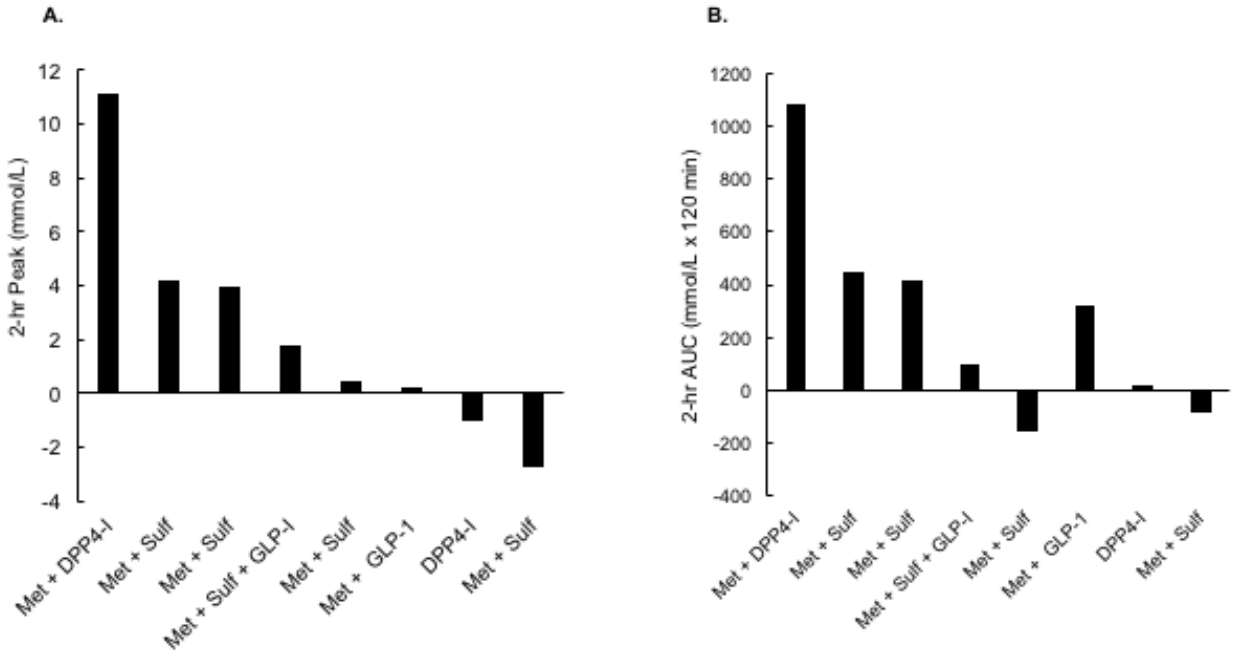

A.
Sedentary
Post-Breakfast Exercise
Glucose (mmol/L)
Post-Breakfast Exercise
Time (min)
B.
Sedentary
Post-Breakfast Exercise
Peak Glucose (mmol/L)
Exercise Window
Breakfast
Lunch
Dinner

Figure 4.3


A.
2-hr Peak (mmol/L)
12
10
8
6
4
2
0
-2
-4
Met + DPP4-I
Met + Sulf
Met + Sulf
Met + Sulf + GLP-I
Met + Sulf
Met + GLP-1
DPP4-I
Met + Sulf
B.
2-hr AUC (mmol/L x 120 min)
1200
1000
800
600
400
200
0
-200
-400
Met + DPP4-I
Met + Sulf
Met + Sulf
Met + Sulf + GLP-I
Met + Sulf
Met + GLP-1
DPP4-I
Met + Sulf

CHAPTER 5

SUMMARY AND CONCLUSIONS

Major Findings

The major finding of these studies was that postmeal exercise reduced postprandial glucose, measured with continuous glucose monitoring (CGM) in people on hypoglycemic agent regimens. Study 1 investigated people being treated specifically with metformin monotherapy. Results showed that postmeal exercise lowered key postprandial outcomes including glucose peak within a 2-hr time window, 2-hr area under the glucose curve (AUC), and glucose spike after a breakfast meal. Study 2 investigated people being treated with add-on hypoglycemic agents. Results showed that postmeal exercise reduced glucose values during the time of the exercise bout, however, this effect was not sustained throughout the day, or even through the duration of the postprandial breakfast period. These findings have important implications for using concurrent use of hypoglycemic agents and postmeal exercise to treat hyperglycemia.

