THE TIMING OF WALKING AND POST-MEAL BLOOD SUGAR LEVELS IN ADULTS WITH TYPE 1 DIABETES

LAUREN V. TURNER

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ABSTRACT

Background and aims: Compared to being sedentary after a meal, a post-meal moderate intensity walk can reduce blood glucose levels in persons living with diabetes. However, it is unclear if post-meal walks confer better, or worse, glucose management than pre-meal walks in people living with type 1 diabetes (T1D), who are prone to dysglycemia. This study examined whether, compared to being sedentary after a meal, a 20-minute moderate intensity walk before or after dinner could reduce post-prandial glucose (PPG) excursions, without eliciting hypoglycemia, in individuals with T1D using hybrid closed loop insulin delivery systems (HCLS).

Methods: Eleven adults with T1D (mean±SD age 42±13 years, BMI 26.3±3.69 kg/m^2, HbA_{1C} 6.3±0.8%, six female) using HCLS participated in this randomized, crossover, at-home observational study. Following two baseline weeks of glucose assessment, using standardized percent time in glycemic target range (%TIR; 3.9-10.0 mmol/L) analysis from continuous glucose monitoring (CGM), participants were assigned to a 20-minute pre- or post-dinner walk at a moderate intensity (~40-50% of their estimated maximal aerobic capacity), every day for two weeks. The participants personal CGM data (Dexcom G6) were analyzed in the 2 hours before and 4 hours following dinner using generalized estimating equations.

Results: Pre-dinner glucose levels were similar between pre- (6.6±2.0 mmol/L) and post-meal (7.1±2.4 mmol/L) moderate intensity walks compared to baseline (7.0±2.3 mmol/L) (p=0.12 and p=0.65, respectively). However, pre-meal walks significantly improved percent TIR (i.e., glucose levels between 3.9 to 10.0mmol/L) by ~6% (B=5.58; 95% CI=[1.24, 9.92]; p=0.01) and decreased time in level 1 hyperglycemia (i.e., glucose levels 10.1-13.9mmol/L) by ~6% (B=5.81; 95% CI=[-10.12, -1.51]; p=0.01) during the 2-hour pre- to 4-hour post-dinner period. In contrast, post-meal walks did not confer any significant differences in %TIR metrics vs baseline (i.e., being sedentary

around the dinner meal). Levels of other PPG metrics, including hypoglycemia incidence or time below glycemic target range, demonstrated no significant differences between the three conditions ($p>0.05$).

Conclusion: In adults with T1D using HCLS who are already achieving target baseline glycemic management, as measured by weekly %TIR metrics, a pre-meal walk offers a slight advantage over a post-meal walk in lowering PPG. The reasons for the advantage of pre-meal moderate intensity walking for PPG management are unclear. However, they may be related to how HCLS responds to the timing of meals in relation to moderate intensity physical activity.

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ABBREVIATIONS

AID	Automated insulin delivery system
AUC	Area under the curve
B	Unstandardized regression coefficient
CGM	Continuous glucose monitor
CI	Confidence interval
CSII	Continuous subcutaneous insulin infusion
HbA_{1C}	Hemoglobin A_{1C}
HCLS	Hybrid closed loop insulin delivery system
HR	Heart rate
fCGM	Flash continuous glucose monitor
GLUT4	Glucose transporters 4
LSM	Least square means
MDI	Multiple daily injections
PAR-Q +	Physical activity readiness questionnaire for everyone
PPG	Postprandial glucose
RPE	Rate of perceived exertion
SE	Standard error
SD	Standard deviation
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TAR1	Time above range 1 (10.0 – 13.9 mmol/L)
TAR2	Time above range 2 (>13.9 mmol/L)
TBR1	Time below range 1 (3.0 – 3.9 mmol/L)
TBR2	Time below range 2 (<3.0 mmol/L)
TIR	Time in range (3.9 – 10.0 mmol/L)
TDD	Total daily dose
VO_{2max}	Maximum volume of oxygen consumption

1.0 INTRODUCTION AND BACKGROUND

Over 300,000 Canadians live with insulin-requiring type 1 diabetes (T1D), and the incidence rate is growing by 5.1% annually [1]. T1D is an autoimmune-driven disease characterized by an inability of the body to produce insulin to bring glucose into the cells, making it hard to manage blood glucose levels, especially in the postprandial periods (following a meal) [2]. Fluctuations in blood glucose can lead to T1D-related complications such as heart disease, kidney disease, nerve damage, limb amputation, blindness, hospitalizations, and premature death, by about ten years [3]. These complications strain the individual, their families, and the Canadian healthcare system [1]. According to recent modelling of Canadian data, the better maintenance of glucose levels in T1D using newer technologies, such as continuous glucose monitors (CGM) and automated insulin delivery (AID) or hybrid closed loop insulin delivery (HCLS) systems, delay disease morbidity and mortality and may even be considered cost-effective for the Canadian healthcare system [4].

Habitual physical activity participation may [5], or may not [6], improve long-term blood glucose management as measured by glycosylated haemoglobin (HbA_{1c}), likely because of the complexity in insulin dosing, but is encouraged for people with T1D for a variety of reasons related to enhanced cardiovascular health and fitness [6–9]. In individuals without T1D, whole-body dynamic aerobic exercise such as walking, running, or cycling largely increases glucose disposal via insulin-independent mechanisms, thereby mitigating blood glucose spikes associated with meals [10]. Similarly, studies have demonstrated that in adults with T1D, walking following a meal attenuated post-meal blood glucose excursions [11,12]. However, it is important to note that these studies were conducted before advancements in T1D technology, such as HCLS and CGMs,

decreasing the generalizability of these results given their recent adoption in North America [11–13].

To date, no studies have used current T1D technology, including HCLS and CGMs, to examine the effects of pre- or post-dinner moderate intensity walks on postprandial glucose (PPG) management in people with T1D in an at-home environment. Furthermore, no studies have looked at the impact of a shorter duration of moderate intensity aerobic activity which may be feasible to implement into an individual's daily routine. This study aims to determine whether 20 minutes of moderate intensity walking before or after dinner can attenuate PPG excursions in individuals with T1D.

2.0 LITERATURE REVIEW

T1D is an autoimmune disease characterized by the destruction of the insulin-producing beta-cells of the pancreas and is often developed in childhood or adolescence [14]. Without the body's natural endogenous insulin production and secretion of the hormone insulin into the portal vein to regulate blood glucose balance, persons with T1D regularly face blood glucose fluctuations outside the normal fasting range (4.0-6.0mmol/L) [15], and even outside the acceptable glucose target range throughout the day for those on insulin therapy (3.9-10.0 mmol/L) [16]. Although there is no cure, current treatment for T1D includes intensive insulin therapy and frequent glucose monitoring [17]. Exogenous insulin can be administered through multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII). More recently, the use of CGMs, along with an AID or a HCLS, have been more widely adopted in countries that can afford the access to these technologies that can clearly improve clinical outcomes [18–22]. While both the HCLS and AID systems aim to automate insulin delivery, the main distinction lies in the degree of automation. HCLS adjusts basal insulin rates but requires user intervention for bolus dosing and calibration, while AID encompasses a fully closed loop system which controls both basal and bolus insulin delivery.

Even with intensive insulin therapy and HCLS and AID systems, individuals with T1D often face dysglycemia (i.e., periods of hypo- or hyperglycemia). A hemoglobin A1C (HbA_{1C}) <7.0% is the clinical objective recommended for individuals with T1D [23]. However, HbA_{1C} values provide a 3-month glycemic average and can fail to depict daily glycemic variation caused by daily events that impact glycemia such as food, stress, and physical activity [24]. As diabetes technology has evolved, more individuals with T1D are using “flash” glucose monitoring (fCGMs), where the user swipes a “reader” over a glucose sensor that is implanted under the skin,

or real-time CGMs that broadcasts data to a reader, insulin pump or smartphone, which reports the percentage time target glycemic range (%TIR) of 3.9-10.0 mmol/L [25,26]. A 70% TIR equates to an HbA_{1C} of ~7.0% and is the clinical target for individuals with T1D, but this still demonstrates that 30% of the time the user is in dysglycemia (either hypo- or hyperglycemia). Each 10% increase or decrease in %TIR changes HbA_{1C} by ~0.5% [27]. Beyond %TIR, CGMs also offer an overview of the percentage of time below (%TBR; <3.9 mmol/L) or above (%TAR; >10.0 mmol/L) the target range, offering a more complete overview of glycemic management [24,28]. To help focus on where the glucose management fails to be within target range in a person with diabetes, various terms have been developed, such as fasting glucose, after a meal post-prandial glucose (PPG), and post-absorptive glucose level (i.e., after the nutrients from a meal are thought to be fully absorbed and assimilated, ~4-5 hours after a meal) [16].

2.1 POSTPRANDIAL GLUCOSE

2.1.1 Definitions

Three primary metabolic states can be discussed while examining a person's blood glucose levels throughout the day. Firstly, ~10-12 hours following the last ingestion of food, the body is in a *fasting state* (catabolic). In a healthy individual, physiological blood glucose level is maintained with insulin levels low in circulation. At the same time, other counterregulatory hormones rise through a balance of glucose entering (appearance) and being removed (disappearance) from circulation [29]. With feeding, termed the *postprandial glucose (PPG) state* (anabolic), the body shifts to a more anabolic state for up to four hours post-ingestion of food or drink, with a concomitant rise in insulin to help combat the rise in glucose concentration [29]. After this, the individual remains in a *post-absorptive* (neutral) state for a few hours with insulin levels dropping

toward fasting levels and glucose levels remaining between 4.0-7.0 mmol/L. However, even with insulin therapy, these physiological processes are challenging to mimic in T1D [30].

2.1.2 Maintaining Blood Glucose in the Fasting State

Non-T1D: In the fasting state, glucose leaves circulation at a constant rate. In a healthy individual, the pancreas maintains physiological blood glucose levels by reducing insulin secretion from the beta cells and increasing glucagon release from alpha cells [31,32]. Additionally, the formation of glucose from glycogenolysis (liver) and gluconeogenesis (lactate and amino acids) are not limited [33–35].

T1D: Individuals with T1D rely on exogenous insulin administration and often face dysregulation in the amount of circulating portal insulin, impacting the production of plasma glucose from glycogenolysis and gluconeogenesis [36,37]. If a person with T1D administers too much insulin, glycogenolysis and gluconeogenesis are suppressed, decreasing blood glucose. On the other hand, if not enough insulin is delivered, these pathways are uninhibited, and blood glucose will increase [36].

2.1.3 Maintaining Blood Glucose in the Postprandial State

Non-T1D: Immediately after carbohydrate ingestion, there is an increase in plasma blood glucose levels [38]. In healthy individuals, insulin is released from the beta cells of the pancreas to mitigate this rise in three primary manners. Firstly, insulin will increase glucose disposal into the periphery (skeletal muscle and adipose tissues). Similarly, blood glucose rises will be mitigated as insulin will act through the paracrine route, to inhibit glucagon production from the alpha cells of the

pancreas. Finally, insulin in portal vein circulation will act directly on the liver to suppress glucose production [39].

T1D: Individuals with T1D depend on exogenous insulin therapy to manage increases in PPG levels [39]. If insufficient insulin is administered during a meal for someone with T1D, hepatic and peripheral glucose uptake will decrease. Simultaneously, exogenous insulin will not effectively suppress glucagon production via the paracrine route. Consequently, glucose appearance may surpass disappearance, leading to plasma blood glucose levels above the target range of 10.0 mmol/L [36].

2.1.4 Postprandial Hyperglycemia

In a person without diabetes, insulin will be secreted into the portal vein, and blood glucose levels will generally peak within ~30-60 minutes of food consumption and return to pre-meal levels within ~2-3 hours [41–43]. However, individuals with T1D have a delayed blood glucose lowering response due to the slower pharmacodynamics of subcutaneously administered insulin [44]. Rapid-acting insulin analogs take ~10-15 minutes until insulin action onset, with peak action occurring after ~1-2 hours, while endogenous insulin typically peaks and disappears within minutes [45]. As such, individuals with T1D often face an increase in PPG hyperglycemia (>10.0 mmol/L) with meals, particularly when a heavy carbohydrate meal is consumed. Various strategies may help reduce the PPG in T1D, such as a delay in eating after administering mealtime (prandial) insulin, a diet higher in fibre and/or lower in carbohydrate content, or moderate intensity aerobic activity [46,47].

2.1.5 Risks Associated with PPG Hyperglycemia

Glycemic Management: PPG is one of the most significant contributors to dysglycemia, even in T1D patients with adequate overall metabolic management [48]. A study by Monnier and Colette (2006) found that PPG contributed to 70% of overall hyperglycemia in 290 T2D subjects with an HbA_{1C} <7.3% [49]. These results imply that PPG influences glucose %TAR (e.g., soon after meals), %TBR (e.g., rebound hypoglycemia long after meals) and glucose variability independent of its influence on overall glycemic control as measured by HbA_{1C}. As such, PPG may be associated with the development of diabetes complications, including macro and microvascular disease [50].

Macrovascular Disease: One of the most considerable complications associated with T1D is the development of macrovascular disease, which can increase the risk of premature morbidity and mortality [51]. In a 14-year longitudinal study of over 500 individuals with T2D, 2-hour post-lunch blood glucose values >10.0mmol/L were significant predictors of cardiovascular events (HR=1.452, p=0.021) and all-cause mortality (HR=1.846, p=0.001) [52]. It has been suggested that oxidative stress caused by acute PPG excursion can increase levels of pro-inflammatory mediators, exacerbating endothelial dysfunction and proatherogenic mechanisms [53,54]. For instance, in persons with T2D, dropping PPG by ~1% if a patient's HbA_{1C} was ≥6.5% reduced the risk of myocardial infarction by 14% over a 10-year follow-up period [55], demonstrating the potential benefit of lowering PPG on oxidative stress and associated macrovascular disease complications in persons with T1D [56].

