BODYWEIGHT EXERCISE AND GLYCEMIC CONTROL

THE EFFECT OF BRIEF BODYWEIGHT EXERCISE ON ACUTE GLYCEMIC CONTROL IN HEALTHY INACTIVE ADULTS.

By FIONA J. POWLEY, B.Sc. Kin

A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Master of Science

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TITLE: The effect of brief bodyweight exercise on acute glycemic control in healthy inactive adults. AUTHOR: Fiona J. Powley, B.Sc. Kin (McMaster University) SUPERVISOR: Dr. Martin Gibala NUMBER OF PAGES: ix, 68

Lay Abstract:

We investigated the effect of brief bodyweight exercise (BWE) on glycemic control. This refers to the ability to maintain blood sugar within a healthy range. Glycemic control was assessed with a small device called a continuous glucose monitor (CGM) that is inserted just below the skin. Healthy adults completed a virtually supervised 11-minute BWE protocol or an equivalent period of sitting. There was no difference in glycemic control measured over 24 hours following the BWE compared to sitting under standardized dietary conditions. Future studies should investigate the effect of repeated sessions of BWE training as well as responses in people with impaired glycemic control.

Abstract

Introduction: Brief vigorous exercise can enhance glycemic control. Limited work has investigated the effect of simple, practical interventions that require no specialized equipment. We examined the effect of bodyweight exercise (BWE) on acute glycemic control using continuous glucose monitoring (Abbott Libre Sense) under controlled dietary conditions This study was registered as a clinical trial (NCT05144490).

Methods: Twenty-seven healthy adults (8 males, 19 females; age: 23±3 y) completed two virtually supervised trials in random order ~1 wk apart. The trials involved an 11-min BWE protocol that consisted of five, 1-min bouts performed at a self-selected pace interspersed with 1-min active recovery periods or a non-exercise sitting control period (CON). Food intake was standardized for each participant using pre-packaged meals supplied over 24 h.

Results: Mean rating of perceived exertion for BWE was 14±2 (6-20 scale). Mean HR over the 11-minute the BWE protocol was 147±14 bpm which corresponded to 75% of age-predicted maximal HR. Mean 24-h glucose after BWE and CON was not different (5.0±0.4 vs 5.0±0.5 mM respectively; p=0.39). Postprandial glucose responses were also not different between trials after ingestion of a 75 g glucose drink, lunch, dinner and breakfast meals after each intervention. Measures of glycemic variability were not different between conditions.

Conclusion: A single session of BWE did not alter acute glycemic control in healthy, young adults. This study demonstrates the feasibility of conducting a remotely supervised BWE intervention using CGM under free-living conditions. Future studies should investigate the effect of repeated sessions of BWE training as well as responses in people with impaired glycemic control.

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List of Abbreviations:

ABBREVIATION	TERM
GLUT 1-4	Glucose transporter 1-4
IRS	Insulin receptor substrate
PI3K	Phosphatidylinositol-3-kinase
AKT	Protein kinase B
AS160	Akt substrate of 160 kDa
TBC1D1/TBC1D4	TBC1 domain family member 1/4
AMPK	AMP-activated protein kinase
ROS	Reactive oxygen species
NO	Nitric oxide
CA+	Calcium
ENOS	Endothelial nitric oxide synthase
P	Phosphate
MAGE	Mean amplitude of glycemic excursions
%PPO	Percentage of peak power output
MG/DL	Milligrams/deciliter
MMOL/L	Millimolar/liter
CGM	Continuous glucose monitoring
MICT	Moderate intensity continuous training
HIIT	High intensity interval training

Declaration of Academic Achievement:

Format and Organization of Thesis:

This thesis is prepared in the standard format as outlined in the School of Graduate Studies' Guide for the Preparation of Master's Theses. The first chapter is a literature review and the second chapter is a draft of a manuscript for submission to a journal.

List of Contributors to Thesis:

F.J. Powley, M.C. Riddell, L.M. Adamo, D. Richards, S. Baumgarten, and M.J. Gibala

Breakdown of Contribution:

F.J. Powley and M.J. Gibala formulated the research question and study design with input from M.C. Riddell. F.J Powley completed data collection with help from L.M. Adamo and S. Baumgarten, input from M.J. Gibala, and oversight from D. Richards. F.J. Powley performed data analysis with help from L.M. Adamo and input from M.J. Gibala. F.J. Powley and M.J. Gibala interpreted the study results with input from M.C. Riddell. F.J. Powley formulated and wrote initial drafts of the literature review and manuscript (Chapter 1 and 2) with input and assistance from M.J. Gibala.

Chapter 1:

1.1 Introduction

Physical activity is associated with a wide range of acute and chronic health benefits (12). Exercise can enhance glycemic control (28), which refers to the ability to manage and regulate blood glucose concentrations in both fasted and postprandial states (76). This can in turn help prevent the onset or progression of type 2 diabetes (T2D) (28). Euglycemia is maintained by balancing the amount of glucose entering and exiting the blood which is characteristic of "tight" glycemic control (14, 44). "Tight" glycemic control involves maintaining blood glucose concentrations between 4.4-6.1 mmol/L (44). The increasing prevalence of T2D worldwide (33) and low adherence to current physical activity guidelines highlights the need to explore novel exercise strategies that might improve glycemic control. Many adults report a perceived "lack of time" as a common barrier to regular physical activity (14). Brief, vigorous, intermittent-style exercise is one strategy to potentially address this barrier (54) due to its time-efficient nature. Another barrier to exercise for some people is access to appropriate equipment and facilities, with the associated cost hindering the capacity to engage in physical activity (76). Hence, there is a need to explore the feasibility of practical exercise strategies to improve glycemic control. This chapter will (a) review the physiological basis of glycemic control and how glycemic control is commonly measured, (b) consider the efficacy of different acute exercise strategies to potentially improve glycemic control, (c) highlight the possible mechanisms related to the beneficial effect of exercise on glycemic control, and (d) consider the impact of nutrition on the measurement of postexercise glycemic control.

1.2 Physiological overview of glycemic control and how it is measured.

1.2.1 The physiological basis of "tight" glycemic control.

Glucose is a monosaccharide which plays a critical role in energy metabolism throughout the body (21). Every cell in the human body utilizes glucose for energy, however the brain typically utilizes the greatest amount at rest (21). Blood glucose concentrations are typically maintained at ~5 mM under normal homeostatic conditions (14). If concentrations fall below 4 mM or rise above 7 mM, this is considered hypoglycemia or hyperglycemia, respectively (14). It is imperative to maintain euglycemia because extended periods of hypoglycemia or hyperglycemia can lead to unfavorable physiological outcomes (14). Hyperglycemia in particular is associated with an elevated risk of both mortality and morbidity (44). The interplay of glucagon and insulin, which are two hormones released from the pancreas, control the concentrations of glucose in the blood (14). Glucagon stimulates the liver to release glucose into the blood and counteracts a reduction in glucose levels (14). In contrast, insulin acts to decrease blood glucose concentrations by promoting glucose uptake into skeletal muscle and adipose tissue cells (14). Insulin tends to predominate in situations where blood glucose levels are high due to the input of glucose into the blood from the digestive system or the liver (14). Skeletal muscle, adipose tissue, and the liver are the three main target tissues of insulin (92) as it exerts an anabolic effect on the metabolism of glucose, fatty acids, and amino acids (37, 92). Therefore, without insulin, individuals would suffer from hyperglycemia, hyperlipidemia, as well as protein wasting (37). As summarized in Figure 1 (56), insulin has several roles including: increasing the uptake of glucose at skeletal muscle and adipose tissue cells, enhancing glycogen storage within the liver, lowering the

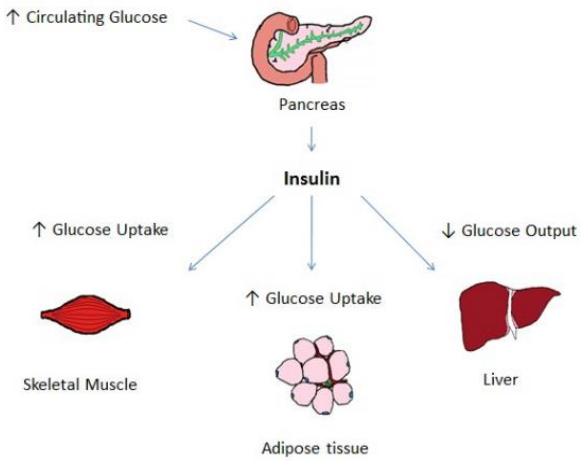


Figure 1. This flowchart displays the roles of insulin across different target tissues (56).

amount of glucose released by the liver, and preventing liver gluconeogenesis (56, 66, 92). The ability of insulin to successfully carry out these roles and achieve a decrease in blood glucose concentration when necessary is a hallmark of adequate insulin sensitivity (92). Reduced insulin sensitivity will lead to lower glycemic control and hyperglycemia as well as the potential development of pancreatic dysfunction and T2D (15). It is important to highlight the role of insulin and the effect of adequate insulin sensitivity on glucose dynamics because it directly impacts the ability to maintain "tight" glycemic control.

1.2.2 The physiology of glucose uptake and the effects of exercise on glucose uptake.

The family of glucose transporter (GLUT) proteins embed into cellular membranes to facilitate the movement of glucose into cells (21). GLUT1-3 are transporters that are typically consistently embedded in the cell membrane of tissues which have a large basal glucose demand such as the brain tissue (21). GLUT4 transporters are mainly found in skeletal muscle and adipose tissue cells and must be signaled to translocate to the cell membrane, otherwise they remain inside the cell and cannot facilitate glucose transport (21, 92). The two major signalling mechanisms involve insulin and muscle contraction which both increase the amount of GLUT4 in the membrane and therefore, glucose uptake (21, 78, 87). GLUT4 can operate in an insulin-dependent and insulin-independent manner to facilitate glucose uptake into cells (7). T2D is characterized by impaired insulin-dependent uptake of glucose, however, the insulin-independent method associated with muscle contraction is intact (7). It is referred to as an insulin-independent method because muscle contraction can stimulate the uptake of glucose without insulin being present (78). Glucose uptake that is insulin-independent is most frequently associated with exercise because this is the easiest method to initiate muscle contraction within the body (7).

Figure 2 summarizes the ability of muscle contraction to activate a signaling cascade which ultimately leads to GLUT4 embedding within the membrane (7).

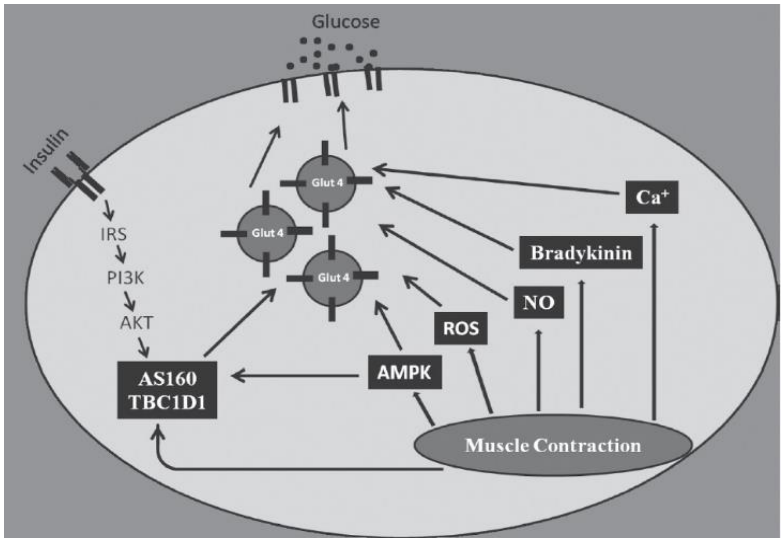


Figure 2. Muscle contractions can influence several proteins within the cell to promote the translocation of GLUT4 (7). Please see the list of abbreviations on page viii for the corresponding protein names. Additional information regarding intracellular mechanisms which impact glucose uptake and GLUT4 can be found in section 1.4.1.

During exercise there is an elevated glucose demand by working skeletal muscle (87). Intramuscular glycogen is the main source of carbohydrates near the beginning of exercise but, as exercise progresses, blood glucose utilization increases (87). Exercise is associated with an increase in skeletal muscle blood flow which results in more glucose and insulin being delivered to the muscle than at rest (87). This occurs despite a lower overall concentration of insulin in the blood during exercise compared to at rest (87). Therefore, during an acute exercise bout, the presence of insulin at the skeletal muscle and the simultaneous muscle contractions, lead to an increase in skeletal muscle glucose uptake, due to a greater number of GLUT4 in the membrane (15, 87). This higher level of glucose uptake at the skeletal muscle cells can also remain elevated for hours after an acute exercise bout (15).

1.2.3 Techniques to measure glucose and insulin dynamics.

There are several different techniques for measuring glycemic control and insulin sensitivity but, for the purposes of this review only a few methods will be discussed. These include fasted blood sampling, hyperinsulinaemic-euglycaemic clamp (HIEC), intravenous glucose tolerance test (IVGTT), oral glucose tolerance test (OGTT), and continuous glucose monitoring (CGM). In

each section below, the method will be described, and the advantages as well as disadvantages of each method will be considered. The measurement techniques vary in terms of expense, complexity, resources, and invasiveness (70). Researchers and clinicians should consider all relevant information when trying to determine the most appropriate technique to utilize in a given situation (70).

I. Fasted blood sampling.

In a clinical setting, glycemic control is typically assessed by measuring fasting glucose or hemoglobin A1c (glycated hemoglobin) in a single blood sample (76). The concentration of fasting glucose would reflect a measure of acute glycemic control whereas, hemoglobin A1c levels represent chronic glycemic control. There are also equations which can predict insulin sensitivity (QUICKI) and insulin resistance (HOMA-IR) by using the concentrations of glucose and insulin obtained from a fasted blood sample (15). This method does not portray postprandial glucose responses and it does not provide insight into glucose fluctuations over time (76) although it is considered the simplest measurement technique.

II. Hyperinsulinaemic-euglycaemic clamp (HIEC).

The HIEC is a very accurate and reliable, gold standard measurement technique (72, 76). This method involves insulin infusion to attain hyperinsulinemia as well as glucose infusion at the same time to achieve euglycemia between 5.0-5.5 mM (15). The level of hyperinsulinemia is meant to reflect concentrations observed in the postprandial state (76). A high level of skeletal muscle insulin sensitivity would correspond with larger rates of glucose infusion during this method (76). A qualified individual is needed for this technique, it is costly from a financial and

time perspective, and the level of hyperinsulinemia achieved could be considered supraphysiological (66, 70).

