Towards a better understanding of the role for continuous glucose monitoring in glycaemic management of athletic cohorts.

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Abstract I

Continuous glucose monitoring (CGM) has been of great benefit to diabetes management, but its use in healthy, physically active populations remains poorly understood. This thesis investigates the accuracy, interpretation, and application of CGM in active individuals, addressing key limitations in how glucose data are applied outside clinical settings.

The first study compares interstitial and capillary glucose responses following ingestion of carbohydrate-containing beverages varying in type, amount, and concentration. It identifies small but consistent differences between compartments during periods of rapid glucose change, highlighting the need to account for physiological lags when interpreting interstitial data. A second study monitors elite female cyclists over a nine-day training camp to characterise glucose patterns during intensified training. Glucose values remain generally stable, yet display some time <70 mg/dL i.e., hypoglycaemia. A third study examines how 28-day high-versus low-glycaemic index (GI) diets affect glycaemia and performance. Although both diets produce glucose values within normoglycaemic ranges, measures of glycaemic variability differ significantly, with the low-GI diet showing reduced variability compared to the high-GI diet. While no performance effects are observed, CGM detects meaningful diet-induced changes in glycaemic profiles, supporting its use for monitoring nutritional strategies aimed at glycaemic stability.

These findings raise important questions about the appropriateness of clinical thresholds and metrics for CGM use in active populations. Many observed fluctuations likely reflect normal responses to exercise, fuelling, and recovery. This thesis highlights the need for context-specific interpretation and the identification of metrics suited to the demands of physically active individuals. CGM is beneficial in helping people understand their glycaemia, which can then support better decisions regarding diet and training. It may also help identify atypical glycaemic patterns and support long-term health monitoring and optimisation in active populations.

Declaration Statement

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Signed.....

Date.....26/6/25.....

This thesis is the result of my own investigations, except where otherwise stated. Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

Signed.....

Date.... 26/6/25.....

I hereby give consent for my thesis, if accepted, to be available for electronic sharing

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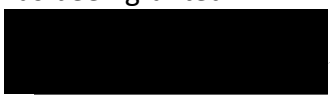
The University's ethical procedures have been followed and, where appropriate, that ethical approval has been granted.



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I always try to keep things brief, though what follows may suggest otherwise.

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List of abbreviations

ACSM	American College of Sports Medicine
ADA	American Diabetes Association
ADP	Adenosine diphosphate
AID	Automated insulin delivery system
Akt	Protein kinase B
ANOVA	Analysis of variance
AMP	Adenosine monophosphate
AMPK	Adenosine monophosphate-activated protein kinase
ANS	Autonomic nervous system
ATP	Adenosine triphosphate
ATTD	Advanced Technologies & Treatments for Diabetes
BASES	British Association of Sport and Exercise Sciences
BG	Blood glucose
Bla	Blood Lactate
BM	Body mass
BMI	Body mass index
CaM	Calmodulin
CaMK	Ca^{2+}-CaM dependent protein kinase
CGM	Continuous glucose monitoring
CHO	Carbohydrate
CK	Creatine kinase
CO_2	Carbon Dioxide
CPET	Cardio-pulmonary exercise test
CRH	Counterregulatory hormone
CSF	Cerebrospinal fluid
CV	Coefficient of variation
DIY	Do it yourself
EDTA	Ethylenediaminetetraacetic acid
ECF	Extracellular fluid
G1P	Glucose-1-phosphate
G6P	Glucose-6-phosphate

GH	Growth hormone
GI	Glycaemic index
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GLUT	Glucose transporters
CMIT	Continuous moderate intensity training
GP	Glucose Polymer
GPS	Global Positioning System
GS	Glycogen Synthase
H^2O	Water
H^+	Hydrogen ion
Hb	Haemoglobin
HbA1c	Glycosylated Haemoglobin
Hct	Haematocrit
HGI	High-glycaemic index
h	Hour
HIIT	High intensity interval training
HR	Heart rate
ICF	Intracellular fluid
IF	Interstitial Fluid
IG	Interstitial Glucose
IL-6	Interleukin-6
IU	Insulin unit
K^+	Potassium
Kcal	Kilocalorie
km	Kilometres
$km.hr^{-1}$	Kilometres per hour
LCHF	Low carbohydrate high fat
LGI	Low glycaemic index
LVL1	Level 1 hypoglycaemia
LVL2	Level 2 hypoglycaemia
MAGE	Mean amplitude of glycaemic excursion
MARD	Mean absolute relative difference

MD	Maltodextrin
mg/DL	Milligrams per decilitre
mmol.l^{-1}	Millimoles per litre
NEFA	Non-esterified fatty acid
NOS	Nitric oxide synthase
O_2	Oxygen
OGTT	Oral glucose Tolerance test
P	Placebo
RER	Respiratory exchange ratio
RPE	Rate of perceived exertion
ROS	Reactive oxygen species
RQ	Respiratory quotient
SD	Standard deviation
S	Sucrose
SGLT	Sodium like glucose transporters
SMBG	Self-monitoring of blood glucose
SST	Serum Separating Tube
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TAR	Time above range
TBR	Time below Range
TBW	Total body water
TIR	Time in range
TITR	Time in tight range
TNF-α	Tumour necrosis factor-alpha
UCI	Union Cycliste Internationale
UDP	Uridine diphosphate-glucose
$VO_{2\ peak}$ (or max)	Peak or maximum oxygen uptake
W	Watts
µmol	Micromole
YSI	Yellow Springs Instrument

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Hamilton R, McCarthy OM, Churm R, Ruiyang X, Nicholas, C Bain, Bracken RM. Glycaemic Impact of Low- and High-Glycaemic Index Carbohydrate diets in Ultra-Endurance Athletes: Insights from Continuous Glucose Monitoring. (*Under review*)

Hamilton R, McCarthy OM, Bain SC, Bracken RM. Continuous measurement of interstitial glycaemia in professional female UCI world tour cyclists undertaking a 9-day cycle training camp. European Journal of Sport Sciences. 24**(11)**: 1573-1582 DOI: 10.1002/ejsc.12201

Hamilton R, McCarthy OM, Churm R, Ruiyang X, Nicholas, C Bain, Bracken RM. Glycaemic and Some Metabolic Responses to Endurance Running and Training Following Low- Or High-Glycaemic Index Carbohydrate Diets in Ultra-Endurance Athletes (2024) *Int J Sport Nutr Exerc Metab* **34:**S1-12

Conference Proceedings

Hamilton R, McCarthy OM, Churm R, Ruiyang X, Nicholas, C Bain, Bracken RM. Intestinal fatty-acid-binding protein (iFABP) responses to prolonged running after a short endurance training programme in ultra-endurance athletes. IBEC, Limerick (2024)

Hamilton R. Tracking Glucose Dynamics: Applications Beyond Diabetes in Athletes and Health Enthusiasts. WIAP, Bangor (2024)

Hamilton R, Bain SC, Bracken RM. A comparison of the interstitial glucose and blood glucose responses to the consumption of carbohydrate-containing beverages in humans. ECSS Annual Conference, Glasgow (2024)

Hamilton R, McCarthy OM, Bain SC, Bracken RM. Continuously Measured Interstitial Glucose Responses Over a 9-Day Training Camp in Female Professional Cyclists. ACSM, Boston (2024)

Hamilton R, McCarthy OM, Bain SC, Bracken RM. Interstitial glucose responses during a 9-day cycle training camp in professional female cyclists. WEDS Spring Meeting, Cardiff (2023)

CHAPTER ONE

Review of the literature

1.1 Thesis introduction

The emergence of continuous glucose monitoring (CGM) in non-diabetic populations has opened new possibilities for understanding metabolism, fuelling, and recovery in everyday settings. Originally designed for diabetes management, CGM was introduced to track glucose levels continuously and support better glycaemic control through metrics such as time in range, glycaemic variability, and mean glucose concentration (Rodbard et al., 2009); Teo, Hassan, Tam, and Koh (2022). These metrics were designed with clinical objectives in mind, primarily the prevention of hypo- or hyperglycaemia and the management of long-term health complications. However, as CGM technologies became more accessible, they gained traction among healthy individuals, particularly athletes and those with an interest in personal health optimisation (Bowler et al., 2022). In this context, CGM is no longer used to monitor disease but now explores how lifestyle behaviours, training, diet, stress and recovery impact glycaemia (Klonoff et al., 2022).

This shift in application raises important questions. While CGM provides a window into glucose dynamics, its outputs are often interpreted using frameworks derived from diabetes care. As healthy users apply CGM data to guide nutrition and recovery strategies, it becomes apparent that glucose regulation in these populations differs in some ways. Healthy, physically active individuals may show glucose patterns that differ from those typically seen in diabetes care. These can present as sharp postprandial rises or occasional dips, but such responses are usually short-lived and well-controlled (American Diabetes Association, 2001, 2021). A key distinction is the presence of intact counterregulatory mechanisms, which act rapidly to stabilise glucose levels and prevent sustained deviations. Influences on sensor accuracy, such as compartmental lag between blood and interstitial glucose, or the effects of movement, temperature, and circulation, are evident in free-living conditions (Bowler et al., 2022; O. Moser, Yardley, & Bracken, 2017). These issues, although recognised in diabetes literature, have not been fully explored in healthy, athletic populations.

This thesis was developed in response to that gap. The work is an examination of how CGM can and should be used in healthy individuals. Rather than assuming that clinical principles apply directly to this new setting, it considers the physiological context in which glycaemic

responses occur, the technical and interpretive challenges of the technology, and the potential for CGM data to be used meaningfully outside of disease management. The original motivation stemmed from observing athletes experimenting with CGM in the pursuit of performance gains. Many sought to fine-tune fuelling strategies, identify recovery needs, or simply gain better awareness of how nutrition affected their energy levels (Abbott, 2020; Flockhart & Larsen, 2023). But the insights generated from this data often lacked appropriate reference points. What constitutes a 'good' or 'bad' glucose response in a healthy, active person? When is a sharp rise or fall meaningful, and when is it simply part of normal physiology? These questions revealed that new interpretive frameworks were needed, ones that accounted for the unique behaviours and demands of non-clinical populations.

As the research progressed, its focus widened. While exercise remained a central theme, the investigation considers broader applications of CGM for health optimisation. Many of the concerns raised by athletes, like maintaining stable energy availability, supporting metabolic health, and aligning dietary intake with physiological demand, also hold relevance for non-athletes (Holzer, Bloch, & Brinkmann, 2022). The thesis has relevance not only to athletes but to anyone seeking to use CGM as a tool for informed decision-making around nutrition and general wellbeing.

A critical piece to effective use is the distinction between measuring glucose and interpreting it. CGM does not measure blood glucose directly, but estimates it through interstitial fluid, which introduces both a time delay and potential sources of inaccuracy, particularly during periods of rapid change, such as during exercise or post-meal periods (Siegmund, Heinemann, Kolassa, & Thomas, 2017). These discrepancies are documented in clinical research but not well understood in the health and performance context, where users may not be aware of how measurement artefacts can distort their interpretation of the data (Holzer et al., 2022). Similarly, many of the standard metrics used to summarise CGM data, offer only a limited picture when removed from a clinical context. A short postprandial spike, for example, may be entirely appropriate following a high-carbohydrate meal or during an intense training session, but could be misinterpreted as harmful if viewed from a clinical perspective. Without appropriate context, CGM risks offering misleading signals, prompting unnecessary dietary restriction, fuelling anxiety, or obscuring more meaningful patterns related to energy availability or adaptation (Bowler et al., 2022).

The research presented here responds to these concerns through a series of studies designed to assess the accuracy, interpretation, and application of CGM in healthy individuals. These studies address both technical and conceptual challenges. The first explores how CGM behaves in controlled conditions where carbohydrate beverages of differing composition, concentration, and volume are administered. This creates a useful context in which to examine blood–interstitial discrepancies, characterise sensor lag, and assess how different types and timings of nutritional intake influence the reliability and interpretability of glucose data (Schierbauer et al., 2022). The second turns to real-world conditions, observing elite female cyclists during a high-volume training camp, to understand how CGM performs in a free-living, high-demand environment. This study provides insight into the natural variation of glycaemia under intensive training and recovery cycles, helping to establish normative data and highlight the complexities of interpreting glucose in such settings. The third study takes a longer view, exploring whether habitual dietary patterns, specifically low versus high glycaemic index intake, can meaningfully influence CGM-derived data in healthy individuals over time. Together, these studies contribute to a broader understanding of what CGM may reveal and how its outputs might be interpreted in healthy active populations.

The work emphasises the value of developing context-sensitive metrics, fostering greater awareness of sensor constraints, and setting realistic expectations about what CGM can reveal regarding health and performance. Ultimately, this research contributes to the broader conversation about how emerging health technologies are being adapted for new populations, highlighting the importance of advancing the scientific evidence base to support their informed and effective use.

Section 1.2: Carbohydrate metabolism in humans

1.2.1 What are carbohydrates?

Carbohydrate is a major macronutrient in the diet. It is the main source of glucose and other sugars but most carbohydrate foods also contain some vitamins and minerals. One gram of carbohydrate will yield 4 Kilocalories (Kcals) of energy. Recommendations for what are considered healthy diets will source approximately 50-60% of energy intake from carbohydrate (European Food Safety Authority, 2010; Institute of Medicine National Academy of Sciences, 2020; Sceintific Advisory Committe on Nutrition (SACN), 2025; World Health Organization,

2023). This number may be even higher for active individuals. Endurance athletes often achieve as much as 70% overall energy intake through carbohydrate (LM Burke, Cox, Cummings, & Desbrow, 2001) in order to adequately fuel performance.

1.2.2 Types of carbohydrate

Carbohydrates are generally classified by molecular structure. In basic human nutrition, three main classes exist (**Figure 1.1)**:

- *Monosaccharides*: Single simple sugars i.e.. Glucose & Fructose
- *Disaccharides or Oligosaccharides*: Two bonded sugars or short chains i.e.. Glucose and Fructose to form Sucrose.
- *Polysaccharides*: Multiple bonded sugars forming a chain i.e.. Glycogen.

In addition, **Fibre** is also a type of carbohydrate which resists digestion and absorption in the small intestine, reaching the large intestine largely intact. Unlike sugars and starches, which are broken down into glucose, fibre contributes little to direct energy provision but has important physiological roles. Dietary fibre comprises a diverse range of substances that can be classified by their viscosity and fermentability, characteristics that largely determine their physiological effects.

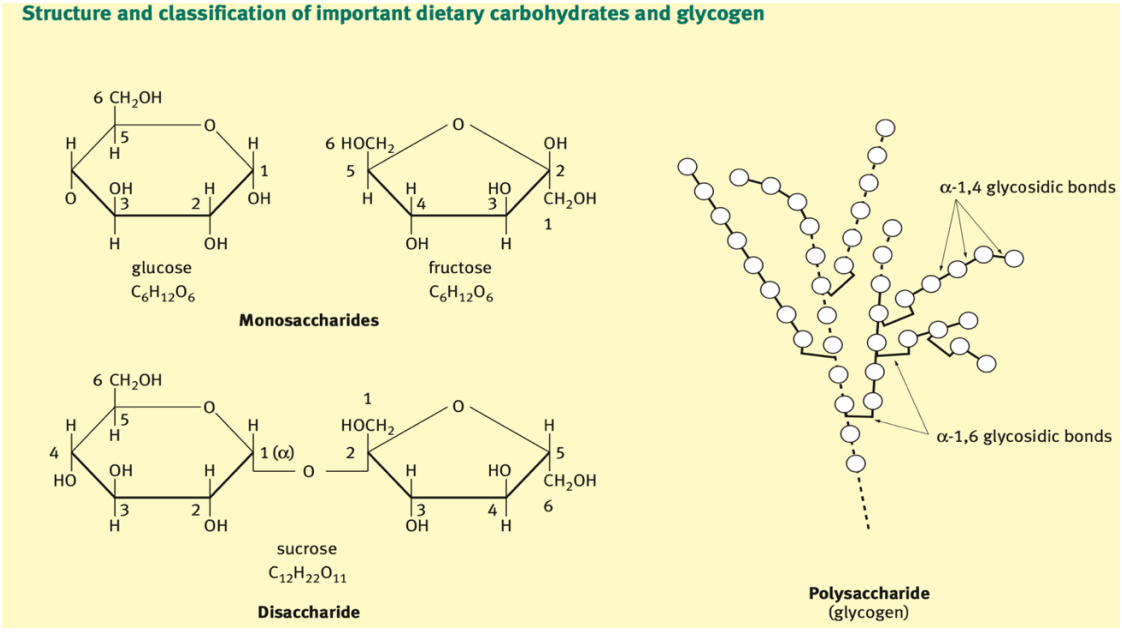


Figure 1.1. Structure and classification of important dietary carbohydrates (Glucose, Fructose, Sucrose & glycogen) illustration taken from R Maughan (2009).

Monosaccharides	Disaccharides	Polysaccharides	Fibre
Glucose Fructose Galactose	Maltose Sucrose Lactose Isomaltulose Trehalose	Maltodextrin Starch Glycogen Pectin Amylose	Cellulose Resistant Starch ß-glucan Inulin Fructo-oligosaccharides

Table 1.1. Classes of carbohydrate.

1.2.3 Digestion of carbohydrates

Carbohydrates must be digested to be broken down into simple molecules which can be utilised by the body for energy. Digestion includes both mechanical and enzymatic processes which take place along the digestive tract and are required to complete the digestion process (**Figure 1.2**).

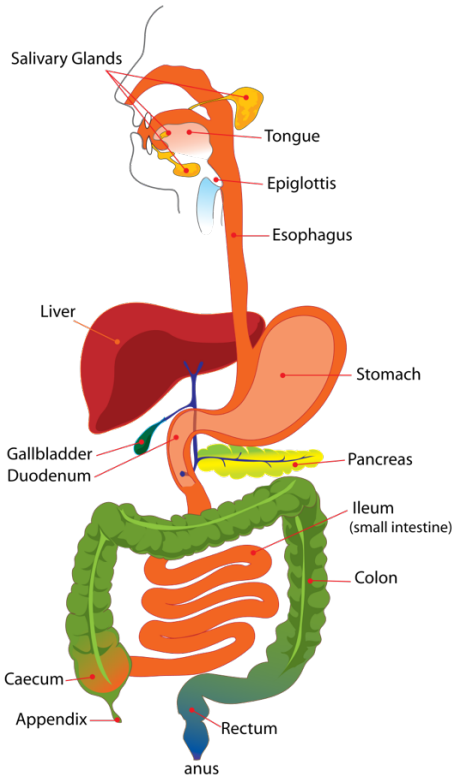


Figure 1.2. The gastrointestinal tract.

Mechanical

Digestion starts in the mouth where, through the process of mastication the solids are broken down, increasing their surface area, and then mixed with digestive enzymes in our saliva. Food is swallowed, where it travels down the oesophagus and into the stomach. In the stomach, further mixing takes place with other foods before entering the small intestine. Gentle muscular contractions gently move food along the digestive tract, a process known as peristalsis. Eventually, peristalsis will push whatever food waste is left to the rectum, where it can then be expelled from the body during defecation.

Enzymatic

Enzymes play a substantial role in digestion (**Table 1.2**) and are introduced immediately in the mouth. The salivary glands release α-amylase to hydrolyse polysaccharides, splitting up chains of sugar molecules. These shorter chains and other macronutrients enter the stomach where further mixing takes place with hydrochloric acid and protein-digesting enzymes known as proteases. This mix is referred to as chyme. The acidity in the stomach hinders α-amylase activity which decreases the rate of carbohydrate breakdown. From the stomach, the chyme enters the small intestine, where more α-amylase is released by the pancreas, along with sodium bicarbonate (buffering the acidity), allowing carbohydrate breakdown to continue. Starches continue to be hydrolysed in the small intestine, where remaining carbohydrates are broken down by specific enzymes along the surface villi known as the brush border.

Enzyme	Site of action	Source	Substrate	Product
Salivary amylase	Mouth	Salivary Glands	Starch	Maltose
Pancreatic amylase	Duodenum	Pancreatic Juice	Starch	Maltose and other oligosaccharides
Maltase	Small intestine	Brush border	Maltose	Glucose
Sucrase	Small intestine	Brush border	Sucrose	Glucose & Fructose
Lactase	Small intestine	Brush border	Lactose	Glucose and galactose

Table 1.2. Digestive enzymes and functions involved in carbohydrate digestion. Adapted from Jeukendrup and Gleeson (2019).

1.2.4 Absorption from the gut

Carbohydrate-containing foods vary in the rate at which they can raise blood glucose concentrations, and amongst other criteria, have been categorised based on their glycaemic index (GI) (Jenkins, Wolever et al. 1981). The movement of CHO, fluids and other macronutrients from the stomach is referred to as gastric emptying. This rate of emptying can be quite influential when it comes to the appearance of glucose in the circulation. The emptying rate can be influenced or manipulated by a number of factors. Meal size, fibre content and the presence of other macronutrients will impact the rate at which food leaves the stomach. Fibre content is particularly relevant to CHO digestion as many CHO-type foods will contain some fibre. Insoluble fibre slows both the digestion and absorption of these foods. Processing and cooking methods can influence the digestibility of certain grains and cereals, in some cases by removing or breaking down fibre or the structure of the carbohydrate food, making it easier for the body to digest.

Monosaccharides enter the bloodstream via the portal venous system which transports the majority of absorbed nutrients to the liver to be processed. The fate of a monosaccharide depends on what particular carbohydrate it is.

Glucose: Most glucose molecules are absorbed in the upper part of the small intestine. This absorption is facilitated by a family of transport proteins known as sodium-dependent glucose transporters (SGLTs). They facilitate the transport of glucose from the intestine through the apical membrane of the enterocyte cells. SGLT1 is of particular importance as it may be a source of limitation for glucose transport into the blood, and can become saturated (Gromova, Fetissov, & Gruzdkov, 2021; Jeukendrup, 2014b).

To move from the enterocyte cell into the portal vein, glucose must utilise glucose transport proteins or GLUT proteins. There are several GLUTs which serve different functions in the process of glucose metabolism but in this instance, it is the GLUT2 that facilitates the movement through the basolateral membrane and into the portal vein. It is now transported to the liver where it can be stored as glycogen or recirculated into the bloodstream. This process is displayed in **Figure 1.3**.

Fructose can be ingested as a monosaccharide or it can be formed from the splitting of di- and poly-saccharide chains. Unlike glucose, fructose is absorbed through the apical membrane facilitated by GLUT5 transporter proteins. As fructose is transported via GLUT5 and not SGLT1 it does not compete for absorption with glucose. As a result, this alternate pathway may facilitate a greater amount of total carbohydrate absorption.

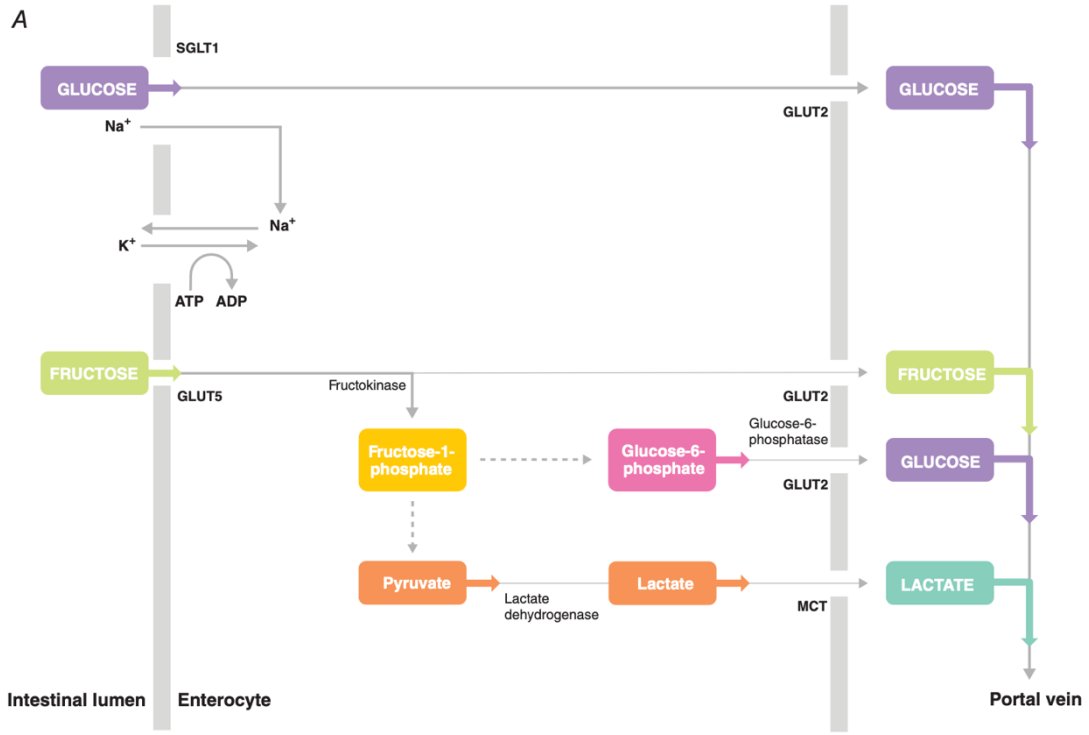


Figure 1.3. The process of glucose and fructose absorption from the intestine into the portal vein. Taken from Fuchs (2009).

1.2.6 Storage

There are several depots for glucose in the body. Glucose may be contained in the body as free glucose or in the more specific storage polymer glycogen. The amount of glucose in each depot varies, so the values mentioned below are approximate and during normal resting conditions. These depots include:

Circulation

At any given time there are approximately 4 grams of free glucose in the bloodstream of an average-sized (non-diabetic) male (70kg) (Wasserman, 2009). The concentration of glucose in the blood is important for maintaining glucose homeostasis in the body. This is generally measured by its concentration which will typically range from 3.9-10 $mmol.l^{-1}$ (70-180mg/dL) (Battelino et al., 2019; Danne et al., 2017). The circulation reflects the total systemic availability of glucose, combining glucose both absorbed from the intestines and glucose released from storage pools (Siegmund et al., 2017).

Interstitial fluid

This is variable and depends on several factors such as the metabolic rate of adjacent cells and the supply of glucose from the circulation. The amount of glucose in this depot is dependent on the flux of glucose, coming from the blood vessel and then leaving into the surrounding cells, or vice versa. Factors such as the metabolic rate of the adjacent cells, blood flow and permeability of the capillaries all influence this rate of flux and the absolute glucose concentration of the interstitial fluid at any given time (Cengiz & Tamborlane, 2009). The concentration of glucose within the interstitial fluid is generally similar to the blood glucose concentration. However, under conditions of rapidly changing BG concentration, differences in diffusion rate may create a lag that may create some discrepancy between the two compartments (Siegmund et al., 2017).

The Brain and cerebrospinal fluid (CSF)

The brain depends on glucose for energy. At rest in healthy normal adults the brain consumption rate of glucose is ~5.6 mg glucose per 100 g human brain tissue per minute (Mergenthaler, Lindauer, Dienel, & Meisel, 2013). The cerebrospinal fluid also contains glucose with a typical concentration of 2.4-4.4 $mmol.l^{-1}$. Similar to interstitial fluid, CSF glucose concentrations correlate closely with changes in blood glucose concentrations.

The kidneys

The kidneys are a filtration centre for blood plasma. They normally filter out metabolic end products and foreign chemicals. Glucose is present in the plasma and so the kidneys must

retrieve glucose and reabsorb it into the bloodstream. Typically this filtration is effective up to a blood glucose concentration of 200mg/dL, at which point glucosuria occurs, resulting in glucose being excreted in urine (Triplitt, 2012). The kidneys are also capable of producing some glucose through glycogenolysis and more substantial amounts through gluconeogenesis (Mather & Pollock, 2011).

The Liver

The liver is one of the main depots for carbohydrate storage in the body. After the ingestion and digestion of carbohydrate, the enzymes glucokinase, glucose-6-phosphatase, and glycogen synthase are responsible for the formation of glycogen in the liver. Gluconeogenesis may also contribute to glycogen formation from glucogenic substrates coming from alternative sources such as lactate, amino acids and glycerol (Radziuk & Pye, 2001) (see **section 1.3.8**). The liver can store approximately 100g of carbohydrate in the form of stored glycogen (Hearris, Hammond, Fell, & Morton, 2018).

Skeletal Muscle

Muscle tissue can store a substantial amount of glucose in the form of glycogen. Glycogen is contained in the sarcoplasm at approximately 13 to 18 g/kg wet weight (Jeukendrup & Gleeson, 2019). This depot is subject to change which may increase its capacity, such as carbohydrate loading (J Bergstrom, L Hermansen, E Hultman, & Bengt Saltin, 1967a). It is estimated that approximately 400g of glycogen is stored in the muscle in the average size male, depending on training status, fatigue and carbohydrate intake (Hearris et al., 2018). There are three main pools for glycogen within the muscle including subsarcolemmal, intermyofibrillar and intramyofibrillar glycogen. These individual pools may serve more specific functions in the cell. For example, the intramyofibrillar glycogen appears to have a relatively larger contribution of glucose than the other pools during exercise (Ørtenblad, Westerblad, & Nielson, 2013).

Section 1.3: Blood Glucose regulation

Blood glucose (BG) is vital to many of the human body's regular functions. To maintain normal glucose levels or "euglycaemia", the body has a complex system in place to coordinate

adequate glucose supplies. Euglycaemia in healthy individuals is considered anywhere between 70 mg/dL (3.9 $mmol^{-1}$) up to approximately 100 mg/dL (5.6 $mmol.l^{-1}$) at rest and in a fasted state (Amercian Diabetes Association, 2023). An overview of blood glucose regulation is displayed in **Figure 1.4**.