Study 1 vs. Study 2: Expanded Discussion

There are two key differences between studies that potentially contributed to differential findings. First is disease severity between participant groups, and second is the applied exercise stimulus. Disease severity may be linked to the duration and magnitude of the postprandial hyperglycemic response, while the size of the exercise dose may be linked to its effectiveness for attenuating glycemic responses. Therefore, the overall effect of postmeal exercise on

postprandial glucose may be a function of the size of the hyperglycemic response in comparison to the size of the exercise dose. Hence, a larger hyperglycemic response may require a larger exercise dose for optimal attenuation, just as a patient with severe diabetes requires a larger medication dose for glycemic control.

Disease Severity: Participants on metformin monotherapy had better glucose control than participants on add-on hypoglycemic agents (HbA_{1C} Met: 6.3 ± 0.6 vs. Add-on: 7.9 ± 2.3). Below is a figure comparing average CGM values during the sedentary conditions between studies.

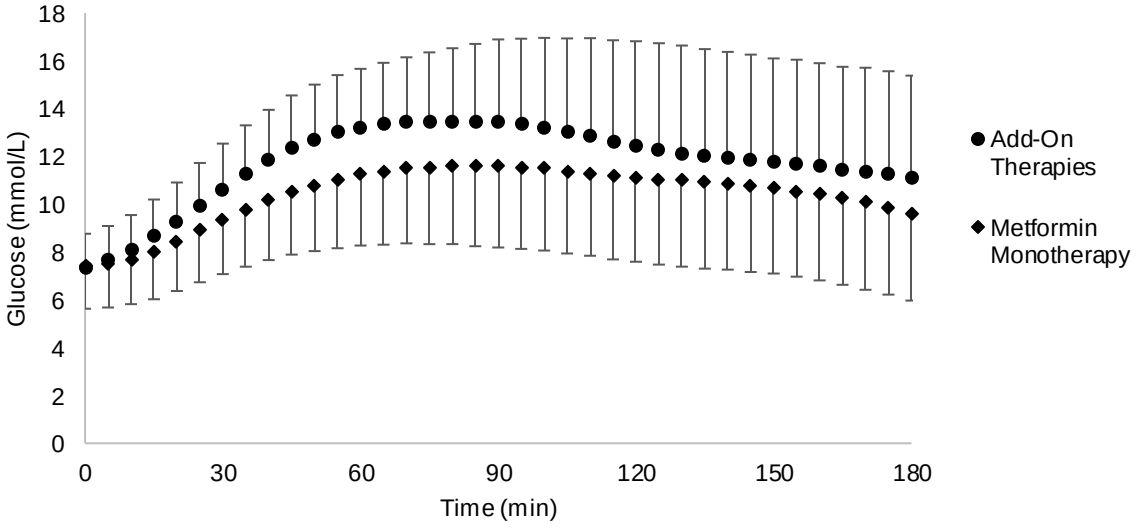


Figure 5.1 shows average CGM values of breakfast postprandial period during sedentary conditions in study 1 (metformin monotherapy) and study 2 (add-on therapies).