III. Intravenous glucose tolerance test (IVGTT).

An IVGTT involves introducing a glucose load into the body through direct injection into the antecubital vein over the span of 2-4 minutes (67, 85). Several blood samples are collected after injection to monitor the body's response to the glucose load (67). An IVGTT typically takes 2 hours to perform in total (30). This method is also considered a gold standard measurement technique along with the HIEC (76). This measurement technique avoids gastrointestinal hormone release because the glucose load bypasses the digestive tract (85). With the use of different indices, data collected during this test can be used to approximate insulin sensitivity (66).

IV. Oral glucose tolerance test (OGTT).

An OGTT involves an individual orally ingesting a 75 g bolus of glucose (15). For 2 hours following ingestion, several blood samples are collected to monitor the body's response to the glucose load (15). Glucose tolerance is measured via this method which is not the same as insulin sensitivity (66, 70). However, validated equations and/or indices (i.e., Matsuda index, Cederholm and Wibell index) have been developed which involve the use of data collected during an OGTT to estimate insulin sensitivity, similarly to an IVGTT (66, 70, 76). An individual who is insulin-resistant at the muscle would experience a slow rate of decline in blood glucose concentrations during an OGTT (3). The OGTT is less costly and more simple in comparison to the HIEC and IVGTT (70, 76). The OGTT introduces the glucose load in a way that reflect our day-to-day physiology (66) where we consume our food orally. However, it is

associated with greater levels of variability (i.e., in the glucose digestion process) and lower reproducibility (66, 70). An effort can be made to counteract this by implementing dietary control in research settings.

V. Continuous glucose monitoring (CGM).

Continuous glucose monitors are sensors that can be worn in various locations on the body to provide a continuous measurement of glucose from the interstitial fluid (5, 27, 43, 55, 69). A very small filament on the device is inserted subcutaneously to facilitate the measurement of glucose (27, 69). This method provides a measure of glycemic control through examining changes in interstitial glucose concentrations (76). This method provides detailed information regarding postprandial glucose responses in a free-living situation (58, 76). CGM effectively captures glycemic variability including all hyperglycemic and hypoglycemic events (55, 75) and displays a more comprehensive and in-depth view of glycemia compared to traditional methods (5, 69). CGM could possibly uncover changes in glycemic control that other techniques could miss because of its detailed nature (58). These devices utilize electrochemical technology which uses glucose oxidase to create an electric current (43). This reaction produces one electron per glucose molecule and the resulting electric current is used to estimate the concentration of glucose in the interstitial fluid (43, 55, 75). The relationship between the electric current and the glucose concentration is proportional (43, 55) and linear across many different physiologic conditions (75). Although, some studies indicate that certain glucose monitoring systems tend to overestimate glucose levels when compared to blood concentrations during exercise (39, 57, 65). The three major manufacturers of CGM devices are, Abbott, Dexcom, and Medtronic. The original purpose of creating CGM devices was to enhance the well-being and quality of life of those living with diabetes (47). However, in 2020, Abbott released a new product called the

Libre Sense Glucose Sport Biosensor (2). This device was not designed for medical purposes and is only meant for recreational use during sport and exercise (2). This device allows individuals without diabetes for the first time to utilize Abbott's glucose monitoring technology (2). Additional information on the application of CGM technology can be found in Appendix C.

1.3 The effect of acute exercise on glycemic control.

Regular physical activity is an effective strategy to improve glycemic control (28). The acute effect of exercise on glycemic control is influenced by numerous factors including the intensity, duration, and modality (40). By manipulating these three factors it is possible to explore the effects of many different types of exercise interventions on acute glycemic control. The different types of exercise that will be discussed in this section include traditional moderate-intensity continuous exercise, high intensity intermittent-style exercise, resistance exercise, as well as practical time-efficient exercise strategies [i.e., stair climbing and bodyweight exercise (BWE)]. High intensity, intermittent exercise could be further divided into high intensity interval training (HIIT) vs sprint interval training (SIT) exercise bouts (48). The former generally involves submaximal efforts performed at an intensity that elicits $\geq$80 % of maximal heart rate (HR) whereas the latter consists of "near maximal" or "all-out" efforts (48). A traditional moderate intensity continuous exercise session would involve completing exercise at a fixed intensity which is lower than that of the high intensity intervals for the entire duration of the session (62). Whereas, high intensity, intermittent exercise involves increases and decreases in intensity to facilitate rest periods in between intervals (48).

Resistance exercise involves completing some form of muscle strengthening activities to promote increases in muscle mass. The aforementioned types of exercise often involve the use of specialized exercise equipment to complete the session. Exercise protocols that require special

equipment or supervision are costly from a financial and time perspective which could influence the level of compliance and adherence to such protocols (53, 76). Stair climbing is an exercise modality that is feasible, inexpensive, and convenient for most individuals (45). BWE is another practical exercise modality that requires no exercise equipment to complete. A form of BWE is plyometrics which incorporates jumping and landing within the exercises (93).

1.3.1 Traditional moderate-intensity continuous exercise.

Many studies have examined the effects of various exercise protocols on glycemic control. This section will focus on the effects of moderate intensity continuous style exercise protocols on glycemic control measured using CGM. For example, a study by van Dijk and colleagues (94) demonstrated the positive effect of a single session of moderate continuous exercise on glycemic control in individuals with impaired glucose tolerance or T2D. These individuals experienced significantly lower 24-hour mean glucose as well as significantly less time spent in hyperglycemia following 45 minutes of moderate continuous cycling compared to a no exercise control condition measured with CGM (94). In contrast, Rees *et al.* (73) found that a single session of moderate intensity continuous walking exercise did not influence glycemic control in individuals with T2D. In the 24 hours following 50 minutes of treadmill walking (5 km/hour) vs sitting, glycemic control measured with CGM was not significantly different (73). These results indicate that an acute bout of traditional moderate intensity, continuous exercise can be beneficial for glycemic control in some instances but ineffective in others. Both of these studies included individuals with T2D and utilized CGM as the measurement technique, however the exercise modalities were different across the studies (cycling vs treadmill walking) (73, 94). It is possible that the walking intervention was a lower overall intensity than the cycling exercise which could explain the lack of influence on glycemic control found in the study by Rees and

colleagues (73). Shambrook *et al.* (80) demonstrated the positive effect of moderate intensity, continuous exercise in healthy, inactive males without any metabolic disorders. Completing 30 minutes of moderate intensity cycling at either ~35% or ~50% of oxygen uptake reserve was able to improve postprandial glycemic control 30 minutes following breakfast compared to a no exercise control condition (80). This suggests that traditional moderate intensity continuous exercise could also be an effective method to enhance postprandial glycemic responses in individuals without impaired glucose control.

1.3.2. High-intensity and intermittent-style exercise.

Chan-Dewar *et al.* (26) demonstrated that a very short but intense exercise bout could improve postprandial glycemic control in healthy, young males after consuming a standardized meal 90 minutes pre-exercise. The postprandial capillary blood glucose responses were significantly lower after completing 2 x 30 s and 4 x 30 s cycling sprints compared to a control intervention (26). This suggests that very short duration but high intensity intermittent exercise is effective to improve postprandial glycemic control in healthy, young individuals (26). Gillen *et al.* (49) demonstrated the positive impact of high intensity, intermittent exercise on glycemic control measured by CGM in individuals with T2D. In the 24 hours following an acute bout of high intensity, intermittent cycling exercise (10 x 60 s intervals at 90% HR max), total time spent in hyperglycemia as well as postprandial hyperglycemia was significantly lower compared to the no exercise control condition (49). Therefore, it is evident that high intensity, intermittent exercise is also an effective method to improve glycemic control in those with T2D (49). Subsequently, Little *et al.* (59) conducted a similar study with overweight/obese participants using the same high intensity exercise protocol from Gillen *et al.* (49). Compared to the control condition, the high intensity, intermittent exercise elicited significant improvements in the postprandial glucose

responses to dinner consumed the same day and breakfast consumed the morning after exercise (59). However, there was no significant difference in 24-hour mean glucose compared to the control condition measured with CGM (59). These studies indicate that various forms of acute high intensity, intermittent exercise across different study cohorts can elicit a consistent positive impact on postprandial glycemic control (26, 49, 59). However, the effect of high intensity, intermittent exercise over the 24 hours following the exercise bout is less clear and requires more research to establish its impact.

1.3.3 Resistance exercise.

To highlight the effect of acute resistance exercise on glycemic control, two studies can be considered with similar designs (71, 94). Praet *et al.* (71) and van Dijk and colleagues (94) compared changes in glycemic control using CGM after the completion of an acute bout of resistance exercise (which involved a series of upper and lower body resistance exercises on exercise machines) and a no exercise control condition. The time spent in hyperglycemia was significantly less in the 24 hours postexercise compared to the control condition in both studies (71, 94). However, the total 24-hour mean glucose was not significantly different between the exercise and control condition in the study by Praet and colleagues (71), whereas van Dijk and colleagues (94) found a significant difference in 24-hour mean glucose. Despite the positive influence of an acute bout of resistance exercise on hyperglycemia this does not always translate into a significant effect on 24-hour mean glucose (71, 94). The inconsistent results between the studies could be attributed to differences in the resistance exercise protocol itself (i.e., types of machines used, and exercises performed or the number of reps vs sets completed) as well as the difference in exercise intensity. In the study by van Dijk et al. (94), the intensity progressively increased with each set up to 75% of the individual's one repetition maximum (1 RM) whereas

all exercises were performed at 50% of 1 RM in the study by Praet and colleagues (71). This suggests that more robust effects on glycemic control could be seen as intensity of the resistance exercises increases. The influence of acute resistance exercise on glycemic control may also provide insight into the effects of BWE protocols on glycemic control due to the muscle strengthening aspect of both modalities.

1.3.4 Time-efficient, practical acute exercise interventions.

The studies presented thus far have all utilized some form of specialized equipment to perform the exercise sessions (i.e., cycle ergometer, treadmill, resistance exercise machines). Two recent studies investigated the effects of three different practical stair climbing exercise protocols (1, 3, and 10-minute stair climbing bout) on glycemic control (11, 64). The main difference between the studies was the study cohort as well as the type of nutritional component provided pre-exercise. Bartholomae *et al.* (11) recruited individuals with prediabetes and completed an OGTT and therefore, the researchers gave participants a 75 g oral glucose drink pre-exercise. Whereas, in the study by Moore and colleagues (64) the glucose load was provided as a mixed meal rather than a liquid drink and the participants were young, healthy adults. Figure 3 displays the blood glucose responses following the stair climbing protocols from the study by Moore and colleagues (64). The key finding from these two studies is that the stair climbing protocols elicited a positive effect on postprandial glycemic control in individuals with and without prediabetes compared to a control sitting condition (11, 64). In both studies, it is evident that the 10-minute stair climbing protocol provided the greatest benefit for

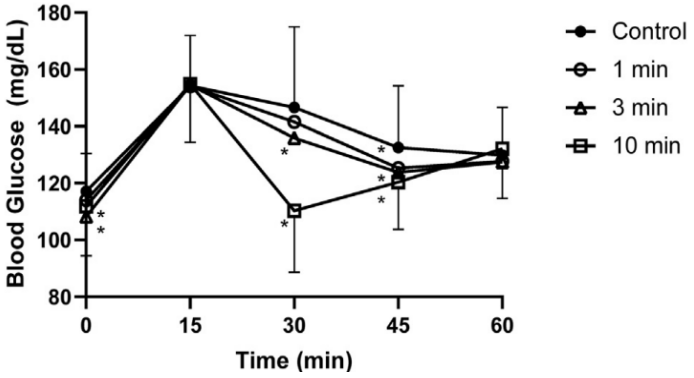


Figure 3. Postprandial glucose responses following the consumption of a mixed meal at 0 minutes. *; significantly different from the control condition (64).

postprandial glycemic control, suggesting a dose-response relationship (11, 64). These results highlight the positive impact of a very practical exercise strategy on glycemic control.

BWE is another important practical exercise modality to explore given that it does not require the use of specialized equipment. Barillas and colleagues (10) demonstrated the benefits of an acute bout of plyometric BWE on glycemic control in young, healthy adults. Participants performed 5 x 10 squat jumps and then immediately consumed a 75 g oral glucose drink (10). Glucose concentrations measured from capillary blood samples were significantly reduced 15 and 30 minutes after consuming the glucose load compared to the control sitting condition (10). This suggests that a very short (~4 -minute) BWE protocol could be effective for improving postprandial glycemic control (10). Similarly, Solomon *et al.* (84) demonstrated the benefits of performing an acute bout of BWE directly after consuming breakfast on glycemic control in healthy adults using CGM. In the 2 hours following the BWE, there was a decrease in the 2-hour postprandial glucose mean, area under the curve, and glycemic variability compared to the no exercise control condition (84). This suggests that glycemic control measured through CGM can improve during a short 2-hour postprandial window following acute BWE (84). More research is needed to further investigate the effects of BWE protocols on glycemic control. Both of these studies examined the influence of BWE over 1 or 2 hours postexercise, respectively therefore, there is a research gap regarding the effects of BWE measured continuously over longer periods of time (i.e., 24-hour glycemic control).