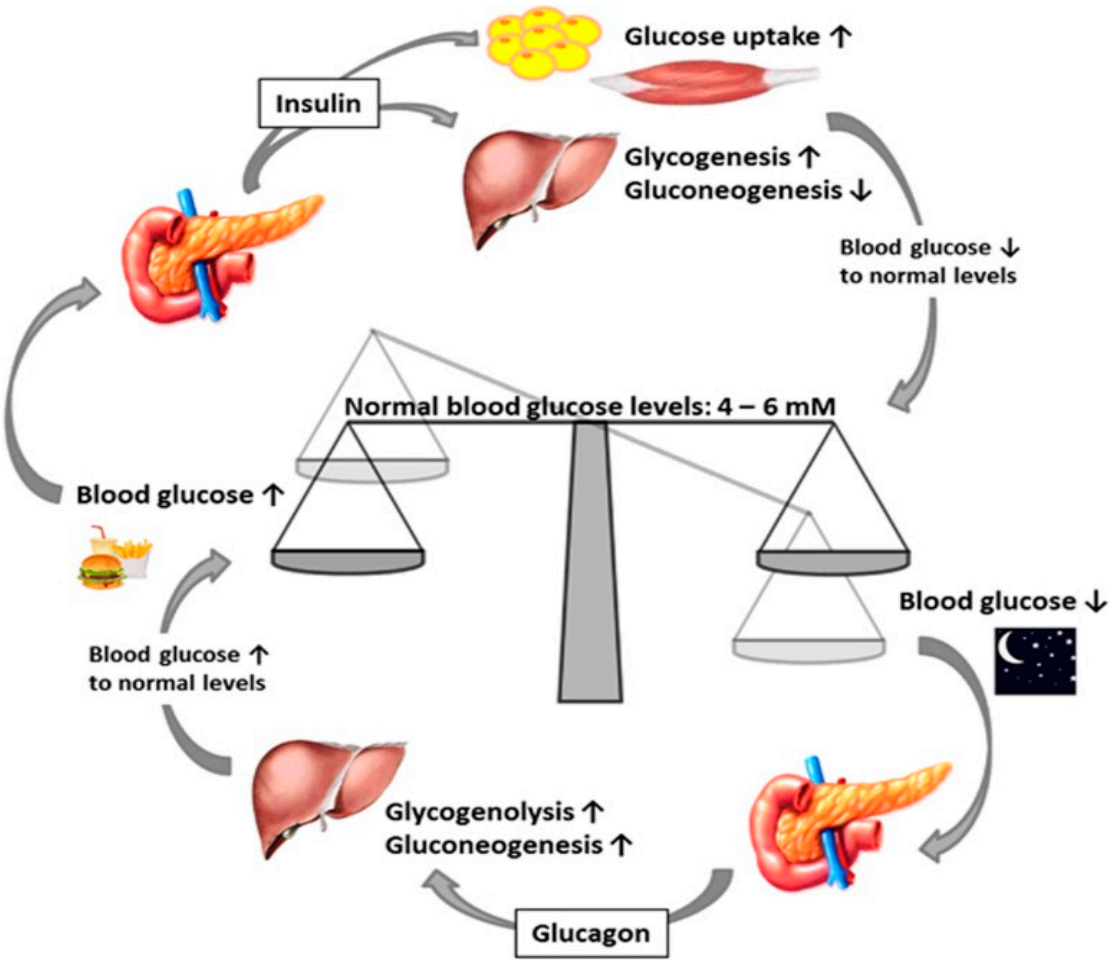


Figure 1.4. An overview of blood glucose regulation. Taken from Roder, Wu, Liu, and Han (2016).

1.3.1 Glucose transport within the body

The transport of glucose throughout the body once absorbed from the gut can have a large impact on how it appears and disappears to and from the bloodstream. Glucose must pass through membranes with the assistance GLUT proteins (**Figure 1.3**). The five GLUT pathways can be insulin-dependent or insulin-independent. GLUT 1, 2 and 3 are insulin-independent. GLUT1 supports the basal uptake of glucose (Pragallapati & Manyam, 2019; Tirone & Brunicardi, 2001b). It is particularly important for the brain, which relies on glucose as a fuel regardless of the BG concentration. GLUT2 is mostly found in the liver and the ß-cells of the

pancreas. GLUT2 enables pancreatic beta cells to sense rising blood glucose levels by allowing glucose to enter the cell independently of insulin, triggering insulin secretion in proportion to glucose concentration (Tirone & Brunicardi, 2001b). GLUT3 is largely associated with the transport of glucose into neurons and nerve tissue. It has a high affinity for glucose which is important during periods where glucose concentration may be low (Haber, Wienstein, E, & Morgello, 1993).

GLUT4 is an insulin-dependent transporter which is particularly important when there is a need to dispose of glucose in the blood. While normally stored intracellularly, insulin will bind to its receptor, increasing protein kinase B (Akt) to translocate GLUT4 from vesicles within the cell, to the cell membrane. When translocated, it can provide a significantly increased access for glucose into the cell. In addition to insulin, exercise can also stimulate the translocation of GLUT4, resulting in large increases in glucose uptake during exercise and for a short time immediately post-exercise (see **section 1.3.7**) (Richter & Hargreaves, 2013b; Thorell A et al., 1999).

The GLUT protein characteristics help ensure glucose goes to the appropriate destinations at the right time. For example, the brain and neurons will have a relatively constant supply even during times when BG concentrations are low. As the BG concentrations increase and there is a more plentiful supply, GLUT2 and GLUT4 will ensure it goes to either storage or metabolically active muscle cells.

GLUT5 is somewhat different in that it only deals with fructose. However, it is insulin-dependent. It is grouped in with the other GLUT proteins as it still has a profound impact on glucose entering the bloodstream. Unlike glucose, fructose does not directly enter the bloodstream after being absorbed through the intestinal wall. It is taken up in the splanchnic area (J. Fuchs, JT, & Van Loon, 2019a) where it is then metabolised into glucose and lactate. These may then either enter the systemic circulation or contribute to glycogen storage in the liver.

In addition, there are sodium-dependent glucose transporters (SGLTs). SGLT1, as previously mentioned, which plays a key role in transporting glucose from the gut into the bloodstream. SGLT2 is in the proximal tubule of the nephron in the kidneys and is essential for the reabsorption of glucose back into the bloodstream after it has been filtered by the kidneys.

1.3.2 Glucose in the postabsorptive (Fasting) state

In a fasted state, such as in the morning, BG concentrations will eventually fall as glucose is naturally utilised by cells. The change in concentration is sensed in the pancreas, where the α-cells will begin to secrete glucagon and simultaneously reduce insulin secretion (E. Cryer, 2007). The main role of glucagon is to upregulate gluconeogenesis and glycogenolysis. The primary source of glucose in a fasting state comes from the liver glycogen stores, accounting for 36% of total glucose production. Gluconeogenesis accounts for the remainder, and as fasts extend in time (>48 h) it will account for a much more substantial contribution (Rothman, Magnusson, Katz, Shulman, & Shulman, 1991; Wahren & Ekberg, 2007). Renal glucose production accounts for a relatively small contribution during short-term fasting but may increase in more prolonged scenarios. Renal glucose can account for a substantial proportion of the glucose supply in a fasted state (Cherrington, 1997; Ekberg et al., 1999; Triplitt, 2012; Wahren & Ekberg, 2007).

When glucose levels begin to fall below normal concentration, the counter-regulatory hormone adrenaline is secreted along with growth hormone and cortisol. Lipolysis is initiated by stimulation of hormone sensitive lipase, consequently increasing the availability of free fatty acids and glycerol. This concert of events induces temporary insulin resistance in the muscle and liver and reduces glucose uptake. As the fast duration extends a parallel increase in proteolysis occurs. The glycerol and amino acids now provide the substrate for gluconeogenesis to occur (Dimitriadis, Maratou, Kountouri, Board, & Lambadiari, 2021; R Maughan, 2009) (**Figure 1.5)**.

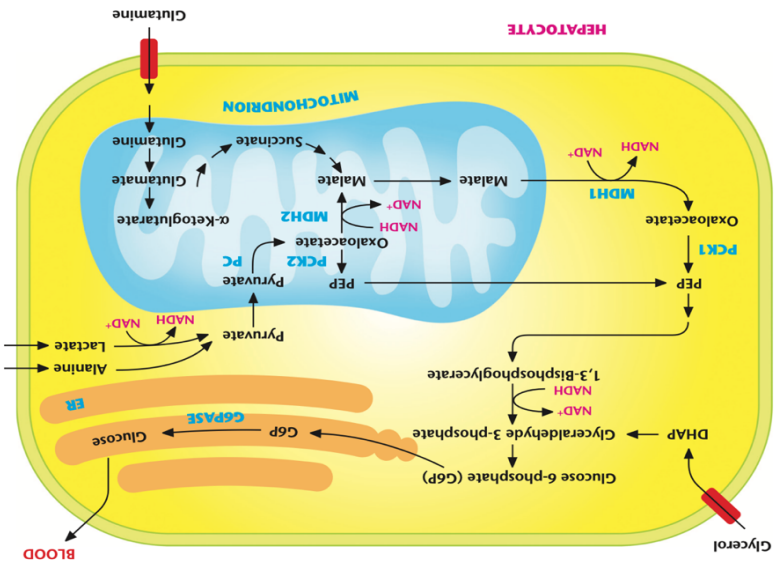


Figure 1.5. Substrates and processes feeding gluconeogenesis. Taken from Chandel (2021).

1.3.3 Glucose regulation in the post-prandial period

After consuming a carbohydrate containing meal BG concentration rises as exogenous carbohydrates are assimilated. To regulate high BG concentrations from occurring, some glucose must be removed from the circulation (**Figure 1.6)**. After a meal, insulin secretion rises due to gut peptides known as incretins. Both glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released in response to glucose absorption through the intestinal wall (Dimitriadis et al., 2021; Unger & Eisentraut, 1969) and stimulate some insulin release from the pancreas. This early release allows for a lesser amount of insulin to be needed in BG regulation. It serves as a preventative mechanism against hyperglycaemia (Giugliano, Ceriello, & Esposito, 2008), initiating some uptake of glucose before more substantial disposal takes place.

From the gut, glucose moves via the portal vein to the liver. Here some of the glucose will be converted into glycogen for storage while the remainder will continue into general circulation. Once in circulation, it can enter the skeletal muscle cells and other organs and tissues for further metabolism and/or storage.

Once BG concentration rises the ß-cells of the pancreas will try and match the level of insulin secretion to the level of BG concentration. This is in an effort to ensure an efficient timing of glucose uptake and storage (Dimitriadis et al., 2021). The release of insulin occurs in a biphasic

manner. Initially, the first phase is quite rapid. This is to quickly inhibit glucagon secretion and suppress glycogenolysis. Then the second phase is longer and more sustained. A consequent decrease in lipase activity will allow the concentration of circulating free fatty acids and glycerol to fall, slowing gluconeogenesis.

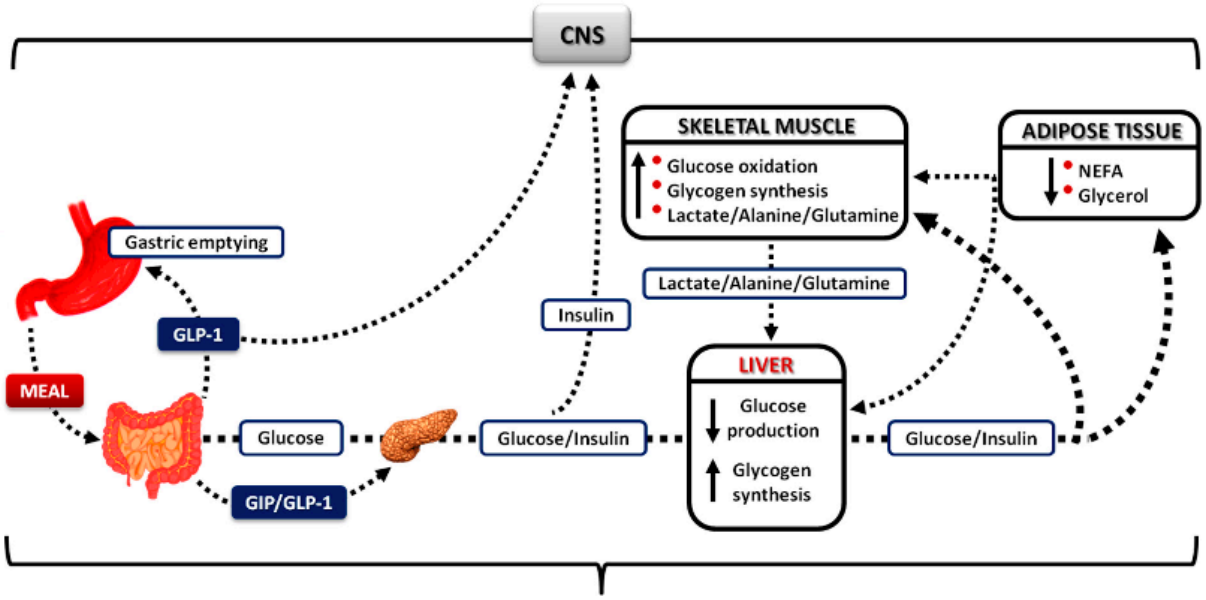


Figure 1.6. Postprandial blood glucose regulation. Taken from Dimitriadis et al. (2021).

1.3.4 Formation of Glycogen

The formation of glycogen is important as it forms an significant glucose store in the body and must be easily accessible. Glucose must go through several steps before a granule of glycogen is formed. This process is illustrated in **Figure 1.7**. Once glucose enters the cell, it is immediately phosphorylated by the enzyme hexokinase to form glucose-6-phosphate (G6P). The glucose-6-phosphate is then converted to glucose-1-phosphate (G1P) via the enzyme phosphoglucomutase. This is followed by the conversion of glucose-1-phosphate to uridine diphosphate-glucose (UDP), an activated form of glucose that is critical for glycogen synthesis.

The process then requires a primer to start building the glycogen chain. Glycogenin forms the tether point from which glycogen can form. Glycogenin attaches the first few glucose molecules from UDP to itself, forming a short chain of glucose units. Once this primer is in place, glycogen synthase (GS) takes over and adds more glucose units from UDP-glucose to the growing chain by creating α1-4 glycosidic bonds.

To create the highly branched structure of glycogen, the branching enzyme amylo-(1,4-1,6)-transglycosylase transfers a portion of the glucose chain to form α-1,6 glycosidic bonds, creating branches. These branches are important because they increase the solubility of glycogen and provide multiple points for glucose release when the body needs energy (R Jentjens & Jeukendrup, 2003).

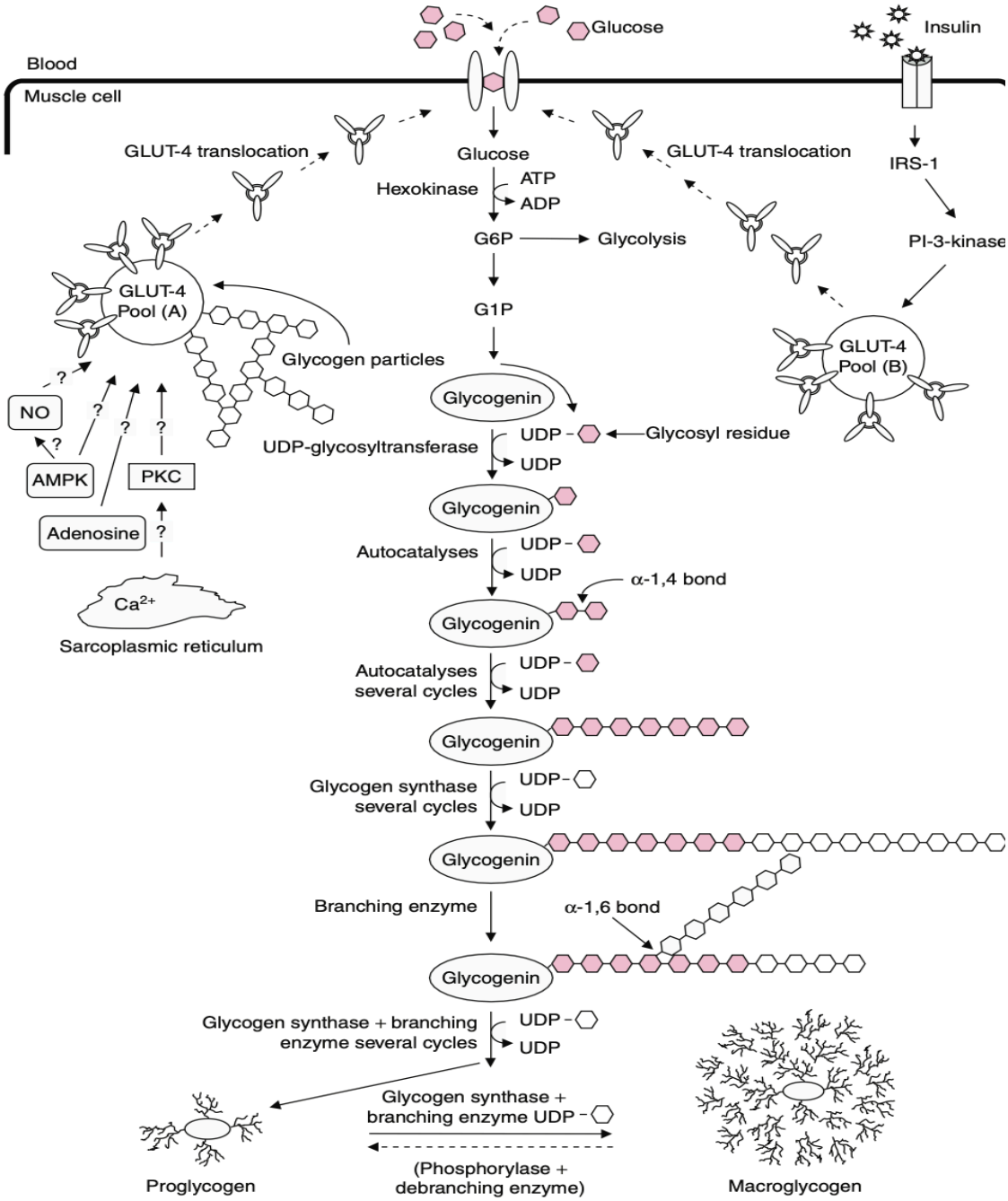


Figure 1.7. Step-by-step representation of glycogen synthesis including the involvement of GLUT4 in a post-exercise period. Taken from R Jentjens and Jeukendrup (2003).

1.3.5 Hypoglycaemia

Hypoglycaemia refers to abnormally low blood glucose levels that pose a risk of harm. The American Diabetes Association defines hypoglycaemia in diabetes as a plasma glucose concentration of $\leq$3.9 mmol.l^{-1} (70 mg/dL), a conservative alert threshold designed to prompt timely action and account for monitoring device limitations (American Diabetes Association, 2021). In contrast, healthy individuals typically experience counter-regulatory responses and symptoms at lower glucose levels (around 3.0 mmol.l^{-1} or 53 mg/dL) (Boyle, Schwartz, Shah, Clutter, & Cryer, 1988), reflecting differences in glucose regulation between diabetic and non-diabetic populations. When we are in a state of hypoglycaemia, cognitive function can be dramatically reduced and prolonged periods at very low levels may lead to brain damage and potential death (Guettier & Gorden, 2006; Tirone & Brunicardi, 2001a). Severe hypoglycaemia is a very rare occurrence in non-metabolically dysfunctional healthy individuals (E. Cryer, 2007). The first mechanisms responsible for preventing hypoglycaemia are hormonal. Counter-regulatory hormones are released and act to initiate glycogenolysis and gluconeogenesis. Then there will be a behavioural influence with an increased feeling of hunger to replenish the body's glucose reserves (Gais et al., 2003) (**Figure 1.8)**. These mechanisms effectively promote the recovery of blood glucose concentrations to safe levels.

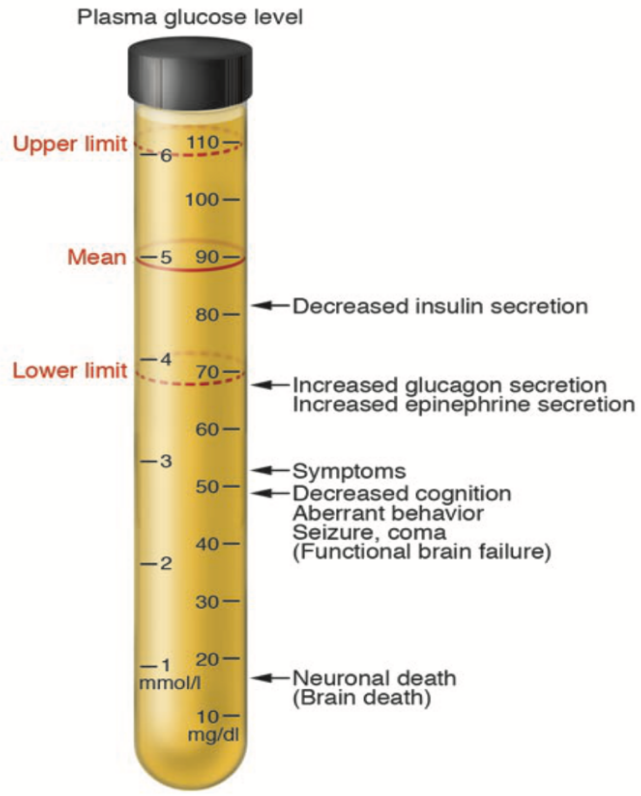


Figure 1.8. Symptoms associated with falling blood glucose concentrations. Taken from E. Cryer (2007).

1.3.6 Hyperglycaemia

To prevent excessive blood glucose (BG) concentrations, termed hyperglycaemia, glucose must be removed from circulation, primarily via insulin-mediated uptake. In individuals with diabetes, hyperglycaemia is often defined as a postprandial (2 hours following a meal) BG level exceeding 11.0 $mmol.l^{-1}$ (240 mg/dL), reflecting impaired glucose clearance (Diabetes.co.uk, 2021). In contrast, healthy individuals typically experience only modest and short-lived glucose excursions due to rapid and effective counterregulatory mechanisms (American Diabetes Association, 2001; Jarvis, Cardin, Nisevich-Bede, & McCarter, 2023). The magnitude of such excursions is also quite tightly related to the glycaemic index and load of the meal ingested (Augustin et al., 2015; Jenkins et al., 1981). Insulin secretion, glucose uptake in peripheral tissues, and hepatic glucose suppression all work in concert to maintain euglycaemia.

As a result, defining hyperglycaemia in healthy populations is challenging; transient elevations are common after carbohydrate intake but are usually well controlled through counterregulatory mechanisms. In individuals with type 2 diabetes, hyperglycaemia typically arises from impaired insulin secretion and insulin resistance. By contrast, healthy individuals may exhibit some degree of insulin resistance, but normal β-cell function allows for adequate compensatory insulin release to maintain glycaemic control (Reaven, 1988). Nevertheless, frequent or prolonged postprandial hyperglycaemia, even within what is considered the "normal" range, has been associated with early markers of metabolic dysfunction, including increased insulin demand, low-grade inflammation, and dyslipidaemia (Blaak et al., 2012; Pazos-Couselo et al., 2025). These effects, though subtle, suggest that repeated exposure to elevated glucose may carry long-term metabolic risks (Pazos-Couselo et al., 2025). Despite the suggestions made from these observational studies, direct evidence of hyperglycaemia causing harm as a sole cause is inconclusive, and the consensus on specific thresholds for concern in healthy individuals remains lacking.

1.3.7 Blood glucose during endurance exercise

As muscle glycogen content begins to decline, signals upregulate the uptake of blood glucose into the muscle. There are a number of possible signals, and it is unlikely that any one pathway has sole responsibility. There are three rate-limiting stages to glucose uptake; delivery, transport and metabolism (Richter & Hargreaves, 2013a; Rose & Richter, 2005; Sylow, Kleinert, Richter, & Jensen, 2017).

Delivery

Increased blood flow is the first mechanism which increases the amount of blood glucose reaching the muscle. This is a product of increased cardiac output, vasodilation of the blood vessels and muscle contractions which help direct blood through the vasculature and to the working muscles. There are a number of potential vasodilatory mechanisms which contribute to the vascular changes in blood flow and muscle perfusion, such as the release of nitric oxide, Adenosine, ADP and ATP itself (Sylow et al., 2017). This vasodilation helps maintain the interstitial-venous plasma glucose relationship.

Transport

The translocation of GLUT4 during exercise increases the amount of glucose entering the cell. Several mechanisms can contribute to the GLUT4 translocation, summarised in **Figure 1.9** below. These include both mechanical and metabolic stress, the release of nitric oxide and reactive oxygen species (ROS). Some of these mechanisms have been indicated through various studies, but remain largely inconclusive as to the exact mechanism of contribution (Sylow et al., 2017).

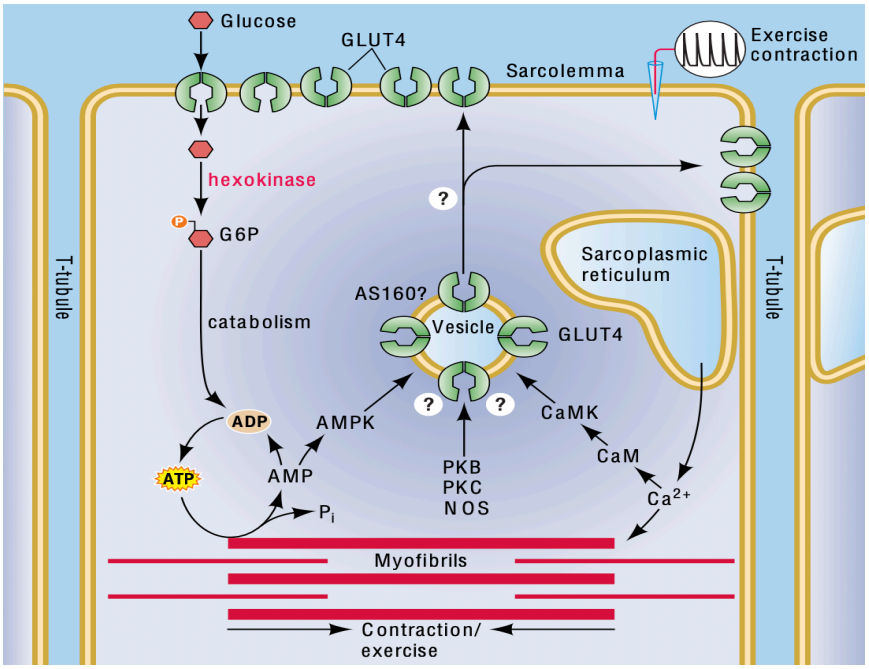


Figure 1.9. Molecular mechanisms of exercise-regulated glucose uptake by skeletal muscle. The mechanisms behind this are unclear but may involve several kinases that sense and transduce signals relating to changes in the intracellular environment during contractions (i.e., higher Ca^{2+}, AMP concentrations) to other undefined proteins involved in GLUT4 movement and insertion into membranes. Question marks refer to unidentified signalling and structural molecules that are involved in this process. G6P, glucose-6-phosphate; AS160, Akt substrate of 160 kDa; AMPK, 5-AMP-activated protein kinase; CaM, calmodulin; CaMK, Ca^{2+}-CaM dependent protein kinase; PKB, protein kinase B (also known as Akt); PKC, protein kinase C; NOS, nitric oxide synthase. Taken from Richter and Hargreaves (2013a).

Glucose metabolism during endurance exercise

Early in exercise, when glycogen breakdown (glycogenolysis) is high, considerable glucose-6-phosphate is produced, which inhibits hexokinase from working. This causes a build-up of free glucose inside the muscle, creating an equal gradient and making it harder for more glucose to

enter. As exercise continues and glycogen stores reduce, glucose-6-phosphate decreases, removing the inhibition of hexokinase. This, along with the increased movement of GLUT4 transporters to the muscle cell membrane, allows more glucose to be taken up from the blood. This shows the role of hexokinase in controlling how much glucose muscles can use during exercise (Sylow et al., 2017). There is a need for such a rate-limiting mechanism to allow for some transition of preference towards blood glucose. This process plays a major role in the regulation of glucose uptake from the blood.

1.3.8 Liver Glycogen

The liver functions as an endogenous glucose store. Liver glycogen provides glucose which maintains basal blood glucose concentrations at rest and becomes an important contributor during exercise. Through glycogenolysis, it releases glucose into the circulation to match rising metabolic demands. In this context, the liver serves as an endogenous energy reserve, mobilising glucose to meet increased metabolic demands during exercise (Trefts & Wasserman, 2022).

Assessing liver glycogen is more challenging than measuring muscle glycogen, but indirect methods have enabled reasonable estimates. Evidence suggests that untrained individuals deplete liver glycogen more rapidly than trained individuals. This difference may be due to a blunted hormonal response in trained individuals at moderate exercise intensities (e.g., 60% VO_2 peak), which slows the rate of hepatic glycogenolysis (Gonzalez, Fuchs, Betts, & van Loon, 2016). Nonetheless, as muscular glucose demand rises during exercise, hepatic glucose output correspondingly increases to help maintain euglycaemia.

Carbohydrate ingestion during exercise reduces the liver's endogenous glucose production by increasing circulating glucose and insulin levels, which suppress hepatic glucose output (Bosch, Dennis, & Noakes, 1994; Jeukendrup, Wagenmakers, et al., 1999). This suppression helps preserve liver glycogen stores, which is critical for sustaining prolonged exercise performance. Additionally, maintaining stable blood glucose through exogenous carbohydrate consumption delays fatigue and supports endurance. The magnitude of hepatic glucose suppression depends on exercise intensity, duration, and carbohydrate dose and type, and may vary among individuals based on training status (Gonzalez et al., 2016; Jeukendrup, 2004; Newell, Wallis, Hunter, Tipton, & Galloway, 2018; Rollo, Gonzalez, Fuchs, Van Loon, & Williams, 2020).

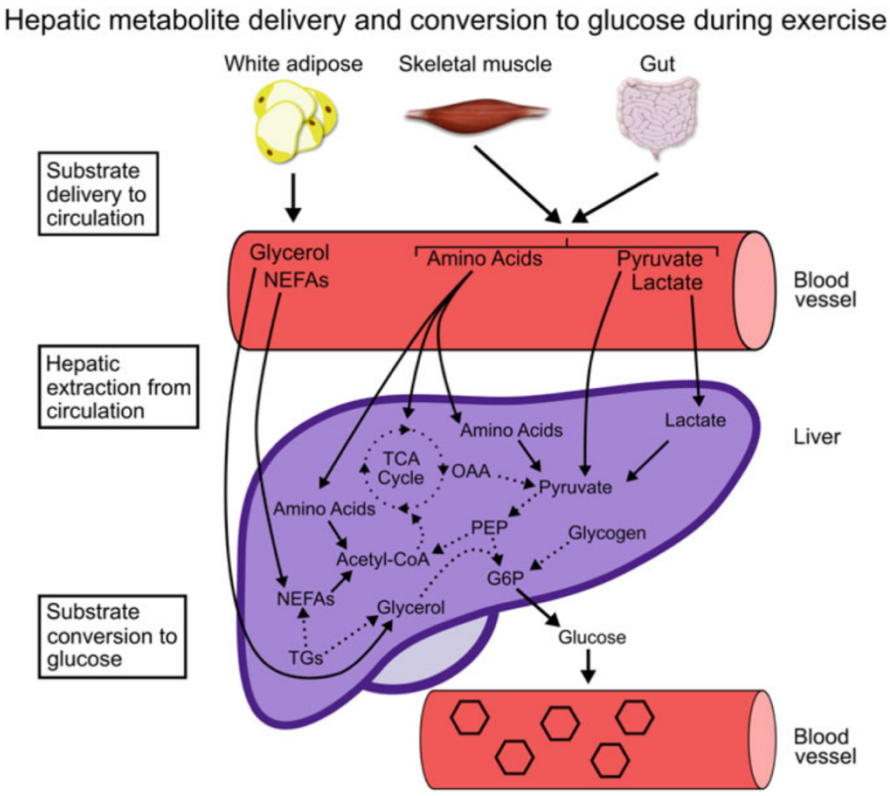


Figure 1.10. Liver nutrient metabolism and gluconeogenesis. Modified from Trefts, Williams, and Wasserman (2015). Taken from Trefts and Wasserman (2022).