Microvascular Disease: Microvascular complications of T1D, including retinopathy, nephropathy, and neuropathy, can also increase one's risk of morbidity and mortality [57,58]. While research is limited in individuals with T1D, studies in populations of inactive, overweight and/or obese individuals with T2D have demonstrated an association between PPG and

microvascular complications [59,60]. In one study of 151 persons with T2D who had a BMI of 25.7±4.4 kg/m^2 and an Hb_{A1C} of 8.15±1.51%, PPG levels independently correlated with the progression of diabetic retinopathy ($p<0.001$) [60]. However, further research is needed to establish the direct mechanisms behind this relationship.

2.2 CONVENTIONAL PPG MANAGEMENT STRATEGIES FOR T1D

Finding strategies to improve PPG dysglycemia in persons with T1D is essential to limiting diabetes-related complications. Conventional strategies to reduce PPG (i.e., hyperglycemia post-meals) include newly developed faster-acting insulins, understanding and/or changing the meal composition, the use of newer T1D technologies such as CGM and insulin delivery systems, and potentially adding physical activity before or after meals.

2.2.1 Insulin

The time lag to peak action while using rapid-acting insulins for meals has influenced the development of fastest-acting insulins, such as faster-acting aspart and ultra-rapid lispro [61]. Ultra-rapid lispro, which appears to be the fastest-acting injected/infused insulin available to date [62], includes treprostinil to induce local vasodilation and citrate to increase vascular permeability. Together, these compounds improve PPG by accelerating insulin absorption and reducing the insulin action period [63]. For example, with the same meal-to-dose timing in 30 persons with T1D, ultra-rapid lispro had better PPG-lowering effects than Humalog. Moreover, the glucose excursion over 5 hours when using ultra-rapid lispro was reduced by 40-44%, which may have the additional benefit of lowering one's risk of late-onset hypoglycemia [64].

2.2.2 Meal Composition

Carbohydrate Counting: Carbohydrate content is a primary determinant of PPG management in T1D [65], and individuals with the disease must closely monitor and count carbohydrate intake to accurately administer a meal insulin bolus [66]. However, carbohydrate counting is a challenge for many individuals. A study of 50 adults with T1D examined patients' 72-hour food records and glucose excursions. Compared to a dietitian using a computerized analysis program, persons underestimated carbohydrate content in 62.7% of their meals [67]. This could influence PPG hyperglycemia as the greater the discrepancy in carbohydrate counting, the greater the variation in PPG [67].

Glycemic Index: The glycemic index of a food containing carbohydrates indicates how quickly the carbohydrate will be broken down during digestion and absorbed into the bloodstream [68]. Foods with a 'high-glycemic index' are broken down and absorbed quickly, rapidly increasing blood glucose. Foods with a low glycemic index are recommended to reduce glucose peak and optimize overall PPG response in individuals with T1D [69]. Moreover, the content of other macronutrients in a food or meal can further influence glycemic response. For instance, consuming 75 to 100g of protein in isolation significantly increased glucose concentrations with a peak from 3 to 5 hours, but 12.5 to 50g of protein did not [70]. Although all aspects of meal composition are essential to PPG management, carbohydrate counting alone is challenging for many individuals living with T1D, as noted above. The glycemic index of a mixed meal is difficult to assess particularly when whole foods are combined (e.g., chicken breast with a sauce, potato salad, brown bread, green and/or root vegetables that contain trace or high levels of carbohydrate, depending on the type).

2.2.3 Technology

Glucose Monitoring: CGMs and fCGMs have significantly contributed to understanding overall patterns of glycemia and PPG in persons with T1D [25,26]. These sensors use a subcutaneous sensor to measure glucose levels in the interstitial fluid. Every 5 minutes (CGM) or when scanned (fCGM), glucose readings are sent to a patient's glucose device, smartphone, and/or insulin pump [26]. Although CGMs are a reasonable reflection of blood glucose concentrations, there is a physiologic lag between sensor glucose and blood glucose readings [71,72]. It takes time to move glucose from the vasculature, where a blood glucose meter can measure the glucose level, to the interstitial fluid space, where the CGM is placed [73]. In times of rapid blood glucose changes, such as post-meal or with vigorous intensity anaerobic exercise (such as sprinting or weightlifting) [74], there is often a time delay in plasma glucose readings ranging from 3-12 minutes [72,75,76]. Nonetheless, glucose sensors offer individuals the opportunity to understand how different meal types, insulin timing relative to meal, behaviour, and physical activity can influence PPG [39,77].

Insulin Pumps: Hybrid closed-loop therapy, requiring user-initiated prandial insulin doses, are the most advanced closed-loop systems commercially available [18]. Automating insulin delivery reduces the input required from those wearing the device, leading to better physiological and psychosocial outcomes [18]. Typically, every 5-minutes, the algorithm will use CGM readings to automatically increase, decrease, or suspend basal insulin infusion to maintain a target glycemic range (often 6.0-10.0mmol/L). However, HCLS still rely on user-inputted information on activities that could influence glycemic management, including physical activity, stress, and meals [18]. As such, HCLS are not always effective at glucose excursions.

2.3 PHYSICAL ACTIVITY AND EXERCISE AS A PPG STRATEGY

Regular physical activity [78] Click or tap here to enter text.offers numerous long-term benefits in persons with T1D, including physical improvements in health and overall well-being and quality of life [7]. Physical health improvements include increased aerobic fitness [7], improved lipid profiles [79,80], increased insulin sensitivity [81,82], and a lower risk of premature all-cause cardiovascular disease and mortality [83]. Moreover, physical activity can improve diabetes-related complications, including nephropathy, neuropathy, and retinopathy.

To reap these health benefits, it is generally recommended that adults with T1D participate in 150 minutes of physical activity per week, including resistance training exercise sessions 2-3 times per week and no more than two days of consecutive rest [3,84,85]. It is important to note that while physical activity includes any body movement produced by skeletal muscles that requires energy expenditure, exercise is a subset of physical activity that is structured, planned, repetitive, and intended to improve or maintain physical fitness. Exercise can involve activities like running, swimming, weightlifting, cycling, or participating in fitness classes. Specific to exercise sessions, a recent review by Helleputte et al. (2023) has highlighted that further research is necessary to investigate the influence of exercise timing and intensity, individual physiological characteristics, and current technology on early and late-phase PPG responses in the T1D population [86].

2.3.1 Exercise Duration and Intensity

During exercise, lipids and carbohydrates are the primary fuel sources, obtained from both within and outside muscle tissue. Fuel utilization and glucose variations during exercise in individuals with T1D depend on the intensity and duration of the activity.

In the early stages of exercise, the body relies on fuel stores within the muscles, such as high-energy phosphates (adenosine triphosphate and phosphocreatine) and muscle glycogen. However, as exercise duration increases, the body gradually shifts its reliance to fuel sources outside the muscles, including free fatty acids and circulating glucose [87]. Glucose is taken up from the bloodstream into the muscles. In individuals without diabetes, the release of glucagon, catecholamines, and growth hormone during exercise (which stimulate gluconeogenesis) in conjunction with low insulin levels helps maintain a safe glycemic range [88,89]. As exercise continues and the levels of counter-regulatory hormones rise, additional fuel sources such as triglycerides mobilized from fat stores, become available. However, individuals with T1D may experience impaired counter-regulatory hormone response to exercise, which is essential for gluconeogenesis and lipolysis [90]. Consequently, blood glucose levels tend to decrease during prolonged moderate intensity exercise (such as sustained running or cycling) [87,91,92].

Lower-intensity aerobic activities, like planned walking sessions, often decrease blood glucose levels in T1D, primarily due to the body's inability to lower circulating insulin concentrations at the onset of exercise [93]. Additionally, elevated blood flow and insulin absorption due to a translocation of GLUT-4 with aerobic activity can increase insulin concentrations, further lowering blood glucose [94]. Conversely, vigorous-to-maximal intensity activities, like sprinting or weightlifting, generally have the opposite effect on glycemia, attenuating the drop in blood glucose levels or even causing an increase [95]. During these higher-intensity activities, the shift in fuel utilization from fat to carbohydrates occurs, and there is an increase in counter-regulatory and metabolic hormones, such as catecholamines, cortisol, and growth hormone. These hormonal responses restrict glucose uptake and can lead to elevated blood glucose levels [96].

2.3.2 Exercise Time of Day

The timing of exercise, whether in the morning or afternoon, can influence blood glucose responses in individuals with T1D. Understanding the effects of morning versus afternoon exercise on blood glucose management is crucial for managing glycemic management in this population.

When examining longer-term glycemic management for individuals with T1D, participating in morning structured exercise sessions may have certain advantages. Morning exercise has been associated with improved overall physical activity adherence [97] and appears to be associated with a lower risk of exercise-associated hypoglycemia in the following 36 hours compared to when the same type of exercise is completed in the afternoon [98]. On the other hand, afternoon exercise has shown benefits in individuals with pre-diabetes or T2D, particularly when vigorous-intensity exercise is performed. Studies have demonstrated that afternoon high-intensity training or endurance exercise can result in improved glycemic outcomes, such as lower overnight and next-day blood glucose levels [99,100]. This might be attributed to enhanced insulin sensitivity following the afternoon exercise sessions.

The acute glucose responses to morning and afternoon structured exercise sessions in individuals with T1D differ. Late-day whole-body moderate intensity aerobic exercise, particularly walking or running, tends to promote a greater drop in glucose during exercise, increasing the risk of nocturnal hypoglycemia [101,102]. On the contrary, morning high-intensity anaerobic exercise, such as heavy resistance training performed in a fasted state, can lead to hyperglycemia, especially in individuals with significant increases in circulating lactate levels [103,104]. Therefore, precautions should be taken to manage glucose levels during and after exercise sessions, including insulin bolus corrections, continuous glucose monitoring, and carbohydrate intake.

2.3.1 Exercise Timing Around a Meal

A single bout of structured exercise, such as participating in a 20-minute bout of moderate intensity endurance exercise, can increase insulin action and glucose uptake during and following exercise. During exercise, blood flow and glucose delivery increase to the working muscle to help facilitate glucose disposal [105–107]. The activation of AMPK within the contracting muscle will facilitate the translocation of the glucose transporters 4 (GLUT4) to the skeletal muscle membrane to further enhance glucose uptake [108]. This increase in glucose disposal rate, without a concomitant increase in glucose rate of appearance in T1D, tends to decrease blood glucose levels [109,110]. Moreover, insulin sensitivity and glucose disposal rates are increased in recovery from a single bout of exercise for several hours [111], thereby helping individuals with T1D to maintain lower blood glucose levels and higher %TIR for about 24 hours after a single exercise session is done [112–114]. Participating in an aerobic exercise before (pre-prandial) or after (post-prandial) a meal may be a promising way to attenuate PPG hyperglycemia.

Pre-Meal Exercise: The influence of pre-meal exercise on PPG has been primarily investigated in individuals living with T2D, insulin resistance/pre-diabetes, or healthy populations, as reviewed elsewhere [115–117]. Reductions in PPG from 0-150 minutes post-lunch ($p<0.05$) have been reported in healthy subjects following 20-minutes of aerobic exercise (i.e., walking at 4-6 km/h) performed before the meal [118]. Consistent with these findings, 60-minutes of aerobic exercise at 60% heart rate reserve significantly improved the 4-hour PPG area under the curve (AUC) ($p=0.02$) in individuals living with T2D [119]. The authors of this study believed that these glucose-lowering benefits were due to increased GLUT4 content and improved vascular function following exercise [119]. However, pre-meal exercise has not improved PPG in all cases. For example, it was found that following 20 minutes of walking at a comfortable intensity before or

after a standardized meal in individuals with T2D, glucose 90-minutes post-meal was significantly lower in the post-meal walk group (6.1±0.4 mmol/L, p=0.048) compared to the pre-meal walk group (8.8±1.0 mmol/L) [120]. However, it is essential to note that these studies have not been widely conducted in individuals with T1D whose levels of circulating insulin pre-exercise may influence these responses.

Post-Meal Exercise: The benefits of light- to moderate intensity post-meal exercise has been reported to improve PPG in most groups (T2D, healthy, T1D). In persons with T2D, 45 minutes of moderate-intensity cycling (~50% VO_{2max}) starting 45 minutes after a meal improved PPG AUC by 50%, likely by a markedly enhanced rate of glucose disappearance as carbohydrate oxidization increased by 53.4±5.7% [121]. Similarly, in 7 untrained males with T1D, 30-minutes of cycling at ~65% VO_{2max} 15 minutes after a meal reduced PPG AUC by approximately one-third (34 ± 12%, $p<0.01$) compared to the 180-minute AUC following a no exercise meal. There were also small reductions in peak glucose values following exercise, but the differences were not statistically significant (13.7 ± 0.3 vs. 12.0 ± 1.3mmol/l, p = 0.09) [122]. The authors speculated that improvements in PPG were caused by improved insulin-mediated glucose uptake caused by a higher muscle glycogen synthase activity following exercise [122]. Another study of six individuals with T1D (43±13 years old) on a basal/bolus multiple daily injection insulin regime found that compared to controls, walking 30 minutes following a meal significantly lowered the glucose AUC (3.8[mmol/L]*hr vs 11.8[mmol/L]*hr, p=0.043) [110]. However, a potentially important consideration of the results of the T1D studies is that patients had to reach normoglycemia (4.0-11.2 mmol/L) before exercise, which may not be reflective of daily fluctuations in glucose seen in at-home settings for individuals living with T1D. Moreover, the patients were told the exact carbohydrate intake associated with their meal, limiting carbohydrate

counting bias. Thus, the results of these studies may not be indicative of living in an open at-home environment with T1D. Taken together, however, these studies demonstrate the potential benefits of post-meal exercise on PPG in individuals with T1D, although the implication in an at-home setting requires further examination.

2.4 ADDITIONAL CONSIDERATIONS

As discussed above, both pre-and post-meal moderate intensity aerobic exercise sessions show strong promise for improving PPG in individuals living with T1D. However, current research regarding "prescribed" moderate intensity walks and PPG in individuals with T1D is limited (Table S1). There are presently several research gaps and additional considerations that require further investigation before meal-timed exercise can be considered to improve PPG in the T1D population (Table S2).