In addition, postprandial glucose excursions tended to be worse in participants on add-on hypoglycemic agents than participants on metformin monotherapy (2-hr peak Met: 12.0 ± 3.4 vs. Add-on: 14.5 ± 4.2 mmol/L; 2-hr AUC Met: 1301 ± 309, vs. Add-on: 1473 ± 328 mmol/L x 120-min). Higher glycemic outcomes seen in the add-on study suggest that these participants have

larger physiological defects contributing to increased hyperglycemia. However, it is not possible to pinpoint specific defects from the current glucose data alone. It is worth noting that differences among studies were not due to differences in participant characteristics (Table below).

Table 5.1

Characteristic	Study 1: Metformin Monotherapy (n = 10)	Study 2: Add-on Therapies (n = 8)
Sex (M/F)	2/8	5/3
Age (years)	57 ± 10	60 ± 10
Height (cm)	166.1 ± 10	167.8 ± 6
Weight (kg)	94 ± 20	94 ± 24
BMI (kg/m^2)	33.8 ± 4.7	33.8 ± 10.3
HbA_{1C} %	6.3 ± 0.6	7.9 ± 2.3
Estimated VO_2 peak ($ml/kg/min^{-1}$)	24.7 ± 6.4	26.7 ± 8.6
Fasting Glucose (mmol/L)	6.8 ± 1.8	7.9 ± 1.9
Tissue Fat (%)	45.6 ± 6.9	41.9 ± 10.3
Fat Tissue (kg)	43.8 ± 15.2	41.2 ± 19.2

The tendency for participants on metformin monotherapy to have lower glycemic outcomes than those on add-on hypoglycemic agents was expected to a degree. Typically, prescription to add-on hypoglycemic agents occurs after metformin monotherapy is deemed inadequate. Therefore, it is reasonable to suspect that individuals requiring add-on hypoglycemic agents have more severe defects in insulin secretion/action when compared to those who can achieve glucose control with metformin alone.

Some may find this argument counter-intuitive; instead, expecting those who are on more medications to have better glucose outcomes. However, this simply is not the case. Type 2 diabetes is a progressive disease, and treatment with hypoglycemic agents typically cannot match this progression. This point is best illustrated by the figure below:

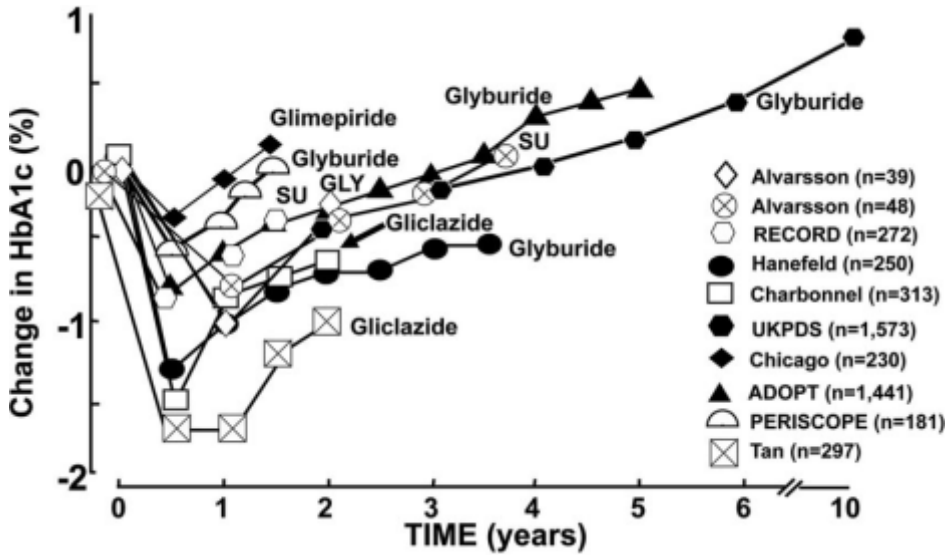


Figure 5.2 illustrates long-term effects on HbA_{1C} after sulphonylurea treatment in several landmark diabetes studies(39).