1.4 Mechanistic basis for effects of acute exercise on glycemic control.

1.4.1 Intracellular factors.

Mechanisms involving GLUT4, signaling proteins/molecules, glycogen depletion, and glycogen synthase (GS) could contribute to observed changes in glycemic control following acute exercise. These mechanisms can be classified as intracellular factors due to the fact that they originate from within the skeletal muscle cells. Increases in glycemic control following exercise are greatly attributed to an improvement in whole-body insulin sensitivity (95). This suggests that mechanisms related to changes in insulin sensitivity have a direct impact on glycemic control. One of the most supported and well-established mechanisms involved in changes to glycemic control is the role of GLUT4. During an exercise session and for ~2 hours postexercise there is enhanced capacity to uptake glucose due to the greater amount of GLUT4 embedded in the sarcolemma and T-tubules as a result of muscle contraction (18). Therefore, an acute bout of exercise can upregulate glucose uptake at the active skeletal muscle cells in both healthy adults as well as those with T2D (18). Glucose uptake stays elevated for many hours afterwards due to an exercise-induced increase in insulin sensitivity at the muscle cells (18, 52). Postexercise there is a greater level of GLUT4 translocation to the membrane in response to a given amount of insulin (18, 41). Essentially, the same amount of insulin is able to stimulate the translocation of a larger number of GLUT4 postexercise (41). This effect is illustrated in Figure 4 (88). Furthermore, intracellular signaling molecules like AMP activated protein kinase (AMPK) could play a role in enhanced GLUT4 translocation postexercise (88). Figure 5B displays the intracellular process involving

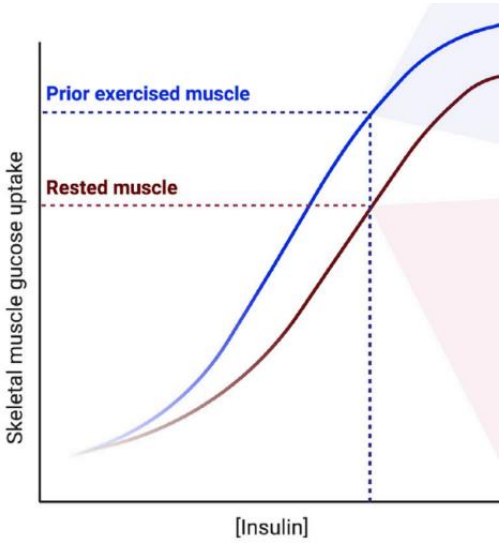


Figure 4. The same insulin concentration pre and post exercise can stimulate a different level of glucose uptake into the muscle cell (88).

AMPK in a previously exercised muscle cell (88). AMPK is activated with exercise which phosphorylates TBC1D4 ultimately enhancing GLUT4 translocation to the membrane and therefore glucose uptake (88). It is also thought that glycogen depletion during exercise might partially contribute to the initiation of greater GLUT4 translocation to the membrane (18) in order to uptake more glucose to synthesize glycogen (99) to replenish the lost stores. The rate limiting enzyme in the glycogen formation process is GS (18). Insulin as well as a decrease in the amount of muscle glycogen are two factors which can increase the activity level of GS (99). Kinases are able to phosphorylate GS within the cell which work to deactivate the enzyme (99) which would ultimately decrease glycogen synthesis. AMPK is an example of a kinase that can deactivate GS (99). This suggests that AMPK might play a competing role in the postexercise period having both a positive impact on GLUT4 translocation (88) but simultaneously, hindering GS activity (99). The intracellular response to exercise is highly integrated and complex. It is likely that the many intracellular factors, such as the activity of GLUT4, AMPK, and GS work together synergistically to facilitate an improvement in glycemic control following exercise.

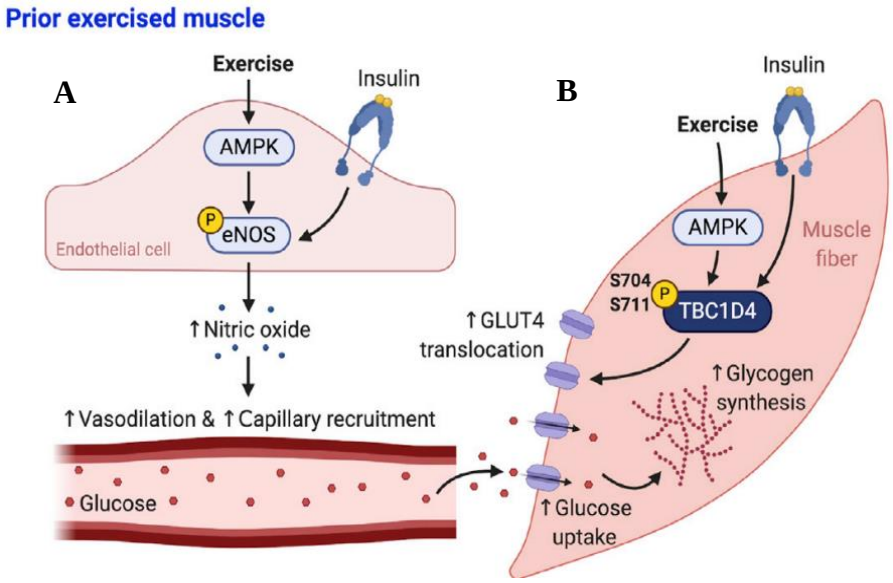


Figure 5. (A) Extracellular influences on glucose dynamics postexercise. (B) Intramuscular impact of exercise on GLUT4 translocation, glucose uptake, and glycogen synthesis (88).

1.4.2 Extracellular factors.

There are other mechanisms which can contribute to changes in glycemic control following acute exercise that are more extracellular in nature. During an exercise session and for ~2 hours postexercise, glucose supply to the skeletal muscle cells is elevated due to an increase in blood flow (18). Figure 5A displays how exercise promotes increases in nitric oxide which results in vasodilation, greater blood flow, and greater glucose delivery to the muscle cells (88). This cascade also involves enhanced capillary recruitment (88). An advantage of greater capillarization includes superior glucose and insulin delivery to the muscle cells (6) which will in turn enhance the amount of glucose uptake (101). Participating in aerobic exercise could lead to skeletal muscle angiogenesis which would enhance the amount of capillarization (101). Vascular endothelial growth factor is involved in the process of angiogenesis (19). A study found that completing one bout of knee extensor exercise for 45 minutes resulted in an improvement in the amount of vascular endothelial growth factor mRNA within the muscle (50). This suggests that a single bout of acute resistance exercise is a sufficient stimulus to elicit angiogenic processes at the skeletal muscle cells. Akerstrom *et al.* (6) utilized prazosin in the drinking water of rats to stimulate angiogenesis which resulted in an ~20% elevation in skeletal muscle capillarization. This was associated with an improvement in both whole-body and skeletal muscle insulin sensitivity (6). Prazosin does not influence GLUT4, GS, AMPK, or insulin signaling (6) therefore, these results are independent of changes in these intracellular factors. A study by Snijders *et al.* (83) further supports the hypothesis that capillarization is influential for glycemic control and insulin sensitivity. The researchers measured baseline skeletal muscle capillarization in older, healthy males and found that those with lower levels of capillarization experienced significantly higher postprandial insulin responses during an OGTT (83). This suggests that the

level of muscle capillarization could have implications for glucose control and insulin sensitivity (83).

Another mechanism to consider is the influence of fibre-type recruitment during exercise on glycogen depletion. There is variation in fibre-type recruitment between different intensities of exercise, such that as intensity increases so will the amount of fibres recruited (97). High intensity exercise is also associated with larger levels of type II muscle fibre recruitment (15). More fibre recruitment can coincide with greater degrees of glycogen depletion (97). Vøllestad and Blom (97) discovered that cycling at both 43% and 61% of VO_{2max} resulted in glycogen depletion within type I and type IIA muscle fibres but cycling at 91% of VO_{2max} was associated with glycogen depletion in type I, IIA, IIAB and IIB muscle fibres. The researchers concluded that higher exercise intensities can elicit greater muscle fibre recruitment and glycogen depletion compared to lower intensities (97). Greater fibre recruitment during exercise could be associated with a greater magnitude of metabolic change because a larger number of fibres are contributing to the effect (76). The results from this study suggest that high intensity exercise may have a greater positive impact on glycemic control based on the mechanisms related to glycogen depletion.

1.4.3 Mechanisms related to no change or a decrease in glycemic control postexercise.

Figure 6 displays different mechanistic pathways that can lead to various effects on blood glucose control (46). The first two pathways have already been addressed however, it is important to consider the effects of counter-regulatory hormones released during brief vigorous exercise on glycemic control. For example, intense exercise can elicit increases in catecholamine concentrations (100). Catecholamines promote glycogen breakdown and gluconeogenesis in the liver which directly results in an increased level of glucose production by the liver (81). This

mechanism could produce a counteracting effect postexercise which might lead to an observable decrease in glycemic control (i.e., greater blood glucose concentrations) or no change in glycemic control (i.e., if paired with other beneficial effects promoting decreases in blood glucose).

The type of exercise performed could also contribute to the observed changes in glycemic control. For example, Asp *et al.* (9) discovered that an acute bout of eccentric exercise was associated with a decrease in GLUT4 content within the working skeletal muscle. Therefore, eccentric exercise could have short-term negative effects on glucose uptake and the resynthesis of glycogen in previously exercised muscles (9). The researchers suggested the possibility of eliciting similar effects with an intense session of concentric exercise (9). Therefore, depending on the nature of the exercise bout this could explain a decrease, or no change observed in glycemic control following acute exercise.

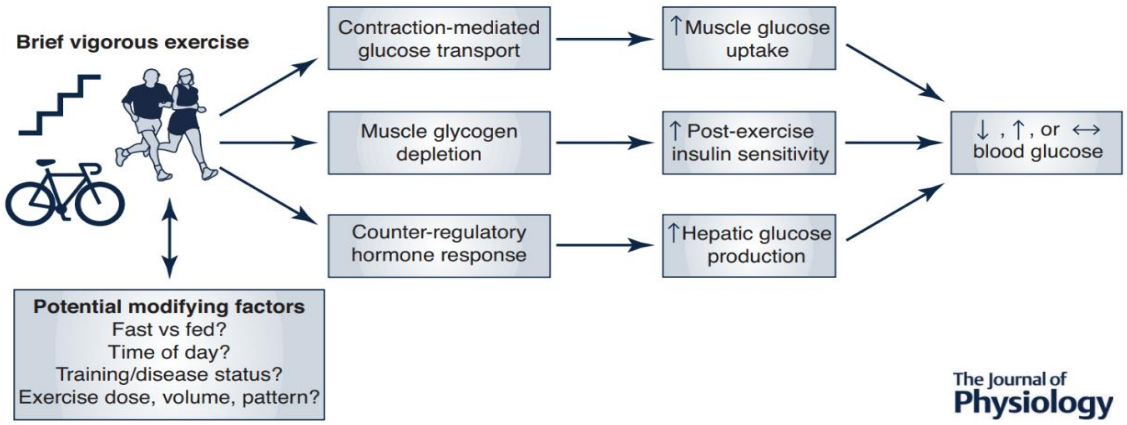


Figure 6. Different mechanistic pathways which could lead to an increase, decrease, or no change in glycemic control following brief vigorous exercise (46).

1.5 The impact of nutritional status and energy balance on glycemic control postexercise.

It is important to consider factors that might modulate the relationship between exercise and glycemic control. Nutritional status (i.e., being in fasted vs fed state while exercising) has the

potential to influence the effects of exercise on glycemic control. For example, a study by Terada and colleagues (90) found that completing an acute bout of treadmill exercise in fasted state was more beneficial for postprandial glycemic control and glycemic variability (MAGE) compared to exercising in a fed state in those with T2D. This suggests that exercising after an overnight fast may be a more beneficial nutritional state to promote positive changes in glycemic control. Furthermore, two recent studies compared the effects of 8 weeks (20) or 12 weeks (96) of exercise training completed in either a fasted or fed state in individuals with T2D. The 8 weeks of training had a positive impact on glycemic control outcomes but showed no difference in the outcomes between the fasted and fed groups (20). Whereas, the 12-week training study found that completing exercise in fed state results in better improvements in hemoglobin A1c levels compared to exercising in fasted state (96). The conflicting results could be attributed to the difference in training duration (8 vs 12 weeks) or training modalities (combined strength and endurance vs endurance training only, respectively) (20, 96). Future studies examining the effects of performing an acute high intensity exercise bout or HIIT in fasted vs fed state on glycemic control in healthy individuals is warranted.

Changes in energy balance (i.e., energy surplus vs deficit postexercise) can also play a contributing role in the relationship between exercise and glycemic control. A study by Schleh and colleagues (79) demonstrated that an exercise-induced energy deficit could be beneficial for postprandial glycemic control in healthy adults. The researchers found that the glucose responses to breakfast the morning following exercise was significantly lower compared to an energy balanced state (no surplus or deficit). Despite this, 24-hour mean glucose as well as glycemic variability (MAGE) was not different between the conditions (79). This highlights the potential value of a negative energy balance for postprandial glycemic control. Similarly, Estafanos *et al.*

(35) also demonstrated the benefit of an exercise-induced energy deficit for glycemic control in postprandial periods following an acute bout of high intensity interval exercise compared to an energy balanced state. The researchers also found a positive impact on 24-hour mean glucose in the energy deficit condition (35). These studies provide evidence in support of achieving an exercise-induced energy deficit in the postexercise period to benefit glycemic control (35, 79). Future studies could investigate the influence of slightly larger energy deficits as well as compare states of acute energy deficit to acute energy surplus rather than only comparing to a state of energy balance or maintenance.

1.6 Purpose

BWE may be an effective method to improve glycemic control, but more research is needed to establish the potential efficacy of practical exercise protocols that may be more feasible and accessible for the general population. To our knowledge, no previous study has employed CGM to examine the effects of an acute BWE protocol on 24-hour glycemic control.

The purpose of this study is to investigate the efficacy of an 11-minute brief BWE protocol on acute glycemic control using CGM. The primary outcome is 24-hour mean glucose and secondary outcomes are glycemic variability, peak postprandial glucose concentration, 2-hour postprandial glucose means, and the maximum positive postprandial glucose change from baseline (MPPC). We hypothesize that mean 24-hour glucose will be lower after the BWE intervention compared to a control sitting condition. We also hypothesize that glycemic variability, glucose peaks, postprandial glucose means, and MPPC will be lower after BWE compared to the control condition.

Chapter 2:

Introduction

Glycemic control is defined as the ability to manage and regulate blood glucose concentrations in both fasted and postprandial states (76). For healthy individuals, so called "tight" glycemic control entails maintaining blood glucose concentrations between 4.4-6.1 mM (44). In a clinical setting, glycemic control is typically assessed by measuring fasting glucose or hemoglobin A1c in a blood sample (76). The concentration of fasting glucose provides a snapshot of acute glycemic control whereas, hemoglobin A1c reflects chronic glycemic control. A limitation of these measures is neither provides insight into rapid glucose fluctuations over time (76) or in response to acute interventions. Continuous glucose monitoring (CGM) is another technique which detects changes in interstitial glucose concentrations and provides comprehensive information regarding postprandial glucose responses in a free-living situation (58, 76). The nature of CGM makes it a very useful and beneficial technique to measure changes in glycemic control following acute exercise interventions (58).