The liver is also a site for gluconeogenesis. It may convert a number of metabolites to glucose. Fatty acids and glycerol, amino acids from protein deamination and circulating lactate can all be converted to glucose (**Figure 1.10)**. The liver is of particular interest during exercise as it may act as an alternative pathway for exogenous carbohydrate to enter the circulation. Increasing overall carbohydrate availability may be of benefit during exhaustive exercise (C. Fuchs et al., 2016; J. Fuchs, JT, & Van Loon, 2019b; Gonzalez et al., 2016). In times of extreme starvation, the liver can also convert fatty and some amino acids into ketone bodies; acetoacetate, beta-hydroxybutyrate, and acetone. This process is called ketogenesis. Ketones can provide fuel to the brain and heart when glucose supply is extremely low (Trefts & Wasserman, 2022).

1.3.9 Glucose uptake in the post-exercise recovery period

In the post-exercise period, glycogen replenishment is an important process in recovering from exercise. It occurs in two distinct phases: the fast and slow phases, both driven by several key physiological changes that upregulate glycogen synthase (GS) activity (R Jentjens & Jeukendrup, 2003). During the fast phase (0–2h post-exercise), GS is highly active due to the

significant glycogen depletion that occurs during exercise, which sensitises the enzyme to glucose uptake. Muscles are also more sensitive to insulin during this phase (Holloszy, 2005), which promotes the dephosphorylation and activation of GS. The GLUT4 transporters which have been translocated to the membrane surfaces also remain elevated (Maarbjerg, Sylow, & Richter, 2011). This increases glucose entering muscle cells, providing the substrate for rapid glycogen synthesis (Alghannam, Gonzalez, & Betts, 2018; LM Burke, van Loon, & Hawley, 2017). In addition, increased microvascular perfusion elevates the concentration of glucose in the interstitial fluid, facilitating glucose uptake from the blood (Maarbjerg et al., 2011).

Following the initial rapid replenishment, the slow phase (2–48 h post-exercise) takes over, where glycogen synthesis continues at a slower rate but remains active due to ongoing insulin action. This is provided that there is available glucose in the blood coming from ingested carbohydrate (LM Burke et al., 2017). Throughout both phases, there is a reduction in stress hormones like adrenaline, lifting any inhibition of GS. Energy-sensing pathways such as AMPK also shift towards further support of glycogen restoration (Jensen & Richter, 2012). These processes make the post-exercise period, especially the fast phase, an optimal window for refuelling muscle glycogen.

There are some instances where glycogen restoration and glucose uptake may be hindered. Where eccentric-type muscle contractions have induced damage, GLUT4 expression appears to be decreased (Asp, Daugaard, & Richter, 1995) and insulin resistance increased (Kirwan, Yarasheski, Kohrt, Wiethop, & Holloszy, 1992), reducing the muscles' ability to take up glucose. In addition, inflammatory cytokines produced during intense exercise, such as tumour necrosis factor-alpha (TNF-α), may interfere with insulin signalling pathways (Gonzalez, Barwood, Goodall, Thomas, & Howatson, 2015).

Section 1.4: Carbohydrate and exercise

1.4.1 The role of carbohydrates during exercise

The role of carbohydrate during exercise was first identified by Krogh and Lindhard (Krogh & Lindhard, 1920). Their investigation used expired gases to establish the relative oxidation of both fat and carbohydrate during exercise. They showed that diets low in carbohydrate and high in fat increased fatigue during exercise. Soon after, S. Levine, Gordon, and Derick (1924) observed symptoms of hypoglycaemia in some Boston Marathon runners. They also noticed that those who consumed carbohydrates before and during the race maintained normal blood glucose and had better performance.

Decades later, muscle biopsy techniques allowed Bergstrom et al. (1967a) to demonstrate that high-carbohydrate diets improved glycogen restoration and subsequent exercise capacity (**Figure 1.11)**. Hypoglycaemia was experienced across trials during this study, but it was delayed when carbohydrate intake was high. Several other studies detailed similar findings soon after (Bergstrom & Hultman, 1967; Hermansen, Hultman, & Saltin, 1967; Karlsson & Saltin, 1971; Widrick et al., 1993).

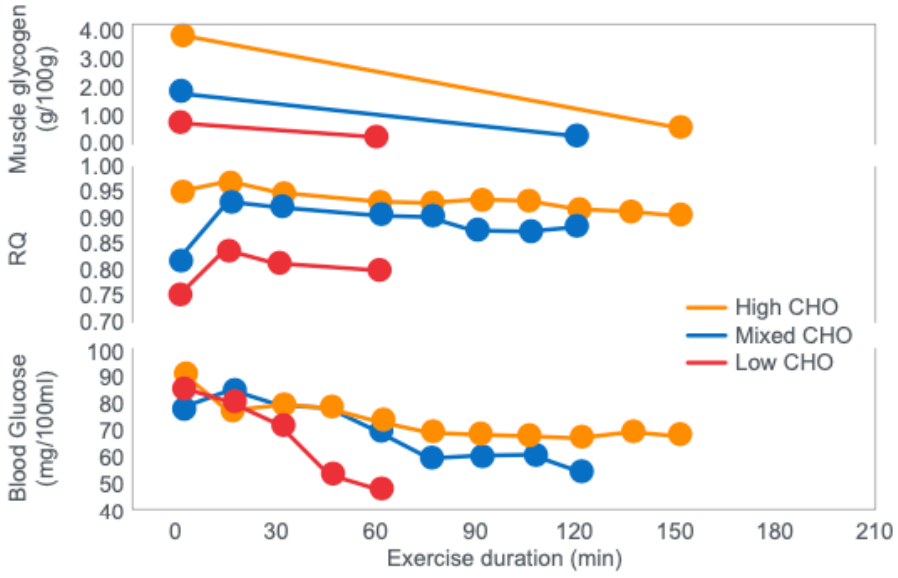


Figure 1.11. Changes in muscle glycogen concentrations, respiratory quotient (RQ) and blood glucose concentrations in subjects after acute adaptation to either high, mixed or low-carbohydrate diets. Adapted from (J Bergstrom, L Hermansen, E Hultman, & B Saltin, 1967b). Taken from (TD Noakes, 2022).

Karlsson and Saltin (1971) showed that carbohydrate loading after glycogen depletion increased muscle glycogen stores. Later research revealed that depletion was unnecessary. Adequate carbohydrate intake for at least 24 hours before exercise was sufficient (Bussau, Farichild, Rao, Steele, & Fournier, 2002; Hawley, Schabort, Noakes, & Dennis, 1997; Sherman, Costill, & Miller, 1981). This approach led to the concept of carbohydrate loading pre-event, and it is now a popular strategy used to prepare for competition (LM Burke, Hawley, Wong, & Jeukendrup, 2011).

The importance of carbohydrate extends to intake during exercise. Ahlborg and Felig (1976) demonstrated that ingesting glucose mitigated hormonal responses to exercise, reversing glucagon secretion. Subsequently, studies by Coyle (Coyle et al., 1983) and Hargreaves (Hargreaves, Costill, Fink, & Nishibata, 1984) showed that ingesting carbohydrates during exercise helped maintain blood glucose concentrations and delay fatigue. AR Coggan and Coyle (1989) showed that fatigue and hypoglycaemia could be reversed after ingesting carbohydrate late in exercise. Declines in plasma glucose were mirrored by declines in carbohydrate oxidation, demonstrating a positive interaction between blood glucose concentration and carbohydrate oxidation rates (Coyle, Coggan, Hemmert, & Ivy, 1986a).

Carbohydrate ingestion also slowed glycogen depletion during prolonged exercise (>4h) (Hargreaves et al., 1984). However, other studies struggled to show the same level of sparing (Coyle, Coggan, Hemmert, & Ivy, 1986b; Fielding et al., 1985; Hargreaves & Briggs, 1988). Ultimately, the focus shifted from glycogen alone to the importance of maintaining glucose availability for sustained oxidation (Saltin & Karlsson, 1971; Widrick et al., 1993).

Despite a body of evidence supporting the role of glucose and glycogen in preventing fatigue, some studies reported fatigue even when glycogen and glucose levels were adequate (A Coggan & Coyle, 1987; Grisdale, Jacobs, & Cafarelli, 1990). This suggests the brain and autonomic nervous system (ANS) played a role in glucose homeostasis and fatigue. Under normoglycaemia, central motor drive supports the motor units involved in exercise. Under hypoglycaemia, reduced central motor drive may act as a protective mechanism (TD Noakes, 2022), feeding into a ‘central governor’ theory. Perception of effort (RPE) may reflect this, with fatigue rates related to initial glycogen content (T Noakes, 2004), as shown in **Figure 1.12**.

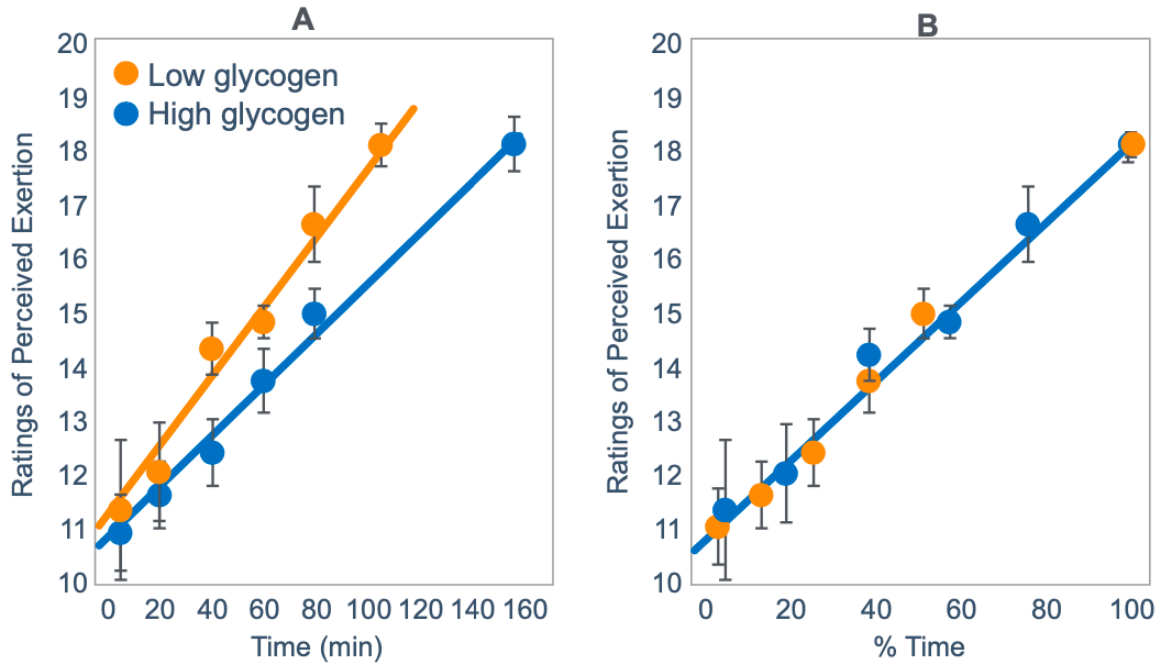


Figure 1.12. A: plot of ratings of perceived exertion (RPE) against exercise duration for groups starting with either low or high glycogen content. B: plot of both groups' RPE against % time of total exercise duration. Suggesting a relationship between the rate of RPE increase and the remaining duration of exercise. From T Noakes (2004).

The relationship between carbohydrate and central drive is further demonstrated by carbohydrate mouth rinsing. Several studies have shown that just the mere sensing of carbohydrate in the oral cavity can stimulate the nervous system and support exercise (Carter, Jeukendrup, & Jones, 2004; Chambers, Bridge, & Jones, 2004; Rollo & Williams, 2011)

More recent research has focused on optimising carbohydrate use during exercise. Both the type and quantity of carbohydrate influence its effectiveness. A key limitation is the rate at which exogenous carbohydrate can be absorbed in the gut (Jeukendrup & Jentjens, 2000). Combining multiple carbohydrate sources, such as glucose and fructose, enhances absorption by utilising different intestinal transporters, leading to higher oxidation rates and reduced gastrointestinal discomfort. This strategy supports sustained carbohydrate availability during prolonged moderate to high-intensity exercise (Currell & Jeukendrup, 2008; J. Fuchs et al., 2019b; RLPG Jentjens, Moseley, Waring, Harding, & Jeukendrup, 2004; Jeukendrup et al., 2006). A summary of some seminal studies investigating the effect of carbohydrate on endurance performance under different conditions is displayed in **Table 1.3,** underpinning current guidelines detailed by LM Burke et al. (2011).

Author (Year)	CHO Amount (g/h)	Exercise Modality	Intensity (% VO2max)	Duration/Task	CHO Type	Physiological outcome	Effect (CHO vs. Placebo)
Bonen, Malcom, Kilgour, MacIntyre, and Belcastro (1981)	234	Cycling to exhaustion	80	Time to exhaustion	20% Glucose	(CHO) Decline in [glucose] without intra intake. (p) fell to hypo	26.1 min (CHO) vs. 29.9 min (P) - No
Ivy et al. (1983)	29	Walking to exhaustion	45	Time to exhaustion	Glucose polymer	(CHO) Initial rise then steady decline. (p) fell to hypo.	299 min (CHO) vs. 268 min (P) - Yes
Coyle et al. (1983)	124	Cycling to exhaustion	74	Time to exhaustion	Glucose polymer	(CHO) fatigued without hypo. (p) Some experienced hypo	157 min (CHO) vs. 134 min (P) - Yes
Hargreaves et al. (1984)	43	Intermittent cycling + sprint	100	4-h intermittent cycling with sprints	Candy bar (43 g sucrose, 6 g fat, 3 g protein)	(CHO) despite reduction in glycogen sprint performance was better.	27 min (CHO) vs. 87 (P) - Yes
Björkman, Sahlin, and Wahren (1984)	53	Cycling to exhaustion	68	Time to exhaustion	5% Glucose, 7% Fructose	(CHO) maintained BG and spared muscle glycogen	137 min (CHO) vs. 116 min (P) - Yes
Fielding et al. (1985)	22	Cycling + sprint	100	240-min cycling followed by sprint	5% CHO, Glucose polymer	(CHO) BG was elevated but glycogen reduced. Sprint performance was better.	116 min (CHO) vs. 116 min (P) - No
Coyle et al. (1986a)	100	Cycling to exhaustion	71	Time to exhaustion	Glucose polymer	(CHO) Maintained BG and oxidation. (p)	121 min (CHO) vs. 81 min (P) - Yes

						BG declined as did oxidation.	
Coggan and Coyle (1987)	100	Cycling to exhaustion + recovery + sprint	73	Cycling to exhaustion followed by 20-min recovery & sprint	Glucose polymer	(CHO) Maintained both BG and oxidation. (p) BG declined as did oxidation.	4.02 h (CHO) vs. 3.02 h (P) - Yes
Flynn et al. (1987)	45	Cycling for 120 min	NA	Time trial for maximum effort	3% Glucose polymer + 2% Glucose	Glycogen stores were elevated and sufficient to maintain intensity.	184 W (CHO) vs. 186 W (P) - No
Murray et al. (1987)	24	Intermittent cycling + sprint	55-65	Intermittent cycling followed by sprint	5% Glucose polymer	(CHO) Greater glucose availability later in trial	400 s (CHO) vs. 432 s (P) - Yes
RJ Maughan, Fenn, and Leiper (1989)	24	Running to exhaustion	70	Time to exhaustion	8% Sucrose	(CHO) Glucose availability produced better performance but composition of drink important.	90.8 min (CHO) vs. 70.2 min (P) - Yes
Mitchell et al. (1989)	37	Cycling to exhaustion + time trial	70	105-min cycling followed by 15-min time trial	5% CHO, Sucrose	(CHO) Maintained BG and increased availability.	79.0 min (CHO) vs. 70.2 min (P) - No
Wright, Sherman, and Dernbach (1991)	35	Cycling to exhaustion	70	Time to exhaustion	12% CHO	(CHO) Maintained BG and oxidation. (p) BG declined as did oxidation.	213 kJ (CHO) vs. 201 kJ (P) - Yes

Wilber and Moffat (1992)	50	Running to exhaustion	80	30-km running time trial	5.5% CHO (Glucose polymer + Glucose + Fructose)	(CHO) Greater BG and oxidation.	115.4 min (CHO) vs. 92.0 min (P) - Yes
Maughan et al. (1996)	12	Cycling to exhaustion	70	Time to exhaustion	Glucose	BG maintained in both	110 min (CHO) vs. 93 min (P) - Yes
Tsintzas et al. (1996)	16	Running to exhaustion	76	Time to exhaustion	5.5% CHO (Glucose polymer + Glucose + Fructose)	(CHO) Greater BG availability and glycogen sparing	132 min (CHO) vs. 114 min (P) - Yes
Madsen et al. (1996)	66	100-km time trial	-	Time to completion of 100-km trial	MD (50% Glucose polymer + Gatorade)	No differences	160 min (CHO) vs. 160 min (P) - No
Angus et al. (2000)	60	Cycling to exhaustion	-	100-km time trial	6% CHO + Glucose + Sucrose	(CHO) Greater BG and oxidation.	166 min (CHO) vs. 178 min (P) - Yes
Patterson and Gray (2007)	43	Intermittent Runs to Exhaustion	55-95	5X15mins shuttles followed by shuttles to exhaustion	Glucose Gel	(CHO) Greater glucose availability	4 (CHO) vs. 6 min (P)- Yes
Currell and Jeukendrup (2008)	108	Cycling + time trial	55	120-min cycling followed by time trial	14.4% Glucose or Glucose+Fructose	(CHO) Greater oxidation and sparing of glycogen stores	61-67mins (CHO) vs. 56 min (P)- Yes
O'Brien and Rowlands (2011)	108	Cycling to exhaustion	NA	150mins followed by	Glucose + Fructose	Greater availability of Glucose	10 (CHO) vs. 9 mins (P)- Yes

				incremental test			

Table 1.3. Summary of studies investigating the effect of carbohydrate on endurance performance under different conditions. CHO: carbohydrate; F: fructose; GP: glucose polymer; MD: maltodextrin; P, placebo; S, sucrose; VO_{2max}, maximal oxygen consumption; W, watt.

1.4.2 Pre-Exercise Carbohydrate

Maximizing muscle and liver glycogen is critical for prolonged endurance performance. Carbohydrate loading (10–12 $g \cdot kg^{-1} \cdot day^{-1}$) can be achieved without prior depletion and typically requires 24–48 hours (Bussau et al., 2002). For shorter or high-intensity events (<20 min), loading offers limited benefit (Hawley et al., 1997).

Even without loading, pre-exercise intake (1–4 $g \cdot kg^{-1}$ 1–4 hours prior) supports performance by replenishing overnight liver glycogen losses (Podlogar & Wallis, 2022). Timing and composition are important to avoid gastrointestinal distress and manage glycaemic fluctuations, which can cause transient hypoglycaemia in some but do not reliably impair performance (Jeukendrup & Killer, 2010).

Low-GI carbohydrate meals may help stabilise glucose levels and modestly improve endurance performance, particularly when in-exercise feeding is limited (Moore, Midgley, Thurlow, Thomas, & McNaughton, 2010; Wong et al., 2008). They also promote greater fat oxidation, potentially sparing endogenous carbohydrate stores (Stevenson, Williams, Mash, Phillips, & Nute, 2006; Wee, Williams, Tzintzas, & Boobis, 2005), though some studies suggested carbohydrate oxidation may still increase due to sustained glucose availability (Moore et al., 2010; Onuma et al., 2023).

1.4.3 In Exercise Carbohydrate

Carbohydrate ingestion during exercise maintains blood glucose and spares liver glycogen, enhancing endurance (Jeukendrup, Wagenmakers, et al., 1999). Glucose oxidation was once thought to be limited to ~60 g/h due to SGLT1 transporter saturation (Jeukendrup & Jentjens, 2000), but combining glucose with fructose via alternate pathways can raise oxidation rates to ~90 g/h or more (RLPG Jentjens et al., 2004; Jeukendrup, 2010). Gut training can further increase tolerance and absorption (Hearris et al., 2022; Jeukendrup, 2017). Recommendations now align intake to exercise duration and athlete training status (Jeukendrup, 2014a).

Gastric Emptying and Beverage Concentration

Carbohydrate concentration influences both gastric emptying and intestinal absorption, with more dilute solutions (typically 4–8%) emptying more rapidly from the stomach (Murray,

Bartoli, Stofan, Horn, & Eddy, 1999). Beverage formulation should therefore balance carbohydrate concentration with fluid delivery and gastrointestinal comfort.

Gastrointestinal Distress

GI symptoms can severely impair performance and are common in endurance events (Jeukendurp et al., 2000; Stuempfle, Hoffman, Weschler, Rogers, & Hew-Butler, 2011). Causes include reduced gastrointestinal blood flow and mechanical or osmotic stress, with both acute and chronic implications (Costa, Hoffman, & Stellingwerff, 2019; Costa, Snipe, Kitic, & Gibson, 2017). Managing intake type, volume, and concentration is key to reducing risk.

1.4.4 Post-Exercise Carbohydrate

Post-exercise carbohydrate intake is essential to replenish glycogen stores, especially when recovery time is short (<8 h) or repeated exercise is planned (LM Burke et al., 2017; Ivy, Brozinick, & Reed, 1988). Muscle glycogen resynthesis rates are highest within the first hours post-exercise due to increased insulin sensitivity and glucose uptake (Zawadski, Yaspelkis, & Ivy, 1992). Recommendations typically suggest 1.0–1.2 $g \cdot kg^{-1} \cdot h^{-1}$ for the first 4 hours to maximise resynthesis (L Burke, Kiens, & Ivy, 2004).

Carbohydrate type influences the rate of glycogen storage, with high-GI sources producing faster restoration compared to low-GI options (R Jentjens & Jeukendrup, 2003). When carbohydrate intake is suboptimal (<1.0 $g \cdot kg^{-1} \cdot h^{-1}$), adding protein (0.3–0.4 $g \cdot kg^{-1}$) can further enhance glycogen synthesis and support muscle repair (Betts & Williams, 2010; van Loon, Saris, Kruijshoop, & Wagenmakers, 2000). However, when carbohydrate is provided in sufficient quantities, the addition of protein offers limited further benefit for glycogen replenishment (LM Burke et al., 2017).

The timing and distribution of carbohydrate and protein across the recovery window can influence outcomes, particularly in scenarios involving multiple training sessions or competitions per day. Strategic post-exercise nutrition, therefore, plays a key role in optimising recovery and subsequent performance.

Section 1.5: Glucose monitoring technology

1.5.1 Background

Blood glucose has long been examined during laboratory studies for investigating a wide range of health, disease and exercise-related physiology. In a disease management context, the ability to monitor glucose is essential for improving clinical outcomes in certain conditions such as diabetes. As a result, non-laboratory measurement techniques are necessary to bridge the gap between the laboratory and real-world use.

The first commercially available glucometer emerged in the 1970s. It measured a drop of blood on reactive paper strips called "Dextrostix" which could then be read with a colour-sensing meter. This system was known as the "Ames reflectance meter" and was the first of the DIY blood glucose monitoring options (Clarke & Foster, 2012; Mendosa, 2000). This technique of assessing the enzymatic reaction is known as colorimetric detection. This led to several companies emerging with similar options to fulfil the demand for what was at the time, a novel but effective piece of equipment for helping individuals to manage their diabetes.

Through a series of technological advancements, meters became battery-powered, smaller and more portable. Internal memory, visual displays and audible sounds were added to help with user interfacing. The amount of blood required to sufficiently operate the sensor also reduced as they developed. The overall reliability and accuracy also improved somewhat.

In the late 1980s, MediSense (eventually bought by Abbott) launched the Exactech glucometer. This was an amperometric sensor which came with the development of the Clarke error grid, now providing a reference tool to compare to laboratory standards and the gold standard Yellow spring analyser. Glucometer development accelerated as the reliability, ease of use and processing times of newer devices progressed. User error was reduced, and their use improved disease management and patient outcomes (Clarke & Foster, 2012).

While finger prick sampling is still an effective method of checking BG quickly, it is somewhat invasive and not convenient in many situations. In addition, the insights provided are limited to the number of samples taken during the day. They also require accurate record-keeping to allow for patient-clinician communication to be effective. This inspired the development of

continuous glucose monitors (CGM). These devices collect information constantly without the user having to initiate a measurement. The CGM allows for readings to be recorded at regular intervals providing a real-time trace of their glucose levels. The extra measurements over time offer significant insight into the dynamics of glycaemic variability.

1.5.2 Continuous interstitial glucose monitoring technology

Most currently available CGM sensors use interstitial glucose as a proxy measurement of BG. Glucose in the blood plasma diffuses through the walls of capillaries into the surrounding interstitial fluid (IF) (Koschinsky & Heinemann, 2001; Thome-Duret et al., 1996). The rate of blood glucose delivery and concentration dictates the amount of glucose which ends up in the IF. As a result, glucose detected in the IF can be used to estimate the level of BG (Cengiz & Tamborlane, 2009; Jansson, Fowelin, Smith, & Lonnroth, 1988).

The skin and subcutaneous area provide easy access to interstitial spaces which allows for much less invasive access to measure glucose (Cengiz & Tamborlane, 2009; Koschinsky & Heinemann, 2001). As a result, this has become the most feasible option for CGM as opposed to measuring blood from intravascular sources (Rossetti, Bondia, Vehi, & Fanelli, 2010).

CGMs work by using a small implantable filament in the subcutaneous region of the skin. This filament sits in the interstitial fluid and measures the flux of glucose through this fluid. The sensor body containing the battery, transmitter and memory unit is attached to the skin with adhesive backing (**Figure 1.13)**.

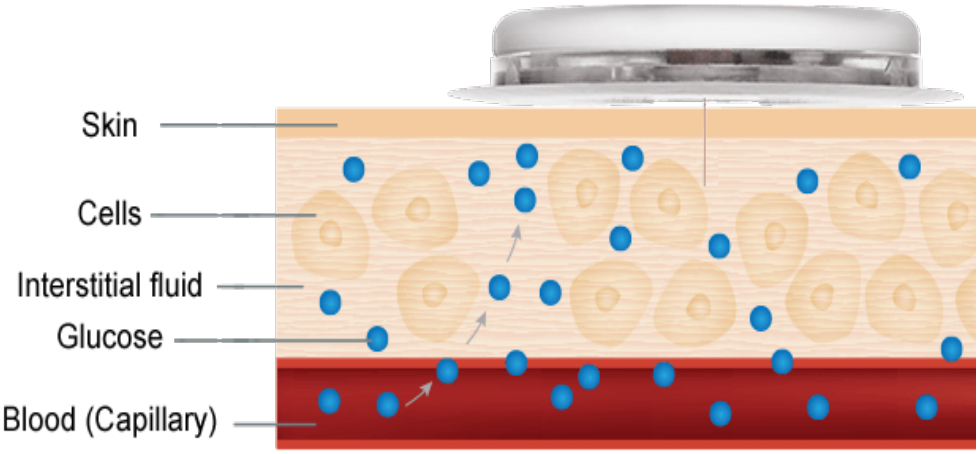


Figure 1.13. Continuous glucose monitor applied to the skin with a filament inserted into the subcutaneous region. The sensor measures the flux of glucose moving through the interstitial fluid. Taken from Abbott.com.

CGM sensors use electrochemical detection methods. These use similar enzymatic reactions to traditional glucometers. The first generation of CGM electrochemical sensors used a glucose oxidase reaction, where the oxidation of glucose produces glucolactone and hydrogen peroxide. The concentration of hydrogen peroxide is proportional to the concentration of glucose. This can then be detected when hydrogen peroxide is oxidised at an electrode housed in a sensor, creating an electric current. These first-generation sensors were particularly susceptible to interference by electroactive substances like acetaminophen, ascorbic acid, and uric acid. They were also dependent on oxygen which may not always be sufficient in the IF to maintain accurate readings (Zou et al., 2023). Second-generation glucose biosensors replaced oxygen with synthetic mediators (e.g., ferrocene, ferricyanide, and methylene blue) to facilitate electron transfer. These mediators operate at lower potentials, reducing interference from electroactive substances. Third-generation biosensors aim to achieve direct electron transfer between the enzyme glucose oxidase and electrodes, bypassing the need for mediators. Enzyme-based biosensors are also limited by enzyme instability under pH, temperature, and chemical conditions, leading to poor reproducibility when these exceed operating ranges.

Fourth-generation sensors attempt to use non-enzymatic methods, directly catalysing glucose on the electrode surface using materials like metal oxides and polymers (Zou et al., 2023). These are not yet clinically approved or commercially available.

1.5.3 Interstitial fluid

Total body water accounts for approximately 60% of body mass in adults and is divided into two primary compartments: intracellular fluid (ICF) and extracellular fluid (ECF). The ECF, which comprises roughly 20% of total body water, includes plasma and interstitial fluid (IF), which resides between capillary walls and cell membranes (Feher, 2012) (**Figure 1.14)**. Interstitial fluid plays a central role in nutrient and metabolite exchange between blood and tissue, including the transport of glucose. As continuous glucose monitors (CGMs) measure glucose in the interstitial rather than the vascular compartment, understanding the physiology and transport dynamics between these compartments is crucial for interpreting CGM data accurately in both clinical and athletic contexts.