This figure illustrates the inadequacy of sulphonylureas to maintain glycemic control in the long term. In fact, on average, glycemic control is only improved by approximately 1.5% for 2 years. The inadequacy of hypoglycemic agents should NOT be interpreted as becoming tolerant or immune to medication. Instead, this inadequacy is a reflection of progressive beta-cell decline, which is part of the natural process of diabetes development.

Exercise Dose: Another key difference among studies is the applied exercise stimulus. Study 1 used 5 x 10 min bouts at 60% maximal oxygen uptake, while study 2 used 3 x 10 min bouts at 50% maximal oxygen uptake. One major difference between these two exercise stimuli is the duration (study 1: 62 min vs. study 2: 36 min). Therefore, the percentage of intervention time is smaller in the add-on study than in the metformin study (add-on: 16 ± 7% vs. met: 34 ± 11%). The figure below shows comparisons between study 1 and study 2 sedentary and post-breakfast exercise conditions.

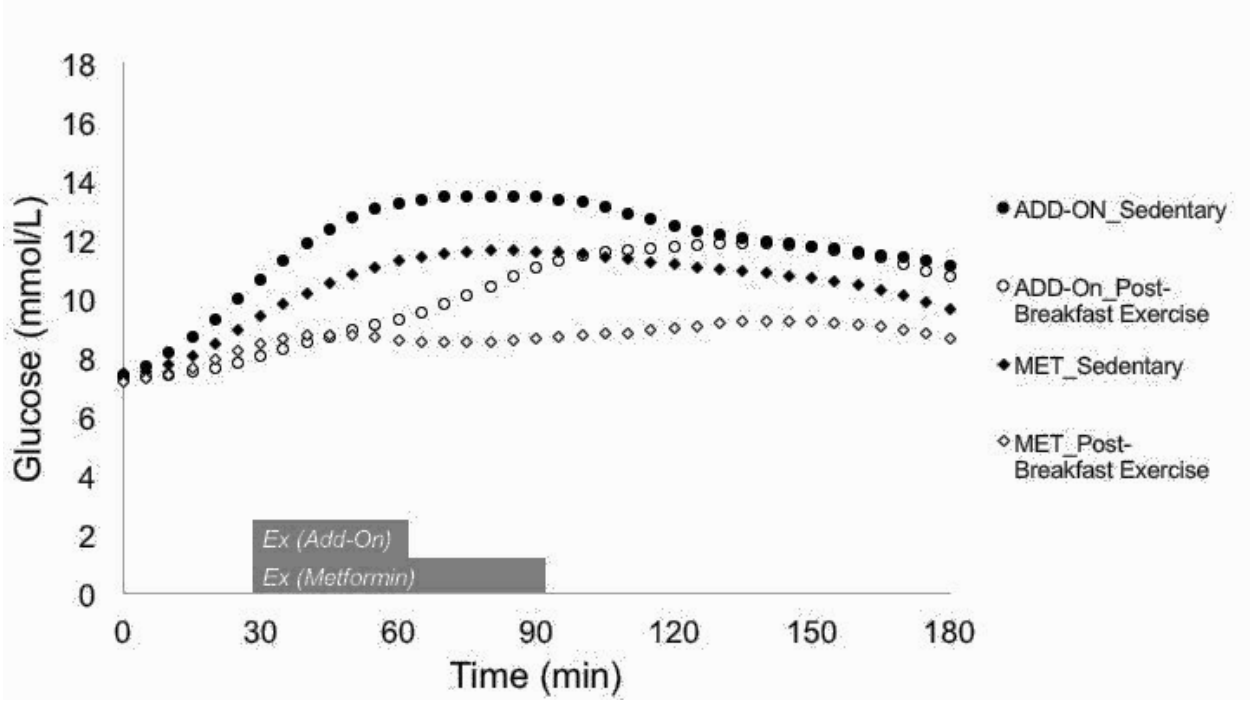


Figure 5.3 shows average CGM values of sedentary and post-breakfast exercise conditions for study 1 (Met) and study 2 (Add-on) during the breakfast postprandial period. Measures of variance omitted for clarity.