2.4.1 Potential Sex Differences

Sex-related differences in fuel utilization and hormonal responses during and following exercise in nondiabetic individuals have been established in past literature [123–128]. While there is limited research examining these differences in individuals with T1D, they seem to be generally consistent between the two populations [129,130]. For instance, males tend to have a higher respiratory exchange ratio during exercise compared to females, indicating they may oxidate more carbohydrates during an exercise bout [131]. Moreover, hormones work in addition to insulin and glucagon during exercise and may influence PPG homeostasis differences in males and females (Table S3).

2.4.2 Exercise Adherence and Hypoglycemic Concerns

Individuals with T1D face similar barriers to adherence to structured exercise sessions as those without diabetes. A considerable percentage of adults with T1D, ranging from 19% to 32%, do not meet the recommended physical activity guidelines [132–134]. Time constraints, limited access to fitness facilities, and financial limitations are commonly reported barriers for adults who are prioritizing personal and professional development. However, research suggests that shorter exercise bouts of less than 20 minutes are more feasible and adherable for adults compared to longer duration exercise sessions of 20 to 60 minutes [135–137]. Walking, in particular, offers the flexibility to be performed in an at-home environment and at one's own pace, possibly making it an achievable exercise mode to improve PPG responses in individuals with T1D.

In addition to the general barriers associated with exercise, individuals with T1D have specific concerns regarding the fear of or actual occurrence of hypoglycemic events during exercise. Unlike healthy individuals, who rely on insulin and glucagon for glucose regulation during exercise, those with T1D experience disruptions in this hormonal balance. In healthy populations, insulin secretion decreases rapidly at the onset of exercise while hepatic glucose production increases [138]. Simultaneously, counterregulatory hormones such as glucagon, catecholamine, growth hormone, and cortisol are elevated to prevent excessive glucose elevations [129].

However, replicating this response in individuals with T1D is challenging. Administered endogenous insulin, which may be in the correct amount for a resting state, will not reduce portal vein circulation at exercise onset [139]. Individuals with T1D often begin exercise in a relative hyperinsulinemia state because of insulin delivery in the subcutaneous tissues, thereby promoting increased glucose disposal rates during exercise [8,140]. This might decrease blood glucose into a

hypoglycemic state [141,142]. Such episodes of hyperinsulinemia are more common following a meal bolus [143]. Therefore, pre-meal exercise may be a manner to reduce hypoglycemic events for individuals with T1D while maintaining PPG-lowering benefits. Further research is needed to explore the adherence and safety of pre- or post-meal exercise protocols to mitigate hypoglycemia in the T1D population.

2.5 REVIEW CONCLUSIONS

Based on the influence of PPG on overall glycemic management and the presence of diabetes-related complications in the T1D population, developing exercise interventions to promote adherence and limit PPG excursions is needed in this population. Both pre-and post-meal 20-minute moderate intensity walking interventions (3-4 on the Borg RPE 10-point scale, easy to breathe and hold a conversation) may be a time-efficient protocol; however, more research is needed.

3.0 STUDY OVERVIEW AND HYPOTHESIS

This was a 6-week, at-home cross-over observational study of the timing of moderate intensity walking on dinner-related PPG levels in men and women with T1D on a HCLS. Following one virtual assessment visit, individuals were asked to complete 2-weeks of baseline data collection followed by 4-weeks of data collection under different walking conditions. Anthropometric data (self-report) was documented following a virtual assessment visit, and each participant performed an at-home fitness evaluation test (estimation of maximal aerobic capacity) during the baseline data collection period.

Primary Objectives: The primary objective of this study was to determine whether moderate intensity walking before or after dinner is more effective than the baseline (sedentary) condition in improving the %TIR (3.9-10.0 mmol/L) and the area under the curve (AUC) during the 2-hour pre-meal to 4-hour post-meal period.

Primary Hypothesis: We hypothesized that while both pre- and post-meal walking sessions would attenuate PPG excursions, resulting in improved AUC and %TIR compared to the baseline condition, pre-meal walks may offer additional benefits with protection against hypoglycemia.

Secondary Objective: The secondary objective of this study was to assess AUC and %TIR metrics during the 3 hours post-meal. Additionally, %TIR metrics were examined over 24 hours to evaluate the influence of walk timing on overall glycemia and the risk of hypoglycemia.

Secondary Hypothesis: We hypothesized that pre- and post-meal walks would reduce the AUC immediately following a meal compared to the baseline condition. Furthermore, we anticipated that both walking conditions would lower glucose levels across 24 hours, potentially increasing exposure to hypoglycemia.

4.0 RESEARCH DESIGN AND METHODS

4.1 PARTICIPANTS

A total of 30 adults diagnosed with T1D for over one year and currently using an HCLS and CGM were screened for this study. All participants were asked to complete a questionnaire confirming their eligibility (Appendix A) and to screen for cardiometabolic complications using the Physical Activity Readiness Questionnaire for Everyone (http://eparmedx.com/). Participants also answered a questionnaire including self-reported anthropometric (height, weight, and waist circumference), demographic, medical history, diabetes management, and habitual physical activity data.

4.2 STUDY PROTOCOL

4.2.1 Virtual Visit

The participants were asked to attend one Zoom call to review the informed consent form and become familiarized with the study protocols. The virtual visit and completion of the forms took ~1 hour. During the virtual visit, the participant was assigned to a moderate intensity walking condition of either (1) pre-meal: within 30 minutes before their dinner meal or (2) post-meal: within 30 minutes after the end of their dinner meal. For this study, dinner was defined as the largest meal of the day consumed after 3:00 PM.

4.2.2 Baseline Data Collection

Each participant had two weeks of baseline data collection following the virtual visit. For these two weeks, participants were asked to refrain from participating in any structured form of

physical activity (such as purposeful walking, aerobic exercise, or resistance exercise) within two hour before the start or after the end of their dinner meal.

Participants were also asked to complete the Rockport 1-mile walk test, a submaximal field test which estimates VO_{2max} in sedentary and active adults (aged 20-69). Participants walked 1 mile (1.6km) on an indoor track or outside on any uninterrupted course as quickly as possible without speed walking or running. Immediately following the test, they tracked heart rate (HR) using a watch or a 15-second count from the radial or carotid artery. The following equation was used to estimate VO_{2max}:

Estimated VO_{2max} (mL/kg/min) = 132.853 – [0.0769 x weight (lb)] – [0.3877 x age] + [6.315 x gender (male=1, females=0)] –[3.2649 x time (min)] – [0.1565 x HR (bpm)]

4.2.3 Walking Observations

Following baseline (sedentary control) data collection, each participant had two weeks of a daily 20-minute moderate intensity walk at their assigned pre- or post-meal condition. Walks were self-paced at a low to moderate intensity with an RPE of 3-4 on the Borg CR-10 Scale and took place within 30 minutes of the beginning or end of the dinner meal [144,145]. The participant was informed how to use the RPE scale during the virtual visit (Appendix B). The walk could be completed on a treadmill, indoor or outdoor track, or outside on a walking path of the participants' choosing. To minimize confounding effects, participants were asked not to participate in any other form of physical activity within the two hours before the start and after the end of their dinner meal. After two weeks, each participant received an email reminder to switch the timing of their walking protocol. Across the two weeks, if there was a day in which the participant could not complete their walk, they were asked to add that day to the end of their current period.

4.3 OUTCOME AND PREDICTOR VARIABLES

4.3.1 Outcome Measures

Primary Objective: This study aimed to compare the effects of moderate intensity walking before or after a meal on glucose excursions during the 2-hour pre-meal to 4-hour post-meal period, compared to a baseline no-walk condition. The following measures were used to assess the glycemic response:

(1) Area Under the Curve ([mmol/L]*time): AUC was computed on Prism Version 9.5.1 (GraphPad Software, San Diego, California, USA) using the trapezoid rule. Interstitial glucose at the start of the meal is considered baseline, with peaks above and below 10% included in the AUC calculation. There were four additional metrics examined which were associated with AUC

   a. Peak glucose (mmol/L): maximum interstitial glucose value
   b. Nadir glucose (mmol/L): minimum interstitial glucose value
   c. Glucose excursion (mmol/L): peak glucose minus baseline blood glucose
   d. Time to peak glucose (minutes): time point 0 at the start of dinner meal

(2) Percent time in range (%TIR) metrics: According to consensus guidelines [146], %TIR metrics were calculated using the participants' CGM data and defined as:

   a. Time below range 2 (%TBR2): <3.0 mmol/L
   b. Time below range 1 (%TBR1): 3.0-3.9 mmol/L
   c. Time in range (%TIR): 3.9-10.0 mmol/L
   d. Time above range 1 (%TAR1): 10.0-13.9 mmol/L)
   e. Time above range 2 (%TAR2): >13.9 mmol/L).

Secondary Objective: To comprehensively investigate glucose responses, the above outcome measures were also examined during the 3-hour post-meal period and across a 24-hour period (from 06:00 to 05:59). While both %TIR and AUC measures were analyzed during the 3-hour post-meal period, only %TIR metrics were examined across the 24-hour period. A sub-analysis was conducted to examine the day (06:00 to 11:59) and overnight (00:00 to 05:59) periods, with a focus on assessing the risk of hypoglycemia.

4.3.2 Predictor Variables

Primary Exposure Variable: The primary exposure variable examined was the walking condition, which was categorized as either (1) baseline, (2) pre-meal walk, or (3) post-meal walk, with the walk duration at a fixed prescribed moderate intensity of 3-4 on the Borg CR-10 scale for 20 minutes.

Additional Variables: Additional predictor variables (Table S4) were also examined in three main categories (1) anthropometrics, (2) physical activity, and (3) diabetes-specific variables. Participants were asked to log walk-specific data using a digital spreadsheet (Excel, Appendix C).

4.4 STATISTICAL ANALYSIS

4.4.1 Sample Size

Using G*Power (Heinrich Heine University Düsseldorf, Düsseldorf, Germany, version 3.1.9.3), the sample size calculated was 28 subjects. The sample size estimation was based on a repeated measure within-factor ANOVA design (alpha 5%, power 80%); 30 participants were screened to account for dropouts.

4.4.2 Univariate Analysis

All Statistical analyses were performed using SPSS V.28.0 (IBM Corp., Armonk, N.Y., USA SPSS) with a $p \leq 0.05$ considered statistically significant. Descriptive participant statistics were performed at baseline. Continuous variables are presented as mean±SD and categorical variables are presented as frequency (percentage).

4.4.3 Generalized Estimating Equations

A one-way repeated measures ANOVA was initially proposed to examine the effects of the walking condition (baseline, pre-meal, post-meal) on time in range and AUC outcome variables. However, due to drop-outs (Figure S1), the small sample size (N=11), non-normal distribution of the data, and correlation within measurements (i.e., 14 days across three time points for each participant), generalized estimating equations (GEE) were determined to be a more appropriate statistical test for this analysis.

GEE is a statistical test that assesses the difference between outcome measures for each time point while accounting for within-participant correlation. GEE results will present population-averaged effects that reflect within-participant changes. Compared to an ANOVA, GEE is more robust to non-normal data, can deal with smaller sample sizes, and can account for the correlation among repeated measures within each participant.

Analyses using GEE with a linear scale response model and exchangeable correlation structure (which assumes that the correlation between any two measurements within the same subject is constant over time) were used to access differences in %TIR metrics between the pre- and post-meal moderate intensity walking conditions and baseline.

Additional GEE analyses, with the same model and correlation structure, were conducted to include covariates when examining AUC outcome variables. The models were adjusted for carbohydrate intake at the meal and blood glucose at the start of the meal. As this study was a crossover design, we did not adjust for demographic variables (such as age, gender, and BMI). Least square means (LSM), standard error (SE), unstandardized regression coefficients (B), 95% confidence intervals (CI), and significance values (p-values) are reported for each GEE analyses.

4.4.4 Data Loss

Only days with >20 hours of CGM data and with complete CGM data in the 2 hours before and 4 hours following dinner were included in the analysis. CGM data was available in 426 out of 462 days of data collection in total (91.8% of total days). There was 90.9% of baseline data included, 92.2% of pre-meal walk data, and 93.5% of post-meal walk data included in analyses.

5.0 RESULTS

5.1 DESCRIPTIVE STATISTICS

A total of 30 participants were screened for the study, out of which 11 (6 females and 5 males) completed the protocol (Figure S1). The participants had an average age of 42±13 years, a BMI of 26.3±3.69 kg/m^2, and an HbA_{1C} of 6.3±0.8%. All participants used a Dexcom G6 with an HCLS (73% using tandem and 27% looping). Participants used either insulin lispro (Humalog® or Lyumjev™; Eli Lilly and Company, Indianapolis, IN) (N=5, 45%) or insulin asprat (NovoRapid® or Fiasp®, Novo Nordisk, Bagsværd, Denmark) (N=6, 55%). Participant VO_{2max} was estimated at 38.3±13.8 mL/kg/min. The average days per week of moderate intensity physical activity was 2±3 days per week (at 49±63 minutes per session), and vigorous intensity physical activity was 1±2 days per week (at 27±34 minutes per session) based on the International Physical Activity Questionnaire (i.e., moderately to highly active). Further details on participant characteristics, including anthropometric, diabetes-specific, and physical activity-related metrics, are presented in Table 1.

Dinners were most frequently consumed between 5:00 PM and 8:00 PM. The average carbohydrate intake was 44±24 grams per meal. There were no statistical differences in carbohydrate consumption between baseline (47±22 grams per meal) and pre-meal (44±22 grams per meal, p=0.17) or post-meal (43±28 grams per meal, p=0.13) walk conditions. No study participants reported any severe hypoglycemic events requiring third-party intervention during the study.