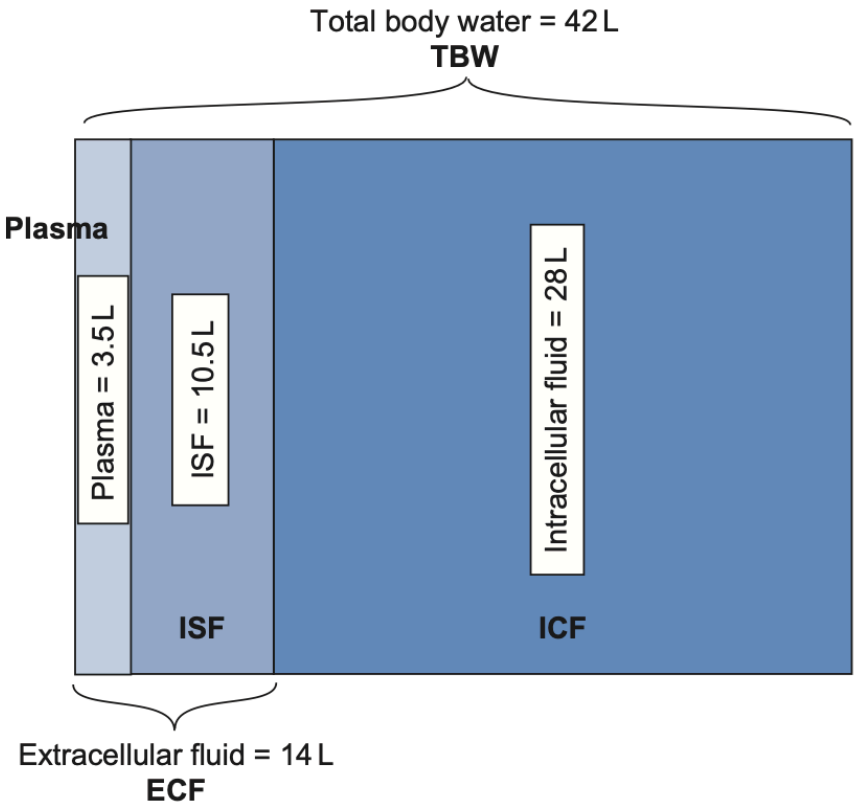


Figure 1.14. The distribution of fluid volume in the body (based upon a 70 kg male). Taken from Feher (2012).

Exchange of fluid and solutes between plasma and interstitial fluid is governed by Starling forces, which include hydrostatic pressure and colloid osmotic (oncotic) pressure across the capillary membrane (S. Evans & Evans, 1968). Capillary hydrostatic pressure, driven by arterial blood pressure, promotes fluid movement from the plasma into the interstitial space, whereas

colloid osmotic pressure, determined primarily by plasma proteins such as albumin, draws fluid back into the capillary. The net movement of fluid, known as ultrafiltration, ensures that nutrients such as glucose are delivered to tissues while maintaining circulatory and osmotic balance (Feher, 2012). These mechanisms are illustrated in **Figure 1.15**.

Beyond Starling forces, several structural and physiological features influence the distribution of glucose between plasma and interstitial fluid. The interstitial space is not a simple fluid-filled void but a structured environment called the extracellular matrix, which can help or hinder solute diffusion and glucose mobility (Wiig & Swartz, 2012). Solute transport from plasma to interstitial fluid primarily occurs via passive diffusion across capillary walls. However, capillary density, perfusion rates, and permeability vary between tissues, affecting both the speed and extent of glucose equilibration. While glucose generally equilibrates rapidly between compartments at rest, a physiological delay of approximately 5–15 minutes has been observed between changes in blood and interstitial glucose concentrations (Rossetti et al., 2010). This lag is more pronounced during rapid glycaemic fluctuations such as postprandial periods or exercise transitions (Pleus et al., 2015; Schmelzeisen-Redeker et al., 2015).

Exercise significantly alters circulatory and fluid dynamics. At rest, muscle blood flow is relatively low and much of the blood volume resides in the venous system. During exercise, vasodilation and capillary recruitment in active muscles lead to up to a 100-fold increase in local blood flow. Simultaneously, a reduction in plasma volume often in the range of 10–20% occurs due to fluid shifts from the intravascular compartment into the interstitial and intracellular spaces. This leads to an estimated 15–20% increase in interstitial fluid volume in working muscle tissues, driven by elevated hydrostatic pressure, increased capillary surface area, and osmotic gradients from accumulated metabolites (Kjellmer, 1964).

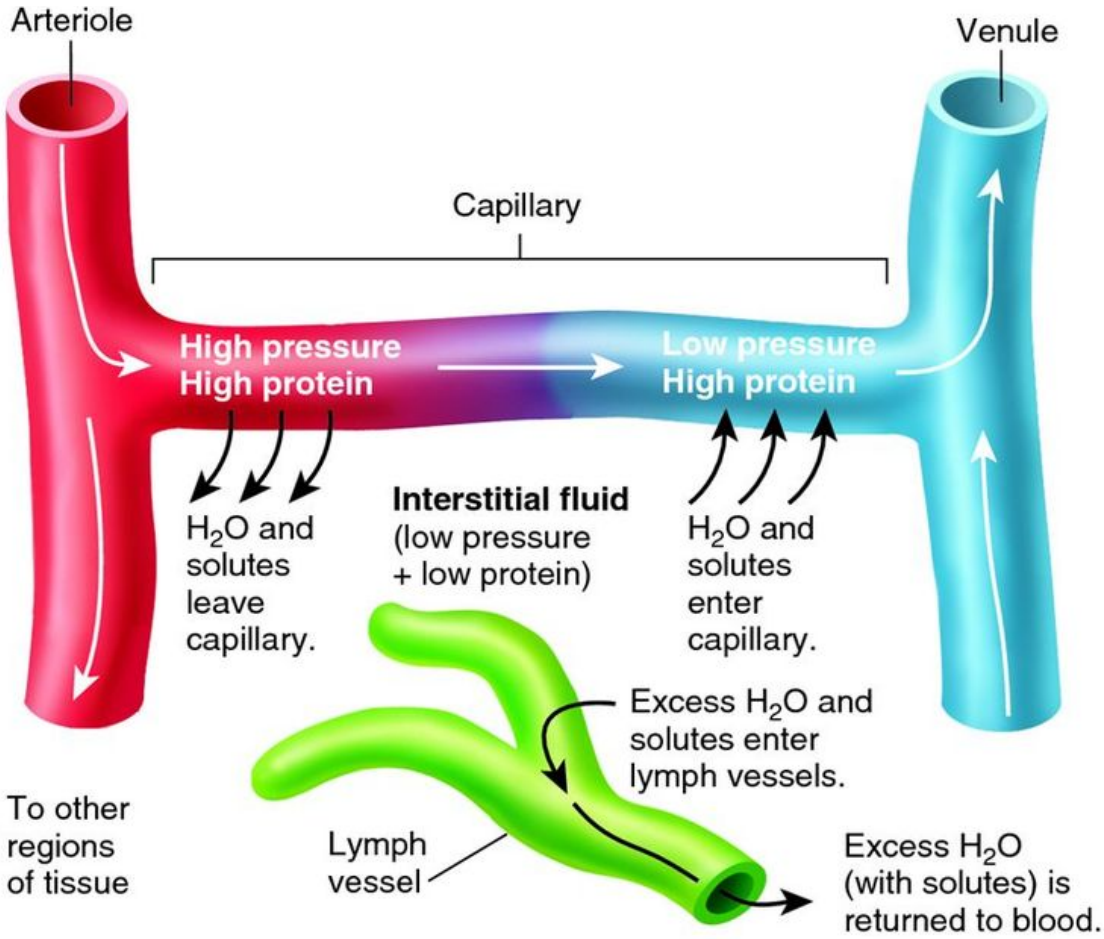


Figure 1.15. Summary of fluid movement from circulation to interstitium and returning to circulation, taken from J. Levine and Miller (2019).

The lymphatic system plays a critical role in maintaining interstitial homeostasis. It serves as the primary route for fluid and solute return from the interstitium to the bloodstream, particularly for macromolecules and excess interstitial fluid not reabsorbed by capillaries (Sawdon & Kirkman, 2023) (**Figure 1.15)**. In active muscle, rhythmic contractions enhance lymphatic flow through a mechanical pumping effect, helping to regulate local pressure, volume, and solute composition.

These changes have important implications for glucose transport and CGM data interpretation. Increased interstitial fluid volume can transiently dilute glucose concentrations and slow equilibration from the blood, particularly in the early stages of exercise. While lymphatic return and redistribution from non-working tissues gradually help stabilise fluid balance, muscle contractions further facilitate reabsorption by increasing lymphatic flow (Schmelzeisen-Redeker et al., 2015). However, under conditions of intense or prolonged exercise, glucose

dynamics may become more variable, and inter-compartmental lag effects may be more pronounced (Richter, Bilan, & Klip, 2025).

Environmental and physiological stressors such as heat exposure, sweating, and hydration status further influence interstitial fluid dynamics and consequently, may impact CGM readings. In hot conditions or during prolonged exertion, thermoregulatory mechanisms cause a redistribution of blood flow toward the skin to facilitate heat dissipation (Périard, Eijsvogels, & Daanen, 2021). This can reduce perfusion to other tissues, such as visceral organs or inactive muscles. Additionally, elevated sweat rates contribute to overall fluid loss and can lead to progressive dehydration if fluid intake does not match losses (Périard et al., 2021). Dehydration reduces plasma volume, which in turn elevates capillary oncotic pressure and may decrease capillary filtration into the interstitium. As a result, interstitial fluid volume may contract, potentially leading to more concentrated interstitial solute levels or impaired glucose equilibration. Conversely, in hyperhydrated states or early exercise when fluid shifts are rapid, interstitial dilution may transiently suppress CGM glucose readings. These factors introduce additional variability in CGM accuracy and lag time, particularly under fluctuating thermal and hydration conditions.

1.5.4 Limitations of CGM use

While CGM sensors offer great benefits, they are not without their limitations. The most obvious limitation is that the sensor measures interstitial glucose flux, and it does not measure glucose in the blood. As glucose in IF is a product of glucose delivery from the bloodstream, there is an inevitable delay in sensing (Boyne, Silver, Kaplan, & Saudek, 2003; Facchinetti et al., 2013; Rossetti et al., 2010; Thome-Duret et al., 1996). Algorithms have been used to correct for potential time lags, but these algorithms have also displayed some issues with reliability (Mazze et al., 2009). In addition to any time lag in sensing, the sensors are also susceptible to noise and general interference, which can impact their accuracy. Sensor placement, skin temperature and physical compression or movement may contribute to sensor noise (Coates, Cohen, & Burr, 2023; Helton, Ratner, & Wisniewski, 2011; Mensh, Wisniewski, Neil, & Burnett, 2013).

The question of accuracy is always one for consideration when assessing the functionality of CGM sensors. Over time, the accuracy of commercially available sensors has improved

considerably (**Figure 1.16)**. The most common metric for tracking and comparing the accuracy of sensors is the mean absolute relative difference (MARD). This metric typically quantifies the difference between the sensor and the gold standard, Yellow Springs Instrument (YSI) (Bailey & Alva, 2021). The more recently developed sensors are displaying some of the most favourable MARD scores to date.

During exercise, CGM accuracy has been known to lose accuracy when compared to blood based measurements (Bauhaus, Erdogan, Braun, & Thevis, 2023; Da Prato et al., 2022; Fabra, Diez, Bondia, & Sanz, 2021; O. Moser, Eckstein, Mueller, et al., 2019). Time lags may be heightened due to a few factors, many relating to the rapid changes which occur in the body during exercise. CGM sensors also appear to lose some of their accuracy at lower concentrations. Work by Moser (O. Moser, Eckstein, McCarthy, et al., 2019) detected a mean absolute relative difference (MARD) of 31.6% during hypoglycaemia in comparison to 16% during euglycaemia. The accuracy and MARD values have improved with developments in technology. Regardless, CGM technologies are shown to be effective for improving clinical outcomes, and they are approved for use in glycaemic management during exercise with those with type 1 diabetes (E. Moser et al., 2020).

There are several factors which can cause interference affecting the sensor's accuracy. Certain medications have been known to influence readings, such as acetaminophen, ibuprofen and Vitamin C (ascorbic acid) (Anhalt, 2016; Bailey & Alva, 2021). In addition, trauma to the site of insertion may cause inflammation and a build-up of metabolically active macrophages. These may also create issues for both sensor function and glucose sensing in the area affected (Joseph et al., 2018; Rigla et al., 2018).

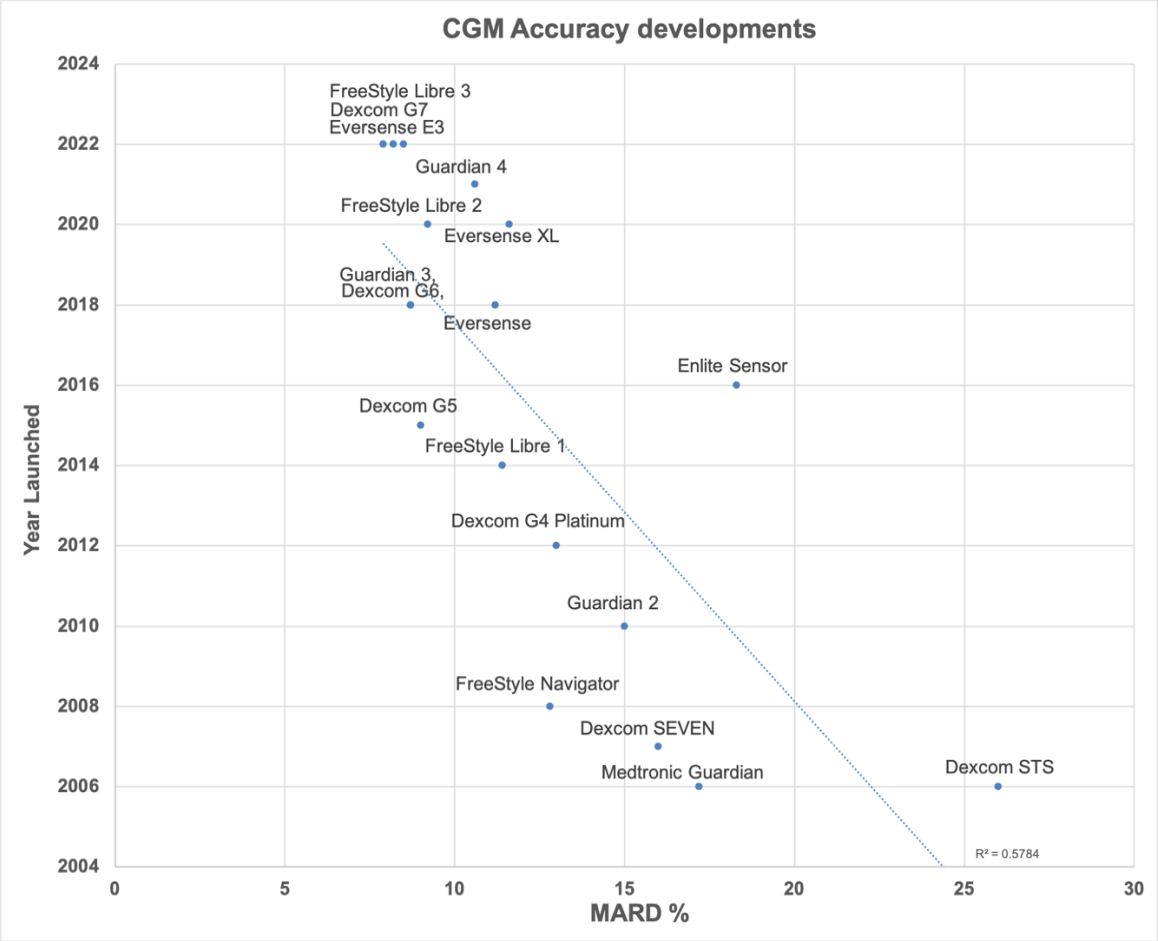


Figure 1.16. The development of continuous glucose monitor (CGM) accuracy with the most prominent companies since the launch of the first commercially available monitor in 2006.

1.5.5 CGM sensor development

The first commercially available monitors were launched in 2006. Since then, there have been continued developments leading to multiple generations of sensors. In general, accuracy is the focus of improvement from one generation to another. However, several other features have improved the user experience and convenience. Most of the major sensor companies have developed sensor form and design. Smaller devices with smaller needles make the units much less cumbersome and more discreet. This may also help with sensor placement, allowing it to be conveniently positioned under clothing. The inclusion of alerts at first helped warn the user of highs and lows. Now these alerts can be customised for specific thresholds and different alarms can be assigned to certain bespoke concentrations. Battery life and sensor durability has been improved, extending the sensor wear time and reducing applications. There is also a reduced need for calibration, as most of the latest generation sensors are calibrated before leaving the factory and no longer require additional calibrations. Early sensor iterations

required a receiver to display or upload data to other software. In some cases, these sensors needed to be wired directly to the receiver (Medtronic). Bluetooth-enabled sensors remove the need for a receiver, which might also require battery replacement or charging. More recently, the development of closed-loop systems has integrated CGM with insulin delivery, allowing real-time glucose data to automatically inform insulin dosing. While primarily used in clinical populations, these systems highlight the potential for CGM to progress from monitoring toward automated glucose management. Overall, sensors have seen continuous improvements to their function and ease of use, making them more popular as an option. A summary of major CGM devices and developments is displayed in **Table 1.4** below.

Brand	Device	Year Launched	MARD (%)	Key Features	Display	Calibration
Abbott	FreeStyle Navigator	2008	12.8	First Abbott CGM, 5-day wear	Receiver	Manual
Abbott	FreeStyle Libre 1	2014	11.4	Improved accuracy, Flash glucose monitoring, 14-day sensor wear	Smartphone	Auto
Abbott	FreeStyle Libre 2	2020	9.2	Improved accuracy, Bluetooth enabled, Alert alarms	Smartphone	Auto
Abbott	FreeStyle Libre 3	2022	7.9	Improved accuracy , smallest sensor, continuous data streaming	Smartphone	Auto
Dexcom	Dexcom STS	2006	26	First Dexcom CGM, 72-hour wear	Receiver	Manual (6 h)
Dexcom	Dexcom SEVEN	2007	16	Improved accuracy, 7-day wear, low warning alerts.	Receiver	Manual (6 h)
Dexcom	Dexcom G4 Platinum	2012	13	Improved accuracy, improved range, customised alerts, 30-day memory.	Receiver	Manual (6 h)
Dexcom	Dexcom G5	2015	9	Compatible with smartphone app via Bluetooth, reduced calibration requirements	Smartphone or receiver	Manual (6 h)
Dexcom	Dexcom G6	2018	8.7	No calibration required, improved applicator, 10-day wear, first approved with looped AID system.	Smartphone	Auto
Dexcom	Dexcom G7	2022	8.2	Smaller, faster warm-up period (30min)	Smartphone	Auto
Dexcom	Dexcom One+	2024	8.7	Smaller, High waterproof rating, Multiple wear locations	Smartphone	Auto
Eversense	Eversense	2018	11.2	Implantable sensor, 90-day wear, requires calibration	Smartphone	Manual (12h s)
Eversense	Eversense XL	2020	11.6	180-day wear, implantable with rechargeable transmitter	Smartphone	Manual (12 h)
Eversense	Eversense	2022	8.5	Improved design,	Smartphone	Manual (12 h) for first 21-

						days, then once per day.
Medtronic	Medtronic Guardian	2006	17.2	First at home CGM approved for use, 3-day sensor wear	Wired to transmitter then to receiver	Manual (12 h)
Medtronic	Guardian 2	2010	15	Real-time display, high and low alerts	Wired to transmitter then to receiver	Manual (12 h)
Medtronic	Enlite Sensor	2016	18.3	Paired with Medtronic pumps, requires calibration	Wired to transmitter then to receiver	Manual (6 h initially then every 12 h)
Medtronic	Guardian 3	2018	8.7	Improved accuracy, 7-day sensor wear, integration with first hybrid closed loop system. Wireless connection	Receiver	Manual (12 h)
Medtronic	Guardian 4	2021	10.6	No calibration, smaller device, paired with AID 780G insulin pump, Bluetooth enabled	Smartphone	Auto

Table 1.4. A summary of major continuous glucose monitor (CGM) companies and model/feature progression over the past decade.

1.5.6 Future of glucose sensing

The demand for less invasive, convenient sensing options continues to be an area receiving attention. There are several alternative technologies gaining traction in both clinical and health-related contexts. Non-invasive techniques fall mostly into one of two categories. The first is optical-based sensing, which includes fluorescence, near-infrared reflectance spectroscopy (NIRS), polarised optical rotation, Raman spectroscopy and optical coherence tomography (OCT) (Siddiqui, Zhang, Lloret, Song, & Obradovic, 2017; Tang, Chang, Chen, & Liu, 2020). The second category is via electrochemical methods. These include reverse iontophoresis technology and bodily fluid analysis (saliva, sweat and tears). All of these have shown some efficacy in their ability to detect glucose but come with their limitations. However, there are some interesting possibilities when considering the trends in wearable technology. These newer technologies may provide future opportunities for CGM to be integrated into fitness trackers, smartwatches and other wearable technologies. Nonetheless, sensors which do not require either blood or a needle would increase the ease of use and allow it to become more accessible to a wider user group.

1.5.7 Effectiveness of CGM

Continuous glucose monitoring (CGM) has become a foundational technology in modern diabetes management (**Figure 1.17**), with substantial evidence supporting its clinical efficacy, particularly in individuals with type 1 diabetes, but increasingly also in type 2 diabetes. Unlike traditional self-monitoring of blood glucose (SMBG) via intermittent fingerstick testing, CGM provides near-continuous data, enabling users to track real-time fluctuations in glucose and observe trends over 24 h periods. This allows for more dynamic adjustments to insulin therapy, dietary intake, and physical activity, facilitating tighter glycaemic control.

Clinical trials and large observational studies in those managing diabetes have consistently demonstrated that CGM use reduces the frequency and duration of both hyperglycaemic and hypoglycaemic events, and is associated with significant improvements in HbA1c levels and time-in-range (TIR) metrics, compared to SMBG (Battelino et al., 2019; Danne et al., 2017; Lin, Brown, James, Jones, & Ekinci, 2021; Teo et al., 2022). The benefits are most obvious in type 1 diabetes, particularly for individuals using multiple daily insulin injections, not just insulin pumps. For example, the DIAMOND and GOLD trials showed that CGM significantly

improved glycaemic outcomes over SMBG in adults with type 1 diabetes, including reductions in HbA1c of up to 1% and fewer hypoglycaemic episodes (Beck et al., 2017; Lind et al., 2017).

Beyond glycaemic outcomes, CGM has been associated with improvements in quality of life, reduced diabetes-related distress, and increased treatment satisfaction (Frost, Dyce, Nazereth, Malone, & Walshaw, 2018; Karakus et al., 2021). Features such as customizable alerts for predicted highs and lows, trend arrows, and retrospective glucose profiling allow both patients and healthcare providers to engage in more informed and responsive care. These alerts can be lifesaving, especially for individuals with impaired hypoglycaemia awareness. Most patients reported concerns around CGM use are related to a lack of access and technical issues such as accuracy and sensor malfunction (Karakus et al., 2021).

In people with type 2 diabetes CGM use has also shown promise. Recent trials and meta-analyses show improvements in HbA1c. In people with type 2 diabetes, CGM use has shown promise, with meta-analyses reporting modest HbA1c reductions (Mean of -0.3% and -4%) and improved time-in-range relative to traditional monitoring (Jancev et al., 2024; Tan, Suan, Koh, Suhairi, & Tyagi, 2024). CGM use appears to support behaviour change, such as increased physical activity and beneficial dietary modifications (Klupa et al., 2023). However, while CGM may indirectly support weight management or dietary adherence, evidence for meaningful effects on body weight, blood pressure, or lipid profiles remains limited and inconsistent. Improved glycaemic control through CGM, although clinically valuable, may not directly translate to reduced cardiovascular risk without broader metabolic improvement.

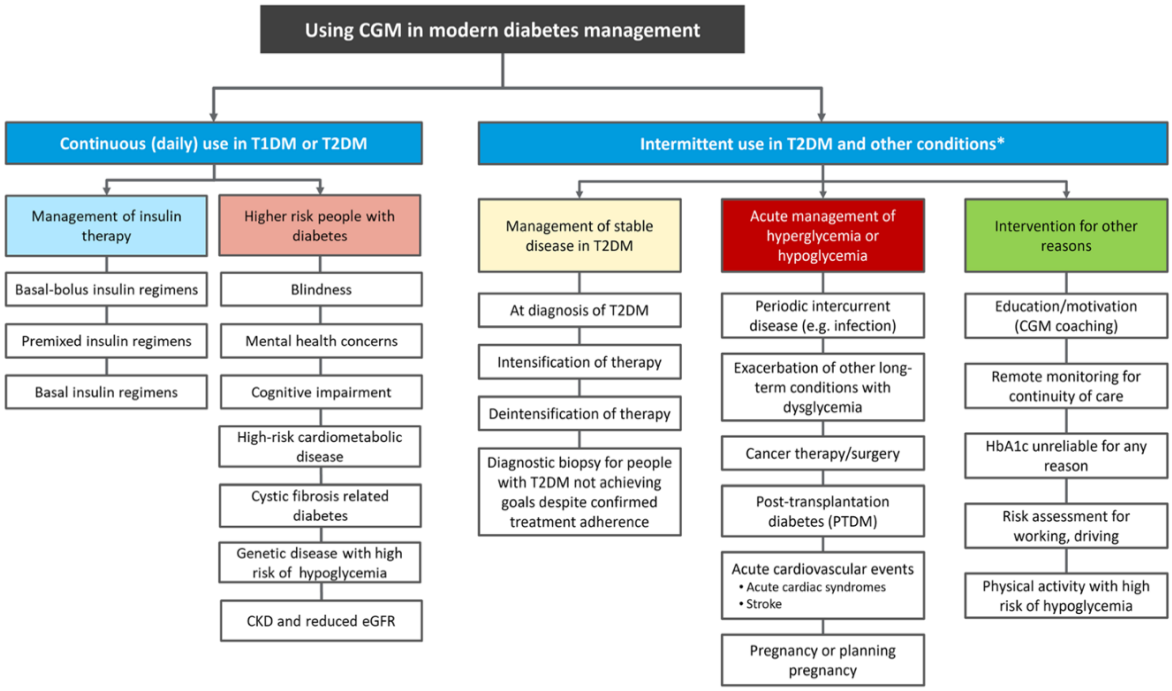


Figure 1.17. Landscape of current CGM use in diabetes management, taken from Klupa et al. (2023).

1.5.8 Insights from CGM

CGM devices are tasked with providing information for both the user and the medical practitioner. Being able to collect glycaemic information continuously over time offers insights into the dynamics of glucose responses to everyday life. Providing a real-time concentration is useful but limited in regard to longitudinal glycaemic management. To assess trends over time, further metrics have been employed to characterise glycaemia. From these metrics it becomes possible for the user to become even more proactive in the management of their glycaemia. Better maintenance of glycaemia is associated with improved metabolic health, as it reduces insulin demand and vascular stress linked to obesity, diabetes, and cardiovascular disease, though direct causal evidence remains limited (Blaak et al., 2012). While initial concerns for blood glucose concentrations were related to acute changes, CGM now provides information which allows for the assessment and management of long-term glycaemia.

Available glycaemic metrics

Glycaemic metrics provide a detailed view of glucose dynamics, capturing not only average levels but also the fluctuations that occur throughout the day. Variability is more than summary

statistics such as standard deviation or coefficient of variation; it also includes measures like time in range, frequency and magnitude of excursions, and patterns of glucose change over 24 hours. Many CGM devices include alert functions that notify users when glucose crosses a defined threshold or follows a concerning trend, such as a rapid decline. These alerts enable timely intervention, whether administering insulin to prevent hyperglycaemia or consuming fast-acting carbohydrates to correct impending hypoglycaemia in individuals with diabetes.

Mean glucose concentration

The mean glucose value represents the average interstitial glucose level over a given monitoring period. It provides a broad indication of overall glycaemic exposure and is often used to estimate HbA1c in clinical settings. In healthy individuals, mean glucose may reflect general dietary intake and metabolic efficiency, but it does not capture the variability or timing of glycaemic excursions.

Maximum glucose concentration

The maximum glucose concentration is the highest recorded value during a CGM monitoring period. It reflects the peak of glycaemic excursions, typically occurring after meals or during stress. In healthy individuals, these peaks are usually transient due to effective counterregulation. In individuals with diabetes, high maximum values, particularly postprandial, can indicate suboptimal glucose control and are associated with health complications.

Minimum glucose concentration

The minimum glucose concentration is the lowest glucose value recorded during monitoring. Minimum glucose concentration is essential for identifying hypoglycaemia risk. In diabetes, values below 3.9 mmol/L (70 mg/dL) signal a need for intervention, as recurrent lows can impair hypoglycaemia awareness and increase the risk of severe events. In healthy individuals, occasional dips are usually well-regulated by counterregulatory hormones.

Standard deviation (SD)

Measuring the standard deviation of [iG] gives insight into the absolute general glycaemic variability. By assessing the spread of concentration from the mean we gain insight into the nature of glycaemic fluctuations over a given time frame.

Coefficient of Variation (CV)

Similar to SD, CV provides insight into glycaemic variability relative to the mean. This can be useful in making comparisons across population groups where individuals' means might be different.

HbA1c

HbA1c is the measure which reflects average glucose concentrations over longer periods of time; typically 90 days. This is a technique which measures the degree to which a haemoglobin protein becomes coated in glucose. This is a good indicator of the exposure someone has had to glucose in their blood over time. It can be a useful tool in the diagnosis of diabetes as well as an indicator of other health risks and complications. The benefits from using CGM have been shown in numerous studies leading to improved HbA1c values (Teo et al., 2022).

Time in range (TIR)

Time in range is an assessment of the percentage of time a person spends in euglycaemic ranges. These ranges have been proposed by the Advanced Technologies & Treatments for Diabetes (ATTD) Congress consensus guidelines (Battelino et al., 2019). The general recommendation sits at a concentration of 70-180mg/dL (3.9 to 10mmol/L). The rationale for this range is that it is a safe level of concentration for which detrimental health outcomes are reduced or unlikely in a diabetic population.

Time in tight range (TITR)

Time in tight range (TITR) represents a recent refinement of the standard time in range (TIR) concept, defining a narrower interstitial glucose band of 70–140 mg/dL (3.9–7.8 mmol/L). This

approach reflects the recognition that individual clinical targets should account for differences in glucose tolerance. For example, patients with severe type 1 diabetes may struggle to achieve tight control, yet still derive benefit from maintaining glucose within a wider target range. By contrast, healthy individuals and those with gestational or type 2 diabetes may benefit from tighter glucose regulation, as glycaemic ranges in non-diabetic populations should align with physiological homeostasis rather than therapeutic thresholds. (Battelino et al., 2019; Dunn, Ajjan, Bergenstal, & Yongjin, 2024; Passanisi et al., 2024; Siddiqui et al., 2017).