Exercise doses used in previous postmeal exercise studies have varied considerably(30). A study in older individuals with impaired glucose tolerance showed that an exercise bout as short as 15 minutes can lead to reductions in 24-hr average glucose(42). When interpreting the effects of this exercise bout, it is important to consider the magnitude of hyperglycemia experienced among participants. The breakfast peak reported in an individual was approximately 8.3 mmol/L, which is considerably lower than the glucose breakfast peaks measured in the current studies (Met: 12.0 ± 3.4 vs. Add-on: 14.5 ± 4.2 mmol/L). A lower peak could be considered an easier target for attenuation by postmeal exercise.

Overall, it is reasonable to suspect those who cannot achieve glycemic stability with metformin alone, thus necessitating add-on therapies, have increased disease severity. This has important implications on the size and magnitude of the postprandial glucose excursions from

the experimental breakfast meal. Taken together, these studies suggest that a "one size fits all" approach may not be appropriate when applying postmeal exercise bouts for the purpose of attenuating postprandial glucose excursions. Just as a higher dose of medication is required for a patient with poor glycemic control, it is possible that more severe glucose excursions will require a higher exercise dose for optimal attenuation.

Inadequacies of Hypoglycemic Agents

The notion that hypoglycemic agents are inadequate for achieving glycemic control is not new. Studies using continuous glucose monitoring have shown that even during regular treatment with hypoglycemic agents, glucose excursions are well above non-diabetic controls (97) (shown in fig below).

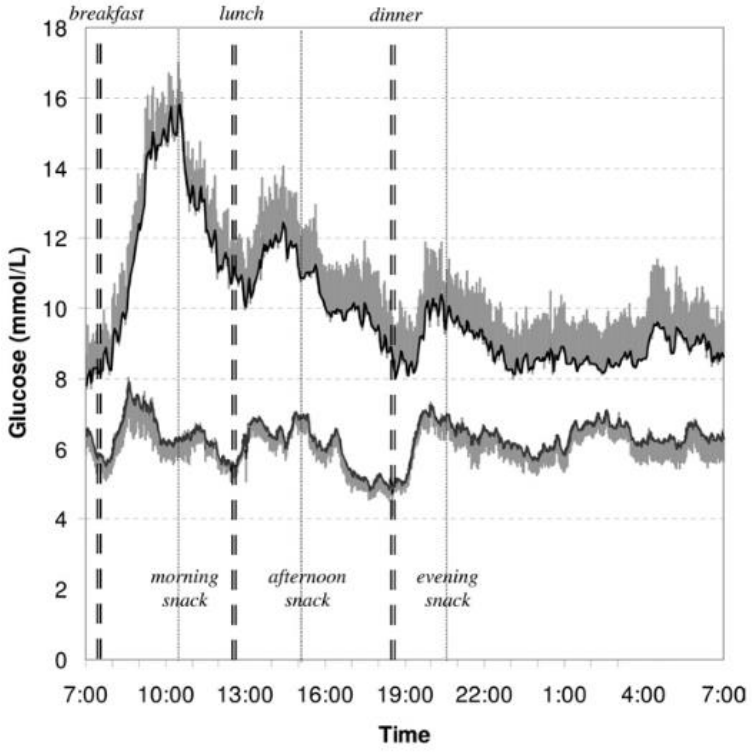


Figure 5.4 shown glucose excursions in people with type 2 diabetes taking hypoglycemic agents in comparison to non-diabetic healthy controls(97).

Results of the current studies also support this. Peak glucose within a 2-hr time window reached 12.0 ± 3.4 mmol/L in people on metformin, and 14.5 ± 4.2 mmol/L in people in add-on agents. Conversely, non-diabetic controls rarely exceed 10 mmol/L(97).