5.2 TWO-HOURS PRE- TO FOUR-HOURS POST-MEAL

5.2.1 Area Under the Curve

Descriptive statistics of AUC and related variables are presented in Table 2, while Figure 1 demonstrates AUC in the pre-and post-meal periods by walking time point. After adjusting for carbohydrate intake and blood glucose at the start of dinner, GEE models indicated that there were no significant differences in the AUC and related variables between the baseline and pre- or post-meal walking conditions during the 2-hour pre to 4-hour post-meal period (Table 4, Figure 2). Although not statistically significant, pre-meal walks resulted in a decreased peak (LSM±SE=10.7±0.2mmol/L; B=-0.09; 95% CI= [-0.47, 0.29]; p=0.64) and nadir (LSM±SE=4.3±0.1mmol/L; B=-0.18; 95% CI= [-0.44, 0.08]; p=0.18) glucose relative to baseline (peak and nadir LSM±SE=10.8±0.2 and 4.5±0.2 mmol/L, respectively). In contrast, compared to baseline, post-meal walks showed a slight but non-significant increase in peak (LSM±SE=11.0±0.2mmol/L; B=0.26; 95% CI= [-0.16, 0.68]; p=0.23) and nadir (LSM±SE=4.6±0.1mmol/L; B=0.08; 95% CI= [-0.22, 0.39]; p=0.59) glucose levels. Additionally, the time to reach peak glucose concentration was less for pre-meal (LSM±SE=41±10 min; B=-21.45; 95% CI= [-49.14, 6.23]; p=0.13) and post-meal (LSM±SE=62±10 min; B=-0.65; 95% CI= [-25.34, 24.04]; p=0.96) moderate intensity walks relative to baseline (LSM±SE=62±10 min), although these differences were not statistically significant.

5.2.2 Time in Range

During the 2-hour pre- to 4-hour post-dinner period, pre-meal walks were associated with a significant improvement in %TIR (LSM±SE=84.9±1.5%; B=5.58; 95% CI= [1.24, 9.92]; p=0.01) and a significant decrease in %TAR1 (LSM±SE=11.1±1.4%; B=5.81; 95% CI= [-10.12,

-1.51]; p=0.01) compared to baseline (%TIR and %TAR1 LSM±SE=79.3±1.9% and 15.8±17%, respectively). Post-meal walks did not show any significant differences compared to the baseline condition. While both walking conditions had a minimal (~0.2%) elevation in %TBR2 and %TBR1 relative to baseline after adjusting for covariates, these and other %TIR metrics did not show any significant differences compared to baseline (p>0.05, Table 5).

5.3 THREE HOURS POST-MEAL

5.3.1 Area Under the Curve

In the 3 hours following dinner, there were no significant (p>0.05) differences between baseline and post-meal AUC and related variables (Table 6, Figure 3). However, GEE models did demonstrate that AUC had a non-significant tendency for being lower for the post-meal walk condition (LSM±SE=361.1±18.8 [mmol/L]*120min; B=-13.30; 95% CI= [-57.24, 30.65]; p=0.55) when compared to baseline (LSM±SE=374.1±18.1 [mmol/L]*120min). On the other hand, there was a significantly lower nadir glucose for the pre-meal walk condition (LSM±SE=4.9±0.1mmol/L; B=-0.40; 95% CI= [-0.74, -0.06]; p=0.02) relative to baseline (LSM±SE=5.3±0.1mmol/L). While time to peak, peak glucose, and AUC values were lower in the pre-meal walk condition than in baseline, none of these outcomes demonstrated statistical significance.

5.3.2 Time in Range

In the three hours following dinner, there were no significant differences in %TIR between post-meal and baseline walk conditions (p>0.05, Table 7). However, as seen with the 2-hour pre to 4-hour post-meal period, %TIR compared to baseline (LSM±SE=78.0±2.5%) was significantly

improved for the pre-meal (LSM±SE=84.6±1.9%; B=6.58; 95% CI= [-0.75, 12.41]; p=0.03), but not post-meal (LSM±SE=78.5±2.2%; B=0.28; 95% CI=[-4.96, 5.52]; p=0.92) moderate intensity walk condition. Pre-meal walks also had an associated significant decrease in %TAR1 (LSM±SE=11.8±1.8%; B=-5.25; 95% CI= [-10.53, 0.04]; p=0.05) and %TAR2 (LSM±SE=0.2±0.1%; B=-2.54; 95% CI= [-4.39, -0.69]; p=0.01) relative to baseline (%TAR1 and %TAR2 LSM±SE=17.0±2.1% and 2.8±0.9%, respectively). There were no differences in %TBR1 or %TBR2 between baseline and pre-meal or post-meal walk conditions.

5.4 TWENTY-FOUR HOURS

The mean glucose levels at the start of meals were similar between the pre-meal (6.6±2.0 mmol/L) and post-meal walk (7.1±2.4 mmol/L) conditions when compared to baseline (7.0±2.3 mmol/L) (p=0.12 and p=0.65, respectively).

The 24-hour %TIR metrics between walking conditions are presented in Figure 4 and Table 3. As per the GEE analyses, there were no significant differences in 24-hour %TIR metrics (Table 8). There was a slight elevation in %TIR for the pre-meal walk condition (LSM±SE=86.3±0.9%; B=1.65; 95%CI=[-0.66, 3.96]; p=0.16) compared to baseline (LSM±SE=84.7±1.0%), which was accompanied by a decrease in %TAR1 and %TAR2 and an elevation in %TBR1 and %TBR2. However, these differences were insignificant (p>0.05, Table 8). Conversely, post-meal moderate intensity walks were associated with a slightly worsened %TIR (LSM±SE=84.5±1.0%; B=-0.16; 95%CI=[-2.6, 2.8]; p=0.90) and elevated %TBR1 and %TBR2 compared to baseline.

Sub-analysis (Overnight and Day): When split into overnight (00:00 to 05:59, Table 9) and day (06:00 to 23:59, Table 10) periods, similar patterns for pre- and post-meal walks compared to baseline were observed. However, in the overnight period, %TBR2 was significantly elevated for the post-meal walk condition (LSM±SE= 0.5±0.1%; B=0.2; 95%CI=[0.01, 0.39]; p=0.04)

compared to baseline (LSM±SE=0.3±0.1%). This elevated hypoglycemia risk was not seen when comparing the baseline to the pre-meal walk condition (LSM±SE=0.3±0.1%; B=0.01; 95%CI=[-0.22, 0.24]; p=0.95). No significant risk for hypoglycemia was observed during the day for either walking condition. Time in hyperglycemia was not different during the overnight (Table 9) or day (Table 10) periods for pre- or post-meal moderate intensity walk conditions relative to baseline.

6.0 DISCUSSION

6.1 PRINCIPAL FINDINGS

To our knowledge, studies have yet to examine the impact of pre- versus post-meal moderate intensity walks on PPG in adults living with T1D on HCLS. Thus, in the present study, we aimed to investigate the effects of at-home pre-and post-meal 20-minute moderate intensity walks on PPG management immediately before and following a dinner meal in already active adults with T1D using HCLS. Our results demonstrated that while AUC was lower in the pre-meal (mean±SD=694.6±360.9 [mmol/L]*360min) and post-meal walk (mean±SD=689.3±342.5 [mmol/L]*360min) conditions compared to baseline (mean±SD=714.4±338.9 [mmol/L]*360min) in the 2-hours pre to 4-hours post-meal when examined with GEE analyses, these differences were not significant (p=0.78 and p=0.45, respectively). Conversely, mean %TIR was elevated at 84.6% for the pre-meal walk condition compared to 77.7% in the post-meal walk condition and 79.5% at baseline, showing the potential benefits of pre-meal walks for overall glycemic management.

6.1.1 2-hours Pre to 4-hours Post-Meal

We observed that pre-meal moderate intensity walks significantly improved mean %TIR by 5.6% (p=0.01) and decreased %TAR1 by 4.7% (p=0.02) during the 2-hour pre to 4-hour post-meal period compared to baseline, while post-meal walks did not (p=0.48 and p=0.49, respectively). Although there was a trend towards lower peak and nadir glucose (by 0.3 mmol/L) in the pre-meal walking condition, this difference was not significant.

The reasons for the advantage of pre-meal walking over post-meal walking for PPG management during this period are unclear. However, it may be related to how participants' HCLS responds to the timing of meals in relation to activity. In the T1D population, endogenous insulin

levels administered at the start of dinner will not decrease at exercise onset [93,147]. Therefore, individuals in this study cohort may have been initiating their post-meal walks in a hyper-insulinemic state, causing blood glucose to drop dramatically during the post-meal moderate intensity walk condition [147]. In response, HCLS would suspend insulin delivery until individuals returned to a safe glycemic range. However, if the insulin suspension persisted for an extended period, individuals could face rebound hyperglycemia. This may be evident in this study cohort by peak glucose occurring after ~60 minutes in the post-meal walk condition compared to after ~40 minutes in the pre-meal walk condition. Further research is needed to identify the mechanisms of HCLS and how they work with pre- and post-meal exercise to optimize glucose management in this population.

6.1.2 3-Hours Post-Meal

This study's results indicate no significant differences in %TIR or AUC metrics between the baseline and post-meal walk conditions in the three hours following a meal. However, significant differences were observed when examining the pre-meal walk condition relative to the baseline (no walk) condition. Specifically, pre-meal walks were associated with a 0.4 mmol/L lower mean nadir glucose in this period, leading to an improved %TIR and decreased %TAR1 and %TAR2. Previous research has demonstrated that a single bout of moderate intensity aerobic exercise can induce glucose-lowering effects by increasing GLUT4 translocation and blood flow to the active skeletal muscles [148–151]. Additionally, increased blood flow can elevate insulin absorption rate [152] and sensitivity by up to 50% in the hour following a 60-minute bout of moderate or high intensity continuous aerobic exercise [147]. Therefore, pre-meal walks may aid in attenuating blood glucose excursions after a meal, as the participant will be more responsive to

insulin delivery. This finding is significant as it suggests the physiological responses to physical activity or exercise intensity or timing relative to a meal may play a critical role in managing PPG excursions in individuals with T1D.

6.1.3 24 Hours Post-Meal

Moderate intensity pre-meal walks were associated with a slight increase in mean 24-hour %TIR (1.7%) and a decrease in %TAR1 (-1.8%). However, the changes were not statistically significant (p=0.16 and p=0.10, respectively) compared to baseline no-walk conditions. Conversely, post-meal walks were associated with a non-significant worsening of %TIR (-0.2%, p=0.90) and an elevation in %TBR1 metrics (0.4%, p=0.18).

Our analysis of 24-hour time in range metrics separated by the day and overnight periods showed that the risk of overnight hypoglycemia <3.0 mmol/L was 0.2% higher for the post-meal walk condition than baseline (p=0.04) but not for the pre-meal walk condition (p=0.95). These findings are consistent with previous research demonstrating the impact of time-of-day exercise on glycemic management in individuals with diabetes [153]. For example, a study by Gomez and colleagues (2015) found that 60-minutes of fasted moderate-intensity treadmill exercise in the morning significantly reduced the risk of hypoglycemia in the subsequent 24-hour period in 35 adults with T1D compared to afternoon exercise (5.6 vs 10.7 events per participant, p<0.001) [98]. The authors attributed this decreased risk, in part, to the absence of bolus insulin in the morning exercise sessions. In line with this thought, one study demonstrated that peak blood glucose values in 39 persons with T1D were found to occur within 73±24 minutes of meal consumption, with a rate of blood glucose decrease occurring at 0.93±0.68 mg/dL/min [154].

Together, the findings of these previous studies, in conjunction with our current study, suggest that walking at a moderate intensity before a meal may decrease the risk of PPG hyperglycemia without promoting hypoglycemia. This may be partially attributable to lower circulating levels of prandial insulin during a pre-meal, but not post-meal, walk. This is an important consideration for individuals with T1D who engage in post-meal exercise, even if it is short duration. Additional precautions, such as ingesting a bedtime snack or overnight basal rate reductions, may be necessary for optimal glycemic management in the overnight period if even a short exercise bout occurs following a meal.

6.2 STRENGTHS

This study has several strengths, primarily associated with the at-home nature of the study design. Firstly, it allowed for the inclusion of participants from diverse geographic locations (Canada, US, UK). It also allowed for the examination of multiple physiological factors (such as age, fitness level, and T1D duration) using GEE for analysis. Additionally, unlike previous studies in this population, we were able to examine late phase, and overnight, post-exercise blood glucose responses through the evaluation of participants' individual CGM data. This provides a more comprehensive understanding of the overall effects of pre-and post-meal walking on glucose management. Furthermore, the 6-week real-world data collection of this study means that the results may be more indicative of a T1D lifestyle as it naturally includes day-to-day variations of variables that can influence glycemia, such as stress, preceding exercise, and carbohydrate consumption. These strengths provide important insights for developing effective exercise interventions for PPG management in individuals with T1D.

6.3 LIMITATIONS AND FUTURE DIRECTIONS

Several limitations are important to mention in this study. The sample size of participants with T1D was small and comprised individuals who were in reasonable glycemic management, active, and well-versed in using their HCLS. Similarly, the exclusion of individuals on MDI and the lack of access to insulin delivery data may limit the generalizability of the results. Future studies could examine the inclusion of this patient population and access to insulin delivery data. Moreover, there is a limitation in the accuracy and completeness of the data, as participants carried out the study protocols independently. While GEE statistical modelling was used to partially control for this limitation, additional information which may have contributed to differences in glycemic responses to pre- and post-meal walks, such as the macronutrient content of meals, was not analyzed. Future studies could include photos of meals to access this information. Finally, the high drop-out rate of this study (N=9, 41%) suggests that achieving 20 minutes of walking at a moderate intensity surrounding a meal per day may be difficult for individuals to fit into their daily routine. Therefore, future research should investigate whether shorter, high-intensity, exercise protocols can produce similar glycemic benefits as walking.

6.4 CLINICAL IMPACT

Achieving the physical activity guidelines of 150 minutes of moderate to vigorous intensity exercise a week is widely recognized as beneficial for the overall health and well-being for individuals with T1D. However, current guidelines for this population do not focus on the influence of planned physical activity or exercise timing relative to a meal to address PPG excursions. The findings of this study suggest that a 20-minute premeal walk may be a time-effective protocol that can be applied to this patient population to limit PPG excursions and

associated complications. Combined, T1D and T2D complications cost the Canadian healthcare system upwards of $3.9 billion annually [51]. Between 5-10% of overall diabetes prevalence in Canada is individuals with T1D. For these individuals, yearly out-of-pocket costs, including supplies and medical support for diabetes related-complications, range from $1,100-$4,900 [51]. Therefore, the initial study results regarding exercising surrounding a meal are promising as a cost-effective manner to reduce patient and healthcare burdens. However, more research examining is required to further elucidate the optimal timing, duration, and intensity of physical activity or structured exercise sessions to optimize glucose management in individuals with T1D.