Regular physical activity is an effective strategy to improve glycemic control (28). The acute effect of exercise on glycemic control is influenced by numerous factors including the intensity, duration, and modality (40) as well as nutritional state and particularly carbohydrate ingestion before and after the session. Recent studies have investigated the influence of relatively brief but vigorous-intensity exercise on glycemic control. For example, Little *et al.* (59) demonstrated that completing a single session of high-intensity interval exercise [10 bouts x 60 s at 90% of peak heart rate (HR)] improved postprandial glucose responses within the immediate 24 hours following the protocol as measured via CGM in participants who were overweight or obese.

These results highlight the potential efficacy of high intensity exercise protocols to acutely improve glycemic control (26, 59).

Brief vigorous exercise that does not require specialized equipment [e.g., bodyweight exercise (BWE)] has the potential to enhance the accessibility and practicality of physical activity strategies to enhance glycemic control (53). Barillas and colleagues (10) demonstrated the benefits of an acute bout of plyometric BWE on glycemic control in young, healthy adults. Participants performed 5 x 10 squat jumps and then immediately consumed a 75 g oral glucose drink (10). Glucose concentrations measured from capillary blood samples were reduced 15 and 30 minutes after drink ingestion compared to the control sitting condition (10). This suggests that a very short (~4 -minute) BWE protocol could be effective for improving postprandial glycemic control (10). Similarly, Solomon *et al.* (84) showed the benefits of performing an acute bout of BWE directly after consuming breakfast in healthy adults using CGM. In the 2 hours following the BWE protocol, there was a decrease in the 2-hour postprandial glucose mean, area under the curve, and glycemic variability compared to the no exercise control condition (84). This suggests that glycemic control measured with CGM can improve during a short 2-hour postprandial window following acute BWE (84). These studies reveal that BWE could be used to improve glycemic control, but more research is needed to establish the efficacy of feasible and accessible BWE protocols. The two aforementioned studies (10, 84) only examined the influence of BWE over a 1 or 2 hour period postexercise and there is a research gap regarding potential changes over a longer period of time (e.g., 24-hour glycemic control). To our knowledge, CGM has not been used to examine the effects of an acute BWE protocol on 24-hour glycemic control. Therefore, exploring the use of BWE to improve glycemic control in the immediate 24 hours postexercise measured via CGM addresses a current gap in the literature.

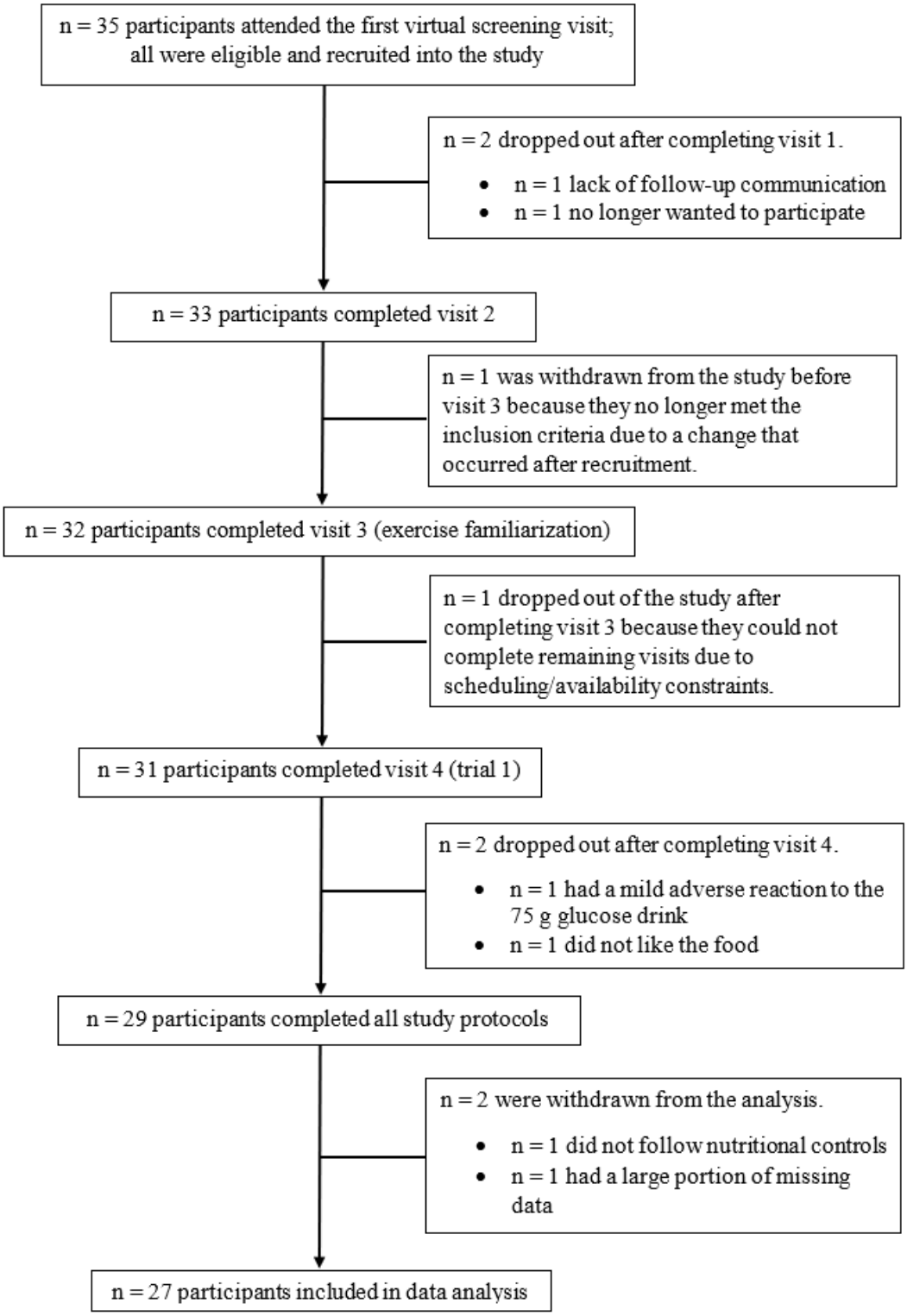
The purpose of this study was to investigate the efficacy of a brief BWE protocol on acute glycemic control using CGM. The primary outcome of this study was 24-hour mean glucose. Secondary outcomes were 2-hour postprandial glucose means, peak postprandial glucose concentrations, the maximum positive postprandial change from baseline (MPPC), and glycemic variability. Glycemic variability was assessed through the mean amplitude of glycemic excursions (MAGE), the 24-hour glucose standard deviation (SD), and the coefficient of variation (CV). We hypothesized that mean 24-hour glucose would be lower after the BWE intervention compared to a control sitting (CON) condition. We also hypothesized that postprandial glucose peaks and means as well as MPPC would be lower after BWE compared to the CON condition. Lastly, we hypothesized that glycemic variability would be lower in the BWE condition compared to the CON condition.

Methods

Participants. Twenty-seven healthy inactive adults volunteered to participate after providing informed consent (19 females and 8 males, age: 23±3 y, mass: 70±15 kg, height: 168±10 cm, body mass index: 25±4 kg/m^2; means ± SD). This study was approved by the Hamilton Integrated Research Ethics Board (project # 13864) and registered on ClinicalTrials.gov (NCT05144490). A calculation performed using an online program (G*Power; version 3.1.9.7) for a one-tailed dependent means (matched pairs) t-test estimated that a sample size of 27 was required to detect a medium effect size (dz=0.5) with 80% power at an alpha level of 0.05. A medium effect size was deemed reasonable based on determinations made in G*Power using our hypothesized minimum meaningful difference of 0.2 mM as well as typical means and SD reported in the literature for 24-hour mean glucose. Participants were recruited from the community surrounding McMaster using word of mouth, posters, and social media. Figure 7

displays a CONSORT diagram illustrating the number of total participants enrolled in study compared to the number of participants that were included in the final data analysis.

Figure 7. Study participant CONSORT diagram.



Study overview. This study involved an acute, experimental, within-subjects, crossover design where each participant completed both a BWE protocol and a CON protocol in random order. The study included six steps which involved either virtual interactions or in-person visits to the Human Performance Laboratory at McMaster University: 1) screening (virtual interview), 2) fitness assessment and CGM familiarization (in-person), 3) exercise familiarization (virtual), 4) BWE or CON trial (virtual), 5) opposite BWE or CON trial (virtual), and 6) CGM removal (in-person). The exercise familiarization was completed at least one week prior to visit 4. The two experimental trials were completed one week apart for most participants (n = 20) while the number of days between trials for a limited subset of participants (n = 7) was different (6-17 days between trials) due to scheduling constraints. All trials started in the morning or early afternoon (1000 h – 1330 h). The two trials started at the same time of day for most participants (n = 22) whereas a small number of participants (n = 5) started the second trial within 30 minutes of their first trial start time. The exercise familiarization and the experimental trials were completed approximately 3 hours after breakfast was consumed. For the two experimental trials, participants completed an 11-minute BWE or CON condition in a randomized order using simple randomization to avoid an order effect.

Pre-experimental procedures. The first virtual screening visit was completed over video call where participants were recruited into the study if they met the eligibility criteria. These criteria included being cleared to participate in physical activity as per the CSEP Get Active Questionnaire, being physically inactive, and being between the ages of 18-35 years. The CSEP Get Active Questionnaire was used to initially screen participants for underlying conditions that might preclude their participation and to determine habitual weekly physical activity levels. Inactivity was defined as not meeting the physical activity targets in the Canadian 24-Hour

Movement Guidelines for Adults. These targets include accumulating at least 150 minutes of moderate-to-vigorous aerobic physical activity weekly and performing muscle strengthening activities using major muscle groups at least twice per week (24). During the screening visit, participants also completed a short medical screening questionnaire to gather information regarding health status, medication usage, allergies, food/dietary preferences or restrictions, and, for the female participants, their contraceptive usage and menstrual cycle. Female participants who were currently using some form of contraception (e.g., pill, IUD, ring; n = 8) completed both experimental trials during the active hormone period rather than the placebo phase. Naturally cycling female participants (n = 11) completed both experimental trials between day 1-15 of their cycles which typically corresponds to the follicular phase (22). The next visit involved participants coming into the laboratory at McMaster University to complete an in-person fitness assessment and CGM familiarization. The latter involved showing participants a short video to inform them about the CGM device (Abbott, Libre Sense Glucose Sport Biosensor) and insertion procedures. Height and body mass were measured prior to the completion of a graded exercise test to volitional fatigue on a cycle ergometer (Lode Excalibur Sport version 2.0, Groningen, The Netherlands). Peak power output was recorded at the end of this test to calculate maximal oxygen uptake (VO_{2max}) using validated equations as previously described (59, 86). The fitness test consisted of a 4-minute warm-up at 0 watts (W) followed by a stepwise increase in intensity of 15 W per minute thereafter. Participants were asked to maintain an RPM between 70-90 during the test and the test was stopped when the participants RPM fell below 60, at which point peak power output (W) was recorded. Participants were given a study kit to keep at home for the remote visits which included a Polar HR monitor (Polar H7 Bluetooth Smart Heart Rate Sensor & Strap), an activity monitor (ActiGraph wGT3X-BT v1.9.2), and a 6-

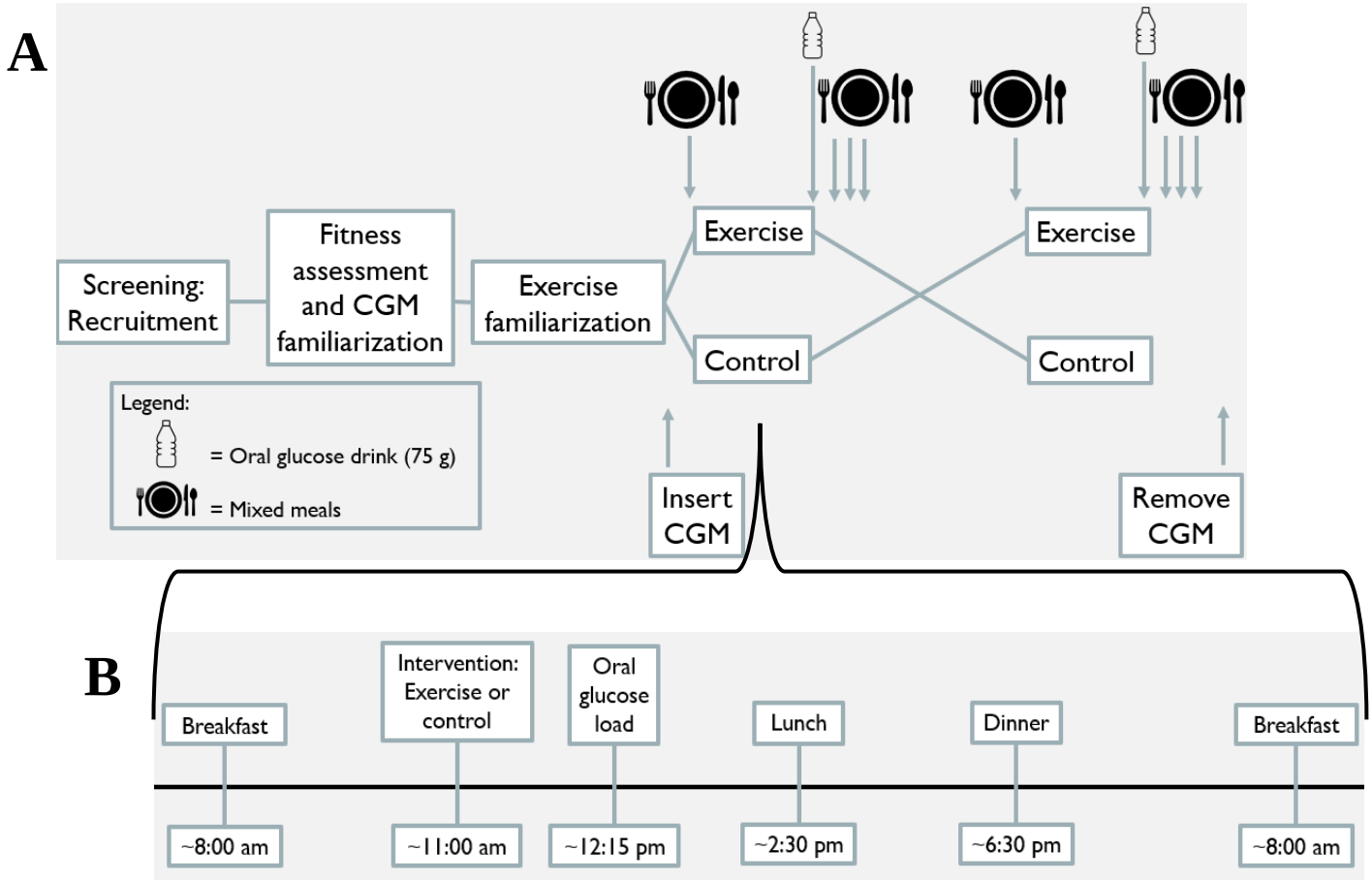
20 Borg rating of perceived exertion (RPE) scale (17). Participants subsequently completed a virtual exercise familiarization which involved performing the 11-minute BWE protocol remotely under the supervision of a researcher over a video call. This enabled the participants to become accustomed to the protocol before the main experimental trials. HR was measured during the exercise protocol and RPE was obtained immediately upon completion of the exercise bouts during the workout. Participants were given the option to subsequently insert the CGM device on the back of their upper arm ~24 hours prior to the first experimental trial or arrange to have a study investigator perform the insertion for them. Additionally, a researcher delivered individualized meals prepared by a commercial company (Heart to Home Meals) and two 75 g glucose drinks (NERL™ Trutol™ Glucose Tolerance Test Beverages, Thermo Fisher Scientific; Unflavoured OGTT, VWR Scientific) to the participants before the experimental trials.