Some propose that this shortcoming is due our adoption of a non-physiologically based treatment approach (39). For example, clinical treatment decisions are based primarily on the HbA_{1C} value, which quantifies red blood cell glycation over approximately 120 days. That is, treatment success or failure is defined by maintaining an $HbA_{1C} \leq 7\%$. While the HbA_{1C} value is clinically advantageous because it is stable and easily obtained, it does not provide any information about the underlying physiological defects contributing to hyperglycemia. As a result, current methods of type 2 diabetes have been criticized as being too glucose-centric, versus being guided by correcting the underlying pathophysiological defects that contribute to hyperglycemia.

The above criticism could be addressed by employing treatment strategies that center on beta cell preservation, which is essentially a prevention strategy. Exercise has long been advocated as a prevention tool for type 2 diabetes. Another beta cell preservation approach is earlier initiation of pharmacological therapies such as GLP-1 analogs(39).

Study 1 and Study 2: Summary

Study 1 and study 2 investigated the effects of postmeal exercise on postprandial glucose excursions in people on hypoglycemic treatment regimens. Study 1 used people on metformin monotherapy. The applied exercise stimulus was 5 x 10 minutes of treadmill walking at 60% maximal oxygen uptake, with 3-min rest periods. The duration of this stimulus was 62 minutes in total, which spanned 34% of the postprandial response. Study 2 used people on add-on

hypoglycemic agents. The applied exercise stimulus was 3 x 10 minutes of treadmill walking at 50% maximal oxygen uptake, with 3-min rest periods. The duration of this stimulus was 36 minutes in total, which spanned 16% of the postprandial response.

Study 1 showed that the applied exercise dose in the study 1 was sufficient to reduce postprandial outcomes including 2-hr peak, 2-hr AUC and glucose spike. Study 2 showed that the applied exercise dose was sufficient to reduce glucose during the time of exercise, but this effect was not sustained throughout the duration of the postprandial period. Taken together, these findings suggest that the effectiveness of the postmeal exercise may be function of the applied exercise dose to the severity of the hyperglycemic response. This concept is similar to "increasing the dose" of a hypoglycemic agent in someone with severe hyperglycemia.

Clinically, treatment of hyperglycemia is primarily done with hypoglycemic agents. However, the long-term inadequacies of hypoglycemic agents are well documented. This suggests that novel strategies of glucose management are needed. Postmeal exercise has been shown to reduce postprandial glucose, however, there is a lack of evidence of how these strategies work in the background of hypoglycemic agents. The vast majority of postmeal exercise studies are small-scale experimental studies. A future avenue of the postmeal exercise field would ultimately be to investigate if such an intervention would have beneficial effects on HbA_{1C}.

Future Experiments

Since the success or failure of diabetes treatment is determined by the HbA_{1C} value, a clinically-impactful study would involve assessing the effects of a postmeal walking intervention on HbA_{1C}. There are several experiments that could be completed first that would help guide the development of such trials. For example, it will be valuable to make assessments of insulin and

C-peptide to further characterize the acute physiological effects of postmeal walking. Furthermore, glucose and insulin assessments could be completed across the hyperglycemia spectrum, as well as in the background of various hypoglycemic regimens.

Hyperglycemic spectrum: Studies addressing the relationship of postmeal exercise effects across the HbA_{1C} spectrum would help guide the development of longitudinal studies aimed at using postmeal exercise to reduce HbA_{1C}. The two major glucose components of HbA_{1C} are fasting and postprandial glucose components. Percentagewise, the contribution of fasting glucose increases as HbA_{1C} increases. For example, postprandial glucose is the larger contributor when HbA_{1C} is low (5-7%). As disease severity increases, fasting glucose rises and ultimately becomes the larger contributor to HbA_{1C} (8-10%). Since postmeal exercise primarily targets the postprandial component, it is likely that a postmeal walking intervention would have detectable effects at the lower range of HbA_{1C}. While this seems logical, it has yet to be confirmed empirically.