6.5 CONCLUSION

In conclusion, our study provides evidence to suggest that a 20-minute moderate intensity pre-meal walk can effectively attenuate PPG excursions in adults living with T1D who are already in reasonable glycemic management using a HCLS. It also demonstrated that additional precautions such as a decreased basal rate or bedtime snack might be required prior to engaging in moderate intensity post-meal walks as they may lead to elevated dysglycemia or overnight hypoglycemic events in the T1D population. The benefits of moderate intensity pre-meal walks may be attributed to lower insulin levels in circulation in conjunction with the hypoglycemia protection offered by HCLS. Although our findings are promising, further research is warranted to examine a larger T1D population sample using different insulin modalities and to investigate the influence of different exercise types performed pre- or post-meals on PPG excursions. Our study highlights the potential benefits of a 20 minute moderate intensity pre-meal walk as a non-pharmacological intervention to improve PPG management in individuals with T1D.

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8.0 TABLES

Table 1. Descriptive Statistics of the Study Population at Baseline. Participant demographic, diabetes-specific, and physical activity characteristics (n=11). Values reported as mean±SD or frequency (percent).

Characteristics	**Baseline (n=11)**
Age (years)	42±13
Sex (female)	6 (55)
Body Mass Index (kg/m^2)	26.3±3.69
Diabetes Specific	
Type 1 Diabetes Duration (years)	17±14
Total Daily Dose (U/day)	43±18
HbA1C (%)	6.3±0.8
Insulin Pump (%)	
Looping	3 (27)
Tandem	8 (73)
Dexcom CGM (%)	11 (100)
Carbohydrate Consumption (grams/day)	44.34±24.25
Physical Activity	
Estimated VO_2max (mL/kg/min)	38.3±13.8
Vigorous intensity physical activity (days/week)	1±2
Vigorous intensity physical activity (minutes/session)	27±34
Moderate intensity physical activity (days/week)	2±3
Moderate intensity physical activity (minutes/session)	49±63
Walking (days/week)	5±2
Walking (minutes/day)	51±44
Sitting (hours/day)	8±4

Table 2. Descriptive Statistics of Glycemic Metrics. The unadjusted area under the curve and related glycemic metrics by walking condition (n=11 for each condition). Values reported as mean±SD.

	Baseline	**Pre-Meal Walk**	**Post-Meal Walk**
2-hours Pre to 4-hours Post-Meal			
Start of Meal Glucose(mmol/L)	7.0±2.3	6.6±2.0	7.1±2.4
Peak Glucose (mmol/L)	10.8±2.5	10.6±2.4	11.1±2.6
Nadir Glucose (mmol/L)	4.5±1.4	4.3±1.1	4.6±1.5
Time to Peak (minutes)	62.4±119.0	41.5±113.5	61.1±120.5
Glucose Excursion (mmol/L)	3.8±2.2	3.9±2.5	4.0±2.6
Area Under the Curve ([mmol/L]*360min)	714.4±338.9	694.6±360.9	689.3±342.5
3-Hours Post-Meal			
Peak Glucose (mmol/L)	10.0±2.5	9.5±2.2	10.1±2.7
Nadir Glucose (mmol/L)	5.3±1.9	4.8±1.4	5.2±1.9
Time to Peak (minutes)	90.6±60.2	87.8±59.2	89.7±64.7
Glucose Excursion (mmol/L)	3.0±2.2	2.9±2.4	3.0±2.9
Area Under the Curve ([mmol/L]*180min)	375.6±216.2	346.2±209.8	363.0±228.7

Table 3. Descriptive Statistics of Time in Range Metrics. Unadjusted time in range metrics by walking condition (n=11 for each condition). Values reported as mean±SD.

	Baseline	Pre-Meal Walk	Post-Meal Walk
2-hour Pre to 4-hour Post-Meal Time in Range			
% TBR2 (<3.0 mmol/L)	0.6±2.6	0.8±2.88	0.7±2.6
% TBR1 (3.0-3.9 mmol/L)	2.8±5.0	3.1±5.0	3.2±5.7
% TIR (3.9-10.0 mmol/L)	79.5±22.8	84.6±17.7	77.7±22.2
% TAR1 (10.0-13.9 mmol/L)	15.7±19.7	11.4±16.4	17.3±20.3
% TAR2 (>13.9 mmol/L)	2.1±7.5	1.0±3.8	1.8±6.1
3-hour Post-Meal Time in Range			
% TBR2 (<3.0 mmol/L)	0.5±2.5	0.9±4.2	0.9±3.8
% TBR1 (3.0-3.9 mmol/L)	2.3±5.7	3.5±6.9	3.3±8.2
% TIR (3.9-10.0 mmol/L)	78.1±29.3	84.3±22.6	78.1±27.0
% TAR1 (10.0-13.9 mmol/L)	16.9±25.2	11.9±21.7	16.0±23.9
% TAR2 (>13.9 mmol/L)	2.8±11.0	0.3±1.6	2.3±7.7
24hr Time in Range (05:59 to 06:00)			
% TBR2 (<3.0 mmol/L)	0.3±0.7	0.3±0.4	0.5±1.1
% TBR1 (3.0-3.9 mmol/L)	1.6±1.3	2.0±1.3	2.0±2.0
% TIR (3.9-10.0 mmol/L)	84.7±8.3	86.4±6.7	84.5±7.5
% TAR1 (10.0-13.9 mmol/L)	12.5±8.0	10.7±6.3	11.9±7.3
% TAR2 (>13.9 mmol/L)	1.6±1.2	1.3±1.2	1.7±2.6
Overnight Time in Range (00:00 to 05:59)			
% TBR2 (<3.0 mmol/L)	0.3±1.4	0.3±1.2	0.5±1.7
% TBR1 (3.0-3.9 mmol/L)	1.8±3.1	2.2±2.8	2.1±3.2
% TIR (3.9-10.0 mmol/L)	83.9±14.2	85.8±12.1	83.6±13.6
% TAR1 (10.0-13.9 mmol/L)	12.8±12.5	11.0±10.7	12.8±12.7
% TAR2 (>13.9 mmol/L)	1.8±4.0	1.4±3.6	1.6±3.8
Day Time in Range (06:00 to 23:59)			
% TBR2 (<3.0 mmol/L)	0.3±2.2	0.4±2.4	0.4±3.1
% TBR1 (3.0-3.9 mmol/L)	1.2±4.1	1.7±6.6	1.6±4.3
% TIR (3.9-10.0 mmol/L)	86.6±22.1	87.4±20.3	87.4±20.1
% TAR1 (10.0-13.9 mmol/L)	11.6±20.2	10.0±17.5	9.3±16.7
% TAR2 (>13.9 mmol/L)	1.1±5.2	1.1±5.7	1.9±9.5

Abbreviations: TBR2, time below range 2 (<3.0 mmol/L); TBR1, time below range 1 (3.0-3.9 mmol/L); TIR, time in range (3.9-10.0 mmol/L); TAR1, time above range 1 (10.0-13.9 mmol/L); TAR2, time above range 2 (>13.9mmol/L).

Table 4. Glycemic Metrics for 2-Hour Pre to 4-Hour Post-Meal. GEE models for the area under the curve and related glycemic metrics during the 2-hours pre-to-4-hours post-meal period for each walking condition (n=11 for each condition). GEE models and least square means adjusted to include carbohydrate intake and blood glucose at the start of the dinner meal as covariates. *Significantly different from reference condition "baseline" ($p \leq 0.05$).

Variable	LSM±SE	B	SE [95% CI]	p-value
Peak Glucose (mmol/L)				
Baseline	10.8±0.2	Reference		
Pre-Meal Walk	10.7±0.2	-0.09	0.20 [-0.47, 0.29]	0.64
Post-Meal Walk	11.0±0.2	0.26	0.21 [-0.16, 0.68]	0.23
Nadir Glucose (mmol/L)				
Baseline	4.5±0.1	Reference		
Pre-Meal Walk	4.3±0.1	-0.18	0.13 [-0.44, 0.08]	0.18
Post-Meal Walk	4.6±0.1	0.09	0.15 [-0.22, 0.39]	0.59
Time to Peak (min)				
Baseline	62±10	Reference		
Pre-Meal Walk	41±10	-21.45	14.13 [-49.14, 6.23]	0.13
Post-Meal Walk	62±10	-0.65	12.60 [-25.34, 24.04]	0.96
Glucose Excursion (mmol/L)				
Baseline	3.8±0.2	Reference		
Pre-Meal Walk	3.7±0.2	-0.09	0.20 [-0.47, 0.29]	0.64
Post-Meal Walk	4.1±0.2	0.26	0.21 [-0.16, 0.68]	0.23
Area Under the Curve ([mmol/L]*360min)				
Baseline	711.0±28.3	Reference		
Pre-Meal Walk	701.0±29.4	-10.02	36.61 [-81.78, 61.75]	0.78
Post-Meal Walk	683.9±28.1	-27.09	36.00 [-97.64, 43.46]	0.45

Abbreviations: LSM, least square means; SE, standard error; B, unstandardized regression coefficient; CI, confidence interval.

Table 5. Percent Time in Range 2-Hours Pre to 4-Hours Post-Meal. GEE models for percent time in range metrics during the 2-hours pre-to-4-hours post-meal period for each walking condition (n=11 for each condition). *Significantly different from reference condition "baseline" ($p \leq 0.05$).

Variable	LSM±SE	B	SE [95% CI]	p-value
% TBR2 (<3.0 mmol/L)				
Baseline	0.6±0.2	Reference		
Pre-Meal Walk	0.7±0.2	0.14	0.28 [-0.41, 0.70]	0.62
Post-Meal Walk	0.7±0.2	0.08	0.23 [-0.37, 0.54]	0.72
% TBR1 (3.0-3.9 mmol/L)				
Baseline	2.8±0.4	Reference		
Pre-Meal Walk	3.1±0.4	0.26	0.60 [-0.91, 1.43]	0.66
Post-Meal Walk	3.1±0.5	0.38	0.59 [-0.78, 1.53]	0.52
% TIR (3.9-10.0 mmol/L)				
Baseline	79.3±1.9	Reference		
Pre-Meal Walk	84.9±1.5	5.58	2.22 [1.24, 9.92]	**0.01***
Post-Meal Walk	77.7±1.8	-1.59	2.24 [-5.98, 2.80]	0.48
% TAR1 (10.0-13.9 mmol/L)				
Baseline	15.8±1.7	Reference		
Pre-Meal Walk	11.1±1.4	-4.70	1.97 [-8.55, -0.84]	**0.02***
Post-Meal Walk	17.3±1.7	1.46	2.09 [-2.64, 5.55]	0.49
%TAR2 (>13.9 mmol/L)				
Baseline	2.1±0.6	Reference		
Pre-Meal Walk	0.9±0.3	-1.24	0.71 [-2.64, 0.15]	0.08
Post-Meal Walk	1.7±0.5	-0.41	0.65 [-1.68, 0.85]	0.52

Abbreviations TBR2, time below range 2 (<3.0 mmol/L); TBR1, time below range 1 (3.0-3.9 mmol/L); TIR, time in range (3.9-10.0 mmol/L); TAR1, time above range 1 (10.0-13.9 mmol/L); TAR2, time above range 2 (>13.9mmol/L); LSM, least square means; SE, standard error; B, unstandardized regression coefficient; CI, confidence interval.

Table 6. Glycemic Metrics for 3-Hours Post-Meal. GEE models for the area under the curve and related glycemic metrics during the 3-hours post-meal period for each walking condition (n=11 for each condition). GEE models and least square means adjusted to include carbohydrate intake and blood glucose at start of the dinner meal as covariates. *Significantly different from reference condition "baseline" ($p \leq 0.05$).

Variable	LSM±SE	B	SE [95% CI]	p-value
Peak Glucose (mmol/L)				
Baseline	10.0±0.2	Reference		
Pre-Meal Walk	9.6±0.2	-0.32	0.23 [-0.77, 0.14]	0.17
Post-Meal Walk	10.0±0.2	0.07	0.24 [-0.40, 0.54]	0.76
Nadir Glucose (mmol/L)				
Baseline	5.3±0.1	Reference		
Pre-Meal Walk	4.9±0.1	-0.40	0.17 [-0.74, -0.06]	**0.02***
Post-Meal Walk	5.1±0.1	-0.19	0.19 [-0.55, 0.18]	0.32
Time to Peak (min)				
Baseline	91±5	Reference		
Pre-Meal Walk	85±5	-6.36	6.67 [-19.45, 6.71]	0.34
Post-Meal Walk	91±5	-0.65	7.11 [-14.60, 13.31]	0.93
Glucose Excursion (mmol/L)				
Baseline	3.0±0.2	Reference		
Pre-Meal Walk	2.7±0.2	-0.32	0.23 [-0.77, 0.14]	0.17
Post-Meal Walk	3.1±0.2	0.07	0.24 [-0.40, 0.54]	0.77
Area Under the Curve ([mmol/L]*180min)				
Baseline	374.1±18.1	Reference		
Pre-Meal Walk	350.2±17.2	-24.88	23.00 [-68.98, 21.20]	0.30
Post-Meal Walk	361.1±18.8	-13.03	24.46 [-60.97, 34.91]	0.59

Abbreviations: LSM, least square means; SE, standard error; B, unstandardized regression coefficient; CI, confidence interval.

Table 7. Percent Time in Range 3-Hours Post-Meal. GEE models for percent time in range metrics during the 3-hours post-meal period for each walking condition (n=11 for each condition). *Significantly different from reference condition "baseline" ($p \leq 0.05$).