Experimental procedures. Each experimental trial involved a controlled nutritional period starting on the morning of the trial up until 24 hours after the 11-minute BWE or CON protocol ended. All meals consumed during this controlled nutritional period were provided to the participants in advance and participants were asked to only consume the food provided to them during that time. The macronutrient breakdown of each controlled meal was ~50% carbohydrates, ~30% fats, and ~20% protein. Daily total caloric need of each participant was calculated using the Harris-Benedict equation with the activity factor set to 1.4 (51, 98). Based on the meal plans we created for participants, the average energy intake over 24 hours was 2260 ± 380 kcal which included the energy supplied from one breakfast, lunch, and dinner. The first controlled meal (breakfast the morning before the remote experimental trial) made up ~25% of the daily energy total in kcal. The second, third, and fourth meals (lunch, dinner, and breakfast the next morning) made up ~30%, ~45%, and ~25% of the total daily energy, respectively.

Participants consumed the same 4 controlled, individualized meals for both experimental trials. Participants were asked to replicate the time of meal consumption between the trials. Participants were able to consume any beverages they wanted but they were asked to replicate beverage consumption patterns between the two trials. Participants were provided with a meal timing and beverage log to facilitate the replication process. All participants were asked to consume their first individualized, controlled breakfast in the morning 3 hours prior to the start time of the remote experimental trial. The exercise condition started by completing the 11-minute BWE protocol whereas, the CON condition involved quietly sitting for the same duration. Participants remained on the video call with a researcher for a 1-hour rest period after completing either 11-minute protocol. After the 1-hour rest period, participants were given 5 minutes to consume the 75 g oral glucose drink under the supervision of the researcher on the video call. For the immediate 24 hours following the 11-minute BWE or CON condition, glycemic control was measured using the CGM device. Participants were asked to eat the second meal (lunch) at least 2 hours after consuming the 75 g glucose drink and the third meal (dinner) at least 2 hours after lunch. This was to provide a distinct 2-hour postprandial window to examine the glucose responses to the 75 g glucose drink and each controlled meal. These procedures were conducted twice for each experimental trial with the only difference being what was performed during the first 11 minutes of the remote video call visit (BWE vs quiet sitting). Participants were also asked to avoid alcohol consumption and to refrain from structured exercise for the 24-hour glucose measurement period (the 24 hours following the 11-minute protocol). Activity data (total kcals, average METs, average percent sedentary time, and total steps) was collected for approximately 24 hours following the completion of the 11-minute BWE and CON conditions to compare activity levels between the trials using a wrist-worn ActiGraph activity monitor. After

the completion of the second experimental trial, participants returned to the laboratory to have their CGM device removed.

Figure 8. A) Study overview. B) Sample trial day overview.



BWE protocol. The BWE protocol was modelled on an 11-minute workout previously utilized by Archila *et al.* (8) in our laboratory. The specific exercises were modified to reduce joint impact forces with the goal of increasing the overall accessibility of the protocol. The protocol started with 60 s of jumping jacks to warm-up and was followed by five exercises performed for 60 s each and interspersed with 60 s periods of walking on the spot for recovery. The protocol ended with 60 s of walking on the spot to cool-down. The specific exercises were:

Squat thrusts (modified burpees)
Knee tucks (left leg for 30 s, right leg for 30 s)
Mountain climbers

Knee tucks (left leg for 30 s, right leg for 30 s)
Squat thrusts (modified burpees)

Participants were asked to follow along to a custom workout video made by a researcher that demonstrated the entire exercise protocol. Participants were encouraged to complete as many repetitions as possible of each of the five exercises in the allotted time.

Measurements and calculations. The CGM data was automatically transferred to an online cloud-based system (Supersapiens Dashboard) which was used to download csv files of the interstitial glucose data collected for each participant. The 24-hour period of glucose data we extrapolated from these files started from the minute that each participant completed the 11 minutes of BWE or sitting on the trial day. An open access Excel spreadsheet (EasyGV 9.0.R2, University of Oxford) as previously described (98) was used to calculate the 24-hour mean glucose as well as MAGE over the 24 hours. CV was calculated as follows: SD / 24-hour mean glucose. Postprandial glucose peaks, 2-hour postprandial glucose means, and MPPC were calculated within Excel. Postprandial periods include the 2-hour window after the consumption of the 75 g glucose drink, lunch, dinner, and breakfast the following morning. Postprandial glucose peaks were recorded as the maximum glucose concentrations achieved in each respective 2-hour window. 2-hour postprandial glucose means were calculated as the average glucose over each respective 2-hour window. MPPC was calculated by subtracting the pre-meal baseline glucose from the postprandial peak glucose concentration. The pre-meal baseline glucose was determined to be the 15-minute mean glucose prior to the meal start time. The CGM devices utilized in this study have a standard glucose reading interval of <1 – 15 minutes under normal measurement conditions. Missing data was identified as any glucose reading interval of >15.5 minutes. The percentage of missing data over the 24-hour measurement period was calculated by determining the number of minutes missing above and beyond the largest glucose sampling interval (15

minutes in this case) and then dividing the total number of missing minutes by the number of minutes in 24 hours (1440 minutes). The percentage of missing data over a 2-hour postprandial period was calculated in the same way except, the total number of missing minutes in the respective 2-hour window was divided by 120 minutes instead. We set 10% as the missing data cut-off threshold, such that participants with more than 10% missing data over the entire 24-hour period or in any one of their 2-hour postprandial periods would be excluded from the respective analysis. In our data set, n=9 participants had no missing data whereas n=18 had small portions of missing data throughout the 24-hour measurement periods. Among these participants the approximate average percentage of missing data across the 24-hour period was <2%. Therefore, no participants exceeded the cut-off threshold for the entire 24-hour period, however, n=2 participants exceeded the missing data threshold for the postprandial breakfast response during one trial. These 2 participants were excluded from the breakfast postprandial analysis (postprandial glucose peak, 2-hour postprandial mean glucose, and MPPC) and therefore, those outcomes are based on n=25. The activity monitoring data was collected using ActiGraph wrist-worn devices and several different activity outcome measures were calculated using the ActiLife 6 Data Analysis Software (v6.13.4). The ActiLife software produces csv files whereby total kcals, total steps, average percent time in sedentary behaviour, and average METs were calculated within Excel. HR was measured to characterize the intensity of the 11-minute BWE protocol vs the CON protocol. Polar HR chest straps were worn during each protocol, and they were paired via Bluetooth to the ActiGraph wrist-worn devices to record HR data. The HR data for each 11-minute intervention was extrapolated from the ActiLife 6 Data Analysis Software (v6.13.4) into csv files where the mean HR and peak HR was calculated within Excel.

Statistical analysis. The independent variable was condition (BWE vs CON) and the dependent variables were 24-hour mean glucose, 2-hour postprandial mean glucose, postprandial glucose peaks, MPPC, glycemic variability, and activity factors including total kcals, total steps, average METs, and average percent in sedentary behaviour. Outliers were identified in the CGM data by creating a modified boxplot for the data set and implementing the use of quartiles and the interquartile range (91). If a data point sat below the first quartile or above the third quartile by more than 1.5 times the interquartile range, then the data point was deemed an outlier in the data set (91). There were no outliers detected for the postprandial peak glucose or MPPC following the 75 g glucose drink as well as CV. The remaining CGM outcome measures had between 1-4 detectable outliers depending on the specific outcome of interest. We conducted the statistical analysis of the CGM data with and without the presence of the said outliers and this did not alter the significance of the outcome measures. All measures remained nonsignificant. A Shapiro-Wilk test was completed to assess normality of the data set. All data that were normally distributed were analyzed using a one-tailed paired t-test. If the data set was not normally distributed, we conducted a Wilcoxon signed-rank test which is the non-parametric equivalent (61). Significance was set as $p \leq 0.05$. Statistical analysis was completed using GraphPad Prism 9.3.1. All data are presented as mean±SD for n=27 except where specifically noted in a few instances.

Results

Descriptive Data:

Average peak power achieved during the fitness test was 198±63 W. The mean indirect VO_{2max} calculated based on the fitness test was 36±7 mL/kg/min. RPE for the BWE protocol was 14±2 vs 6±0 for CON. The BWE protocol elicited a peak HR of 173±14 bpm and mean HR of 147±14

bpm (n=26) with the latter corresponding to 75% of age-predicted maximal HR. The mean HR for the CON was 73±11 bpm (n=22).

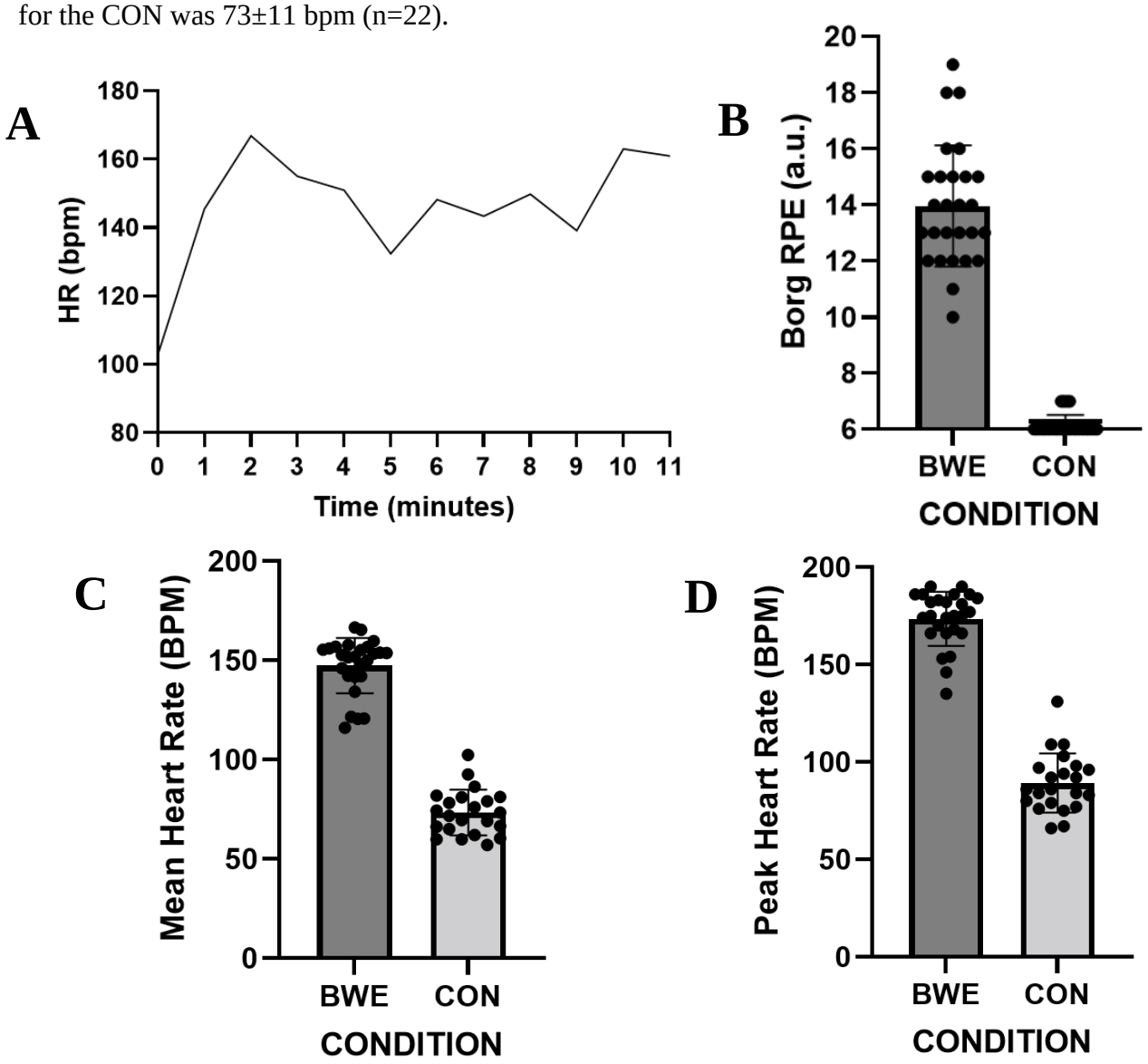


Figure 9. The following graphs characterize the intensity of the BWE protocol. (A) Representative HR tracing for one participant during the 11-minute BWE protocol. (B) RPE responses. (C) Mean HR vs (D) Peak HR for each 11-minute intervention with n = 26 displayed for BWE and n = 22 for CON.

Activity Monitoring Data:

Total kcals, total steps, average METs, and average percent time in sedentary behaviour are displayed in Table 1. There were no differences between conditions for any variable ($p>0.05$).

Table 1. Differences in activity monitoring data between BWE and CON conditions assessed with a Wilcoxon matched-pairs signed rank test for all outcomes except average percent sedentary time which was assessed using a paired t-test (n=25).