Hypoglycemic regimens: It will also be important for future studies to document interactions of postmeal exercise and hypoglycemic agent regimens. Findings from study 2 did not shown patterns among drug classes and exercise effects, however, this topic is still worthy of investigation. Future studies could evaluate whether postmeal exercise during treatment with hypoglycemic agents are additive or complementary. For example, some hypoglycemic agents target postprandial glucose and it would be interesting to test if there is additivity among treatments. In addition, some hypoglycemic agents are targeted at lowering fasting glucose; thus, postmeal exercise may provide complimentary benefits.

Broader Views

Disease Severity

As mentioned previously, a key difference between study 1 and study 2 was disease severity. Applying postmeal exercise to two different disease groups is a major strength of this dissertation because it provides valuable insight into how postmeal exercise should be used across various stages of the hyperglycemic spectrum. Participants from study 1 experienced more glucose lowering benefit than participants in study 2. In fact, findings from study 1 suggest that the effective size of postmeal exercise alone is comparable that of glucose-lowering drugs. Thus, postmeal exercise could be considered another version of an "add-on therapy." Whether adoption of postmeal exercise delays the need for additional add-on therapies warrants further investigation. Results from study 2 suggest that the source of variability in glucose responses mostly occurs during the post-exercise phase. While there are several possible reasons for this, it suggests that postmeal exercise may be more effective when applied to earlier disease stages. Future studies that further characterize postmeal glucose lowering effects across various diabetes phenotypes are needed.

Carbohydrate Dose/Overeating

When it comes to glucose management, another important consideration is food intake. Meal type and macronutrient composition have a direct influence on plasma glucose concentrations. Results from study 2 show that participants had difficulty handling the carbohydrate dose from the experimental meal (65% carb, 15% fat, 10% protein). As mentioned previously, the average peak glucose value in the add-on study was 14.5 ± 4.2 mmol/L, while healthy controls are not expected to exceed 10 mmol/L. The severe hyperglycemic response is

an indicator of how poorly the carbohydrate dose was tolerated by participants. This suggests that consuming large carbohydrates doses and/or repeatedly overeating could pose health risk in the long-term. Thus, eating behavior should remain a foundation of diabetes treatment.

The application of postmeal exercise did not completely blunt the glucose excursions seen in the study 2. This suggests that while small bouts of postmeal exercise cause some glucose reduction, it will likely not cure diabetes or replace the need for pharmacologic therapies. It is possible that the carbohydrate dose given to participants was simply too large for postmeal exercise to have a highly significant influence. Perhaps meals that are smaller in carbohydrates dose would be more amenable to postmeal exercise.

Exercise Timing

Exercise is a cornerstone of diabetes prevention and treatment, and it is recommended to patients at all stages of disease severity. However, there is no guidance on *when* to exercise, in relation to meal consumption. The strategy of "postmeal" exercise is a relatively novel concept that further sophisticates the approach of using exercise as a tool for glucose management. The historical view was that exercising after eating is uncomfortable and not recommended. While this may be true for high intensity exercise, this usually does not carry over into moderate intensity exercise. In the current studies, all participants were able to tolerate exercise after eating.

Public Health Message

Regulation of postprandial glucose is an important concern in the treatment of type 2 diabetes. Exercise *after* eating, such as walking at a moderate intensity, may be a strategy for

lowing postprandial glucose responses. The amount of benefit of exercising after eating may vary by disease severity, however, this concept is still being explored by the scientific community.

Final Thoughts

Postmeal exercise is not necessarily a cure for diabetes, however, it should be considered a cost effective tool for blood glucose management. Adequate diabetes treatment plans should involve complex regimens including routine exercise, eating behaviors/management of carbohydrate dosing, as well as effective hypoglycemic agents. The optimal time to implement postmeal exercise may be during disease onset, while waiting until the disease becomes more severe may reduce its effectiveness. Future studies should investigate if postmeal walking regimens can reduce HbA_{1C}.

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