Variable	LSM±SE	B	SE [95% CI]	p-value
% TBR2 (<3.0 mmol/L)				
Baseline	0.5±0.2	Reference		
Pre-Meal Walk	0.9±0.3	0.42	0.37 [-0.31, 1.15]	0.26
Post-Meal Walk	0.9±0.3	0.44	0.39 [-0.32, 1.21]	0.26
% TBR1 (3.0-3.9 mmol/L)				
Baseline	2.3±0.5	Reference		
Pre-Meal Walk	3.5±0.6	1.15	0.74 [-0.31, 2.60]	0.12
Post-Meal Walk	3.3±0.7	1.01	0.81 [-0.59, 2.60]	0.22
% TIR (3.9-10.0 mmol/L)				
Baseline	78.0±2.5	Reference		
Pre-Meal Walk	84.6±1.9	6.58	2.97 [0.75, 12.41]	**0.03***
Post-Meal Walk	78.3±2.2	0.28	2.67 [-4.96, 5.52]	0.92
% TAR1 (10.0-13.9 mmol/L)				
Baseline	17.0±2.1	Reference		
Pre-Meal Walk	11.8±1.8	-5.25	2.70 [-10.53, 0.04]	**0.05***
Post-Meal Walk	15.9±2.0	-1.09	2.42 [-5.84, 3.66]	0.65
% TAR2 (>13.9 mmol/L)				
Baseline	2.8±0.9	Reference		
Pre-Meal Walk	0.2±0.1	-2.54	0.94 [-4.39, -0.69]	**0.01***
Post-Meal Walk	2.2±0.6	-0.54	0.92 [-2.34, 1.27]	0.56

Abbreviations TBR2, time below range 2 (<3.0 mmol/L); TBR1, time below range 1 (3.0-3.9 mmol/L); TIR, time in range (3.9-10.0 mmol/L); TAR1, time above range 1 (10.0-13.9 mmol/L); TAR2, time above range 2 (>13.9mmol/L); LSM, least square means; SE, standard error; B, unstandardized regression coefficient; CI, confidence interval.

Table 8. Percent Time in Range Across 24 Hours. GEE models for percent time in range metrics over 24-hours following a dinner meal for each walking condition (n=11 for each condition). *Significantly different from reference condition "baseline" ($p \leq 0.05$).

Variable	LSM±SE	B	SE [95% CI]	p-value
% TBR2 (<3.0 mmol/L)				
Baseline	0.3±0.1	Reference		
Pre-Meal Walk	0.3±0.1	0.003	0.11 [-0.21, 0.22]	0.98
Post-Meal Walk	0.5±0.1	0.19	0.11 [-0.02, 0.41]	0.08
% TBR1 (3.0-3.9 mmol/L)				
Baseline	1.6±0.2	Reference		
Pre-Meal Walk	2.0±0.2	0.44	0.29 [-0.12, 1.00]	0.12
Post-Meal Walk	2.0±0.2	0.37	0.28 [-0.17, 0.91]	0.18
% TIR (3.9-10.0 mmol/L)				
Baseline	84.7±1.0	Reference		
Pre-Meal Walk	86.3±0.9	1.65	1.18 [-0.66, 3.96]	0.16
Post-Meal Walk	84.5±1.0	-0.16	1.24 [-2.60, 2.28]	0.90
% TAR1 (10.0-13.9 mmol/L)				
Baseline	12.5±1.0	Reference		
Pre-Meal Walk	10.7±0.8	-1.75	1.05 [-3.81, 0.31]	0.10
Post-Meal Walk	11.9±0.9	-0.56	1.10 [-2.72, 1.60]	0.61
% TAR2 (>13.9 mmol/L)				
Baseline	1.6±0.3	Reference		
Pre-Meal Walk	1.3±0.2	-0.30	0.34 [-0.97, 0.37]	0.38
Post-Meal Walk	1.7±0.3	0.08	0.36 [-0.63, 0.80]	0.82

Abbreviations: TBR2, time below range 2 (<3.0 mmol/L); TBR1, time below range 1 (3.0-3.9 mmol/L); TIR, time in range (3.9-10.0 mmol/L); TAR1, time above range 1 (10.0-13.9 mmol/L); TAR2, time above range 2 (>13.9mmol/L); LSM, least square means; SE, standard error; B, unstandardized regression coefficient; CI, confidence interval.

Table 9. Percent Time in Range Overnight (00:00 to 05:59). GEE models for percent time in range metrics in the overnight period following a dinner meal for each walking condition (n=11 for each condition). *Significantly different from reference condition "baseline" ($p \leq 0.05$).

Variable	LSM±SE	B	SE [95% CI]	p-value
% TBR2 (<3.0 mmol/L)				
Baseline	0.3±0.1	Reference		
Pre-Meal Walk	0.3±0.1	0.01	0.12 [-0.22, 0.24]	0.95
Post-Meal Walk	0.5±0.1	0.20	0.10 [0.01, 0.39]	**0.04***
% TBR1 (3.0-3.9 mmol/L)				
Baseline	1.8±0.3	Reference		
Pre-Meal Walk	2.2±0.2	0.43	0.31 [-0.19, 1.04]	0.17
Post-Meal Walk	2.1±0.3	0.29	0.31 [-0.32, 0.90]	0.35
% TIR (3.9-10.0 mmol/L)				
Baseline	83.9±1.1	Reference		
Pre-Meal Walk	85.8±1.0	1.94	1.33 [-0.67, 4.54]	0.15
Post-Meal Walk	83.6±1.1	-0.31	1.39 [-3.03, 2.41]	0.82
% TAR1 (10.0-13.9 mmol/L)				
Baseline	12.8±1.0	Reference		
Pre-Meal Walk	11.0±0.9	-1.84	1.15 [-4.09, 0.42]	0.11
Post-Meal Walk	12.8±1.0	-0.09	1.26 [-2.55, 2.38]	0.95
% TAR2 (>13.9 mmol/L)				
Baseline	1.8±0.3	Reference		
Pre-Meal Walk	1.4±0.3	-0.41	0.40 [-1.20, 0.38]	0.31
Post-Meal Walk	1.6±0.3	-0.15	0.42 [-0.98, 0.67]	0.72

Abbreviations: TBR2, time below range 2 (<3.0 mmol/L); TBR1, time below range 1 (3.0-3.9 mmol/L); TIR, time in range (3.9-10.0 mmol/L); TAR1, time above range 1 (10.0-13.9 mmol/L); TAR2, time above range 2 (>13.9mmol/L); LSM, least square means; SE, standard error; B, unstandardized regression coefficient; CI, confidence interval.

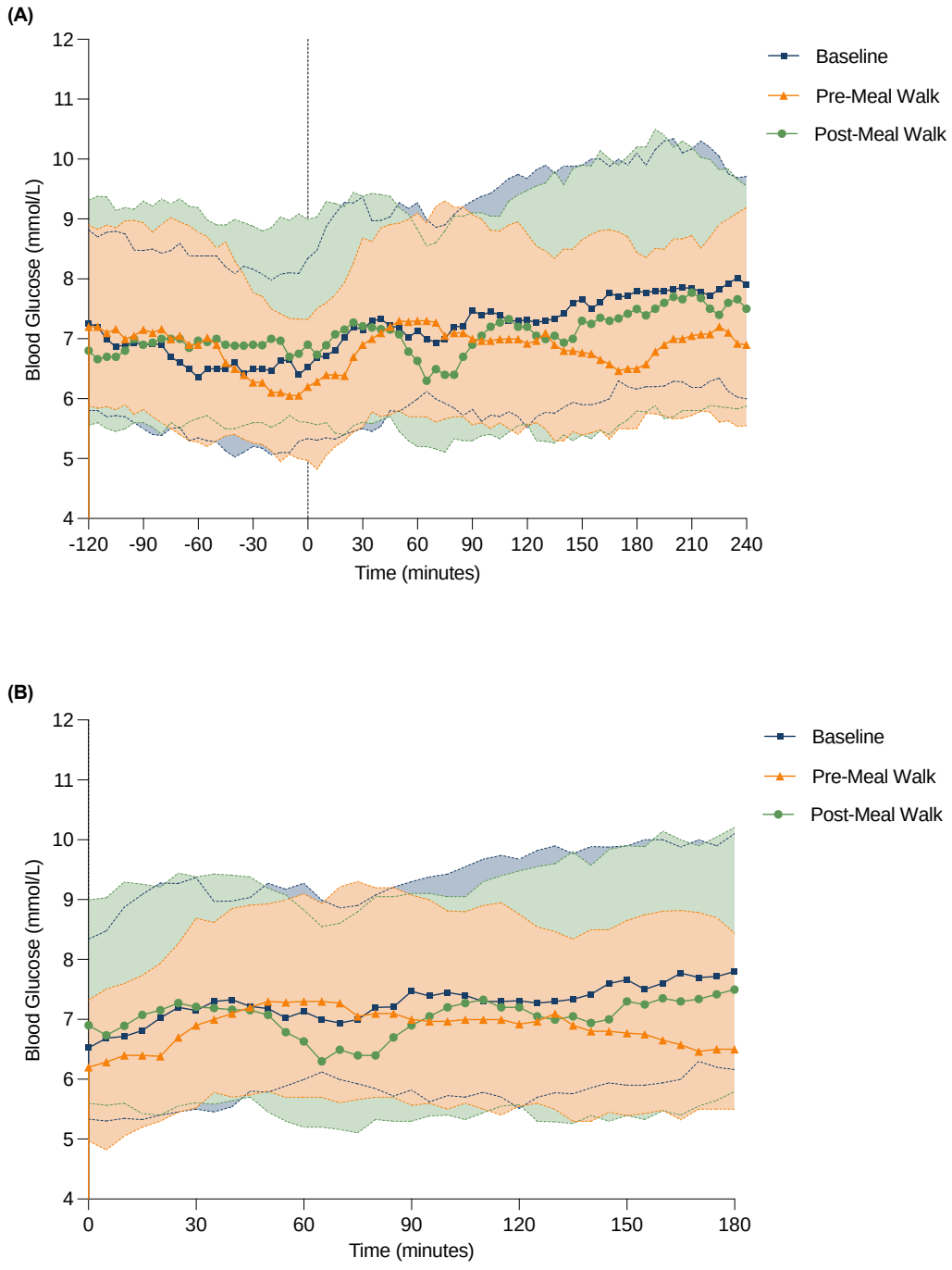
Table 10. Percent Time in Range in the Day (06:00 to 23:59). GEE models for percent time in range metrics during the day following a dinner meal for each walking condition (n=11 for each condition). *Significantly different from reference condition "baseline" ($p \leq 0.05$).

Variable	LSM±SE	B	SE [95% CI]	p-value
% TBR2 (<3.0 mmol/L)				
Baseline	0.3±0.2	Reference		
Pre-Meal Walk	0.4±0.2	0.04	0.26 [-0.47, 0.55]	0.88
Post-Meal Walk	0.4±0.3	0.10	0.30 [-0.50, 0.69]	0.75
% TBR1 (3.0-3.9 mmol/L)				
Baseline	1.2±0.3	Reference		
Pre-Meal Walk	1.7±0.5	0.58	0.64 [-0.67, 1.83]	0.37
Post-Meal Walk	1.6±0.4	0.41	0.46 [-0.49, 1.31]	0.37
% TIR (3.9-10.0 mmol/L)				
Baseline	86.6±1.8	Reference		
Pre-Meal Walk	87.4±1.6	0.78	2.31 [-3.74, 5.31]	0.73
Post-Meal Walk	87.4±1.6	0.74	2.35 [-3.87, 5.35]	0.75
% TAR1 (10.0-13.9 mmol/L)				
Baseline	11.5±1.6	Reference		
Pre-Meal Walk	9.9±1.4	-1.62	1.99 [-5.53, 2.29]	0.42
Post-Meal Walk	9.3±1/4	-2.24	2.00 [-6.16, 1.68]	0.26
% TAR2 (>13.9 mmol/L)				
Baseline	1.1±0.4	Reference		
Pre-Meal Walk	1.1±0.5	0.01	0.64 [-1.23, 1.26]	0.98
Post-Meal Walk	1.9±0.8	0.83	0.86 [-0.85, 2.52]	0.33

Abbreviations: TBR2, time below range 2 (<3.0 mmol/L); TBR1, time below range 1 (3.0-3.9 mmol/L); TIR, time in range (3.9-10.0 mmol/L); TAR1, time above range 1 (10.0-13.9 mmol/L); TAR2, time above range 2 (>13.9mmol/L); LSM, least square means; SE, standard error; B, unstandardized regression coefficient; CI, confidence interval.