At present, these ranges are the only standards proposed as appropriate for healthy individuals, though they are based on observed norms rather than direct evidence for optimal health outcomes. Healthy individuals typically exhibit a high proportion of time within this range (JDRF, 2010). There is limited evidence to suggest that meeting these targets confers any additional health benefits. This range is also adopted within the Supersapiens™ ecosystem to represent the euglycaemic zone for its target user group.

Time above range (TAR)

Time above range refers to the percentage time spent above euglycaemic ranges. In the current application of CGM this is any time captured with [iG] above 140 mg/dl (7.8mmol/L). TAR indicates time accumulated in a state of hyperglycaemia. It has been proposed that concentrations above 140 mg/dL are not necessarily an indication of diabetes, but they indicate abnormally high concentrations (American Diabetes Association, 1997). This range (70 to 140 mg/dL) is widely used in the assessment of glycaemia in healthy participants (Klonoff et al., 2022). Shah et al (Shah et al., 2019) propose the use of TITR and perhaps an even tighter range, based on the data they collected in a normal population.

Time below range (TBR)

Time below range refers to the percentage time spent below euglycaemic range. In the current application of CGM this is any time captured with [iG] below 70 mg/dl (3.9 mmol/L). TBR indicates time accumulated in a state of hypoglycaemia.

Level 1 Hypoglycaemia (LVL1)

TBR has been adapted further to present a more meaningful picture of the severity of hypoglycaemia. The clinical significance of level 1 hypoglycaemia is somewhat questionable in healthy individuals, with the suggestion that values below 70 mg/dL are more an indication of falling glucose (Danne et al., 2017) rather than clinically concerning. It marks an alert value for corrective intervention for those with type 1 diabetes. More clinically concerning values begin at approximately 55 mg/dL (3.1 mmol/L) (E. Cryer, 2007; P. Cryer, 2009). For this reason, LVL1 is considered to be any time accumulated in the range 55-70 mg/dL (3.1 to 3.9 mmol/L).

Level 2 Hypoglycaemia (LVL2)

In healthy individuals it is recommended that the threshold for level 2 hypoglycaemia be adopted as a more appropriate value. This is defined as any time spent at or below 54 mg/dL (3.0 mmol/L). These values are somewhat arbitrarily set, as symptoms of hypoglycaemia can begin to occur at a wide range of concentrations (Jeukendrup & Killer, 2010; Simpson, Holdsworth, & Macdonald, 2008). While clinically concerning values may occur at approximately 54 mg/dL, (E. Cryer, 2007) physiological, correctional responses may begin to occur at higher concentrations (Choudhary et al., 2009; P. Cryer, 2009). It is worth noting that current guidelines are determined by clinical symptoms.

Current literature exhibits variation in the adopted ranges. While most generally follow the above target ranges, there still appears to be a lack of established targets for healthy population groups. A summary of literature and their range choices are displayed in **Table 1.5** below.

Author (Year)	Duration	Age	Group	n	TBR	TBR%	TBR LVL 2	TIR	TIR %	TAR	TAR %
JDRF (2010)	**3-7 days**		Healthy	74	<70 mg/dL	1.70 %	<60 mg/dL	71-120 mg/dL	91%	>140 mg/dL	5.60 %
Thomas, Pretty et al. (2016)	**6 days**	28	Athletes	10	<72 mg/dL			72-108 mg/dL		>108 mg/dL	
Hall (2018)	**14-28**	44.8±12.9	Healthy	57 (32 F, 25 M)							
Rodriguez-Segade, Rodriguez et al. (2018)	**7 days**	42±12		254	<70 mg/dL	1.6		70-140 mg/dL	97.4	>140 mg/dL	2.2
Sundberg and Forsander (2018)	**7 days**	5.4±1.6	Healthy	15	<72 mg/dL	9		72-140 mg/dL	89		2
Shah, DuBose et al. (2019)	**8 Days**	70-80	Healthy	153	<70 mg/dL	1.1		71-140 mg/dL	96	>140 mg/dL	2.1
DuBose, Li et al. (2020)	**10 Days**	Age 7-80	Healthy	153	<54 mg/dL						
Kulawiec (2020)	**4-6 days**	23-50	Athletes	10 (3 F, 7 M)							
Selvin, Wang et al. (2021)	**14 Days**	27 Age 77-91	Healthy	19	<70 mg/dL	2.2	<54 mg/dL	71-140 mg/dL	92.3	>140 mg/dL	4.7
Bergia (2022)	**84 days**	55±11	At risk	160 (86 F, 74 M							
Sofizadeh, Pehrsson et al. (2022)	**7 days**	43	Healthy	60	<72 mg/dL	3.5	<54 mg/dL	72-144 mg/dL	90.7	>180mg/dL	
Prins, Noakes et al. (2023)	**31 Days**	40±5	Athletes	10				70-110 mg/dL			
Kashiwagi et al. (2023)	**14 days**		Healthy	40 (20 F, 20 M)			<70	70-140	90.5 ±7.2	>180	9±7.1
Yoshimura (2023)	**7 days**	40±12	Healthy	104							
Zignoli, Fontana et al. (2023)	**NA**	38	Active	6761	<70 mg/dL						

Bowler, Burke et al. (2024)	**4 days**	22±4	Athletes	12	<72 mg/dL	0.5		72-144 mg/dL	96.3 ± 2.4	>144 mg/dL	2.4±1.6
Chaudhry (2024)	**14 days**	32.8±6.6	Healthy	53	<70 mg/dL	1.6 ± 6.4		70-180mg/dL	95.3 ± 10.4	>180mg/dL	0.1 ±0.7
Skroce, Zignoli et al. (2024)	**NA**	40±11	Active	12,504	<70 mg/dL	3.4		71-140 mg/dL		>140 mg/dL	3.8
Weijer, van der Werf et al. (2024)	**14 Days**	35±8	Athletes	13	<70 mg/dL	2.1		70-140 mg/dL	90.8	>140 mg/dL	5.4
Zignoli, Martinez-Gonzalez et al. (2024)	**12 Days**	23±4	Athletes	26	<70 mg/dL	NA	<52 mg/dL	70-140 mg/dL	NA	>140 mg/dL	Na
Daya (2025)	**14 Days**	83	Healthy	1,150	<70 mg/dL	7.42		70-140 mg/dL	87.2		5.1

Table 1.5. Studies observing glycaemia chronically, utilizing CGM in the study design with chosen ranges and subcategories for time in range characterisations. Employed concentration ranges for time spent below range (Hypoglycaemia) (TBR), in level 2 hypoglycaemia (LVL 2), time spent in range (TIR) and time spent above range (TAR) are displayed. The reported time in range data is also expressed as a percentage of time. All data expressed as mean ± SD where possible.

1.5.9 Consumer use of CGM for health, performance, and wellness goals

The wearable technology market is experiencing significant growth, fuelled by increasing interest in health monitoring, biohacking, and tech-driven health trends. This surge is driven by the rise of smartwatches, fitness trackers, and continuous glucose monitors (CGMs) that offer users real-time insights into their health. Wearables are evolving beyond fitness to include biohacking trends, where enthusiasts use technology to optimise physical and cognitive performance. Innovations in sensors and non-invasive biomonitoring systems reflect a growing demand for more personalised health solutions. These trends align with a broader movement toward preventive health care and the quantified self, where individuals take charge of tracking and improving their well-being through data-driven decisions.

CGM fits into this space quite well, offering insights into personal physiology. In recent years, there have been a number of companies utilising existing CGM technology to leverage insights into lifestyle factors which may influence health. These are summarised in **Table 1.6**. These companies have subtly different approaches in their use of CGM, proposing a list of potential benefits. However, the research supporting some of the claims is limited, and in certain cases, may not yet be strong enough to ensure consistent outcomes. These claims include the following:

Stabilising glucose (reducing variability) appears to be the foundation for many of the proposed benefits that come from using CGM. Stabilizing glucose and preventing high glucose concentrations is a common theme, although few companies have effectively demonstrated how this might be beneficial in those without diabetes. A paper by Bermingham et al. (2023) has been cited, demonstrating lesser glucose variability and the association with reduced HbA1c, achieved with CGM use. A key limitation of this study is its cross-sectional, observational design, which prevents any inference of causality. While associations were observed between lower glucose variability and reduced HbA1c, these findings only reflect concurrent relationships and cannot determine whether one influences the other. As such, the results may represent coincidental or confounded patterns rather than true physiological effects. In order to help guide users, some companies have adopted the Advanced Technologies & Treatments for Diabetes (ATTD) Congress consensus "Time in Range" guidelines (Battelino et al., 2019). For those with type 1 diabetes, these provide targets which can help them manage their glycaemia which supports positive clinical outcomes (Anderson et al., 2011; DeSalvo et

al., 2021; Parkin, Graham, & Smolskis, 2017; Rodbard et al., 2009). From a preventative perspective, these ranges can also help identify those at risk of developing, or who may already have type 2 diabetes without knowing (Acciaroli et al., 2018; Klupa et al., 2023).

At present, there is little evidence that managing variability offers any health benefit beyond helping to prevent or detect those at heightened risk. While this may provide some benefit, there may be little need to monitor variability over the long term if short-term investigations show no cause for concern. Evidence currently provides little support for long-term continued monitoring of individuals who display good glycaemic control. CGM may overestimate acute glucose values (Hutchins, Betts, D, Hengist, & Gonzalez, 2025), and unlike OGTT or HbA1c, there are no standardised thresholds for prediabetes. Regardless, CGM provides a tool to observe the impact of interventions, such as dietary modification.

Weight management is also an outcome that several companies have offered as a benefit of using their product (Limbo, Veri and Signos). The mechanism for which continuous glucose monitoring helps achieve weight loss is not clear from any of their supporting materials. To date, CGM has been used as an observational or behaviour-support tool but not as a direct intervention for weight management. Most studies employ CGM to provide feedback on glucose responses, but the behavioural or nutritional component, rather than CGM itself, drives any observed changes. Meta-analyses report some improvements in glycaemic control but no consistent or clinically meaningful reductions in body weight, indicating that CGM primarily facilitates self-monitoring and awareness rather than exerting a direct effect on energy balance (Hegedus & Salvy, 2021; Richardson, Jospe, Crawshaw, Saleh, & Schembre, 2024). These companies do, however, suggest some potential mechanisms which might be related to potential weight loss.

The first of these is in relation to insulin resistance***. "Frequent spikes in glucose concentrations contribute to insulin resistance, which is strongly associated with weight gain"***. Being insulin-resistant is associated with greater levels of adiposity and obesity (Barazzoni, Gortan Cappellari, Ragni, & Nisoli, 2018; Ludwig et al., 2021). It may contribute to a predisposition to store fat, but there is little evidence that it prevents fat loss. A calorie deficit is the critical factor (Buscemi et al., 2024). Several studies have shown successful weight loss in insulin-resistant individuals; in fact, those with insulin resistance often show greater weight loss than those with no insulin resistance (Chiu, Wray, & Beverly, 2010;

Mediano & Sichieri, 2011; Pittas & Roberts, 2006; Wedick, Mayer-Davis, Wingard, Addy, & Barrett-Connor, 2001). In addition, as weight is reduced, insulin resistance tends to improve. So while insulin resistance and obesity are associated, the applicability of CGM in supporting weight loss has not been sufficiently established.

Similar to the previous, Signos claims, ***" When glucose is elevated, insulin gets released by the pancreas to move glucose into cells for immediate energy. Glucose that isn't used immediately gets stored for later, often as fat in our tissues".*** This might occur in the case of excessive carbohydrate intake (contributing to an energy surplus), but high blood glucose does not necessarily result in fat deposition. Glucose, if not used for energy in the cells, will be stored as glycogen (see **section 1.3.4**). If glycogen stores are full, then excess glucose may contribute to lipogenesis, but only if an energy surplus exists (Hellerstein, 1999). This process becomes more complex in those with any metabolic disorder, but these devices are not for clinical use, and therefore, this concern should not apply to healthy individuals.

Finally, "Limbo" suggests that CGM provides insights into metabolism (https://www.limborevolution.com/research/toward-a-new-science-of-glucometabology); however, CGM cannot and does not have the capability to provide any data regarding energy intake or expenditure. They propose a concept of "Glucometobiology'; however, there is no peer-reviewed literature available to either confirm its validity or show any proof of concept.

Lifestyle optimisation is another claimed benefit. This includes a number of lifestyle factors, the first of which is **diet**. There is evidence that CGM can help guide personalised nutrition in regard to an individual's response to certain foods and meal types (Berry et al., 2020; Merino et al., 2022; Song, Oh, & Song, 2023; Zeevi et al., 2015). A number of companies utilise the support of a registered nutritionist (**Table 1.6**), either in the form of coaching or some other AI-driven app, to help provide feedback and support based on glycaemic responses. While this appears to be a more responsible approach to CGM application, there is little support other than anecdotal evidence that will have any meaningful health impact. Depending on the level of accompanying support, it is possible that CGM may provide useful data to guide nutritional interventions; however, more robust evidence is required.

Better appetite control is cited by some of the companies. Only one study relating to appetite is mentioned in the marketing material. Wyatt et al. (2021) display a correlation between post-

prandial glucose dips and self-reported hunger, which forms much of the foundation for this claim. The links between glycaemia and hunger have been investigated but are still not fully understood (Campfield & Smith, 2003). There is no clear guide on how one might use their CGM to prevent or manage hunger. It may be that maintaining stable concentrations helps manage hunger cues, but it is unclear which is the actionable insight: absolute concentration or indication of a changing (falling) concentration (Campfield & Smith, 2003). While there may be some associations between blood glucose and appetite, the interaction is not certain, and so the response is also unclear. With that in mind, CGM use in this context is likely to have a limited and inconsistent impact.

Improved energy levels, mood and cognition have also been cited as areas where CGM can be of benefit (https://www.hellolingo.com/the-science). However, the supporting literature provided does not contain the use of CGM. Studies have demonstrated the impact of a High vs. Low glycaemic index on the above factors, and shown some benefit to adopting a low-GI diet (Breymeyer, Lampe, McGregor, & Neuhouser, 2016). In a diabetic population, the occurrence of severe hypo- and hyperglycaemia has been linked to feelings of alertness, mood and cognition but this is in response to clinically concerning concentrations brought on by pharmacological interventions (E. Cryer, 2007). However, these extremes are much less frequent in healthy individuals and are quickly corrected for naturally. On a day-to-day basis, using CGM in this context needs further investigation to support claims on its utility.

Improved sleep is another factor that has been frequently mentioned as a benefit of using CGM, through the stabilising of glycaemia. The literature provided does not include CGM nor demonstrate how it might be used in this context. The literature shows that insufficient sleep may have a detrimental impact on glycaemia through an increase in insulin resistance (Tsereteli et al., 2022). There have been reports of reduced subjective sleep quality associated with nocturnal hypoglycaemia (Gardner, Tan, Lim, Zin, & Chandran, 2023); however, other studies which employed polygraphic sleep analysis showed prolonged REM sleep associated with hypoglycaemic episodes (Bendtson, Gade, Thomsten, Rosenfaclk, & Wildschiødtz, 1992). Regardless of the mixed consensus, the issue with linking CGM use to improved sleep quality relates to how action might be taken. One cannot react to a hypoglycaemic event if they are asleep. While CGM might identify unstable glucose during the night, there is no guideline as to how to respond or if any particular intervention will yield consistent improvements.

In summary, while CGM is often promoted as a tool for lifestyle optimisation, the supporting evidence remains weak and primarily correlational. Most findings describe associations between glycaemic variability and the above-mentioned lifestyle factors without demonstrating cause and effect. These relationships are often inconsistent and likely influenced by multiple confounding factors, making it unclear whether CGM use directly improves any of these outcomes. Therefore, current claims of CGM's lifestyle benefits should be interpreted cautiously until supported by controlled, mechanistic evidence.

Athletic performance is a specific area which one company was specifically targeting. Supersapiens™ (no longer active) was focused primarily on athletes and those partaking in sport. Their goal was to provide a feedback tool similar to power meters or heart-rate monitors that could be used to support performance optimisation. Integration with bicycling head units and sports watches, provided individuals with an activity-friendly ecosystem. This included a fuel-band display for those who wanted to avoid carrying a smartphone during exercise. They were able to collect data which could be read on a simple display and synced to the app post-exercise. They also offered a protective patch to prevent accidental removal or interference with the sensor during intense activity. The app-based platform was constructed with activity in mind, where an individual could log exercise, food intake and sleep for these events to be incorporated into their 24hr glucose trace. They also offered the ability to combine exercise data to help identify any relationship between glucose and exercise. Supersapiens™ also employed the "glucose performance zone" (GPZ), aiming to give users a target glucose range (110–180 mg/dL) that could support performance, though this range appeared arbitrary and only broadly customizable. While there is strong evidence supporting the maintenance of blood glucose for exercise performance (Coyle et al., 1983; Febbraio, Chiu, Angus, Arkinstall, & Hawley, 2000; Hawley & Leckey, 2015).

While strong evidence supports the importance of maintaining blood glucose during exercise for performance (Coyle et al., 1983; Febbraio et al., 2000; Hawley & Leckey, 2015), direct evidence that CGM feedback improves performance in athletes without diabetes is limited. Small pilot studies and observational work suggest that CGM may help athletes better understand fuel utilisation and recovery patterns (Bowler et al., 2022), but definitive performance benefits have not been established. Nonetheless, features such as real-time monitoring, activity-friendly design, and personalised glucose targets are highly relevant to athletes, offering practical tools for training decisions, nutritional strategies, and recovery

optimisation. These examples highlight how CGM features, originally developed for clinical populations, may translate into meaningful applications for non-diabetic athletes, even if strong performance evidence is still emerging.

Company	Target Group	CGM model	Proposed benefit	How?	App features	Major Features
Supersapiens	Athletes	Abbott Libre sense Biosensor (libre 2)	• Maximize performance through glucose monitoring • Optimize fuelling strategies	Maintaining adequate glucose supply	Timeline display, Daily averages, Glucose TIR, excursions, fuelling zones.	Focused on athletic performance, glucose-based energy zones, integration with fitness apps like Garmin, fuelling strategy insights for endurance sports like cycling and running.
Veri	Health	All Abbott Libres	• Enhance metabolic health • Optimize energy levels • Improve lifestyle choices	Reducing variability and preventing insulin resistance	Timeline display, Daily averages, Glucose TIR, Excursions, App integrations	Easy-to-use app, personalized insights into diet and lifestyle, integration with exercise and food logs, data-driven guidance for daily routines and performance improvements.
Limbo	Weight loss	GlucoRX Aidex	• Stabilising glucose promoting the	Reduced variability preventing insulin sensitivity and	Timeline display, Coaching prompts	Focused on weight management and metabolic health,

			use of fat as energy	poor glucose tolerance		features metabolic age assessment, insights on glucose control for weight loss, personalized recommendations for lifestyle improvements, gamified health progress.
Levels	Athletes, health-conscious individuals	Dexcom G7	• Optimize diet, exercise • Optimize lifestyle based on glucose response • Improve metabolic health	Reduce variability	Timeline display, Averages, Spike Time, Stability score, Calibration, integration with Apple health, coaching insights	Real-time feedback, personalized insights on food, exercise, and stress responses, food logging, interactive reports, community-based support.
Ultra Human	Health	Abbott Freestyle	• Optimize metabolic health and performance	Reducing variability	Timeline display, Food Score, Ai prompts, App integration	Integration with fitness wearables (Ultrahuman Ring, Oura), personalized

			• Improve recovery • Improve sleep quality			fitness, nutrition, and recovery insights, performance score based on metabolic health, extensive tracking of metabolic biomarkers.
Zoe	Health	Abbott Freestyle	• Improve metabolic health • Improve gut health	Reducing variability	Glucose, microbiome diversity, food impact	Combined glucose and microbiome testing, comprehensive insights into gut and metabolic health, personalized food recommendations, in-depth analysis of food responses and gut health based on blood and stool data.
Nutrisense	Health	Abbott Freestyle	• Improve dietary habits • weight management • Improve metabolic health	Online nutritionist linked to CGM	Timeline display, Daily averages, Glucose TIR, excursions, App integrations, Nutritional summary	Dietitian support, AI-driven recommendations, custom health programs, data tracking integration with

						wearable devices (e.g., Fitbit, Apple Watch).
Signos	Weight loss, Health	Dexcom G7	Real-time feedback for weight management based on glucose levels and metabolic insights	Preventing glucose from being stored as fat.	Real-time blood sugar and trend data, In-app nutritionist support, Predictive glucose for your meals, Fasting and meal timing tips, Exercise and activity recommendations.	Weight-loss focused tracking, meal suggestions based on glucose levels, AI-driven predictions for food impact on glucose, integration with fitness apps.
Vively	Health	Abbott Freestyle	Metabolic optimisation via personalized nutrition	Reducing variability	Timeline display, Daily averages	Focused on real-time glucose insights, meal suggestions, activity and sleep tracking, personalized insights into daily routines for better metabolic health and lifestyle optimization.
Lingo (Abbott)	Health	Abbott Freestyle	• Optimize diet, exercise • Lifestyle based on glucose response		Timeline display, Daily averages	Enhance metabolic health, optimize diet, exercise, and lifestyle based on

			• Improve metabolic health			real-time glucose monitoring
Stelo (Dexcom)	Health	Dexcom Biosensor (dexcom 1)	• Continuous glucose monitoring for lifestyle and behaviour optimization, including diet and exercise impacts on glucose levels		Timeline display, Daily averages	Over-the-Counter Availability: No prescription needed, making it accessible for a wider audience. Optimize diet, exercise, and lifestyle based on real-time glucose monitoring

Table 1.6. Current companies utilising Continuous Glucose Monitoring to achieve health, performance or wellness goals in healthy populations.

1.5.10 Benefits of CGM in a healthy population

The ability to observe glucose response is the central feature of CGM. It has shown to be useful in those with metabolic disorders and other health complications. How that can be used effectively in healthy individuals still requires research to address questions which have come from its early use in these groups. However, some work has begun to fill in the knowledge gaps, and the data is beginning to grow.

A number of studies have examined the potential for CGM to observe the impact of dietary interventions on glycaemia in healthy individuals. Prins et al. (2023) demonstrated that 5 weeks of a low-carbohydrate high-fat (LCHF) diet reduced 24 h mean glucose and resulted in greater fat oxidation during an exercise assessment at the end of the intervention, when compared to a high-carbohydrate low-fat diet. Bergia et al. (2022) also tracked glycaemia over a 12-week period following a low- or high GI diet, reporting a greater reduction in glycaemic variability, MAGE and mean 24 h glucose when following the low-GI diet. (Bergia et al., 2022).

Other studies have used CGM to demonstrate the impact of certain meals on subsequent glucose stability. Xiao, Furutani, Sasaki, and Shibata (2023) showed a reduced postprandial response to lunch and dinner if following a high-protein breakfast on the same day, when compared to a normal breakfast. Fechnar, Eyndt, Mulder, and Mensink (2020) demonstrated lower postprandial glucose area under the curve following low-GI breakfasts, lunches and dinners over 3 days when compared to high-GI versions. Freckmann et al. (2007) used CGM over 2 days to observe glycaemia under everyday life conditions. They observed reduced postprandial responses to meals containing greater amounts of fibre, protein and fat.

Studies have also used CGM to observe the glycaemic response to exercise. Flockhart et al. (2022) displayed a reduction in glucose tolerance post prolonged endurance exercise in comparison to rest or high-intensity interval training (HIIT). This was also shown to occur in response to longer periods of heavy endurance training (Flockhart et al., 2021). Little, Jung, Wright, Wright, and Manders (2014) compared post-prandial glycaemic control following either HIIT or continuous moderate intensity training (CMIT). The HIIT group had a greater reduction in postprandial response to breakfast the following day than the CMIT group. Coates et al. (2024) used CGM to detect a reduction in glucose availability during submaximal exercise in overreached athletes; however, there was no control group in this study.

1.5.11 CGM and athletes

Athletic cohorts are the focus of this thesis. Given the importance of glucose in exercise performance (Coyle et al., 1983; Hawley & Leckey, 2015), CGM has gained considerable interest within the athletic community. Blood glucose has long been an outcome measure of interest for many scientific purposes. In a laboratory setting, collecting blood glucose data has been relatively straightforward, but in a real-world scenario, it is often not practical. CGM has allowed access to glucose data in situations which would not have been feasible previously. In addition, CGM can provide a much larger amount of data with a massively increased sampling rate, allowing for much more detailed insights into glucose dynamics.

With the relative ease of access, this information can now be provided to display units such as watches and cycling head units. With the development of supporting software, the insights are also made more user-friendly and intuitive, meaning an individual needs little education or training to understand the basic dynamics and general trends.

Currently, the main interest in CGM for athletes is in relation to fuelling exercise more effectively. Endurance athletes are concerned with running out of fuel during competition. This is often referred to as "hitting the wall" or "bonking". It is typically considered a sudden but debilitating onset of fatigue which results in a dramatic reduction of intensity or cessation of exercise (Smyth, 2021). In reality, this sudden onset of fatigue is due to a combination of factors, but the depletion of muscle and liver glycogen, alongside the lack of available blood glucose are major contributors. Athletes believe that a real-time display of glucose may act as an early warning system, allowing them to intervene with exogenous carbohydrates. This is not so dissimilar to how an individual with type 1 diabetes might respond to glucose readings which are trending towards hypoglycaemia. This strategy, however, does not consider the time delay or other factors which may influence the accuracy and punctuality of the CGM reading.

CGM during exercise in type 1 diabetes

CGM use during exercise has been problematic due to the rapidly changing physiological processes that occur during exercise. Changes to blood flow rates, body temperature and acidity may all influence CGM accuracy (E. Moser et al., 2020). CGM accuracy has been the subject of many investigations owing to the importance of its use when insulin is being administered

by individuals with type 1 diabetes. The interaction of insulin and exercise may result in very rapid changes in concentration which must be carefully tracked and managed. Improvements in sensing technology as well as developments in the software algorithms have helped to improve these MARD values over time. **Figure 1.18** below displays an appraisal of recent CGM devices and their reported accuracy during different modes of exercise. While reported accuracy does appear to vary from study to study, the use of CGM during exercise in clinical settings has been deemed consistent and reliable enough for it's clinical use (E. Moser et al., 2020).

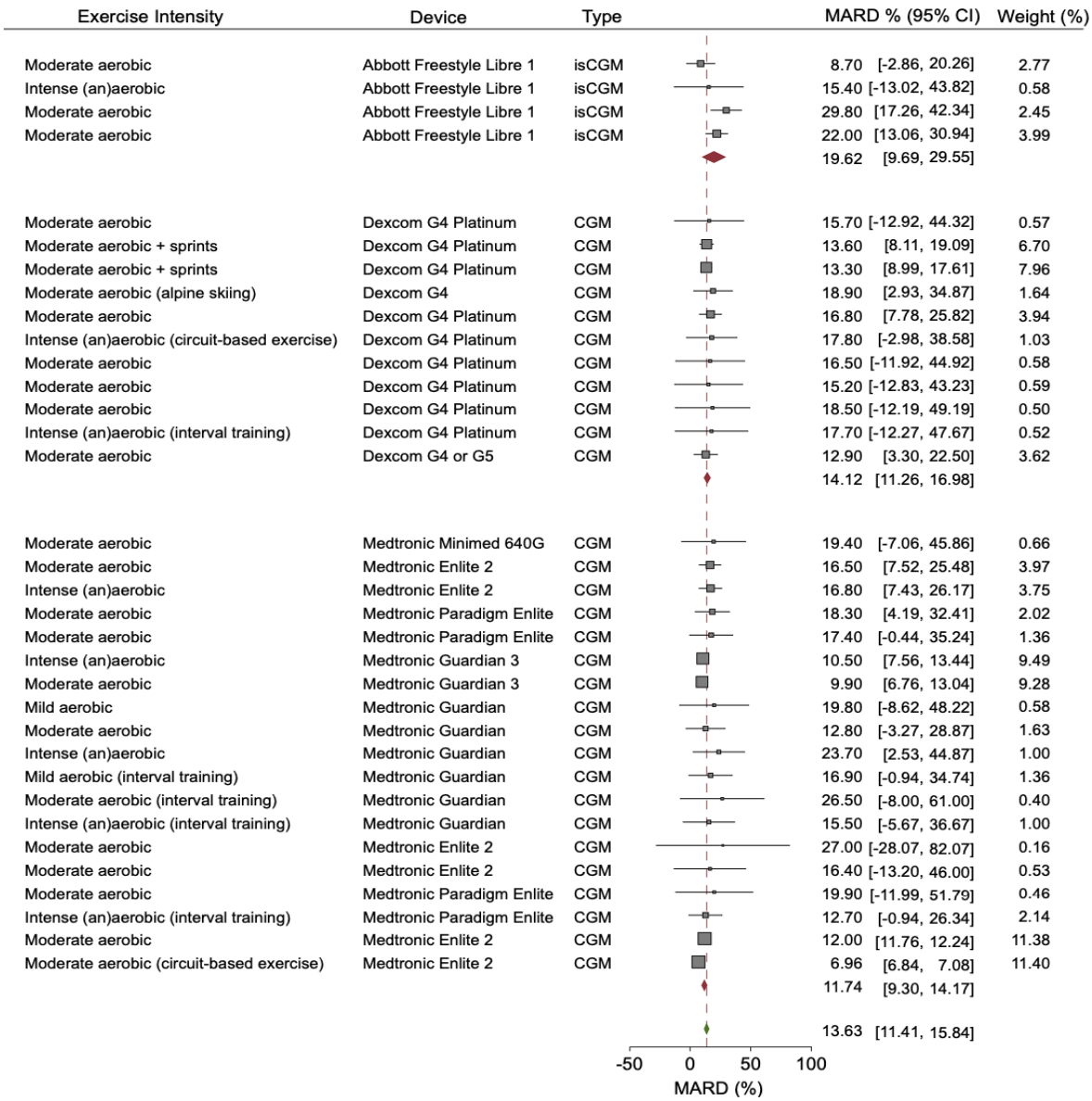


Figure 1.18. MARD (%) of recent CGM devices during exercise. MARD data are weighted for the number of participants and standard deviation of MARD for different manufacturers of all CGM devices. The dashed line represents the MARD of all CGM devices. Horizontal bars represent the 95% CIs for the specific studies. Adapted from (E. Moser et al., 2020).

1.5.12 Current observations from CGM in healthy athletes

Tight glycaemic control during exercise has been observed in studies investigating mixed-sex ultrarunners competing in single-stage events (Hargreaves et al., 1984; Ishihara et al., 2020; Kulawiec, Zhou, Knopp, & Chase, 2021; Sengoku et al., 2015). For example, Ishihara and colleagues (2020) noted normoglycemic iG concentrations in their cohort of runners throughout a 160 km ultramarathon event using an intermittent CGM device (All runners [n=10]: 134±19 mg/dL with a CV of 14.0%. Female only runners [n=3]: 124±18 mg/dL with a CV of 14.2%). Kinrade and Galloway (2021) also observed mean euglycaemic [iG] levels in mixed-sex ultra-endurance runners (n=14) undertaking a continuous 24 hour event (i.e., 124±1 mg/dL).