Activity measure	*BWE*	*CON*	*p-value*
Total kcals (kcals)	1222 ± 771	1084 ± 536	0.27
Total steps (steps)	10983 ± 5134	10152 ± 3725	0.20
Average METs (METs)	1.40 ± 0.24	1.34 ± 0.16	0.15
Average percent sedentary (%)	54 ± 9	54 ± 12	0.46

CGM data:

There was no difference in the glucose responses over the 24 hours following the BWE or CON interventions (p>0.05). The 24-hour mean glucose (5.0±0.4 mM vs 5.0±0.5 mM; Figure 10) was not different between BWE vs CON (p=0.39). The 95% confidence interval (CI) for BWE and CON 24-hour mean glucose was 4.83 - 5.18 mM and 4.79 - 5.19 mM, respectively and the effect size (d_z) was 0.06. There were no significant differences detected for the measures of glycemic variability in the 24 hours following the BWE vs CON interventions (p>0.05) with the results displayed in Table 2 and Figure 11. There was also no significant difference between BWE vs CON for the postprandial measures (p>0.05) which are summarized in Table 3.

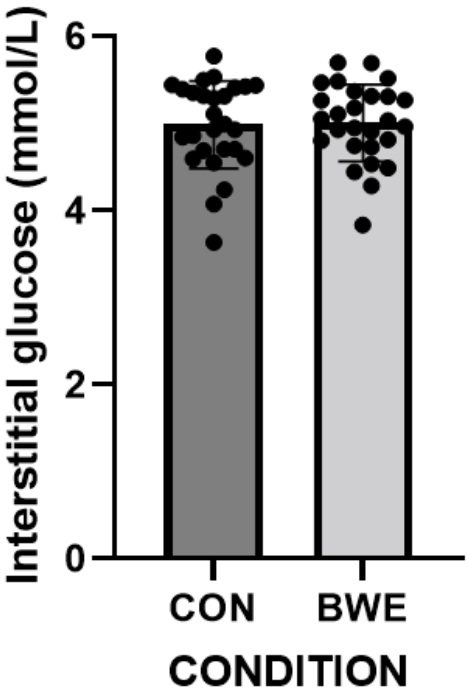


Figure 10. 24-hour mean glucose (p>0.05).

Table 2. Measures of glycemic variability. There were no significant differences detected for the measures of glycemic variability in the 24 hours following BWE vs CON. d_z = effect size.

Glycemic variability measure	BWE	BWE 95% CI	CON	CON 95% CI	Mean difference between conditions	p-value	d_z
MAGE (mM)	2.20 ± 0.67	1.93 - 2.46	2.37 ± 0.63	2.12 - 2.62	0.17	0.06	-0.31
SD (mM)	0.97 ± 0.26	0.87 - 1.07	0.99 ± 0.24	0.90 - 1.09	0.02	0.30	-0.10
CV (%)	19 ± 5	18 - 21	20 ± 5	18 - 22	1	0.21	-0.16

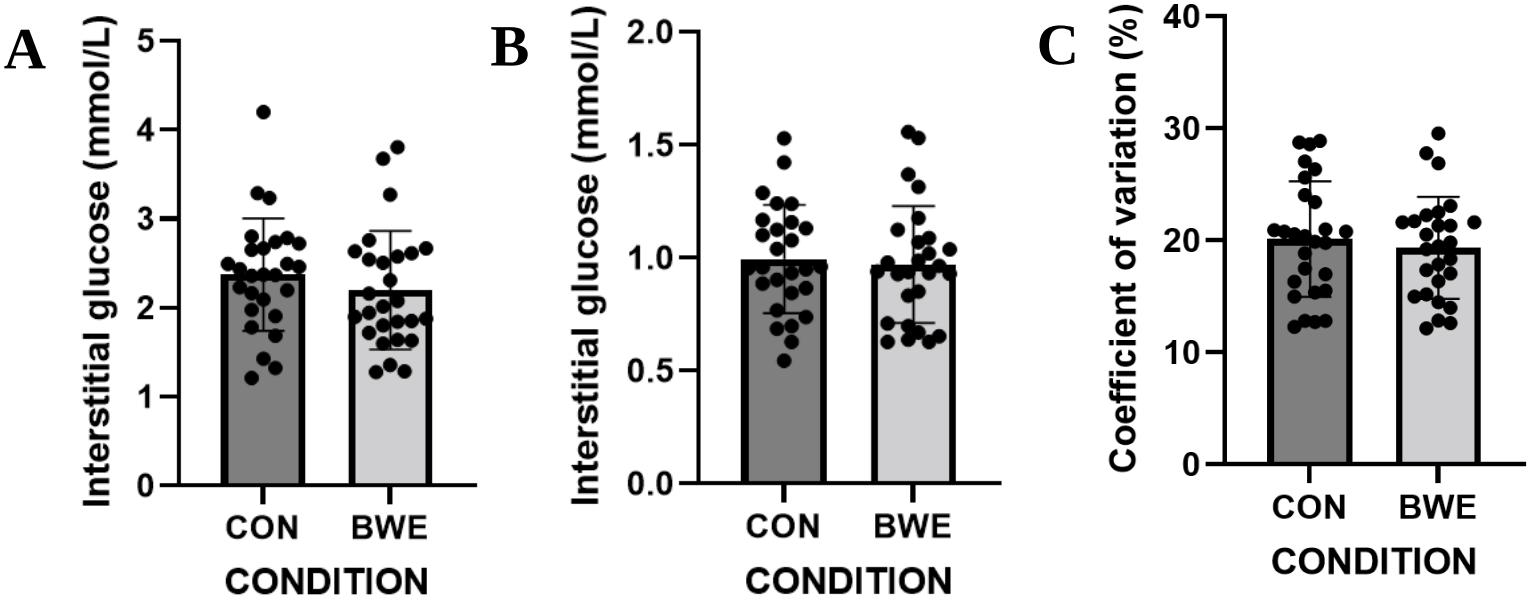


Figure 11. Measures of glycemic variability. (A) MAGE; (B) SD; (C) CV; (p>0.05).

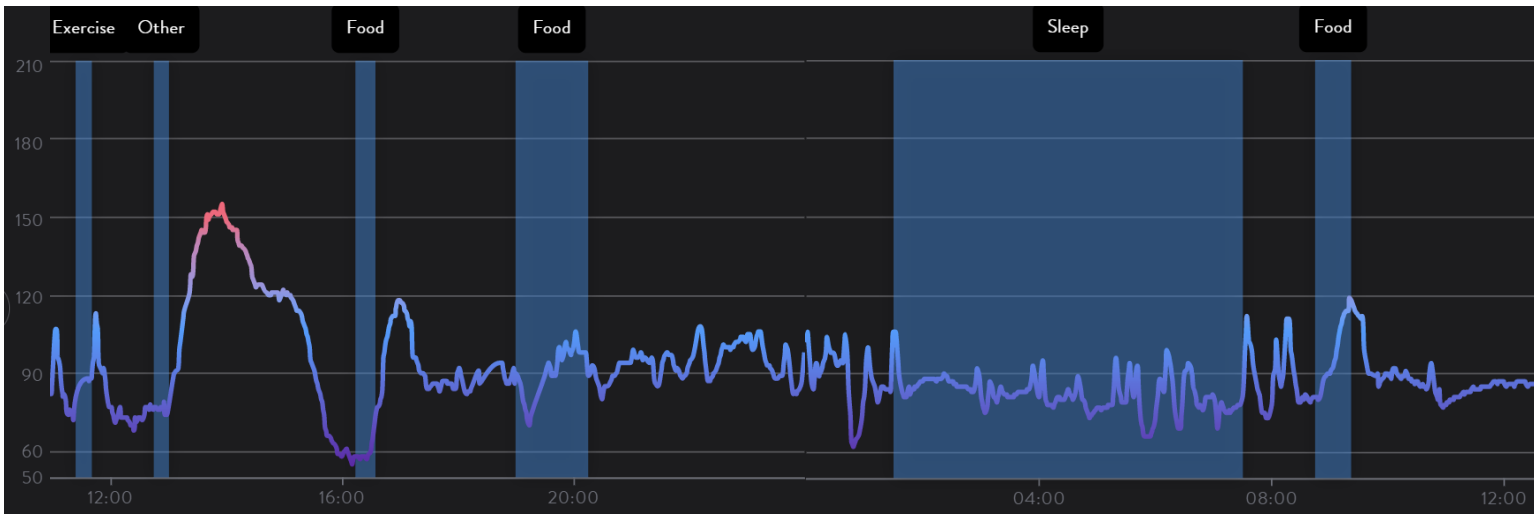


Figure 12. Representative 24-hour CGM tracing from a BWE trial for one participant. This figure displays glucose concentrations (mg/dL) on the y-axis and time of day on the x-axis. Exercise = BWE protocol, Other = 75 g glucose drink, Food = controlled lunch, dinner, breakfast in order from left to right. Conversion between mg/dL and mmol/L: glucose value (mg/dL) / 18 = glucose value (mmol/L).

Table 3. Postprandial glucose responses in the 24 hours following BWE vs CON. Italicized font indicates a Wilcoxon signed-rank test was performed because the data did not pass the normality test. (A) Postprandial glucose peaks, (B) 2-hour postprandial mean glucose, (C) MPPC. d_z = effect size.

A

Postprandial period	BWE peak (mM)	BWE 95% CI (mM)	CON peak (mM)	CON 95% CI (mM)	p-value	d_z
Glucose drink	8.84 ± 1.31	8.33 - 9.36	8.93 ± 1.33	8.40 - 9.45	0.35	-0.07
Lunch	7.00 ± 1.39	6.45 - 7.55	6.88 ± 1.12	6.44 - 7.32	0.35	0.08
Dinner	7.28 ± 1.46	6.69 - 7.87	6.95 ± 1.08	6.51 - 7.38	0.11	0.25
Breakfast	6.53 ± 1.05	6.10 - 6.96	6.71 ± 1.41	6.13 - 7.29	0.26	-0.13

B

Postprandial period	BWE 2 h mean (mM)	BWE 95% CI (mM)	CON 2 h mean (mM)	CON 95 % CI (mM)	p-value	d_z
Glucose drink	6.61 ± 0.79	6.30 - 6.93	6.68 ± 0.89	6.33 - 7.04	0.34	-0.08
Lunch	*5.23 ± 0.88*	*4.89 - 5.58*	*5.08 ± 0.64*	*4.83 - 5.33*	*0.31*	*0.19*
Dinner	*5.61 ± 1.00*	*5.20 - 6.01*	*5.36 ± 0.56*	*5.14 - 5.59*	*0.23*	*0.23*
Breakfast	4.91 ± 0.52	4.70 - 5.13	4.93 ± 0.68	4.65 - 5.21	0.43	-0.04

C

Postprandial period	BWE MPPC (mM)	BWE 95% CI (mM)	CON MPPC (mM)	CON 95% CI (mM)	p-value	d_z
Glucose drink	3.98 ± 1.47	3.40 - 4.56	4.18 ± 1.59	3.55 - 4.81	0.19	-0.17
Lunch	1.93 ± 1.61	1.29 - 2.57	1.69 ± 1.67	1.03 - 2.35	0.30	0.10
Dinner	*2.33 ± 1.28*	*1.81 - 2.85*	*1.90 ± 1.35*	*1.36 - 2.45*	*0.12*	*0.28*
Breakfast	1.94 ± 0.84	1.61 - 2.28	2.03 ± 1.03	1.62 - 2.44	0.35	-0.08

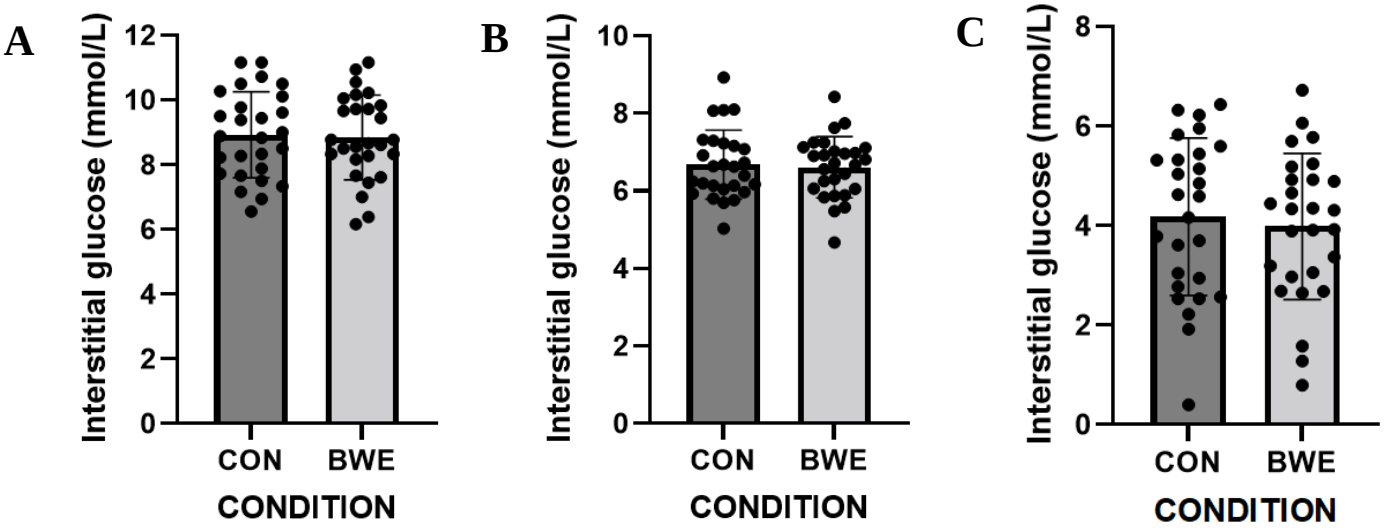


Figure 13. Postprandial glucose responses following the consumption of the 75 g glucose drink. (A) Glucose peak. (B) 2-hour postprandial glucose mean. (C) MPPC. There was no significant difference found between the BWE and CON conditions ($p>0.05$).