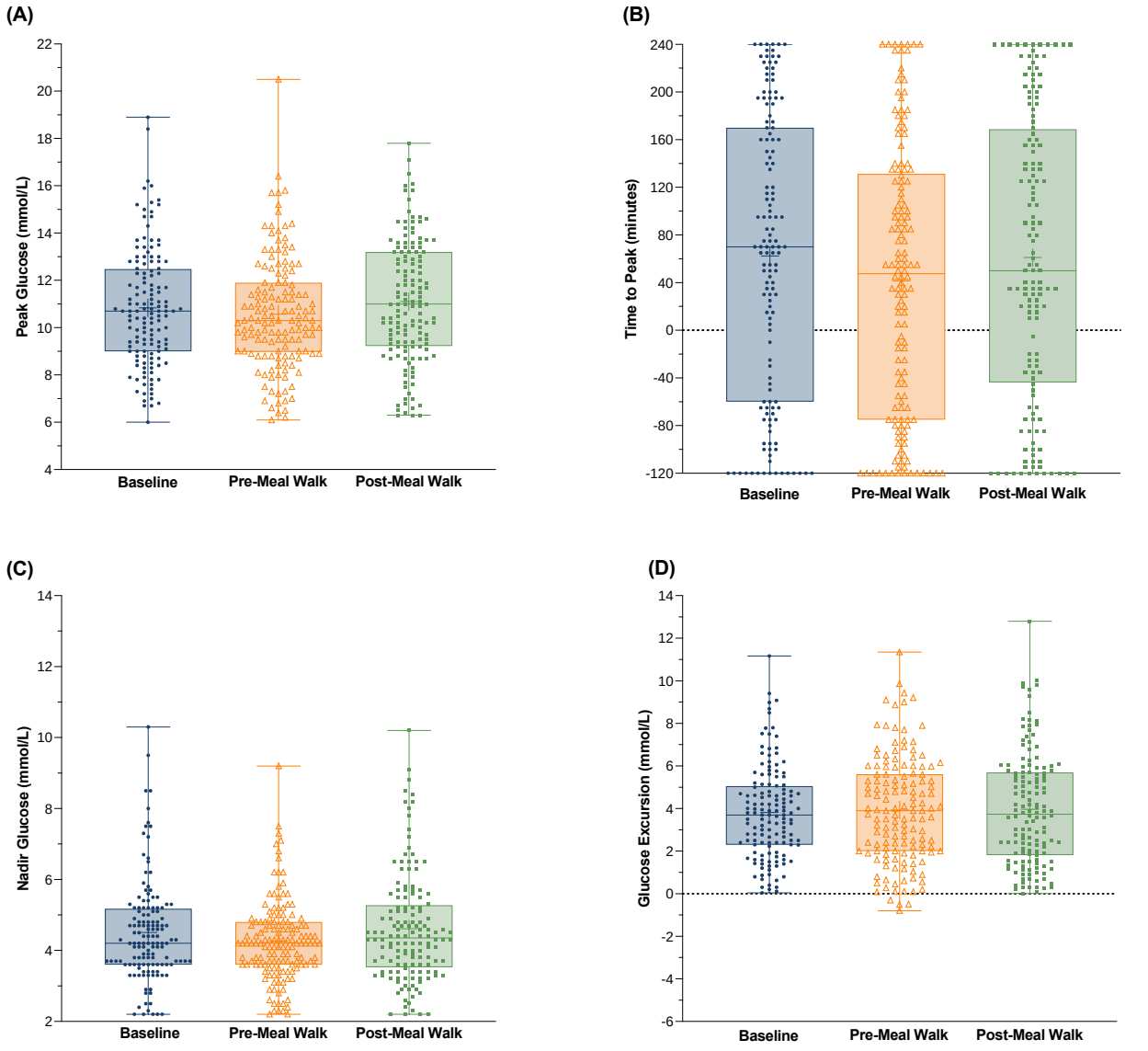
9.0 FIGURES

Figure 1. Area Under the Curve by Walking Condition.



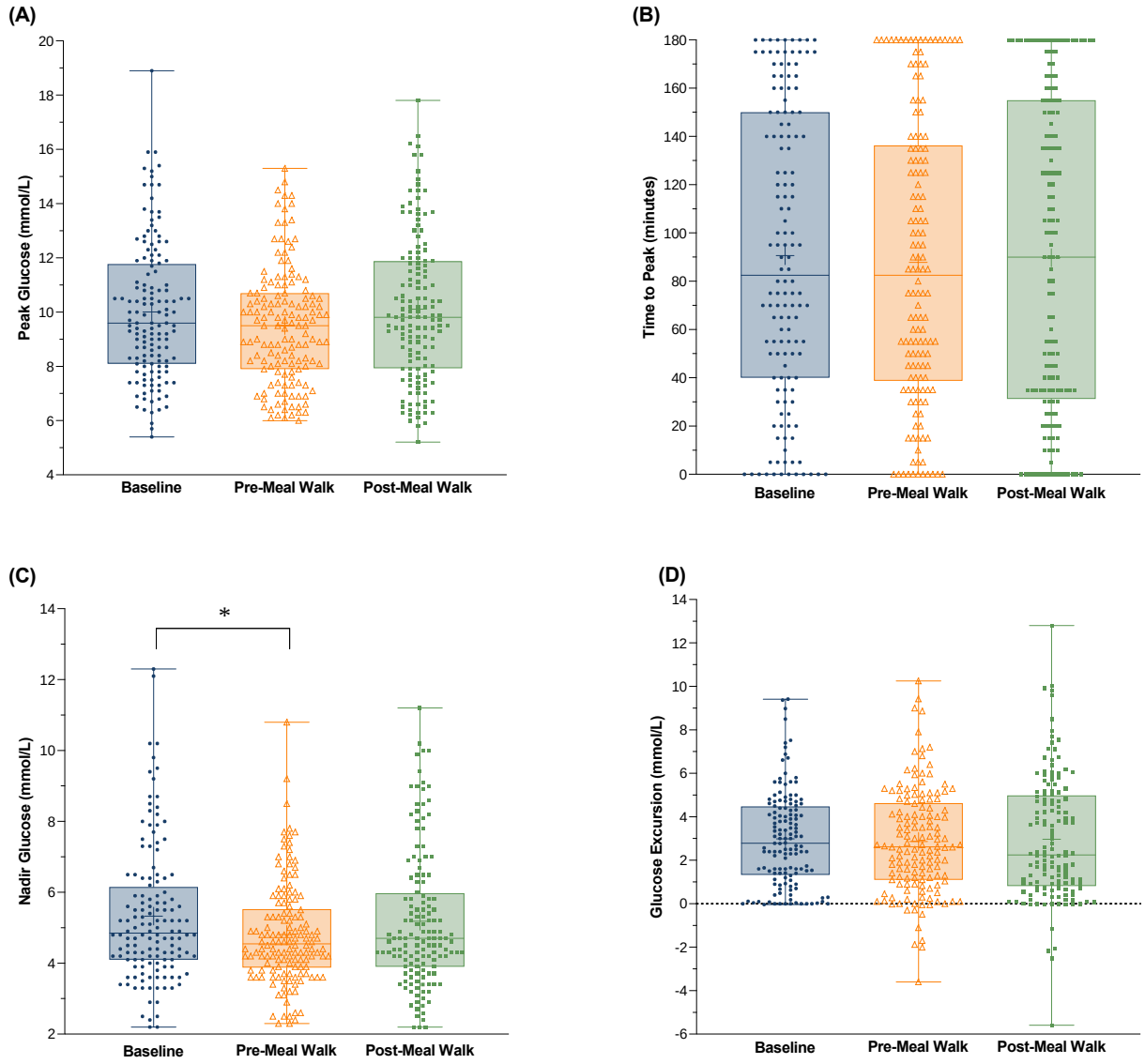
Median (solid lines) and interquartile range (filled area) of blood glucose presented at different time points for (A) 2-hours pre to 4-hours post-meal and (B) 3-hours post-meal. Time 0 is the start of the dinner meal.

Figure 2. Blood Glucose Metrics in the 2-Hours Pre- to 4-Hour Post-Meal by Walking Condition.



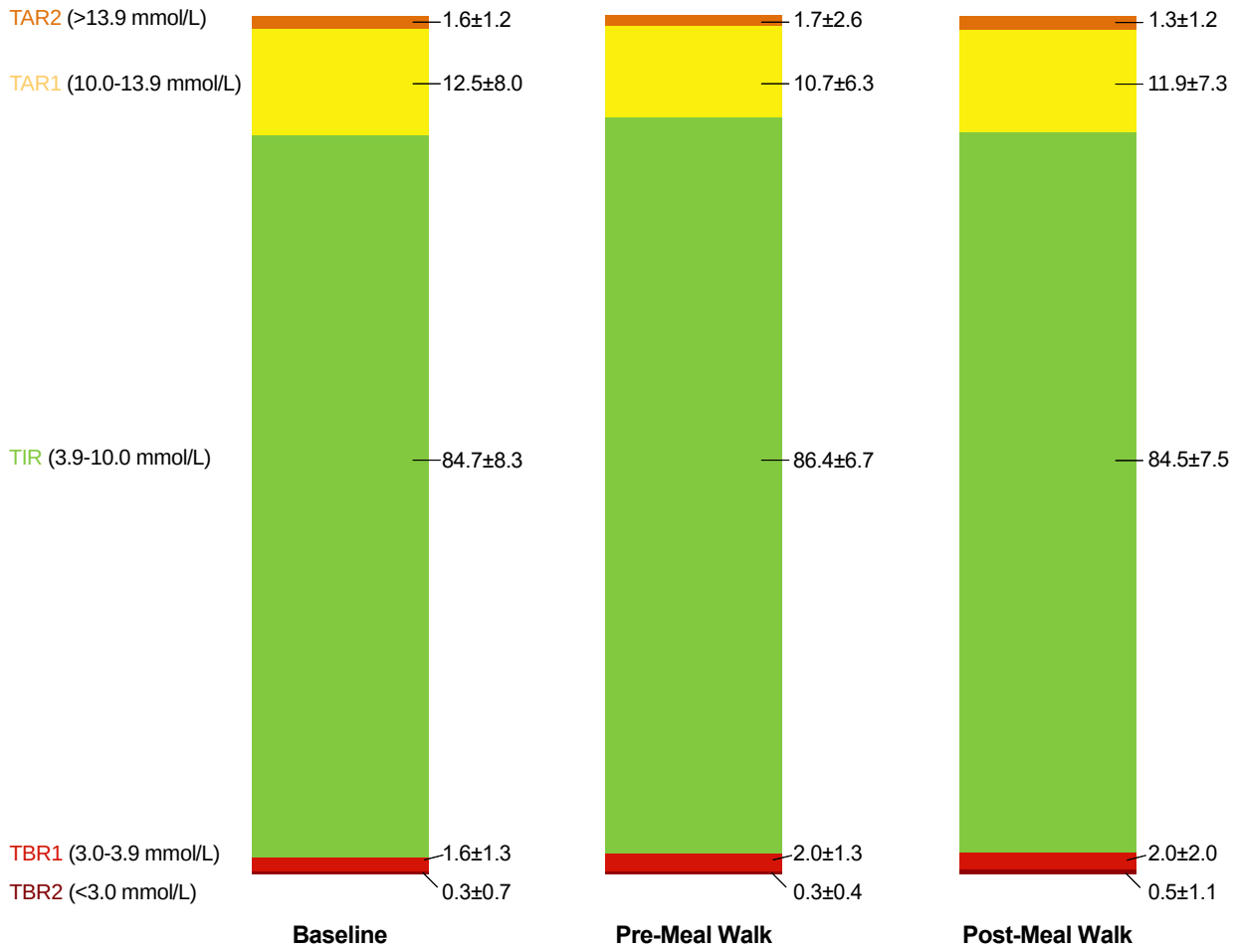
Box and whisker plots of (A) peak glucose, (B) time to peak glucose, (C) nadir glucose, and (D) glucose excursion. Boxplots extend from the 25th to 75th percentiles, line in the box is median, plus sign is the mean. Whiskers show minimum to maximum values. Each participant's by-day values are presented in dots. *Significantly different from reference condition "baseline" ($p \leq 0.05$).

Figure 3. Blood Glucose Metrics in the 3-Hours Post-Meal by Walking Condition.



Box and whisker plots of (A) peak glucose, (B) time to peak glucose, (C) nadir glucose, and (D) glucose excursion. Boxplots extend from the 25th to 75th percentiles, line in the box is median, plus sign is the mean. Whiskers show minimum to maximum values. Each participant's by-day values are presented in dots. *Significantly different from reference condition "baseline" ($p \leq 0.05$).

Figure 4. 24-Hour Time in Range Metrics by Walking Condition.



Percent time above range 2 (TAR2), time above range 1 (TAR1), time in range (TIR), time below range 1 (TBR1), and time below range 2 (TBR2) by walking condition. All values are presented as mean±SD. Pre- and post-meal walk metrics compared the reference "baseline", all $p>0.05$.

10.0 SUPPLEMENTARY TABLES AND FIGURES

Table S1. Summary of the Literature on Walk Timing and Postprandial Glucose in Individuals with T1D. Summary of the existing scientific literature regarding walk timing and postprandial glucose in a T1D population.

STUDY	CHARACTERISTICS	STUDY DESIGN	EXERCISE	MEAL	INSULIN	RESULTS	LIMITATIONS
PRE-MEAL EXERCISE							

Mitchell (1988) [155]	• N=16
	  ○ Male=4
	  ○ Female=4
	• Age=29±2
	• T1D Duration
	  ○ CON=n/a
	  ○ T1D=14±2
		(1) Exercise pre-meal	Bicycle test to exhaustion. Cycling at 80%VO_2max with 50-60 rpm.	• No meal	• CSII	• In T1D patients with baseline glucose of 86±4 and 149±9, glucose was significantly increased by 40-120min following exercise ($p<0.001$ and $p<0.025$).
						  ○ CON had a transient but significant increase as well ($p<0.01$)
							• High-intensity exercise is not always replicable
							• No meal provided
							• Bolus used pre-exercise to correct for hyperglycemia

POST-MEAL EXERCISE							

Hinojosa (2017)[156]	• N=7
	  ○ males=4
	  ○ females=3
	• Age=22.3±4.3
	• BMI=25.4±3.5
	• A1C=7.4±0.5
		(1) No exercise
		(2) Exercise immediately post-meal
			15-minute treadmill walk at 50-60% age-predicted HRmax	• 8oz BOOST drink with 41g of CHO	• Injected fast-acting insulin based on fasting BG level and CHO load	• On walking days, there was a significantly lower magnitude of BG spike ($p=0.016$) and AUC ($p=0.031$).	• Small sample size
							• Only completed exercise once BG 3.8-11.1mmol/L
							• Unclear what insulin regime was being used (i.e. pump, MDI, CGM) by participants

Manohar (2012) [157]	• N=24
	  ○ males=10
	  ○ females=14
	• Age
	  ○ CON=37.7±13.7
	  ○ T1D=37.4±14.2
	• BMI
	  ○ CON=25.6±3.2
	  ○ T1D=24.4±2.6
	• A1C
	  ○ CON=5.23±0.21
		(1) No exercise 6 hours post-meal
		(2) Exercise post-meal
			1.2mph walk for 33.5 minutes followed by 26.5minutes of inactivity repeated. In total, participants walked 5-6 hours each day.	• 10 kcal/kg each meal
				  ○ 55% CHO, 15% PRO, 30% FAT
				• 7:00 breakfast, 13:00
					• MDI injection of fast-acting insulin based on BG level and CHO load
					• Uniform doses for each meal
						• In individuals with and without T1D, the AUC was significantly higher for meals followed by inactivity ($p=0.001$ and $p=0.024$)
						• Percent time hyperglycemia increased by 10% after inactive meals.
							• Small sample size
							• extremely controlled environment
							• pre-bolus for meals to have a BG <8.33 mmol/L
							• 5-6 hours of daily walking may not be transferable to a

	○ T1D=7.0±0.60			lunch, 19:00 dinner			free-living environment.
Ramussen (1994) [11]	• N= 7 (males) • Age=29±4 • BMI=23±0.9 • T1D duration=16±2	(1) No exercise (2) Exercise 15 minutes post-meal	30 minutes of cycling at 65% of VO_2max.	• Breakfast at 11:30 • 100g white bread ○ 50g CHO, 1.5g fat, 8g PRO, 5g fibre	• MDI	• 3-hour AUC response was 34±12% lower during exercise days ($p<0.01$)	• Patients connected to an artificial pancreas to achieve normoglycemia before meal
Pre- and post-meal exercise							
Yamanoushi (2002) [148]	• N=6 ○ male=3 ○ female=3 • age=42.7±13.6 • BMI=20.3±2.3 • A1C=7.4±0.9	(1) No exercise (2) Exercise 30min pre-meal (3) Exercise 30min post-meal	30-minute walk on the treadmill at <50% VO_2max. Subjects maintained a HR range of 90-110bpm	• Breakfast at 7:30 (either pre- or post-exercise)	• MDI • Fast-acting injection 30 minutes before each meal • One injection of NPH at bedtime	• Post-meal exercise significantly improved AUC ($p=0.043$) • The same response was not seen following pre-meal exercise ($p=0.180$)	• Unclear makeup of the meal • Controlled environment • Patients only on MDI

Abbreviations: T1D, type 1 diabetes; CON, control; BMI, body mass index; A1C, hemoglobin A1C; HR, heart rate; CHO, carbohydrate; PRO, protein; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; AUC, area under the curve; BG, blood glucose.