In free-living conditions, Bowler, Burke, and Cox (2024) examined glycaemia in athletes using CGM. They also reported tight control with a mean 24 h glucose of 102.6±5.4 mg/dL with a CV of 0.2 % and 96% time in euglycaemia. Thomas et al (F. Thomas, C. Pretty, T. Desaive, & G. Chase, 2016) have observed heightened iG concentrations in a similar study. Six of ten participants presented a significant proportion of their day (85%) within normal limits, while 4/10 spent 70% above recommended fasting concentrations. Their findings did not warrant major clinical concern but did indicate that athletes may also experience relatively high glucose concentrations for a large portion of their day. Shah et al (2019) and Thomas, Pretty et al. (2016) used upper TIR limits of 120 and 126 mg/dL, respectively. Thomas, Pretty et al. (2017) showed that 40% of their participants would fall into a pre-diabetic classification when applying this methodology. However, this threshold limit is recommended for use in assessing fasted glucose concentrations, which are after an overnight fast (American Diabetes Association, 2003). This approach may result in the reporting of greater TAR than what has been observed in other studies applying wider threshold ranges.

In a broader context, (Skroce et al., 2024) profiled a large cohort of active and healthy individuals. Mean glucose was reported to be 97±11 mg/dL; there was 3.4% TBR (<70mg/dL), 3.6% TAR (>140mg/dL) with the rest of the time considered in range. This study further stratified the cohort into males and females and at different times of the day. They also investigated glycaemia in professional cyclists with a focus on day vs. night differences. Mean daytime glucose was 115±9 mg/dL vs. a night time mean of 94±9 mg/dL. Daytime time in

range was 86±10% vs. 97±10% during the night. Time spent below range was ~1%±2% during the day vs. 3±9% during the night and lastly time spent above range was 13±10% during the day vs. 0±2% during the night. The data suggests that there is a greater variance in glucose during the day than during the night. The standard deviation was greater during the day than at night (day: 20±4 mg/dL vs. night: 9±4 mg/dL).

1.5.13 Additional health insights

Some concerns have been raised in the mainstream media surrounding the development of type 2 diabetes in athletes, which is largely unfounded. However, F. Thomas, C. Pretty, T. Desaive, and G. Chase (2016) appears to be a major source of these concerns, being regularly cited as the study in focus. In addition, Flockhart et al. (2021) and Flockhart et al. (2022) showed some evidence of impaired glucose tolerance in response to acute bouts of exercise and over longer periods of training, which might support some of these concerns. Kulawiec et al. (2021) suggested post-exercise inflammation may be a cause of increased glucose variability and might have a detrimental impact on recovery. While none of these studies confirm any development of type 2 diabetes, there are questions raised over the downstream impacts of heavy exercise on glycaemic control. This is one area in which CGM may be useful to observe potential disturbances in homeostasis and the relationship between glycaemia and exercise stress.

There is growing interest in the potential of continuous glucose monitoring (CGM) for the early detection of prediabetes and the onset of type 2 diabetes (Pazos-Couselo et al., 2025). By providing real-time feedback on glucose fluctuations, CGM can help individuals become more aware of their glycaemic stability and identify periods of dysregulation that may not be captured through traditional fasting glucose or HbA1c tests. This insight can be especially valuable for individuals with obesity who do not yet meet the clinical criteria for type 2 diabetes but exhibit signs of intermediate hyperglycaemia (Battelino et al., 2025). In such cases, CGM may help highlight the need for lifestyle or dietary adjustments that could delay or prevent progression to overt metabolic disease.

Section 1.6: Summary and thesis aims

Currently, it appears CGM is a useful tool for tracking one's interstitial glucose as a proxy for blood glucose. It might be suggested as a useful tool to observe the effectiveness of nutritional interventions, as evidenced in the literature (Bergia et al., 2022; Chekima et al., 2022; Fechnar et al., 2020; Prins et al., 2023). When combined with additional support from a trained professional, these insights could be used to refine and guide existing nutritional strategies. As part of a larger ecosystem of additional sensors, a wide range of data could be coordinated to create quite a detailed picture of one's individual responses to many lifestyle factors. This information might be used to have downstream health and performance benefits. Alone, CGM use provides little standalone benefit, but when combined with some form of intervention, it could offer a valuable contribution to guiding better habits. With the addition of external professional guidance, there is an increased potential to achieve meaningful outcomes. However, to establish best practice protocols and to understand the data sufficiently to provide appropriate guidance, further research is warranted in several areas.

1.6.1 Gaps in the literature

1) Normative data: While there is a reasonable body of work detailing glycaemia in those with diabetes and other health disorders, there is a much smaller amount in those who are healthy. This is in part due to the technology. Only recently has CGM reached a standard of monitoring which can effectively observe glycaemia over prolonged periods of time. The studies that have been done are displayed in **Table 1.5**. Of these studies, many are observations of broad conditions which aim to establish some of the normative standards. Participant characteristics (Daya et al., 2025; JDRF, 2010; Kashiwagi et al., 2023; Rodriguez-Segade et al., 2018; Shah et al., 2019; Skroce et al., 2024; Sofizadeh, Pehrsson, Olafsdottir, & Lind, 2022; Sundberg & Forsander, 2018) and the influence of meals (DuBose et al., 2020; Zignoli, Fontana, Lipman, et al., 2023) were the primary focus of many studies. For obvious reasons the elderly, children and general population are of interest to identify potential health risk factors. The influence of meals also warrants attention as feeding is a major influence on glycaemia throughout the day.

Athletes are somewhat of a niche group who have quite a specific interest in glycaemia. Health aside, their performance in their chosen sport can be profoundly impacted by the maintenance

of glucose supply (see **section 1.4**). They have created a new demand for CGM which is quite different from its original intended use. Nonetheless, these individuals are also in need of a better understanding of glycaemia. Acute scenarios have attracted attention as many studies have assessed glycaemia under either competition or training scenarios. These studies have highlighted some of the physiological processes at play and the impact it has had on performance. CGM is useful in acute scenarios, but it has been shown to be particularly useful over longer periods of observation (Danne et al., 2017). Prior to 2023, only two studies collected data for more than a few days in athletes (Kulawiec et al., 2021; F. Thomas, C. Pretty, T. Desaive, & G. Chase, 2016). The time spent around competition and training has quite an impact on preparation and or recovery. Any potential impact in these time periods is relatively unknown apart from these studies, neither of which included overall glycaemic characterisation, which align to current CGM guidelines (Danne et al., 2017). However, these guidelines are derived from clinical populations and may have limited applicability to healthy individuals. They do, however, provide a useful framework for developing more relevant and population-specific targets."

2) CGM accuracy in response to food intake: Oral glucose tolerance tests (OGTT) are commonly used to assess how someone handles a bolus of glucose. This can effectively identify those who may exhibit some form of dysglycaemia and signal the onset of metabolic disorders such as type 2 diabetes. In addition, the OGTT type test can help characterise foods and their impact on glycaemia. The glycaemic index concept stems from the rate and extent to which a certain food impacts glucose concentration (Jenkins et al., 1981). This work has helped improved many with metabolic disorders better manage their condition through dietary changes.

In the context of athletes, carbohydrate intake is an integral part of many regimens, whether it be training or competition (Jeukendrup, 2014a; Podlogar & Wallis, 2022). Athletes consume many carbohydrate foods and beverages in order to support their performance. Ultimately, the goal is to maintain adequate blood glucose supply to the working muscle. This has generated interest in CGM as a possible tool to provide feedback on one's ability to maintain glucose supply. The ability for CGM to measure blood glucose accurately is limited as it measures the IF. Glycaemic index, carbohydrate amount and fluid concentration are all aspects of these products which are manipulated to deliver different options to suit different fuelling strategies. They are also all potential influencers on the glycaemic response. Rapidly changing

concentrations have the potential to impact CGM accuracy. Different characteristics have the potential to impact accuracy in different ways. This is not something which has been researched from this perspective. However, it could have major implications for the real-world application of CGM, especially in athletes where feedback on their fuelling strategies is of interest.

3) Glycaemia in elite or professional athletes: Until recently, there was no available research examining or characterising glycaemia in a group exclusively made up of elite or professional athletes. Considering the major physical demands placed on elite-level athletes and the potential use of CGM by athletes in general, there is an obvious opportunity to gain a deeper understanding of glucose dynamics in these circumstances. The physiology of an elite-level athlete can be unique in many ways and warrants investigations, particularly when general metabolism is so tightly associated with performance outcomes.

4) Impact of diet on glycaemia: Diet is a key modulator of glycaemia and has been used to effectively manage glycaemia in those with type 1 diabetes and other health conditions (Bergia et al., 2022; Chiavaroli et al., 2021; CJK Henry, Lightowler, Tydeman, & Skeath, 2006; Perin, Camboim, & Lehnen, 2021). Active individuals competing in sport have large carbohydrate demands in their general diet (LM Burke et al., 2011). However, little data exists on how a diet over time might impact glycaemia in athletes who consume greater than normal amounts of carbohydrate on a daily basis. Altering the glycaemic index of a diet could have a significant impact on glycaemia and performance, but it is still unexplored.

5) Glycaemic variability in athletes: Glycaemic variability is a factor which has gained considerable attention for those managing or preventing the development of metabolic disorders (Bermingham et al., 2023; Hjort, Iggman, & Rosqvist, 2024; Suh & Kim, 2015). Initial studies in athletes have raised concerns around glucose variability and impaired glucose handling post-exercise (Flockhart et al., 2021; Parent et al., 2024; Pestell, Ward, Galvin, Best, & Alford, 1993). It is unknown how this response observed after acute exercise might impact over longer periods of training. There is limited evidence regarding the chronic impact of such events. CGM allows for data to be collected and for this variability to be assessed, yet only one study has observed glycaemia for more than 14 days to date.

6) CGM best practice in athletes: A number of reviews have alluded to the potential for athletes to benefit from CGM use and the data it provides (Bowler et al., 2022; Flockhart &

Larsen, 2023; Klonoff et al., 2022). There are also several studies showing its ability to track and profile glycaemia in athletes (**Table 1.5**). There is still very little guidance on how to best implement CGM into an ecosystem of monitoring and feedback. There is no real guidance on how athletes, coaches or nutritionists should interpret the data and what the appropriate actions are to address any concerns. Many of the instructions and recommendations that accompany commercial sensors lack adequate support in the literature in some cases the literature might even be somewhat conflicting. As more studies are completed, the strengths and limitations of continuous glucose monitoring become more apparent. With any new data or observations, it serves to help provide better guidance as to how you can best use the data provided. At present, however, there is still relatively little information available for athletes and practitioners to draw from.

1.6.2 Study aims, objectives and hypotheses

The studies completed in this thesis will have the following aims:

Chapter 3

Aim:

To investigate both the interstitial and blood responses to the consumption of different carbohydrate-containing beverages. Observed using CGM technology.

Hypothesis:

There will be no measurable differences between blood and interstitial glucose concentrations; however, quantifying any existing variation may provide insight into their relationship in non-diabetic individuals.

Primary outcomes:

The comparison of acute glycaemic metrics between blood and interstitial compartments in non-diabetic individuals at rest.

Secondary outcomes:

Changes in plasma volume

Glycaemic metrics such as peak glucose and time to peak

Sensor accuracy indices, including Clarke Error Grid and Bland-Altman analysis.

Chapter 4

Aim:

To characterise the glycaemic variability of professional female UCI world tour cyclists using continuous interstitial glucose monitoring over a 9-day cycle training camp.

Hypothesis: Healthy athletes will spend a similar proportion of time within the target glucose range regardless of time of day or exercise status.

Primary outcomes:

24 h glycaemic metrics

Secondary outcomes:

Time-segmented glycaemic

Exercise glycaemic metrics

Exercise data and relationship to glycaemic metrics

Chapter 5

Aim: To examine the glycaemic impact of adopting a 28-day carbohydrate-rich diet primarily consisting of either low- or high-GI carbohydrates on acute and chronic glycaemia using continuous glucose monitoring and explore the impact on endurance capacity in ultra-endurance athletes.

Hypothesis:

When matched for total carbohydrate intake, consuming a low or high glycaemic index diet for 28 days will have no effect on mean glucose concentration, glycaemic variability, or endurance capacity in trained athletes.

Primary outcomes:

Comparison of glycaemia between each diet.

Differences in endurance capacity between carbohydrate types.

Secondary outcomes:

Anthropometric changes

Substrate utilization

CHAPTER TWO

Methodology

2.1 Study ethics

Ethical approval for the studies used in each of the data chapters 3 and 5 was granted by Swansea University Research Ethics Committee (Ref no. RH_28-07-22 and RH_28-07-22, respectively). Ethical approval for study chapter 4 was granted by Supersapiens^{TM}. An in-house ethical review was conducted by the company's Medical Officer in accordance with internal governance procedures (Ref no. SS-001). These studies were carried out in accordance with the Declaration of Helsinki and International Conference on Harmonisation of Good Clinical Practice. Only data collected from participants that provided informed consent were included in the analysis of the studies (See **Appendices A2, B2 and B3**). Study 5 was registered with clinicaltrials.org (trial number **U1111-1281-5048)**.

2.2 Study Design

Chapter 3 was a randomised, double-blind, cross-over fashion to investigate the impact of glycaemic index, amount of CHO and the concentration of a CHO-containing beverage. Following randomised allocation (via computerised randomising sequence software www.randomizer.org) participants completed seven experimental trial arms.

Chapter 4 was an observational, exploratory study involving nine professional female UCI tour riders. Data was collected over a nine-day training camp undertaken in January 2022 in Majorca, Spain.

C*hapter 5* was a randomised, cross-over study where participants were randomly allocated to either a low- or high glycaemic carbohydrate-rich dietary arm and within this arm attended the laboratory on 2 within-arm trial days at the start and end of each 28-day dietary arm. There was a 2-week washout between arms where athletes returned to their normal diet patterns (study schematic in **Figure 5.1**). They were instructed to maintain their training during both of the dietary intervention periods.

2.3 Participant recruitment

Chapter 3

Participants were recruited from the university students by word of mouth. Those who wanted to participate contacted a member of the research team to express their interest. Interested individuals were sent a participant information form (**Appendix A1**) outlining the general study information and protocol details. They were then asked to opt into the study by written consent if they wanted to continue to be involved (**Appendix A2**). They were allowed to voluntarily withdraw from the study at any time with no penalty. Participants received no remuneration for their participation in this study.

Chapter 4

Participants were recruited via communication with the Canyon Sram Women's UCI cycling team management staff. The head coach and team manager expressed interest in taking part in further research relating to the use of CGM in cycling. After the formation of the study design and discussion concerning team logistics and scheduling a final study schedule was agreed upon. Each member of the team were provided an information leaflet and informed consent form via Supersapiens™ research manager. A member of the research team then attended a team meeting at the beginning of their preseason training camp to brief the team on the study and it their potential involvement. Those interested in taking part and providing their information then returned the informed consent forms to their team manager who then forwarded these to the research team. Their involvement was voluntary with no penalty for not taking part or withdrawing from the study (which they were made aware they could do so at any time). Participants received no remuneration for their participation in this study.

Chapter 5

Participants registered their interest in response to advertisements placed on various social media portals (Facebook, Twitter and Instagram) (**Appendix B6**). These included local running, triathlon clubs and relevant interest groups i.e. Local running groups, coaches and event groups. Once participants registered an initial interest, they were contacted via email. Once they met the overall inclusion criteria. They would then be assessed for breach of any

exclusion criteria before commencing the study via a screening session (**Appendix B2**). Participants were informed that they were free to withdraw from the study at any time without giving a reason, and it would not affect their relationship with the School of Sport and Exercise Sciences or any of the researchers involved in the study. Prior to completing a screening session, each participant was sent a detailed participant information leaflet (**Appendix B1**) detailing the expectations of the study and they were asked to complete an informed consent form, relevant health questionnaires and some background information (**Appendix B2**). Following the screening session and providing they met inclusion criteria and in the absence of any exclusion criteria they were then invited to complete a short familiarisation period. This allowed them to become accustomed to study expectations and procedures, as well as receiving some basic training for any of the relevant study procedures and data collection processes (**Appendix B4**). They were then invited to proceed to the first laboratory test session and book their trial schedule. A flowchart detailing the recruitment process for study 3 is displayed in **Figure 2.1.**

Participants received an inconvenience allowance of £100 per laboratory visit to reflect the time, and inconvenience involved in taking part in the study. This was paid on completion of the study.

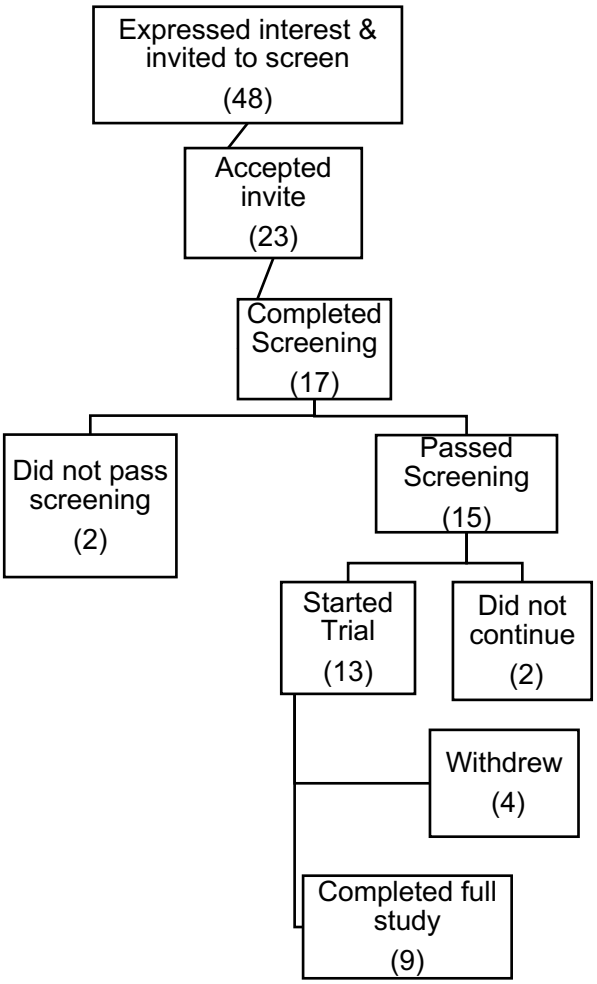


Figure 2.1. Flowchart of study recruitment, completions and withdrawals.

2.4 General information

Prior to any study participants were asked to complete information pertaining to age, gender, date of birth, sporting background and any general information useful to the study. However, they were not assessed for family history, which might have included any family history of diabetes. For laboratory-based studies participants were asked to complete an additional Pre-test health questionnaire (**Appendices A3 & B2**) and Physical Activity Readiness Questionnaire (PAR-Q) (**Appendices A4 & B2**).

2.5 Anthropometric measurements

Height and weight

Participant heights (Holtain Stadiometer, Holtain Ltd, UK) and body mass (Seca Digital Scales, Seca Ltd, UK) were taken for the quantification of body mass index (BMI).

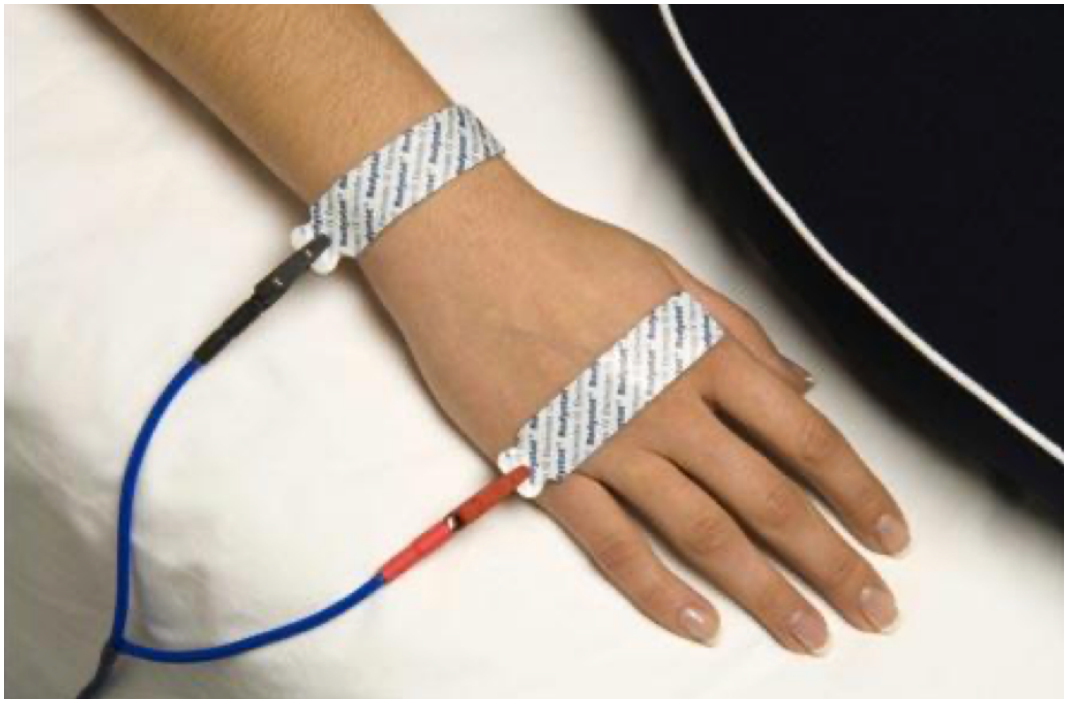
$$BMI = \frac{Body\ mass\ (kg)}{Height\ (m^2)}$$

Bioelectric impedance analysis (BIA) (Chapters 3 and 5)

To complete BIA analysis; height, body mass, waist and hip circumference measurements were manually input to the BIA device (Bodystat Quadscan 4000, Bodystat Ltd, USA). BIA measures body composition through the principle of electrical impedance. A small, safe electrical current passes through the body via electrodes placed on the hand (wrist and knuckle) and similarly on the foot (ankle and toes) (**Figure 2.2**). The resistance encountered by the body is influenced by the composition of various body tissues and water content. From the resistance measured, the machine provided a validated assessment of body composition and other information such as estimated basal metabolic rates (Kushner et al., 1990). Preparation for the analysis involved remaining in a supine position for 15 minutes prior to the test. Electrode sites were prepared using alcohol wipes (Cutisoft, BSN medical, Germany).

The device scan was then activated, completing an assessment in seconds. Data for the scan was then manually recorded in an Excel record sheet for later recall and further analysis.

A)



B)

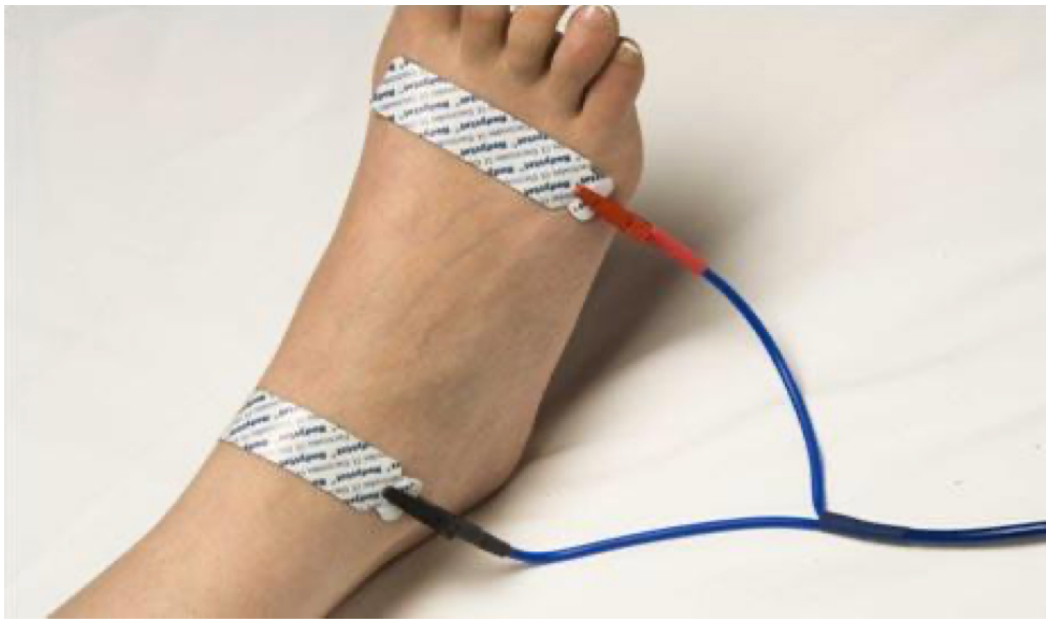


Figure 2.2. Bodystat sensor electrode placement for A) hand position and B) foot position.

2.6 Physiological measures

2.6.1 Heart rate monitoring *(Chapter 5)*

Heart rate was recorded using a Garmin HRM-Dual™ chest strap (HRM-Dual™ , Garmin Ltd. USA). The chest strap was attached to the participant around the torso at the level of the xiphoid process and paired to a relevant recording or display device. Electrodes on the garment were lubricated with ECG gel (Spectra®360 Electrode Gel, Parker Laboratories Inc., USA). Once paired the sensor began transmitting automatically. Data was recorded using the participants' own activity tracking watches when recording data from home or the Garmin Forerunner® 920XT (Foreunner® 920XT, Garmin Ltd. USA) when in the laboratory. Data was uploaded via Garmin express to TrainingPeaks monitoring software (TrainingPeaks, Peaksware LLC, Louisville, USA) to be later downloaded and statistically assessed. During laboratory testing, it was also manually transcribed at five-minute intervals to a separate results sheet and later added to a digital database via excel format.

2.6.2 Continuous Glucose Monitoring (CGM) (*all data chapters)*

The Abbott Freestyle Libre Sense Biosensor (Freestyle Libre®, Abbott, Lake Bluff, Illinois, USA) powered by the Supersapiens™ application (TT1 Products Inc., Atlanta, GA, USA) was provided to participants. The device has a sensor life of approximately 14 days and should be applied approximately 24 h before intended use. This CGM device is designed to be operated by the participant. At the time of the data collection for this thesis, Supersapiens™ provides extensive user guides on application and start-up of the sensor as well as an extensive troubleshooting guidance library. In addition, each participant was trained in the use and application of the sensor and was given time to familiarise themselves with the technology ahead of any study. The sensor is applied to a subcutaneous fat pad located over the triceps brachii, as per manufacturer's instructions (**Figure 2.3**). The sensor transmits data to a smartphone, where the Supersapiens™ application records and displays data. The sensor is intended to measure in one-minute intervals as long as the sensor is in range of the smartphone. If not, the sensor saves data internally for a period of eight hours at 15 minute intervals. Supersapiens™ provided a proprietary a wrist-based watch for real time data display which was also paired with the sensor. This wrist based unit (Supersapiens™ Fuel Band) recorded data in intervals of 2 mins. It also served as a memory device which was used in the absence

of a smart phone. Data from this display unit was uploaded by syncing with the phone application. CGM data was accessible from an online Supersapiens™ coaching dashboard, where it was then exported in Excel format for analysis.

Figure 2.3. Continuous Glucose Monitor (CGM) sensor placement. (Photo courtesy of Supersapiens™).

CGM data analysis

Once the CGM data had been exported to an Excel file it needed to be organised to display [iG] values and timestamps. From here, the data was screened to ensure that a minimum of 70% coverage was collected. This was assessed based on the number of time points present in a 24 h period compared to the expected (1440). This ensured that gaps in the data did not skew the analysis or provide misleading values.

Once the raw data was screened and organised, it was analysed for a range of standard glycaemic characterisations including mean, peak, nadir, standard deviation, coefficient of variation and time in ranges, as detailed by the international consensus on the use of CGM (Danne et al., 2017), a further categorisation of tight time in range (TTIR) was also adopted to provide more applicable insight into a healthy cohort (Dunn, Ajjan, Bergenstal, & Xu, 2024; Passanisi et al., 2024) (see **section 1.5.8**).

Further analysis was made to partition the data into daytime (06.00-10.59), night-time (11:00-5:59) and in exercise time (defined by exercise logs). These time periods are individually assessed and used for further statistical analysis.

The Abbott Biosensor has a lower detection limit of 54 mg/dL, making it unable to capture the full extent of LVL2 hypoglycaemia. However, estimations of the time spent below 55 mg/dL [3.1 mmol/L^{-1}] were made possible by calculating the proportion of time the data displayed a consistent flat line value of 54 mg/dL, indicating the concentration was at or below 54 mg/dL.

2.6.3 Blood glucose (BG) and lactate BLa *(Chapters 3 and 5)*

All trial day BG and BLa samples were analysed using the Biosen C-Line system (Biosen, EFK, Germany). The device was fully calibrated the morning prior to any experimental visit and subsequently set on a timed self-calibration run every 60 minutes. This involved running a series of known linearity and control test solutions, for which the Biosen result needed to fall within a certain acceptable range for both glucose and lactate (linearity standards: 2,5,7 and 18 mmol/L^{-1}. Normal control: glucose 6.06 mmol/L^{-1} and lactate 3.00 mmol/L^{-1}. Pathological control: glucose 15.99 mmol/L^{-1} and lactate 15.00 mmol/L^{-1}) (**Appendix C1**). If any of these test standards failed, biosensor chips were replaced, and the machine was restarted. The calibration samples were run again to ensure acceptable functionality had been restored. A sample of either capillary or canular-derived venous blood was aspirated into end-to-end capillary tubes and then placed into individual Eppendorfs that were pre-filled with 1 ml of haemolysing solution (EKF Diagnostics Holdings, Barleben, Germany). All samples were inverted a minimum of 3 times prior to analysis.

Measurement ranges for the Biosen C-line for were **Glucose**: concentrations from 0.5-50 mmol/L (9-900 mg.dL^{-1}) and **lactate**: concentrations from 0.5-40 mmol/L (5-360 mg.dL^{-1})

(EKF Diagnostics). The manufacturers report a coefficient of variation (CV) of ≤1.5% at 12 mmol/L^{-1}.