Discussion

The primary finding from this study was that a single session of BWE did not alter acute glycemic control in young, healthy adults. In contrast to our hypothesis, we found no differences in 24-hour mean glucose or indices of glycemic variability or postprandial glycemic control in response to an 11-minute bout of self-paced BWE as compared to a non-exercise CON condition. It is unclear whether the lack of effect was related to the exercise stimulus per se or related to other factors including the acute nature of the intervention, the study cohort, or the specific nutritional controls employed. This study nonetheless established the feasibility of performing BWE remotely while simultaneously utilizing CGM in a free-living situation.

Little *et al.* (59) previously showed that an acute bout of high intensity, intermittent exercise performed on a cycle ergometer can improve postprandial glycemic control (59). The protocol involved 10 x 60 s intervals at an intensity corresponding to ~90 % of peak HR. However, that study reported no difference in 24-hour mean glucose compared to the control condition measured with CGM (59). Similarly, the present study found no change in 24-hour mean glucose following exercise compared to the CON condition. In contrast to the results of Little *et al.* (59), we found no significant differences in postprandial glucose responses. This may be due to differences in the study cohort and/or the number and intensity of exercise intervals. The study by Little *et al.* (59) recruited participants who were on average 18 years older and had a BMI that was 11 kg/m^2 greater than the BMI of our participants. It is possible that the group of younger, mainly normal weight adults in the present study were less responsive to a short bout of high intensity exercise as compared to older adults who were overweight or obese. Additionally, more than 50% of the participants in the study by Little and colleagues (59) had impaired fasting glucose at baseline. Individuals with impaired glucose control may be more responsive to an

acute bout of brief, vigorous exercise as compared to our participants who self-reported having no previous diagnosis of a metabolic health condition. Furthermore, our study included five, 60 s BWE intervals that elicited a mean HR of ~75% of maximum over the 11-minute protocol as opposed to the 10 exercise intervals implemented by Little and colleagues which elicited ~87% HR maximum over the ~20-minute session (59). It is also possible that a larger dose of BWE (i.e., a greater number of intervals or the same number of intervals performed at a higher percentage of HR max) may be needed to see an effect in relatively young, healthy individuals.

Two previous studies (10, 84) also showed an effect of BWE on postprandial glycemic control over a 1-2 hour period postexercise. Barillas *et al.* (10) measured glycemic responses using capillary blood samples at specific time points during the 1 hour after consuming a glucose drink whereas Solomon and colleagues (84) measured glycemic indices over 2 hours using CGM. Solomon *et al.* (84) only saw a positive effect when breakfast was consumed immediately before exercise, whereas no effect was seen when breakfast was consumed 30 minutes before exercise or immediately after completing exercise. This suggests that the time course between nutritional manipulations and exercise can influence postprandial glycemic responses. The timing of our nutritional manipulations surrounding exercise differed from these previous studies and this may in part explain the difference observed in postprandial glycemic responses. Solomon and colleagues (84) utilized CGM, but they only reported a 2-hour window of data. Our study expands upon the current literature by introducing the use of CGM to measure 24-hour glycemic responses to acute BWE which, to our knowledge, has not previously been done. Differences in the results of the present study compared to the study by Barillas *et al.* (10) could be attributed to differences in the study cohorts as well. Barillas and colleagues (10) recruited participants who had previously engaged in resistance and plyometric exercise on a regular basis leading up to

their participation. Additionally, it was a requirement that participants could attain 80% of their age predicted HR maximum when completing plyometric exercise (10). Since these participants were athletes experienced with plyometrics, it is possible they exerted a higher level of effort during the workout reflected by a higher HR response. It has been suggested that a relative intensity of $\geq$80% of HR maximum may be the intensity threshold needed to see changes in glycemic responses postexercise (10). As previously noted, our participants achieved a mean HR equivalent to ~75 % of maximum over the 11-minute bout. Our participants performed the BWE protocol at a self-selected pace to mimic at-home BWE workouts where individuals may not have the necessary equipment to monitor their HR or the intensity of the exercises.

The lack of change in glycemic control postexercise may also be related to the nutritional state of participants. Previous research (90) has indicated that fasted state exercise may promote beneficial changes in glycemic control. Terada and colleagues (90) found that completing an acute bout of treadmill exercise in the fasted state was more advantageous for postprandial glycemic control and glycemic variability (MAGE) compared to exercising in a fed state in people with T2D. In the present study, we had participants consume breakfast 3 hours prior to exercise to simulate real-world conditions whereby individuals may not perform exercise in fasted state and/or may avoid consuming a mixed meal directly before performing BWE. The glycemic control responses may have differed if the BWE was completed in fasted state instead. It is also possible that exercise nutritional state may have a greater impact on those with impaired glycemic control including T2D as compared to our study cohort of young, healthy adults. The glycemic index of the controlled meals provided to the participants in our study could have influenced the postprandial glucose responses. Each participant consumed the same meals in both trials therefore, the glycemic index of the meals was consistent within each participant,

however all participants had different individualized meal plans. Hence, the glycemic index of the meals was not standardized across participants. Campbell and colleagues (23) demonstrated that glucose area under the curve was larger after consuming high glycemic index foods compared to low glycemic index foods in individuals with type 1 diabetes. This suggests the possibility of greater glucose responses in some participants compared to others depending on the glycemic index of the foods in their meal plans. The present study opted for an individualized meal plan approach which was based on the height, body mass, age, and sex of each participant. If standard meal plans were provided to all participants whereby everyone consumed identical meals with the same nutritional profile and glycemic index then each participant would have been in a different nutritional state (caloric deficit, maintenance, or surplus) because height, body mass, age, and sex would not have been accounted for.

From a mechanistic standpoint, high intensity exercise elicits a variety of physiological responses that could influence indices of glycemic control postexercise. During an exercise session and for ~2 hours postexercise, glucose supply to the skeletal muscle cells is elevated due to an increase in blood flow (18). There is also an enhanced capacity to uptake glucose due to the greater amount of GLUT4 embedded in the sarcolemma and T-tubules as a result of muscle contraction (18). Therefore, an acute bout of exercise can upregulate glucose uptake at the active skeletal muscle cells in healthy adults (18). A greater level of glucose uptake postexercise would lead to lower blood glucose concentrations and this would be interpreted as an improvement in glycemic control. However, simultaneously there are competing mechanisms which promote increases in blood glucose concentrations. For example, intense exercise can elicit increases in catecholamine concentrations (100). Catecholamines promote glycogen breakdown and gluconeogenesis in the liver which directly results in an increased level of glucose production by

the liver (81). This mechanism contributes to an increase in blood glucose concentrations during and/or after exercise. Furthermore, Asp *et al.* (9) reported that an acute bout of eccentric exercise was associated with a decrease in GLUT4 content within the working skeletal muscle. The researchers suggested the possibility of eliciting similar effects with an intense session of concentric exercise (9). Less GLUT4 content would result in a lower capacity to uptake glucose into the cells, leading to greater blood glucose concentrations. It is evident that there are both positive and negative signals at work in the postexercise period which might lead to no change in glycemic control observed if these signals are in a relative equilibrium. It is possible that the BWE protocol in our study elicited a number of competing mechanisms which ultimately resulted in no change observed in glycemic control compared to the CON condition.

Future studies are needed to further explore the effects of BWE on glycemic control. For example, studies exploring larger doses of acute BWE to help determine the minimum exercise prescription required to see an effect would be warranted. Additionally, investigating the effects of repeated bouts of BWE in the form of training studies would be useful to explore the potential for chronic exercise to alter glycemic control. Furthermore, studying the effects of various nutritional manipulations surrounding BWE interventions would be helpful. For example, looking into how glycemic control is influenced by fasted vs fed state exercise, the timing of meals surrounding exercise, as well as the glycemic indices of foods consumed. Our study was powered to detect changes in our primary outcome of 24-hour mean glucose, therefore future adequately powered studies should further probe the impact of BWE on glycemic variability given the fact that our MAGE data trended towards showing a benefit from BWE although this was not statistically significant. Additionally, future work should explore whether there are sex-based differences in glycemic responses to BWE. Also, studies investigating the mechanistic

basis behind observed increases, decreases, or no changes seen in glycemic control following exercise would be warranted. Such studies should be conducted in a variety of study populations such as healthy adults, individuals with impaired glucose control, or those at risk of developing metabolic diseases. Perhaps other study populations would be more sensitive to the effects of BWE on glycemic control compared to the young, healthy adults we recruited.

Some strengths of the present study include the level of nutritional control, the use of CGM in a free-living situation, the recruitment of both males and females, as well as the menstrual cycle control implemented with the female participants. Whereas some limitations of the design included the use of self-reported dietary logs, conducting remote visits which created less environmental or laboratory-based control, as well as the lack of counterbalancing the number of males and females. We provided participants with controlled, pre-packaged meals to consume during the 24-hour CGM measurement period. This was a strength of the study design because it allowed for an enhanced level of nutritional control within each participant, ensuring that they consumed the same meals on both trials. Meal and beverage consumption patterns (i.e., timing and amount consumed) were self-reported by the participants in a meal and beverage log. This could be considered a limitation of the study given the potential difficulties surrounding self-reported data. We utilized CGM which is considered a very detailed and sensitive measurement tool that produces comprehensive glucose data. This study was designed to simulate a practical, free-living situation where the intervention was completed remotely at-home and the use of CGM facilitated this design due to the fact that participants did not have to be in the lab for the collection of glucose data. Although conducting a free-living study comes with its own benefits it also removes aspects of lab-based studies which have a superior level of environmental and activity control. For example, the free-living nature of this study resulted in the activity levels of

our participants not being standardized in the 2 hours following the consumption of the 75 g glucose drink which could be considered a limitation. A strength of our study was the unbiased recruitment of both males and females. We also controlled for menstrual cycle in our female participants to ensure that hormonal profiles were similar during both trials. However, we did not counterbalance for sex in our recruitment and therefore, we ended up with more females than males (n=19 vs n=8 respectively).

In conclusion, this study found that a brief 11-minute BWE protocol did not alter 24-hour glycemic control compared to 11 minutes of sitting. There were no differences between conditions for 24-hour mean glucose, measures of glycemic variability, and the different postprandial outcomes. This BWE protocol was not a large enough stimulus to show an effect in young, healthy adults. Future studies should investigate the influence of BWE in those with impaired glycemic control as well as BWE training-induced effects. Also, the relationship between BWE and 24-hour MAGE should be probed further in adequately powered studies in the future.

Appendix A: HiREB study approval letter.

HiREB
Hamilton Integrated Research Ethics Board

Nov-05-2021

Project Number: 13864

Project Title: The effect of brief bodyweight exercise on acute glycemic control in healthy inactive adults.

Principal Investigator: Dr. Martin Gibala

The Hamilton Integrated Research Ethics Board (HiREB) has reviewed and approved the above-mentioned study.

The following documents have been approved on both ethical and scientific grounds:

Document Name	Document Date	Document Version
CSEP Get Active Questionnaire (GAQ)	Jul-13-2021	V1
Get Active Questionnaire (GAQ) Reference Form	Jul-13-2021	V1
Research Participant Payment Form V2 - Clean	Oct-06-2021	V2
Meal Timing and Beverage Log V2 - Clean	Oct-06-2021	V2
Medical Screening Questionnaire V2 - Clean	Oct-06-2021	V2
Study Proposal V2 - Clean	Oct-06-2021	V2
Study Consent Form V2 - Clean	Oct-06-2021	V2
Recruitment Poster V2 - Clean	Oct-06-2021	V2
Email Correspondence V2 - Clean	Oct-06-2021	V2
Study Key BWE-GC V2 - Clean	Oct-06-2021	V2
Data Collection Form V2 - Clean	Oct-06-2021	V2

The following documents have been acknowledged:

Document Name	Document Date	Document Version
CITI certificate updated	Sep-15-2021	V1
HiREB 13864 response letter	Oct-07-2021	V1

In light of the current COVID-19 pandemic, while HiREB has reviewed and approved this application, the research must be conducted in accordance with institutional and/or public health requirements.

Please Note: All consent forms and recruitment materials used in this study must be copies of the above referenced documents.

We are pleased to issue final approval for the above-named study for a period of 12 months from the date of the HiREB meeting on August 4, 2021. Continuation beyond that date will require further review and renewal of HiREB approval. Any changes or revisions to the original submission must be submitted on a HiREB amendment form for review and approval by the Hamilton Integrated Research Ethics Board.

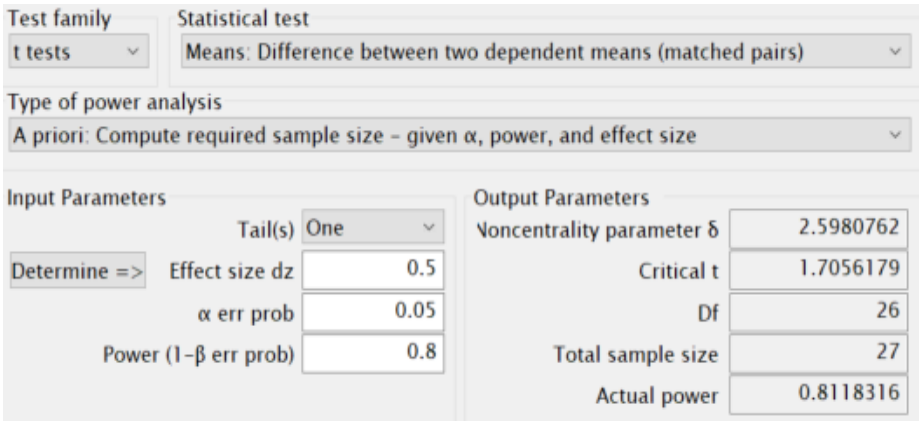
PLEASE QUOTE THE ABOVE REFERENCED PROJECT NUMBER ON ALL FUTURE CORRESPONDENCE

Sincerely,

Frederick A Spencer

Dr. Frederick A. Spencer, MD

Appendix B: G*Power analysis to determine sample size.



Appendix C: An Overview of CGM Technology and Devices.

Introduction

The monitoring of changes in metabolite levels throughout the body can be achieved with wearable sensors (43). Continuous glucose monitors are sensors that can be worn in various locations on the body to provide a continuous measurement of glucose from the interstitial fluid (5, 27, 43, 55, 69). A small filament on the device is inserted subcutaneously to facilitate continuous glucose monitoring (CGM) of the interstitial fluid (27, 69). CGM provides a proportional approximation of blood glucose concentrations by measuring the amount of interstitial glucose (43, 55). CGM devices automatically provide a glucose measurement every 1-5 minutes (25, 55). A subset of CGM devices, referred to as flash glucose monitoring devices, do not automatically provide a glucose measurement at a constant time interval (77). Instead, these devices display glucose measurements upon user initiation whereby the individual must pass a phone or reader by the sensor to see the glucose measurement (77). CGM devices can be used to collect data in a retrospective manner or to provide the user with real-time glucose measurements (5, 77).