Table S2. Current Knowledge Gaps and Future Research Directions. Summary of the current literature knowledge and gaps regarding pre- and post-meal walks in a T1D population, and where future research can expand to limit these gaps.

Research gaps	Current literature	Future directions
Sex-based differences 	• Studies have not directly compared differences in PPG responses in males and females	• Examine **biological sex differences** in response to exercise protocols and ppg • Include female menstrual cycle fluctuations, which could influence blood glucose
Adherence 	• Studies were primarily limited to single-day protocols (i.e., one night in the lab)	• Longer study duration to investigate participant **adherence** to exercise protocols
Exercise timing 	• Post-meal exercise more effective at limiting PPG in healthy and T2D populations than pre-meal exercise (3,6) • Primarily focused on breakfast meals	• **Randomized control trial** comparing pre- and post-meal exercise in individuals with T1D • Examine a variety of meals, including dinner meals which tend to have the largest variation in meal composition
Environment 	• In-lab settings only have been examined for populations with T1D • Different insulin modalities in individuals with T1D	• An **at-home** study examining the effects of activity on PPG in an open environment • Comparison of **different forms of technology** which could be influencing PPG
Hypoglycemia 	• A barrier not specifically examined in applicable T1D studies	• Examine hypoglycemia as a **barrier** to exercise completion and adherence • Study the number of hypoglycemic events

Abbreviations: PPG, postprandial glucose; T2D, type 2 diabetes; T1D, type 1 diabetes.

Table S3. Impact of Hormones on Glycemia in Individuals with T1D. A summary of the influence of various hormones on glycemia, highlighting their roles and potential sex-related differences.

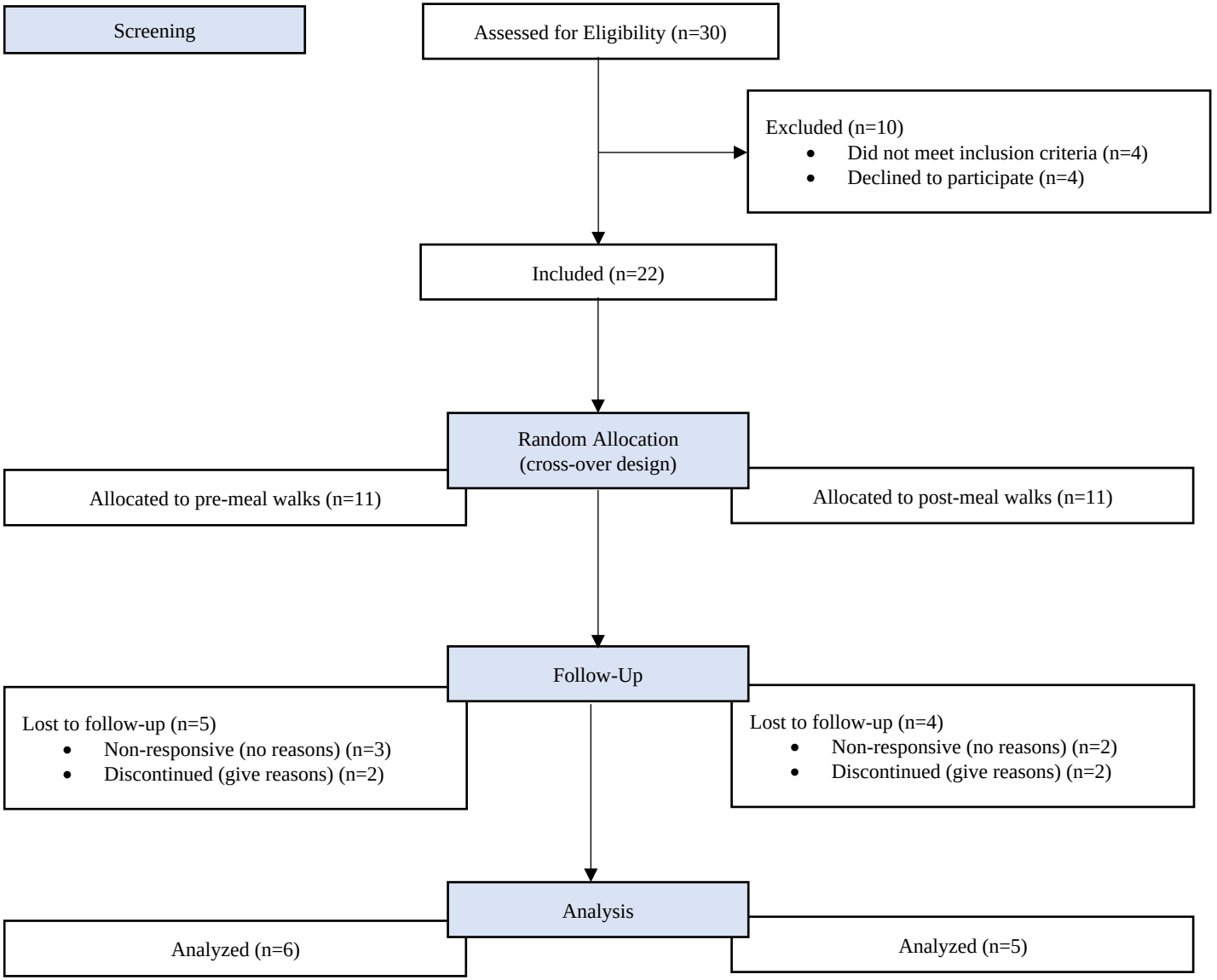
Hormone	Role	Glycemia	Sex Differences
Catecholamines (Epinephrine and norepinephrine)	- Increase hepatic glucose production - Increase glycogenolysis and gluconeogenesis	- Increase blood glucose during exercise - Hypoglycemia following exercise as glycogen stores replenished	- Higher response to exercise in males in fasted and PPG state
Growth Hormones	- Promote lipolysis and lipid oxidization	- Help to maintain blood glucose during exercise	- Similar response during and following exercise >10 minutes - More sustained growth hormone response in men
Estrogen	- Promote lipid oxidization - Glycogen sparing with less depletion of glycogen stores	- Maintained or increased blood glucose during exercise	- Similar levels between sexes in the follicular phase of the menstrual cycle - In the luteal phase of the menstrual cycle, estrogen increases

Table S4. Predictor Variables. Anthropometrics, activity, and diabetes-specific characteristics of interest.

Anthropometrics	Activity	Diabetes-Specific
Age (years): The participant's age at the time of data collection	**I-PAQ***:* Average vigorous, moderate, walking, and sitting activity over the past 7 days	**Disease duration (years):** Participants reported the years they have lived with T1D.
Gender: Participants identified as male or female	**Exercise:** Exercise session type and duration (minutes)	**HbA1C (%):** Average glycated hemoglobin over three months
Body Mass Index (kg/m^2): Calculated by participant's reported height and weight	**Heart Rate (bpm):** Average pulse during an activity session measured by a health tracker or 15-second pulse	**Insulin Modality:** The name of the insulin pump system used
Waist Circumference (cm): Measured by the participant	**RPE:** Subjectively measured by participant and recorded on the activity tracker	**Insulin (U):** Total daily insulin dose.
Medication: Current medication use beyond insulin	**VO_2 (mL/kg/min):** Determined by the subjects' 1-mile walk test	**Food:** Dinner meal content and the estimated CHO (grams)

Abbreviations: IPAQ, international physical activity questionnaire; bpm, beats per minute; RPE, rate of perceived exertion; HbA1C, hemoglobin A1C.

Figure S1. Inclusion of Study Participants Flow Diagram.



11.0 APPENDICES

Appendix A. Eligibility Questionnaire.

Inclusion Criteria: *must answer **yes** to all to be eligible*	
1. 18-60 years of age	☐ Yes ☐ No
2. Diagnosed with type 1 diabetes (T1D) for over one year	☐ Yes ☐ No
3. Been using an insulin pump for over 3 months	☐ Yes ☐ No
4. Living in the community (not in an institutional setting)	☐ Yes ☐ No
5. Able to participate in 20 minutes of light to moderate walking a day without assistive devices	☐ Yes ☐ No
6. Regularly use a continuous glucose monitor or flash glucose monitor	☐ Yes ☐ No
7. Access to a computer with internet	☐ Yes ☐ No
Exclusion Criteria: *must answer **no** to all to be eligible*	
1. Any cognitive, communication, or behavioral concerns that could limit safe exercise involvement	☐ Yes ☐ No
2. Pain worsened with exercise	☐ Yes ☐ No
3. Any neurological or musculoskeletal condition or co-morbidity that would preclude safe exercise participation	☐ Yes ☐ No
4. Any diagnosis of one or more of the following conditions by a physician:	
a. Cardiovascular disease	☐ Yes ☐ No
b. Neuropathy (nerve damage)	☐ Yes ☐ No
c. Nephropathy (kidney disease)	☐ Yes ☐ No
d. Retinopathy	☐ Yes ☐ No
5. Poorly controlled diabetes (hemoglobin A1C >10.0%)	☐ Yes ☐ No
6. Hypoglycemic seizure within the last 12 months	☐ Yes ☐ No
Does the participant meet study requirements? (i.e., answers yes to all inclusion criteria and no to all exclusion criteria)	☐ Yes ☐ No

**** If you, the participant, **do not** meet the study eligibility requirements, please inform the researchers, and do not continue with the questionnaire.*

Appendix B. Borg RPE 10-point Scale.

RPE	Level of Exertion	How it Feels
0	**No exertion**	Complete rest.
0.5	**Very, very slight (just noticeable)**	It doesn't even feel like you are exercising.
1	**Very Slight**	
2	**Slight**	It is easy to breathe and have a conversation.
3	**Moderate**	
4	**Somewhat Severe**	You are breathing heavily but can have a conversation.
5	**Severe**	
6		
7	**Very Severe**	You are short of breath. You can only say one sentence at a time.
8		
9	**Very, very severe (almost maximal)**	You can barely breathe and can only say a few words at a time.
10	**Maximal**	You are completely out of breath and cannot talk.

***you want to maintain a walking pace that feels like an **RPE of 3-4** on this scale.

Appendix C. Participant Log Sheet.

Date	Dinner Meal	Carbohydrates	Time of Dinner**	Exercise Type	Time Exercise Start	Exercise Duration	HR	RPE	Carbs to Treat a Low	Time Treated	Insulin Pump Profile Change	Time of Profile Change	Closed Loop Turned Off	Time	Menstruating
Ex 1: March 10	*Salmon and mashed potatoes*	*20g*	*7:00 PM*	*Walking*	*8:00 PM*	*30 minutes*		*4*	*15g Dex Tablets*	*10:20 PM*	*Exercise Mode*	*8:00 PM*			*yes*
											Normal	*8:30 PM*			
Ex 2: March 11	*Hamburger*	*30g*	*6:30 PM*	*Outside bike*	*4:45 PM*	*45 minutes*	*150pm*	*6*					*yes*	*9:45 PM*	
				Walking for Study	*6:00 PM*	*20 minutes*	*90bpm*	*3*					*no*	*10:30 PM*	
Day 1:															
Day 2:															
Day 3:															
Day 4:															
Day 5:															
Day 6:															
Day 7:															
Day 8:															
Day 9:															
Day 10:															
Day 11:															
Day 12:															
Day 13:															
Day 14:															

1 mile Walk Test Results		Estimated VO2
Name		
RPE		
Weight (lbs)		
Age		
Gender (1=male; 0=female)		
Time (minutes)		
End Heart Rate (bpm)		132.853

1 Mile Walk Test Protocol

1. Walk 1 mile (1.6km) on an indoor track or outside uninterrupted course
2. Walk as quickly as possible without speed walking or running
3. Track heart rate immediately following test using a watch or manually

**PLEASE NOTE

1. Record information in the 2 hours before dinner and 4 hours after dinner
2. If not applicable, leave cells blank
3. Refrain from additional exercise in the one hour before and one hour following dinner
4. Walking for study 3-4 on Borg RPE scale
5. Baseline: refrain from walking within 30 minutes before the start or end of your dinner meal
6. Pre-Meal Walking Condition: walk within 30 minutes before the start of your dinner meal
7. Post Meal Walking Condition: walk within 30 minutes of the end of your dinner meal