2.6.4 Cardio-pulmonary exercise test to determine VO_{2max} and anaerobic threshold

CPET Protocol *(Chapter 5)*

Following completion of a PAR-Q questionnaire, checks for inclusion criteria and contraindications to CPET (**Appendix B2**), an incremental ramp exercise test on a treadmill (Pulsar 3P, Cosmos, Munich) was completed. After a 10 min warmup, participants were given some time to stretch and prepare for the incremental proportion of the run test. This portion of the test began with a standing 5-minute rest phase followed by 3-minute incremental steps test to volitional failure, increasing in 1km.h^{-1} increments per step as per BASES recommendations (BASES, 2006). Treadmill gradient was set at 1% throughout the entire test. At the end of each step, participants were instructed to step off the treadmill using the treadmill safety rails for one minute. During this 60 s period, capillary blood was collected from the participants' fingertip and they were asked to indicate their rate of perceived exertion using (RPE) on a BORG scale (6-20). The treadmill was increased in speed before the next step to allow it to reach its intended velocity. Participants would step onto the moving belt and the next stage commenced. Volitional failure was defined by one or more of the following criteria 1) an inability to maintain a safe position on the treadmill, which was marked with hazard tape on the treadmill rails; verbal warnings were given to ensure safe positioning. Only when a participant failed to respond to repeated warnings would the test be stopped or 2) voluntary termination of test by stepping on rails or signalling to researchers to stop. Following cessation of test, volitional fatigue his was cross-referenced with predicted maximum HR, peak lactate concentration and RPE to confirm the attainment of maximal effort (**Table 2.1)**. At the end of the test, the treadmill speed was reset to 5 km.hr^{-1} for 5 minutes to allow participants to warm down appropriately.

RPE (Borg)	HR (BPM)	Blac (mmol.L^{-1})
20±1	178±12	10.56±2.31

Table 2.1. Physiological measures collected upon exhaustion during the graded exercise test. ***RPE***: Rate of perceived exertion***, HR:*** Heart rate & ***Blac:*** Blood lactate. Data is displayed as mean±SD.

Breath measurements and determination of CPET and Endurance capacity test measurements (Chapter 5)

Breath-by-breath data were measured using a pulmonary gas analyser (MetaMax® 3B; Cortex Biophysik GmbH, Germany) calibrated using certified gases (Gas 1: Ambient Air, Gas 2: 15.08% O_2, 5.03% CO_2) with data displayed for standardised temperature and pressure for dry air. Heart rate (HR) was recorded via a heart rate monitor chest strap and data was integrated into the Metamax software. All cardio-pulmonary data were subsequently averaged in 5-second intervals (Metasoft Software, Cortex Biophysik GmbH, Germany) for statistical processing. Capillary blood samples (20 µl) were taken from the fingertip to determine BG and lactate (BLa) at rest, and immediately after each step. Samples were analysed via an enzymatic-amperometric analyser (Biosen C-line, EKF Diagnostics, Germany) and manually recorded on a results sheet to be later transcribed and saved to an Excel results sheet.

Calculation of substrate oxidation rates (Chapter 5)

Pulmonary gas exchange data was used to assess substrate oxidation during exercise via indirect calorimetry. Respiratory quotient (RQ) indicates the amount of CO_2 produced compared to the O_2 consumed within body tissues. Indirect calorimetry relies on whole lung gas exchange measurements to determine total O_2 consumption and CO_2 production and to estimate RQ, or more so, termed respiratory exchange ratio (RER). The oxidation of different fuel sources produces different amounts of CO_2 and consumes different amounts O_2 (Jeukendrup & Wallis, 2005). From this principle, it is possible to calculate the contribution of energy and the rate of oxidation of carbohydrates, fats and proteins.

The equations used are outlined below;

• CHO Oxidation ($g.min^{-1}$) = 4.210/V̇ CO2 – 2.962/V̇ O2 – 0.40n

• Lipid Oxidation ($g.min^{-1}$) = 1.695/V̇ O2 – 1.701/V̇ CO2– 1.77n

• Energy from 1g of CHO (20% glucose; 80% glycogen) = 4.07kcal

• Energy from 1g of fat = 9.75kcal

In cases where exercise intensity is moderate and above, accumulation of hydrogen ions (H^+) as a result of a higher glycolytic flux will result in bicarbonate buffering. Ultimately, this results in an increase in CO_2 production, which elevates $\dot{V}CO_2$, and an overestimation of carbohydrate oxidation and an underestimation of fat oxidation (Jeukendrup & Wallis, 2005). Oxidation rates were only analysed during the steady state exercise, which was at an intensity below 75% $\dot{V}O_{2peak}$.

In the processing of oxidation rates for statistical assessment, sampling points were taken as the rolling mean of 5 seconds taken every 30 seconds. Where RER values were >1.0, the fat oxidation was corrected to zero grams per minute.

VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$) was also determined from breath-by-breath data. Intensity levels for endurance performance tests were assigned as a % Heart rate or run velocity at VO_{2peak}. This was to ensure that participants were able to have a method to observe and control intensity in a practical way. In addition to providing training intensity zones by heart rate, run capacity intensity was controlled on the treadmill by using a percentage of velocity at VO_{2peak}.

For the retrospective classification of exercise intensity, a three-zone training model was utilised. Intensity zones were defined with heart rate using the corresponding first and second lactate threshold turning points as identified from the generated lactate curve from the CPET (Seiler, 2010).

2.6.5 Blood analytes *(Chapter 5)*

Blood analytes collected in Chapter 5 are detailed below, with processing methods and equipment displayed in **Table 2.2**.

Catecholamines (Adrenaline & Noradrenaline)

Catecholamines were analysed using Eagle Biosciences ELISA assay kit (Eagle Biosciences, Inc. Nashua, USA).

These competitive BI-CAT Adrenaline and Noradrenaline ELISA Assay Kit uses the microtiter plate format. Adrenaline and noradrenaline, respectively, are bound to the solid phase of the plate. Acylated catecholamines from the sample and solid phase-bound catecholamine compete for a fixed number of antiserum binding sites. When the system is in equilibrium, free antigen

and free antigen-antiserum complexes are removed by washing. The antibody bound to the solid phase catecholamine is detected by anti-rabbit IgG/peroxidase. The substrate TMB/peroxidase reaction is monitored at 450nm. The amount of antibody bound to the solid phase catecholamine is inversely proportional to the catecholamine concentration in the sample. The performance characteristics of the assessment kits are displayed in **Table 2.2** below.

Human Insulin Assay

Analysed using Invitron Insulin Assay Kit (Invitron LTD, Monmouth, UK). 'True' insulin in plasma is measured by an immunoassay which does not cross-react with other insulin-like components. The assay is a two-site sandwich immunoassay, employing an insulin-specific solid phase antibody immobilised on microtitre wells, and a soluble antibody labelled with an acridinium ester. Labelled antibody and samples, controls, or calibrators are incubated simultaneously in antibody-coated wells. This incubation leads to insulin being bound to the microwell test plate between the two different antibody-molecules ("sandwiched"). Excess labelled antibody and other components from the sample are removed by washing. The bound luminescence is quantified by a microtitre plate reading luminometer capable of in situ reagent addition. The performance characteristics of the assessment kits are displayed in **Table 2.2** below.

Interleukin-6 (IL-6)

Analysed using R&D systems Assay Kit (R&D systems, Oxford, UK). Samples are incubated in a microtitre plate coated with an IL-6 specific antibody. After a wash step to remove any unbound substances, an enzyme linked polyclonal antibody, specific to IL-6 is added to all wells. Following a second wash step to remove unbound substances, a substrate solution is added to all wells to generate colour. The reaction is then stopped. The absorbance of the stopped reaction is read in a plate reader, colour intensity being directly proportional to the amount of IL-6 present in the sample. The performance characteristics of the assessment kits are displayed in **Table 2.2** below.

Triglycerides

The Randox Triglycerides assay provided a rapid measurement of triglycerides in serum or plasma when it was run on the Randox Daytona Plus analyser. Samples were assayed in batches which allows a large number to be measured simultaneously. The performance characteristics of the assessment kits are displayed in **Table 2.2** below.

TNF-α

The Quantikine Human TNF-alpha Immunoassay is a 4.5-hour solid-phase ELISA designed to measure human TNF-alpha in cell culture supernates, serum, and plasma. It contains E. coli-derived recombinant human TNF-alpha and antibodies raised against this protein. It has been shown to accurately quantify the recombinant factor. Results obtained with naturally occurring TNF-alpha samples showed linear curves that were parallel to the standard curves obtained using the Quantikine kit standards. These results indicate that this kit can be used to determine relative mass values for natural human TNF-alpha. The performance characteristics of the assessment kits are displayed in **Table 2.2** below.

Aspartate Aminotransferase (AST)

The aminotransferases are a group of enzymes that catalyse the interconversions of amino acids and α-oxoacids by transfer of amino groups. AST (aspartate aminotransferase or glutamate oxaloacetate transaminase) has been found in the cytoplasm and the mitochondria of cells that have been studied. In cases of tissue damage e.g. liver, the predominant form of serum AST is that from the cytoplasm, with a smaller amount coming from the mitochondria. Severe tissue damage will result in more mitochondrial enzymes being released. α-oxoglutarate reacts with L-aspartate in the presence of AST to form L-glutamate plus oxaloacetate. The indicator reaction utilises the oxaloacetate for a kinetic determination of NADH consumption. The performance characteristics of the assessment kits are displayed in **Table 2.2** below.

Alanine Aminotransferase (AST)

The aminotransferases are a group of enzymes that catalyse the interconversions of amino acids and α-oxoacids by transfer of amino groups. The enzyme ALT (alanine aminotransferase or glutamate pyruvate transaminase) has been found to be in the highest concentrations in the liver, with decreasing concentrations found in the kidney, heart, skeletal muscle, pancreas,

spleen and lung tissue respectively. ALT measurements are used in the diagnosis and treatment of certain liver diseases (e.g. viral hepatitis and cirrhosis) and heart diseases. Elevated levels of the transaminases can indicate myocardial infarction, hepatic disease, muscular dystrophy and organ damage. Elevated levels of ALT in serum are rarely observed except in parenchymal liver disease, since ALT is a more liver-specific enzyme. The performance characteristics of the assessment kits are displayed in **Table 2.2** below.

α-oxoglutarate reacts with L-alanine in the presence of ALT to form L-glutamate plus pyruvate. The indicator reaction utilises the pyruvate for a kinetic determination of NADH consumption.

L-γ-Glutamyltransferase (GGT)

Gamma-Glutamyltransferase (γ-GT) and isoenzymes measurements are used in the diagnosis and treatment of liver diseases such as alcoholic cirrhosis and primary and secondary liver tumours.

The substrate L-γ-glutamyl-3-carboxy-4-nitroanilide, in the presence of glycylglycine is converted by γ-GT in the sample, to 5-amino-2-nitro-benzoate which absorbs at 405 nm. The performance characteristics of the assessment kits are displayed in **Table 2.2** below.

Glycerol

Measurements are used in the diagnosis and treatment of patients with diabetes mellitus, nephrosis, liver obstruction, other diseases involving lipid metabolism, or various endocrine disorders. A direct colourimetric procedure for the measurement of glycerol is described utilising a quinoneimine chromogen system in the presence of glycerol kinase, peroxidase and glycerol phosphate oxidase. The performance characteristics of the assessment kits are displayed in **Table 2.2** below.

Analyte	Methods	Manufacturer	Assay (kit) Reference	Sensitivity	Assay Range	Intra-assay reliability	Plate Reader/Analyser
Glycerol	Randox	Randox	Randox, GLY RXMONZA (GY105)	4.5 µmol/l.	19 to 1997 µmol/l.	5.4-6.4%	RX Daytona Plus, Randox Plc. Crumlin, UK
Ketones	Randox	Randox	Randox, RANBUT (RB1007)	0.1 mmol/L	0.1 – 5.75 mmol/L	3.80%	RX Daytona Plus, Randox Plc. Crumlin, UK
Triglycerides	Randox	Randox	Randox (TRIGS) (TR8332)	0.2 mmol/L	0.7-56.8 mmol/L	2.6-3.7%	RX Daytona Plus, Randox Plc. Crumlin, UK
ALT	Randox	Randox	Randox, ALT IFCC (AL 3801)	9.70 U/l	6 to 82 U/l.	1.39-4.91%	RX Daytona Plus, Randox Plc. Crumlin, UK
AST	Randox	Randox	GGT IFCC (GT 8320)	18.7 U/l.	10 - 225 U/l.	1.66-4.21%	RX Daytona Plus, Randox Plc. Crumlin, UK
GGT	Randox	Randox	Randox, ALT IFCC (AL 3801)	5.13U/L	8 U/L to 1521 U/L.	3.8-5.6%	RX Daytona Plus, Randox Plc. Crumlin, UK

iFABP	ELISA	R&D Systems, UK	ELISA Enzyme-Linked Immunosorbent Assay (DY3078)	NA	31.2 - 2,000 pg/mL	NA	RX Daytona Plus, Randox Plc. Crumlin, UK
H-FABP	ELISA	Randox	ELISA Enzyme-Linked Immunosorbent Assay (FB10022)	0.25 ng/ml.	0-80 ng/ml	2.2-3.1%	RX Daytona Plus, Randox Plc. Crumlin, UK
CK-MB	Randox	Randox	CK-MB UV-Method RX SERIES (CK 3893)	14 U/l.	8.30 to 1182 U/l		RX Daytona Plus, Randox Plc. Crumlin, UK
IL6	ELISA	R&D Systems, UK	Human IL-6 Quantikine ELISA Kit, R & D Systems (D6050)	0.70 pg/ml	3.1-300 pg/ml-1	1.6 – 4.2%	Multiskan™, Thermo Scientific, Massachusetts, U.S
TNF-a	Thermo	R&D Systems, UK	Human TNF-α Quantikine ELISA Kit, R & D Systems (DTA00C)	4.00 pg/mL	2.09-6.23 pg/mL	4.40%	Multiskan™, Thermo Scientific, Massachusetts, U.S
Insulin	ICMA	Invitron, UK	Invitron insulin assay, IV2-001	0.25 mU/L	0.25 - 250 mU/L	2.4-7.1%%	Centro LB 960 Luminometer,

							Berthold Technologies GmbH and Co, Germany
Adrenaline	Competitive ELISA	Eagle Biosciences, USA	BI-CAT Adrenaline and Noradrenaline ELISA Assay Kit (BCT31-K02)	0.005 ng/ml	0.005 – 50 ng/ml	9.6 – 9.5%	Multiskan™, Thermo Scientific, Massachusetts, U.S
Noradrenaline	Competitive ELISA	Eagle Biosciences, USA	BI-CAT Adrenaline and Noradrenaline ELISA Assay Kit (BCT31-K02)	0.016 ng/ml	0.016 - 150 ng/ml	8.4 – 9.7%	Multiskan™, Thermo Scientific, Massachusetts, U.S

Table 2.2. Methodological overview of the laboratory-based blood analysis employed for the quantification of each biomarker. Table details were taken from individualised kit inserts as provided by the manufacturers. ELISA: enzyme-linked immunosorbent assay.

2.7 Trial day inclusion *(Chapters 3 and 5) (Appendix B2 & B3)*

2.7.1 Screening Day inclusion criteria

1. Informed consent obtained
2. Male or female aged 18-65 years (both inclusive)
3. Completed pre-medical questionnaire
4. Completed International Physical Activity Questionnaire (IPAQ) and deemed eligible for study participation

2.7.2 Screening Day exclusion criteria

1. Known or suspected hypersensitivity to trial product(s) or related products (any known sucrase-isomaltase deficiency)
2. Receipt of any investigational medicinal product within 1 month prior to screening
3. Known haemoglobin <8.0 mmol/L male) or < 7.0 mmol/L (female)
4. Suffer from or history of a life-threatening disease (i.e. cancer judged not to be in full remission except basal cell skin cancer or squamous cell skin cancer), or clinically severe diseases that directly influence the study results, as judged by the Investigator. This did not prohibit the participation of patients taking medications that influences the metabolism (e.g. statin) or cardio-respiratory system (e.g. asthma spray) as long as the therapy is stable and is not adapted throughout the run of the trial. Furthermore, it did not exclude patients who have celiac disease (or similar diseases or allergies), as long as the disease is stable, and patients were able to stay on their specific (e.g.) Low glycaemic diet
5. Cardiac problems defined as decompensated heart failure (New York Heart Association (NYHA) class III and IV)10 at any time and/or angina pectoris within the 12 months prior to screening and/or acute myocardial infarction at any time
6. Blood pressure at screening outside the range of 90-140 mmHg for systolic or 50-90 mmHg for diastolic (excluding white-coat hypertension; therefore, if a repeated measurement on a second screening visit shows values within the range, the participant can be included in the trial). This exclusion criterion also pertained to participants being

on antihypertensives (as long as the blood pressure is within the range, participants on hypertensives can be included)

7. Known ECG abnormalities
8. Proliferative retinopathy or maculopathy and/or severe neuropathy, in particular autonomic neuropathy, as judged by the Investigator
9. Any chronic disorder or severe disease which, in the opinion of the Investigator might jeopardize participant's safety or compliance with the protocol
10. Participant known to be positive for Hepatitis B surface antigen (HBsAg) or Hepatitis C antibodies (or diagnosed with active hepatitis), for HIV-1 antibodies, HIV-2 antibodies or HIV-1 antigen
11. History of multiple and/or severe allergies to drugs or foods or a history of severe anaphylactic reaction (except celiac disease – patient must exclude foods that contain gluten from the diet)
12. Surgery or trauma with significant blood loss (more than 500 mL) within the 3 months prior to screening
13. Treatment with systemic (oral or i.v.) corticosteroids, monoamine oxidase (MAO) inhibitors, non-selective or selective beta-blockers, growth hormone. Furthermore, thyroid hormones are not allowed unless the use of these has been stable during the 3 months prior to screening
14. Significant history of alcoholism or drug/chemical abuse as per Investigator's judgement
15. Smoker (defined as a participant who is smoking more than 5 cigarettes or the equivalent per day)
16. Not able or willing to refrain from smoking, or use of nicotine substitute products during the inpatient period
17. Participant with mental incapacity or language barriers precluding adequate understanding or cooperation or who, in the opinion of their general practitioner or the Investigator, should not participate in the trial
18. Potentially non-compliant or uncooperative during the trial, as judged by the Investigator
19. Any condition that would interfere with trial participation or evaluation of results, as judged by the Investigator
20. Any known history of diabetes mellitus, or the use of any anti-hyperglycaemic drug or insulin to treat diabetes and related conditions

Contraindications to CPET

1. Acute myocardial infarction within 2 days of test
2. Ongoing unstable angina
3. Uncontrolled cardiac arrhythmia with hemodynamic compromise
4. Active endocarditis
5. Symptomatic severe aortic stenosis
6. Decompensated heart failure
7. Acute pulmonary embolism, pulmonary infarction, or deep venous thrombosis
8. Acute myocarditis or pericarditis
9. Acute aortic dissection
10. Physical disability that precludes safe and adequate testing

2.8 Experimental procedures

2.8.1 Oral Glucose Tolerance Test (OGTT) *(Chapter 3)*

Oral glucose tolerance tests were used to assess the glucose dynamics in the blood and interstitial fluid following the ingestion of a carbohydrate-containing beverage (Feng, Cheng, Li, & Cheng, 2021). The participant rested in a seated position for 5 minutes before commencing the test. Initial measurements and finger-prick blood samples were taken. The participants then consumed a carbohydrate-containing beverage in a blinded, randomised order. A timer was started to indicate the time points for additional measurements and samples. Blood samples (approximately 100ul at each time point) at rest, and thereafter at 2.5, 5, 10, 20, 30, 40, 50, 60, 90 and 120 min. At each time point, measures were made of capillary glucose and lactate (Biosen C-line, EKF Diagnostics, Germany). The protocol timeline is displayed in **Figure 3.1**

2.8.2 Venous blood sampling and analysis overview *(Chapter 5)*

Participants were fitted with a 20-gauge catheter (Venflon, Becton Dickinson, Helsingborg, Sweden) into the ante-cubital vein of the non-dominant arm. On all occasions, the procedure was performed by a member of the research team trained in Phlebotomy. Lines were secured with a Veca-C dressing (Venflon, Becton Dickinson, Helsingborg, Sweden) placed over a 10 cm extension with 3-way stop clock (Connect, Becton Dickinson, Helsingborg, Sweden).

Saline solution (Sodium Chloride BP, 0.9%, Braun, UK) was infused periodically to keep the catheter patent. 4ml of blood was aliquoted into an EDTA tube (Thermo fisher, Massachusetts, USA) and placed on ice, while 2ml of blood was aliquoted into a serum separator (SST) tube (Thermofisher, Massachusetts, USA) and left at room temperature for 15 minutes to allow clotting. Both tubes were then centrifuged at 5000 rpm for 5 minutes (Thermo scientific Heraeus 8R centrifuge, Thermofisher, Massachusetts, USA*)* to separate whole blood into haematocrit and serum/plasma. Following centrifugation, serum or plasma samples were aliquoted into individually stored microtubes with anonymous but identifiable codes that detailed the participant ID, trial number and trial timepoint. Samples were then boxed and stored in an alarmed freezer at -80˚C (Liebherr Medline freezer, Bulle, Switzerland) until later analysis.

2.8.3 Fasted run protocol *(Chapter 5)*

In order to investigate the efficacy of the different carbohydrate types in maintaining endurance performance, participants first completed a 3 h fasted run prior to a refeed. This protocol was designed to maintain an element of sport specificity at an appropriate intensity while still depleting glycogen stores. Participants were asked to arrive at the laboratory following an overnight fast (minimum 8 h). Their run protocol involved running for 3 h at an intensity equivalent to 70% $\dot{V}O_{2peak,}$ (ascertained during screening session) and monitored via HR. HR was kept within ± 5 bpm of this pre-determined intensity with run data collected from their own GPS watch to be later download from TrainingPeaks™. This run was completed outdoors on a pre-determined course replicating a trail run type environment. Maunder, Podlogar, and Wallis (2017) and (Casey et al., 2000) used similar exercise protocols to effectively observe the influence of supplementary carbohydrate refeeding on short-term post-endurance exercise recovery. The intensity was chosen to replicate the intensity typical of an endurance-type event. 70% $\dot{V}O_{2peak}$ falls below the lactate threshold of most individuals, allowing them to sustain relatively long durations >90mins exercise (Bergia et al., 2022). This allows for a depletion of glycogen stores without incurring significant metabolic stress or mechanical damage. It is also reflective of the intensity which may be experienced in many long-duration endurance events and training sessions (Muñoz, Cejuela, Seiler, Larumbe, & Esteve-Lanao, 2014). Trial run data was assessed to ensure uniformity and appropriate intensity.

2.8.4 Run capacity testing *(Chapter 5)*

To assess the impact of carbohydrate types on run performance, participants completed a treadmill test in the laboratory. Participants were asked to run on a treadmill (Pulsar 3P, Cosmos, Munich) where they ran at an intensity equivalent to ~74% $v\dot{V}O_{2peak}$ (ascertained from cardiopulmonary exercise testing during screening) until volitional fatigue. This intensity was chosen to reflect the demands of an ultra-endurance event. It is also an intensity that can be greatly impacted by the level of starting glycogen and glucose availability (Bergstrom et al., 1967a; Hermansen et al., 1967; Saltin & Karlsson, 1971). A lesser intensity may not have been challenged by the availability of glucose sufficiently, as the oxidation of lipids might become an influencing factor (Felig, Cherif, Minagawa, & Wahren, 1982), while a greater intensity may have been influenced by other factors such as the accumulation of lactate. Upon cessation of the test, blood lactate was measured to confirm that concentrations were indicative of an aerobic intensity level and associated fatigue.

2.9 Remote data collection

2.9.1 Collection of training data *(Chapters 4 and 5)*

All training data obtained throughout chapters 4 and 5 was collected via the use of the Training Peaks application (Training Peaks, Peaksware LLC, Louisville, USA). As participants in both studies used different devices all data collected from cycling head units and/or activity watches was uploaded directly to this platform. This allowed for a standardisation of data analysis. Once uploaded data could be assessed and downloaded in a raw data file for further processing in Excel®.

2.9.2 Collection of nutrition data *(Chapter 5)*

Collection of nutritional intake was made using the Nutritics™ (Nutritics, Dublin, Ireland) smartphone application. This software had a library of common products and brands with pre-populated nutritional information. Participants could scan the product barcode or manually input and save new foods to recall on further occasions (**Appendix B4**). Participants were provided with weighing scales (Salter, Manchester, United Kingdom) so that they could accurately weigh their foods (dry weight). They then manually selected the quantity via the application which then saved their meal. In addition, they selected additional snacks throughout

the day to ensure all food intake was collected. This information was then made accessible by the research team for later analysis. Both the food log and the daily total nutritional information were organised into exportable reports that were analysed further in Excel and statistical packages.

2.10 Experimental materials

2.10.1 Carbohydrates used *(Chapters 3 and 5)*

Dextrose: Dextrose is another name for the monosaccharide, glucose. Dextrose comes in a powdered form and is soluble in water. It may be produced in both flavoured or flavourless forms. In chapter 3 unflavoured dextrose powder (Bulk powders, Colchester, United Kingdom) was mixed with water and approximately 10 ml of flavoured cordial (Britvic PLC, Hemel Hempstead, UK) to each beverage to increase palatability and mask any distinctive flavour discrepancies between trial beverages.

Maltodextrin: Maltodextrin is a polysaccharide chain of glucose molecules bonded linearly with alpha-1,4 bonds (Hofman, Van Buul, & Brouns, 2016). It is by definition, a complex carbohydrate but due to the rapid splitting of the saccharide chain it takes on characteristics similar to simple sugars. It can be produced and used in both flavoured and unflavoured powder and is easily soluble in water. In chapters 3 and 5, both flavoured and unflavoured Maltodextrin was used (BENEO, Mannheim, Germany) with six different flavours available to avoid any taste fatigue during the at-home phase of the study. The concentration of these beverages varied depending on when they were being consumed.

Isomaltulose: (Palatinose™) is a disaccharide sucrose isomer with an alpha-1,6 glycosidic bond between glucose and fructose. It is naturally found in food sources such as honey. It's taste and sweetness are similar to sucrose (table sugar). It is fully cleaved and absorbed in the small intestine. However, this process is 20–25% the rate of sucrose (Gunther & Heymann, 1998; Lina, Jonkar, & Kozianowski, 2002), giving it a glycaemic index value of 32. Isomaltulose can be produced and used in both flavoured and unflavoured powder and is easily soluble in water. In chapters 3 and 5 unflavoured Isomaltulose powder (BENEO, Mannheim, Germany) was mixed with water and approximately 10 ml of flavoured cordial (Britvic PLC, Hemel Hempstead, UK) to each beverage to increase palatability and mask any distinctive flavour discrepancies between trial beverages. In chapter 5, both flavoured and unflavoured

Isomaltulose was used (BENEO, Mannheim, Germany) with six different flavours available to avoid any taste fatigue during the at-home phase of the study. The concentration of these beverages varied depending on when they were being consumed.

2.11 Statistical analyses

Statistical analyses were carried out using Excel (Microsoft Office) and GraphPad Prism V 9.5. All data are presented as mean ± standard deviation (SD). Data were tested for normal distribution (Shapiro–Wilk test).

Chapter 3

To assess differences across conditions and over time, two-way repeated-measures ANOVAs were performed, with Bonferroni-adjusted post-hoc comparisons applied to control for the increased risk of Type I error associated with multiple comparisons. Paired samples t-tests were used when comparing two related conditions for each glycaemic metric. All tests were two-tailed, and statistical significance was set at $p \leq 0.05$.

To evaluate agreement between interstitial glucose (iG) and blood glucose (BG) measurements, Bland-Altman analysis was conducted to quantify the mean bias and 95% limits of agreement between paired data points. In addition, Clarke Error Grid analysis was applied to assess the clinical accuracy of iG relative to BG by categorising paired values into zones reflecting potential clinical risk and decision-making accuracy.

Chapter 4

A one-way ANOVA and Pearson's product-moment correlation coefficient were used as the data met the assumptions required for parametric testing, including approximate normal distribution (assessed via Shapiro-Wilk tests). Data were measured on an interval, appropriate for mean-based comparisons and correlation analysis. Where significant main effects were found in the ANOVA, Bonferroni-adjusted post-hoc tests were applied to control for the increased risk of Type I error. A two-way ANOVA was used to discern differences between day- and night-time variables as the camp duration progressed. t-tests were employed to make direct comparisons of glycaemic metrics based on the stratified periods. Pearson's correlation was selected to explore linear relationships between continuous variables (e.g., exercise

duration and 24 h time in range), under the assumption of linearity and normally distributed residuals. Significant differences were reported if $p \leq 0.05$.

Chapter 5

Within each dietary intervention arm, daily glycaemic metrics were analysed using repeated-measures ANOVA to assess any differences, Anthropometric, dietary and exercise metrics were also assessed repeated-measures ANOVA, with Bonferroni-adjusted post-hoc comparisons applied to identify where significant differences occurred. Between-arm glycaemic metrics were conducted using paired t-tests. For acute exercise sessions performed at the beginning and end of each intervention period, repeated-measures ANOVA was used to compare responses across time points and conditions, with Bonferroni-adjusted post-hoc comparisons applied to identify where significant differences occurred. Changes across each 28-day intervention period were assessed using paired samples t-tests. Acute trial day glycaemia was assessed using a two-way repeated-measures ANOVA to assess the effects of both condition and timepoint. For blood analyte data, two-way repeated-measures ANOVA was used to assess the effects of condition (dietary arm) and timepoint, including potential interactions between these factors. Statistical significance was set at $p \leq 0.05$ for all tests, which were two-tailed.

2.12 Sample Size

Chapter 3

Sample size was informed by Brouns, Wolever, and Frayn (2005) , who suggested that approximately ten participants can provide precise and statistically meaningful measurements of glycaemic responses under tightly controlled conditions. Given the exploratory aim of characterising acute glycaemic responses and sensor behaviour, rather than detecting population-level effects, a sample size of ten participants was employed. Post hoc inspection indicated sufficient power to detect large within-subject differences (Cohen's $d \approx 0.8–1.0$), as observed for variables such as minimum glucose concentration and time to peak, where differences of 5–9 $mg \cdot dL^{-1}$ or 6–8 minutes were statistically significant ($p < 0.05$). However, for parameters such as peak and mean glucose concentrations or rates of change, between-compartment differences were typically small (< 4 $mg \cdot dL^{-1}$) relative to their variability (SD ≈ 15–25 $mg \cdot dL^{-1}$), resulting in small effect sizes ($d < 0.3$) and correspondingly low power (<

40%). Detecting such small differences with 80% power would require approximately 40–80 participants, which is impractical given the repeated-measures, crossover design with multiple laboratory visits. Thus, the chosen sample size represented a pragmatic balance between statistical rigour and logistical feasibility. While it limits the ability to generalise findings or detect subtle effects, the within-subject design and strict experimental standardisation support the reliability of the observed patterns within this cohort.