Other traditional and commonly used methods of assessing glucose control include frequent capillary blood tests or the measurement of HbA1c (5, 43, 69). HbAlc is a type of glycated hemoglobin which is formed when the hemoglobin protein of a red blood cell acquires a glucose molecule that attaches to an amino group on the protein (60). The former measurement technique can be painful and inconvenient for users (43) and the latter cannot provide detailed information regarding glycemia or glycemic variability (5). CGM effectively captures glycemic variability including all hyperglycemic and hypoglycemic events (55, 75) and displays a more comprehensive and in-depth view of glycemia compared to traditional methods (5, 69). This

paper will address and explore the history and development of CGM technology, the major manufacturers of CGM devices, as well as the uses, limitations, and assumptions of CGM devices and technology.

The development and history of CGM

The most common technology employed in CGM devices that are approved by the US Food and Drug Administration (FDA) is the electrochemical method (43). This involves the use of glucose oxidase which reacts with glucose in the interstitial fluid (25, 43, 55, 75). This reaction produces one electron per glucose molecule and the resulting electric current is used to estimate the concentration of glucose in the interstitial fluid (43, 55, 75). The relationship between the electric current and the glucose concentration is proportional (43, 55) and linear across many different physiologic conditions (75).

CGM technology was established in the late 1990's which makes it relatively new in comparison to other techniques (25, 69). The first method utilized to monitor glucose concentrations was a urine test (69). At-home urine testing was implemented around 1925 (69) to estimate blood glucose concentrations, though the accuracy of this measurement was low (43). Later in the 1900's, capillary blood glucose measurements were introduced which replaced urine testing (43, 82). Finger pricking to measure capillary blood glucose concentrations produce more accurate measurements, but it is associated with several drawbacks (43). For example, it can only provide intermittent glucose measurements, the process can be painful, and there is a frequent need to safely dispose of the materials utilized (43, 82). In 1999, the first CGM device produced by Medtronic MiniMed was approved (47, 69, 82). Soon after the approval of the first device, Dexcom and Abbott also released approved CGM devices in 2006 and 2008, respectively (47, 69, 82). The original purpose of creating CGM devices was to enhance the well-being and

quality of life of those living with diabetes (47). These early devices had limitations surrounding accuracy, usability, calibration, cost, and the duration in which the device could be used for (5, 69, 77). This resulted in low usage rates initially (25).

The mean average relative difference (MARD) in comparison to a reference measurement of glucose is how the accuracy of CGM devices are assessed (47). Devices must have a MARD of ±20 % across glucose values that would be considered biologically relevant in order to obtain approval (47). Recent CGM devices have MARD values of ~10% (43, 77). Originally, CGM devices were approved for adjunctive use only which meant that patients had to confirm CGM data with capillary blood sampling before making a treatment decision (25, 55). Additionally, capillary blood sampling was also necessary for calibration purposes two times a day in some CGM devices (43, 55). Increases in the accuracy of some CGM devices led to approval of nonadjunctive use (25). Also, in 2016, Abbott released the Freestyle Libre Pro Flash CGM device which did not require capillary blood sampling for calibration purposes (69). This device undergoes factory calibration (77) and therefore takes this daily responsibility off the user. The implementation of nonadjunctive use and factory calibration greatly reduced the need for capillary blood sampling (5, 25). Flash glucose monitoring devices, like the one mentioned above by Abbott, also tend to be less costly (5, 77). Since the development of the first CGM device, many steps have been taken to address the initial limitations (25, 47). Some of the most recent devices are smaller, more comfortable, more user-friendly, have better accuracy, and require no daily calibration (25, 47).

The major manufacturers: Abbott, Dexcom, and Medtronic

The FreeStyle Libre by Abbott is a small, round, disposable, factory-calibrated glucose monitoring device that is worn on the back of the upper arm, can be inserted for up to 14 days, and requires no user calibration (1, 5, 16, 27, 29). Obtaining a glucose reading is very easy and quick as it simply involves passing a phone or reader by the device to facilitate the process (1, 16, 27, 29). This device has a compatible FreeStyle Libre app which allows users to easily monitor their glucose concentrations in real-time through their personal smartphones (1, 29). The FreeStyle Libre was designed for use by individuals with type 1 or 2 diabetes who are 18 years and older, as long as they are not critically ill, pregnant, or on dialysis (2, 16). However, the newer FreeStyle Libre 2 system has now been approved for individuals 4 years and older (1). This device can also be used in conjunction with the compatible FreeStyle Libre 2 app which now has the ability to send customizable glucose level alarms/alerts to your smartphone (1). The FreeStyle Libre device is safe to wear in water and while exercising (1) and it can also be used in a nonadjunctive manner in certain countries (29, 36). This device is reported as being easy to use and affordable in comparison to other comparable glucose monitoring devices (29). Although rare, the most notable adverse event observed with this device is associated with the adhesive used to hold the sensor in place (29). The FreeStyle Libre device has a MARD of 11.4% which is an indication of good accuracy that is comparable to other glucose monitoring devices (5, 29). However, it has been noted by the FDA that this device has shown inaccuracies during periods of low glucose concentrations (16). In 2020, Abbott released a new product called the Libre Sense Glucose Sport Biosensor which is based off the technology used in the FreeStyle Libre (2). This device was not designed for medical purposes and is only meant to be used by athletes during sport and exercise (2). This will allow individuals without

Figure 14. This is the FreeStyle Libre device which is approximately the size of a Canadian quarter (1,6).

diabetes for the first time to utilize Abbott's glucose monitoring technology (2). The purpose of this device is to help athletes who are 16 years and older better understand the relationship between their glucose levels and factors such as nutrition, training, competition, and performance (2). Applying the device is usually a painless procedure with manufacturer data stating over 90% of users report no pain upon insertion (2). This device also has a compatible smartphone app similar to the FreeStyle Libre (1, 2).

The Dexcom G6 glucose monitoring device is a competitor to the FreeStyle Libre. It continuously monitors glucose while inserted, requires no user calibration, it can be worn for up to 10 days, and can be used for individuals 2 years and older (32). The device can be worn on the abdomen for anyone 2 years and older, the back of the upper arm for those 18 years and older, or on the upper buttocks for those between 12-17 years of age (32). This device is also compatible to be used in conjunction with a personal smartphone (32). Other competing devices are made by the company Medtronic. The newest device released by Medtronic is the Guardian Sensor [3] which can be worn for up to 7 days (63). Those who are between the ages of 3-13 years can insert this device on the abdomen or buttock, and those 14 years and older can insert it on the abdomen or the back of their upper arm (63). The Dexcom device is suitable for nonadjunctive use (32) however, the Medtronic device is only approved for adjunctive use (36).

Several studies have endeavoured to compare the various glucose monitoring devices. For example, Denham (31) demonstrated that FreeStyle Libre 2 had better accuracy (lower MARD) than the Dexcom G6 during the first day of insertion. Furthermore, Nagl *et al.* (68) compared the accuracy of the FreeStyle Libre by Abbott, the Dexcom G6, and a different device by Medtronic called the Medtronic Enlite in individuals between the ages of 9-14. The Medtronic Enlite demonstrated better accuracy in comparison to both of the factory calibrated models by Abbott

and Dexcom (68). The accuracy of all three devices decreased overnight and during periods of hypoglycemia as indicated by elevated MARD values (68).

Uses, limitations, and assumptions of CGM

The most common application of CGM is for individuals with type 1 or 2 diabetes whereby it can be used to improve glycemic control (25, 42, 43, 47, 77). CGM could also be utilized by other groups of individuals in a more non-traditional manner (25, 47, 77). For example, CGM technology could be advantageous for individuals who are pregnant, in the hospital (i.e., intensive care unit), have renal disease, or have prediabetes (5, 34, 42, 47). CGM could be used as a preventative measure instead of only being used in a reactionary manner (34). Some additional fields that could benefit from CGM include exercise science, sports medicine, recreation, and sport/athletics (43). With the use of CGM, it could help athletes optimize nutrition, training, and recovery (43). As mentioned earlier, the Libre Sense Glucose Sport Biosensor by Abbott is a newly released device that can help facilitate this process (2). CGM can also be utilized in various research settings (43, 77). For example, Abdulrahman *et al.* (4) used CGM to investigate the impact of continuously monitoring glucose levels during moderate to high intensity exercise performed by individuals with type 1 diabetes. The researchers demonstrated that using CGM resulted in a greater amount of time spent in a target interstitial glucose range (4) indicating improved glycemic control. Little *et al.* (59) utilized CGM to explore the postexercise glucose responses to moderate intensity continuous vs high-intensity interval exercise in overweight/obese individuals. Therefore, CGM allows investigators to explore and answer many different types of research questions.

Several studies have investigated the accuracy of the CGM systems developed by Abbott, Dexcom, and Medtronic during exercise in individuals with type 1 diabetes and it is evident that the accuracy decreases when performing different types of exercise (13, 57, 65, 89). Exercise is accompanied by quick changes in glucose concentrations which contributes to the observed inaccuracies (89). Also, studies seem to indicate that certain glucose monitoring systems tend to overestimate glucose levels when compared to blood concentrations during exercise (39, 57, 65). Figure 15 provides a visual representation of the overestimation by a CGM device during exercise from a study by Larose *et al.* (57). Biagi *et al.* (13) demonstrated that the accuracy of CGM was only impacted during aerobic but not anaerobic exercise. Figueira *et al.* (38) showed a similar trend in the accuracy and overestimation of CGM in individuals with type 2 diabetes during exercise. Another limitation of CGM is the 5 to 10-minute lag time between blood glucose concentrations and interstitial glucose concentrations if measurements are being taken in real-time (25). However, when reviewing CGM data in a retrospective manner, lag time is not as much of a concern (25). CGM technology also makes a few assumptions to provide glucose measurements. First, it is assumed that the interstitial glucose concentration at the skin is proportional to blood glucose concentrations (43). There are also assumptions made regarding the equilibrium between the interstitial fluid and the blood (74). Lastly, it is assumed that the interstitial glucose concentration is proportional to the electrical current generated at the continuous glucose sensor (55).

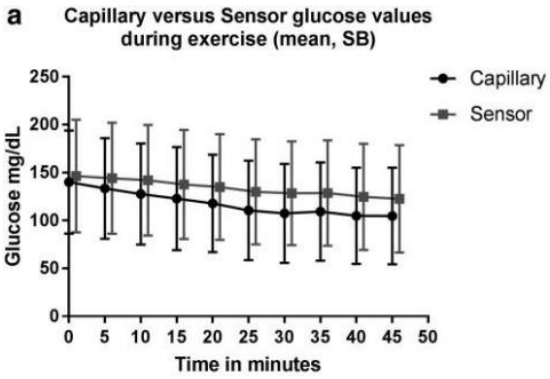


Figure 15. CGM provides overestimated glucose values compared to capillary blood during exercise (57).

Conclusion

Since the development of the first CGM devices, many improvements have been implemented and the initial limitations have been addressed (47). The three major manufacturers, Abbott, Dexcom, and Medtronic, produce competing devices which share some similarities but also have their differences. These devices utilize electrochemical technology which uses glucose oxidase to create an electric current (43). CGM is mainly utilized to help those with diabetes but it also has applications in healthy individuals (47). The Libre Sense Glucose Sport Biosensor can facilitate the process of using CGM for recreational purposes in sport, athletic, and exercise settings (2, 43). There are some limitations and assumptions of CGM technology, but despite these, CGM devices continue to be very useful tools to collect glucose data in a continuous manner. Future directions of glucose monitoring techniques are also addressed in the literature. For example, some future goals include creating an artificial pancreas system (a CGM device used in conjunction with insulin delivery) or a fully implanted CGM sensor (47). Furthermore, other advancements could be made by monitoring glucose in other body fluids such as sweat, tears through contact lenses, or saliva through mouth guards (43). Lastly, in the future, wearable sensors could have the ability to monitor more than just glucose concentrations which could provide a comprehensive view of many metabolites in the body with just one device (43).

Appendix D: Additional participant characteristics.

Height (cm)	Weight (kg)	BMI (kg/m^2)
174.8	107.3	35.11695616
171.5	79.7	27.09755289
169	59.1	20.69255278
163.9	57.2	21.29306215
157.6	63.1	25.40486743
185.3	74.2	21.6099154
159.1	55.1	21.76763465
147.9	48.4	22.12631106
174.5	68	22.33150795
178.3	86.1	27.08323045
172.5	70	23.52446965
163.9	74.9	27.88199921
162	63.3	24.11979881
163.2	53.5	20.0869257
169.5	70.2	24.43417652
167.3	65.6	23.43753629
160.3	58.6	22.80502598
162.2	52.4	19.91725975
165.2	68.5	25.09981298
158	57.7	23.11328313
176	88.9	28.69963843
153.8	64.3	27.18305739
175.2	80.6	26.25831405
154.6	52.4	21.92362212
175.4	90.8	29.51390469
173.2	101.5	33.83531834
191.8	79.5	21.61075416

Appendix E: Additional information regarding contraceptive use and menstrual cycle control for naturally cycling females.

CONTRACEPTIVE USERS			**NATURALLY CYCLING**	
n = 8			n = 11	
Types of contraceptives used:			**Day of menstrual cycle the trial was completed:**	
Hormonal Pill	*IUD*	*Ring*	*BWE*	*CON*
6	1	1	13	6
[redacted]			10	3
			8	15
			5	12
			4	11
			3	10
			12	5
			15	9
			10	4
			12	5
			4	11

Appendix F: Sample meal plan for one participant.

Participant characteristics		Sex: Female Weight: 79.7 kg Height: 171.5 cm Age: 27 years
Breakfast	539 kcal	Pork in Smokey Barbecue Sauce Western Omelette
Lunch	671 kcal	Brazilian-Style Beef Stew Chicken Pot Pie
Dinner	989 kcal	Crustless Vegetable Quiche Chicken and Harvest Vegetable Pie Chicken and Harvest Vegetable Pie Garden Vegetable Soup
Breakfast	539 kcal	Pork in Smokey Barbecue Sauce Western Omelette

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