Chapters 4 and 5 Sample size estimates indicated that the number of participants required to achieve 0.80 statistical power varied considerably depending on the metric assessed, ranging from as few as eight participants for time-below-range (TBR) to as many as 466 for maximum concentration. This wide range reflects the variable effect sizes across different glycaemic outcomes. Given these differences, it was not feasible to recruit a sample large enough to achieve adequate power for every metric within the available timeframe. Tight timelines linked to sponsor obligations and the coordination of athlete training schedules limited recruitment opportunities. Consequently, the study was likely underpowered for certain secondary outcomes, particularly those with smaller effect sizes.

However, the primary intent of these investigations were exploratory, serving as a proof-of-concept to establish feasibility and provide foundational insight into the glycaemic characteristics of competitive endurance athletes. Within this context, the repeated-measures, within-subject design substantially increased power for detecting within-person differences, which were central to the study's objectives. The highly homogeneous sample of trained athletes further reduced inter-individual variability, enhancing sensitivity to detect physiologically meaningful changes. The final sample size aligns with comparable investigations using CGM in athletic cohorts (Bowler et al., 2024; Freckmann et al., 2007; Prins et al., 2023; Weijer et al., 2024).

CHAPTER THREE

A comparison of the interstitial and blood glucose responses following consumption of different carbohydrate-containing beverages in humans: a randomised controlled trial

3.1 Introduction

Continuous interstitial glucose monitoring (CGM) has gained considerable interest within the global athletic and wellness community as a surrogate tool for observing blood glucose concentrations [BG]. With the relative ease of use and practicality of inserting a small coin size, disposable transmitting sensor, the data CGM provides has proven to be clinically meaningful for managing pre- (Chekima et al., 2022; Klupa et al., 2023) and diabetes (DeSalvo et al., 2021; Lin et al., 2021). In individuals without metabolic conditions, real-time glucose monitoring offers a 24-hour glucose profile, capturing fluctuations around meals, physical activity, and sleep (Bowler et al., 2022; Klonoff et al., 2022). These insights might provide some value for understanding the impact composition, size and timing of meals may have in an individual (Bermingham et al., 2023) but the wider implications of understanding nutrient influences on metabolic function (or dysfunction) as well as optimising nutrient intake using this technology is currently unclear (Klonoff et al., 2022).

It is widely acknowledged that in humans, interstitial fluid (IF) volume is approx. 10-12 l (Levick, 2010). Large fluid shifts occur during hyperhydration, hypohydration and with fluid loss during physical exercise. Fluid movements also occur between the interstitium and the bloodstream via fenestrated capillaries. Thus, the volume of interstitial fluid (IF) in which glucose circulates is continuously changing, much like in blood, due to factors that influence the rates of glucose appearance and disappearance. Consequently, notwithstanding that CGM can measure glucose, it is expected that measurement differences arise between IF and blood (Boyne et al., 2003; Facchinetti et al., 2013; Rossetti et al., 2010; Thome-Duret et al., 1996).

When carbohydrate-containing foods are ingested, they go through a process of digestion, assimilation and absorption from the digestive tract into the bloodstream and interstitial fluid. This transfer is aided by several transporter proteins known (GLUTs). The rate of digestion and assimilation of carbohydrates is largely dictated by how much processing is required to break it down into glucose (Jeukendrup & Gleeson, 2019; Wolever, 2006). The amount, type and method of carbohydrate delivery can impact the rate of appearance of glucose into the circulation. In addition, a number of factors such as subject group characteristics, fasting

glucose levels and even time of day can introduce variability in the glucose response to a specific food (Hutchins et al., 2025; Wolever et al., 1985).

In addition, the rate at which glucose appears in the interstitium depends on the forces governing fluid and solute exchange between blood and interstitial fluid. Hydrostatic and osmotic gradients, described by Starling forces (S. Evans & Evans, 1968), determine the direction of fluid movement. Hydrostatic pressure is largely responsible for fluid entry into the IF, while oncotic forces act somewhat in opposition, together maintaining a balance between fluid and substrates such as glucose. In addition to the appearance of glucose in the circulation, local factors such as blood flow, tissue perfusion, membrane permeability, and cellular glucose uptake also influence its presence in the interstitial fluid (Richter et al., 2025; Rossetti et al., 2010; Schmelzeisen-Redeker et al., 2015). SGLT1 influences fluid movement in the gut by co-transporting sodium, which alters osmotic gradients across the membrane. The osmolality and carbohydrate content of an ingested fluid, therefore, can have a large impact on plasma fluid volume, as different characteristics (high or low osmolarity) may cause either a volume expansion or reduction (G. Evans, Shirreffs, & Maughan, 2009; Shi et al., 1994). These shifts can occur rapidly, with notable plasma volume changes detected within 20 minutes of ingestion (G. Evans et al., 2009). Such alterations affect solute flux, potentially increasing differences between interstitial and blood glucose concentrations. With evidence of commonly reported differences between interstitial and blood glucose (lag time, peak concentration, rate of change) (Fellinger, Brandt, Creutzburg, Rommerskirchen, & Schmidt, 2024; Jin et al., 2023; Schmelzeisen-Redeker et al., 2015; Siegmund et al., 2017).

Notwithstanding the many sources of variance between interstitial and blood glucose, useful metrics for characterising (dys)glycaemia in diabetes have substantially advanced diabetes care in recent decades. A shift from simple mean glucose values to detailed measures of acute excursions has enhanced feedback for lifestyle and dietary adjustments (Danne et al., 2017) and improved the effectiveness of drug therapies in diabetes management. However, the adoption of relevant metrics obtainable from CGM for people without diabetes is not as well developed.

Commercial CGM systems promote the use of CGM metrics by healthy individuals, encouraging them to identify and manage personal responses to meals, activity and daily stressors. Feedback centres on metrics that reflect daily glucose stability. However, threats to glucose stability come from nutrient intake, exercise, hydration status and other daily stressors.

Thus, glycaemic variability may be a more useful term that describes fluctuations in glucose concentration (Ajjan, 2024). In acute scenarios, such as following the ingestion of a carbohydrate-containing meal, the rate and direction of change provide insight into the glycaemic response to that food type. A rapid rise in blood glucose triggers a pancreatic insulin release, causing glucose levels to reduce (to sometimes below a pre-ingestion value). On the other hand, if blood glucose levels fall, pancreatic alpha cell glucagon release can stimulate hepatic glycogenolysis and release glucose into the circulation. This daily 'glucose yo-yo' effect influences mood, stress, and appetite, potentially driving calorie intake. As a result, stabilising glucose and minimising peaks and troughs has gained interest among health-conscious individuals.

In addition to providing metrics that help individuals improve daily glucose stability, CGM use in generally healthy individuals has also been proposed as an effective tool for the early detection of emerging metabolic conditions, through the identification of elevated day-to-day glucose variability (Acciaroli et al., 2018; Bermingham et al., 2023; Jarvis et al., 2023; Klonoff et al., 2022). However, improving glycaemic control in people without underlying health conditions has yet to show clear health benefits (Klonoff et al., 2022).

If CGM is to be adopted more widely as an indicator of blood glucose in no diabetes populations, sensor validity and accuracy is crucial. As previously mentioned, the IF is a separate compartment from blood, so some differences in solute concentration are inherent to the fluid and solute flux between them. While CGM algorithms aim to minimise these differences, the displayed metrics are still subject to sensing lags, which should be considered when interpreting CGM data. Time lags between IF and blood glucose concentrations of 5-10 minutes are commonly reported (Kuroda et al., 2017; Schmelzeisen-Redeker et al., 2015). Additionally, although brief, the sensor's internal processing time may contribute to further delay (Schmelzeisen-Redeker et al., 2015).

Sensor accuracy has improved over time, with the mean absolute relative difference (MARD) serving as the primary metric for comparison against the gold standard, blood glucose (usually measured by YSI) (Bailey & Alva, 2021). A MARD of 12.5% for 98% of measurements is considered acceptable (Finfer et al., 2013), yet reported MARDs for modern sensors range from 9.7 to 20.6% (Nielsen et al., 2024) under different feeding or real-life clinical monitoring circumstances. These differences often reflect physiological sensing delays between

compartments, rather than measurement errors (E. Moser et al., 2020). Diabetes research has highlighted greater MARD during exercise than at rest, often exceeding the accepted 12% (Fabra et al., 2021; E. Moser et al., 2020); Similar observations have been made in healthy participants, where glucose is more stable, with MARDs of 34±12% (Weijer et al., 2024) and 22±24% (Bauhaus et al., 2023) being observed during exercise. Following the ingestion of carbohydrate meals, MARDs of 17±12% (Bauhaus et al., 2023) and 25.7% (Jin et al., 2023), have been observed in healthy individuals. These findings highlight the need for careful interpretation of CGM values in response to feeding and exercise. In addition to MARD, Bland-Altman analysis provides further insight into the systematic trends or biases. Identifying the source of MARD influencers and characterising their relative impact might help provide further information to the user to make more appropriate decisions in data obtained from non-diabetes cohorts.

Recent research has begun to advance our understanding of interstitial glucose responses to food intake. Specific investigations of carbohydrate amount (Song et al., 2023), glycaemic load (Bridal et al., 2013), glycaemic index (Hutchins et al., 2025) and the impact of carbohydrate beverage concentration (Schierbauer et al., 2022), collectively begin to highlight the complexity of glucose detection aided by CGM. However, much more research is needed, for example, as noted by Schierbauer et al. (2022), on factors such as the osmolarity of ingested fluids.

Thus, the aim of this study was to investigate the relationship between interstitial and blood glucose concentrations following ingestion of carbohydrate-containing drinks differing in carbohydrate amount, osmolarity and glycaemic index. We hypothesise that there will be no measurable differences between blood and interstitial glucose concentrations; however, quantifying any existing variation might provide insight into their relationship in non-diabetic individuals. The primary outcome of this study was the comparison of acute glycaemic metrics between blood and interstitial compartments in non-diabetic individuals at rest. Secondary outcomes include indices of sensor accuracy, including Clarke Error Grid and Bland-Altman analysis and define plasma volume shifts.

3.2 Methods

3.2.1 Participants and ethical approval

10 healthy adults (9 male, age: 22±1 years, height: 177±12 cm, weight 75±14 kg) took part in this double-blind, randomised, counterbalanced study. Ethical approval was granted by the Swansea University Research Ethics Committee. The study was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonisation of Good Clinical Practice. All volunteers provided written informed consent prior to study involvement. Before undertaking any experimental procedures, participants completed a screening visit during which eligibility for trial inclusion was assessed alongside a review of their medical history via the PAR-Q questionnaire. After confirmation of study suitability, data on anthropometric characteristics were collected and a familiarisation session with the blood sampling procedure was completed.

3.2.2 Study design

This was a randomised, double-blind, cross-over fashion to investigate the impact of glycaemic index, amount of CHO and the concentration of a CHO-containing beverage. The trial day schedule of measurements is displayed in **Figure 3.1** below.

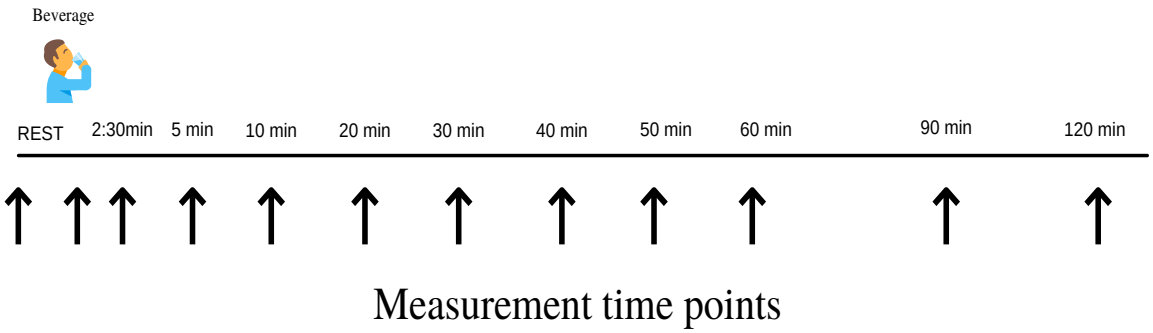


Figure 3.1. Study timeline showing consumption of beverage and measurement timepoints thereafter.

Following randomised allocation to each sub-aim trial (via computerised randomising sequence software) participants completed seven experimental trials. Trial beverages were prepared by a laboratory assistant outside of the research team to ensure double-blinding. Drinks were formulated and labelled with specific codes, also assigned using an online randomiser software (www.randomizer.org). Identification of each trial beverage was only made available to the research team on cessation of study trials.

On each day of the trial, participants would attend a laboratory trial session having applied a CGM sensor a minimum of 24 h prior. They then consumed their assigned beverage and remained in a seated position for the following 2 h, while measurements were taken at fixed timepoints (See **Figure 3.1**).

3.2.3 Beverage formulation

Beverages were formulated using Isomaltulose (Palatinose^{TM}) (ISO) (BENEO, Mannheim, Germany) or Dextrose (Bulk powders, Colchester, United Kingdom). Each beverage had approximately 10 ml of flavoured cordial (Britvic PLC, Hemel Hempstead, UK) which added approximately 2 mg of additional carbohydrate to each beverage. These subgroups are displayed below, with beverage formulation is displayed in **Table 3.1**.

Subgroup	Beverage 1	Beverage 2	Beverage 3
Carbohydrate amount	**50g** (50g Dextrose in 500ml) 1030 ± 0 mOsm.kgH_20	**25g** (25g Dextrose in 500ml) 720 ± 0 mOsm.kgH_20	**10g** (10g Dextrose in 500ml) 360 ± 0 mOsm.kgH_20
Carbohydrate concentration	**5%** (25g Dextrose in 500ml) 720 ± 0 mOsm.kgH_20	**10%** (25g Dextrose in 250 ml) 1270 ± 0 mOsm.kgH_20	**20 %** (25g Dextrose in 125ml) 2540* ± 0 mOsm.kgH_20
Glycaemic Index carbohydrate	**DEX (High GI)** (50g Dextrose in 500ml) 1030 ± 0 mOsm.kgH_20	**ISO (Low GI)** (50g Isomaltulose in 500ml) 970 ± 10 mOsm.kgH_20	**PLAC** (500ml) 73 ±12 mOsm.kgH_20

Table 3.1. Beverage allocation and constituents for each subgroup of investigation measured in grams (g) of carbohydrate per millilitre (ml) water with 10 ml of flavoured cordial added to each. * indicates where measurements were estimated due to values exceeding the measurement range. This estimate was made based on expected osmolarity (2 times the 10% beverage osmolarity).

3.2.4 Collection of interstitial glucose concentration

All interstitial glucose [iG] data were recorded via the Abbot Libre Sense Biosensor (Abbot Laboratories, Chicago, IL, USA). The CGM device was paired to the Supersapiens^{TM} receiver and Software application (TT1 Products Inc., Atlanta, GA, USA) which was installed on the participant's smartphone. Point iG concentration values were recorded manually from the phone app display at each timepoint (simultaneously with capillary blood collection) for later analysis via Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, USA). (See **Section 2.4.2**).

3.2.5 Assessment of CGM accuracy

Mean absolute relative difference (MARD) was used to assess the accuracy of the CGM sensor's [iG] against BG. The absolute relative difference (in percent) reflects the difference between the two measurements. This was calculated for overall MARD as well as during different target ranges: Hypoglycaemia (<70 mg/dL), Euglycaemia (71-140 mg/dL) and

Hyperglycaemia (>140mg/dL). The MARD was also assessed during different rates of concentration change: Quick rate of change (>2 mg/dL/min), Changing (1–2 mg/dL/min) and slow rate of change (<1 mg/dL/min). Surveillance error grids are provided for all measured pairs as well as pairs within each glucose threshold range as per Klonoff, et al. (2014).

A Bland–Altman plot was used to assess the systematic measurement differences between blood and interstitial glucose values. This analysis provides directional insights into any biases that may appear between the measurement compartments. The 95% limits of agreement, calculated as the mean difference ± 1.96 times the standard deviation (Altman & Bland, 1983).

3.2.6 Blood sampling

Capillary blood samples were taken from the fingertip. The sampling site was prepared by cleaning with an alcohol swab before using a lancet to collect the blood sample which was analysed for glucose and lactate (Biosen, EFK, Germany). An additional sample was also analysed for haemoglobin (Haemocue, Ängelholm, Sweden) and haematocrit (Hawksley reader, Sussex, UK) following centrifugation. These were used for the estimation of plasma volume changes as per Dill and Costill (1974).

3.2.7 Statistical analyses

Statistical analyses were carried out using Excel (Microsoft Office) and GraphPad Prism V 9.5. All data are presented as mean±standard deviation (SD). Data were analysed using one- or two-way ANOVAs with Bonferroni adjustment and paired t-tests where appropriate. Significant differences were reported if $p \leq 0.05$. For complete statistical analyses and sample size justification (see **section 2.12)**.

3.3 Results

3.3.1 Glycaemic responses

Carbohydrate amount

The glycaemic responses to differing amounts (**50g**, **25g**, **10g** and a Placebo [**PLAC**]) of carbohydrate (dextrose) in 500mls of water are displayed for [iG] and [BG] in **Figures 3.2A** and **3.2B**, respectively. Detailed glycaemic metrics are displayed in **Table 3.2** with a comparison of [iG] and [BG] measurements displayed in **Table 3.5**.

Influence of carbohydrate administration in different amounts on interstitial glucose concentrations

At rest [iG] was similar between all beverages. From rest, the rate of change to peak was different in all beverages compared to **PLAC** (**50g** +2.2±0.6, **25g** +1.9±0.5, **10g** +1.2±0.7 vs. **PLAC** +0.1±0.3 mg/dL/min, $p<0.05$), and quicker when **50g** was compared to **10g** ($p=0.004$). Peak [iG] was greater in all beverages compared to **PLAC** and larger amounts of carbohydrate displayed larger peaks (**50g** 158±17, **25g** 137±17 **10g** 107±22 vs. **PLAC** 86±8 mg/dL, $p<0.05$). **50g** was also greater than the peak in **10g** ($p<0.001$). The time of peaks was similar in all beverages. The rate of change from the peak to minimum [iG], was different in all beverages compared to **PLAC** (**50g** -1.8±0.8, **25g** -1.6±0.4 and **10g** -1.2±0.8 vs. **PLAC** 0.0±0.4 mg/dL/min, $p<0.05$). The minimum [iG] was lower than **PLAC** in all beverages (**50g** 62±7, **25g** 62±6, **10g** 68±8, vs. **PLAC** 77±8 mg/dL, $p<0.05$), occurring between 70 and 98 mins. Mean [iG] was only greater than **PLAC** for the **50g** beverage (**50g** 104±9 vs. **PLAC** 82±8 mg/dL, $p<0.001$).

Influence of carbohydrate administration in different amounts on blood glucose concentrations

At rest [BG] was similar between all beverages. From rest, the rate of change to peak was different for all beverages when they were compared to **PLAC** (**50g** +2.3±0.1, **25g** +2.3±0.8 and **10g** +1.3±0.7 vs. **PLAC** +0.2±0.4 mg/dL/min, $p<0.05$). Peak [BG] was also greater in all beverages when compared to **PLAC** (**50g** 154±23, **25g** 133±17 and **10g** 107±14 vs. **PLAC** 84±12 mg/dL, $p<0.05$). Peaks were greater in both **50g** and **25g** when compared to **10g**

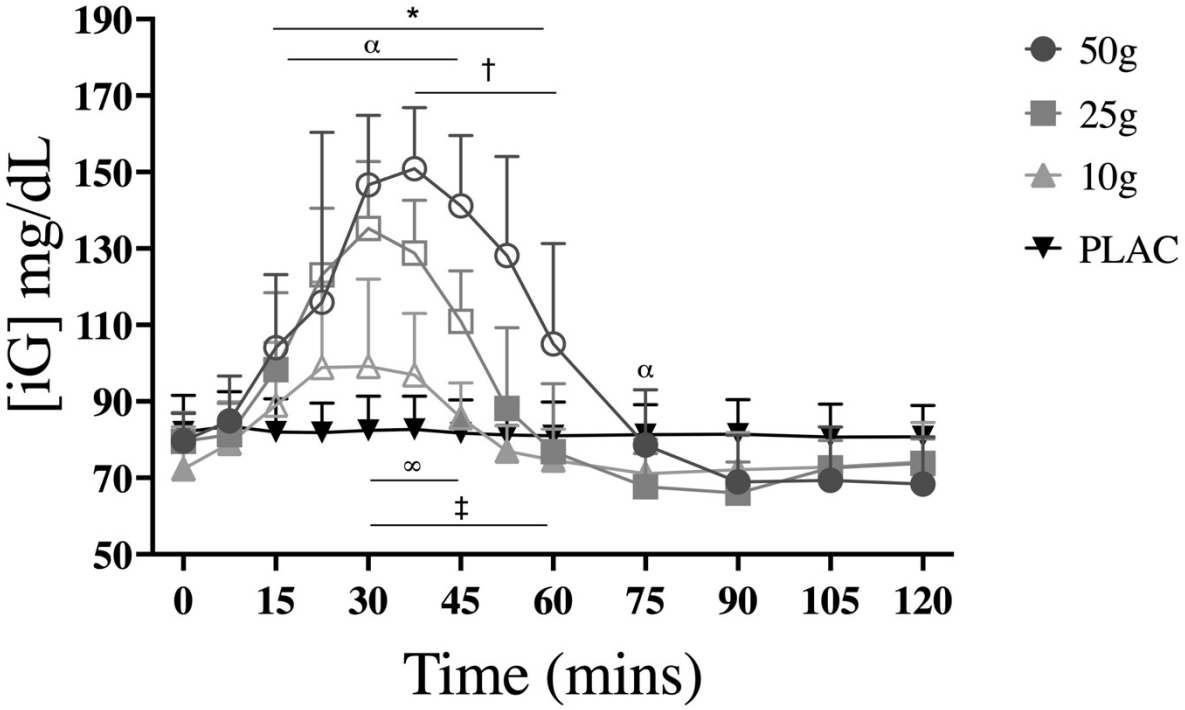
($p<0.05$). The timing of the peak [BG] was similar with all beverages**.** The rate of change from peak to minimum [BG] was different with both **50g** and **25g** compared to **PLAC** (**50g** -1.3±0.4 and **25g** -1.3±0.4 vs. **PLAC** -0.4±0.3 mg/dL/min, $p<0.05$). Minimum [BG] and the timing of the minimum similar between all beverages, occurring between approximately 85 and 102mins. Finally, mean [BG] was greater with all beverages than **PLAC** (**50g** 104±13, **25g** 94±10, and **10g** 85±8, vs. **PLAC** 77±10 mg/dL, $p<0.05$). The mean [BG] was greater in **50g** compared to the **10g** ($p=0.002$).

Comparison of blood and interstitial glucose concentrations in response to consumption of different amounts of carbohydrate

The difference between [iG] and [BG] across the 2 h period have been adjusted to account for the difference between [iG] and [BG] in the PLAC trial and displayed in **Figure 3.2C**. All differences are displayed as (Δ = [iG]-[BG]).

During the **PLAC** trial [iG] and [BG] glycaemic metrics were similar apart from the higher [iG] minimum values (Δ+8.5±11.5 mg/dL, $p=0.035$). At rest in the **10g** trial, [iG] was lower than [BG] (Δ-8±8.9 mg/dL, $p=0.027$). The rate of change for [iG] and [BG] was similar in all beverages, although peak [iG] occurred later than [BG] during both the **25g** and **10g** trial [BG] (**25g** Δ+8±5, and **10g** Δ+5±6 mins, $p<0.05$). Peaks were similar in both [iG] and [BG] for all beverages. In the **10g** trial, the rate of change from [iG] peak to minimum was slower (Δ-0.6±0.7mg/dL/min, $p=0.019$) and the time of the [iG] minimum was earlier than [BG] (Δ30±27 min, $p=0.010$). The minimum [iG] was lower than [BG] in **25g** (Δ5.3±5.7 mg/dL, $p=0.033$). Mean [iG] and [BG] were similar in all beverages.

A)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[iG] mg/dL
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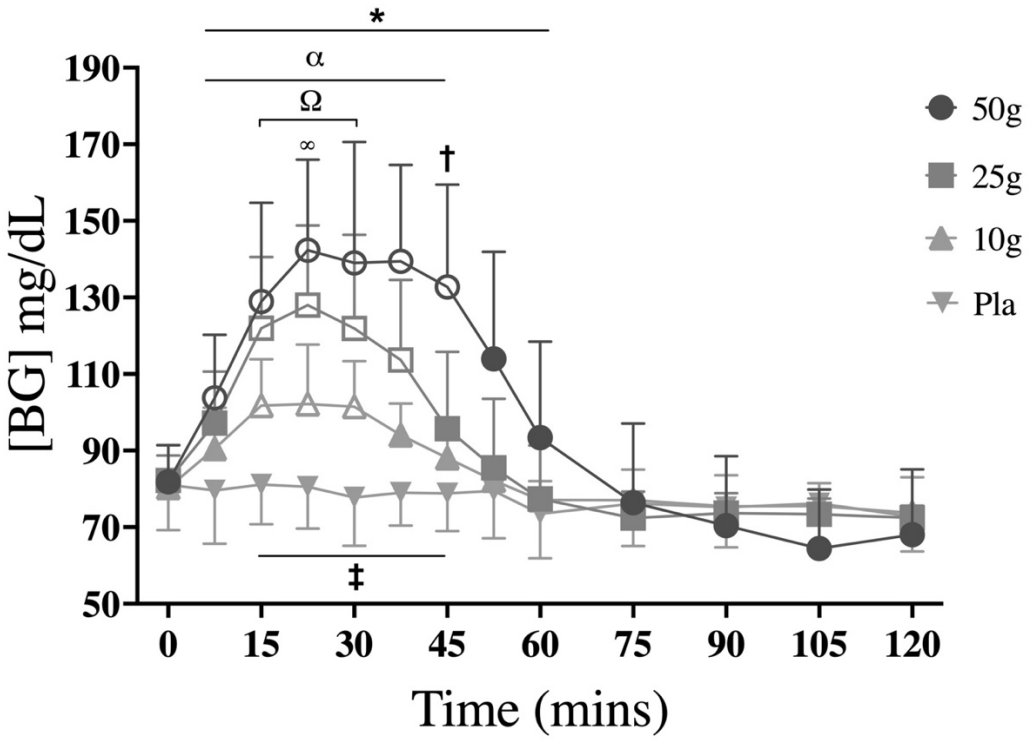
10g
PLAC

B)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[BG] mg/dL
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Time (mins)
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50g
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Pla

C)

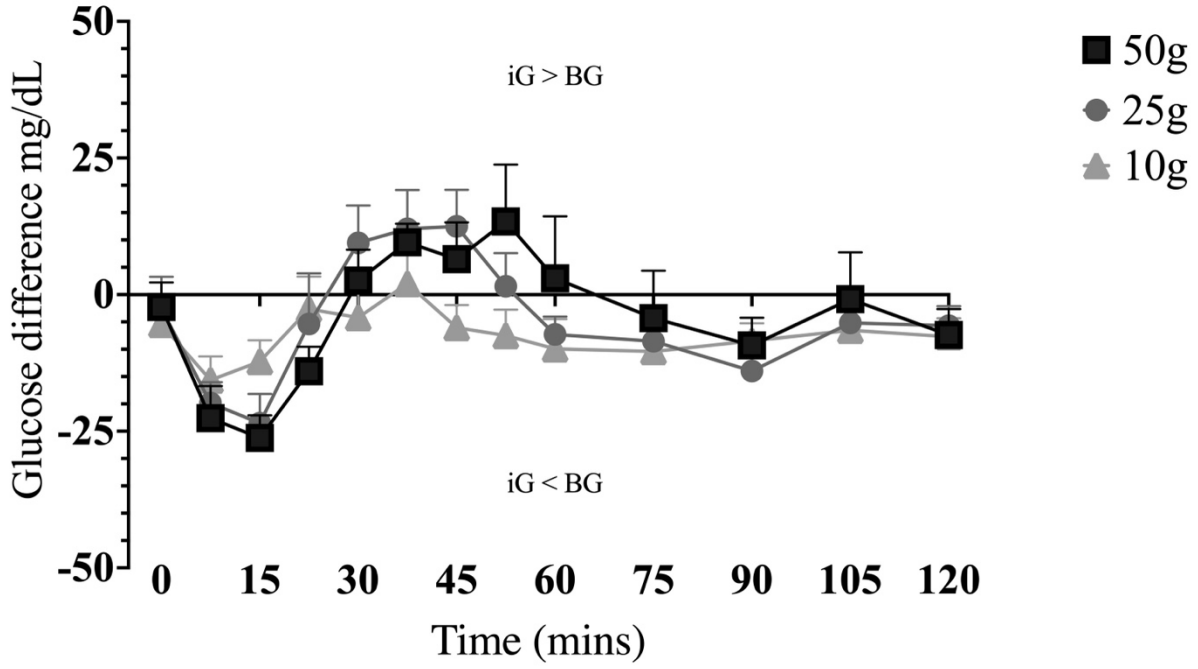


Figure 3.2. Interstitial glucose concentration [iG], B) Blood glucose concentrations [BG] and C) the difference between [iG] and [BG] values in the carbohydrate-containing trials adjusted from the difference between [iG] and [BG] in **PLAC** (C is displayed as Mean ± SEM) following an overnight fast and over 2h following ingestion of **50g** (n=10), **25g** (n=9), **10g** (n=10) or Placebo (**PLAC**) (n=11) of Dextrose. Negative values indicate [iG] was lower than [BG], while positive values indicate where it was greater. All carbohydrates were consumed in 480ml water with 20ml flavouring (**PLAC**). Hollow sample points indicate changes from rest within the condition. * indicates a difference between **50g** and **PLAC** trial, † Indicates a difference between **50g** and **25g**, ‡ indicates differences between **50g** and **10g**. α indicates a difference between **25g** and **PLAC**. ∞ indicates a difference between **25g** and **10g**. Ω indicates a difference between **10g** and **PLAC** (P≤0.05). Data is displayed as mean±SD.

Carbohydrate Amount	[iG]					[BG]				
	50g 500ml (10% soln)	**25g** 500ml (5% soln)	**10g** 500ml (2% soln)	**PLAC** 500ml	**p value**	**50g** 500ml (10% soln)	**25g** 500ml (5% soln)	**10g** 500ml (2% soln)	**PLAC** 500ml	**p value**
Peak (mg/dL)	158±17	137±17	107±22‡	86±8$^{*\alpha\Omega}$	**<0.0001**	154±23	133±17	107±14‡	84±12* $_{\alpha\Omega}$	**<0.0001**
Mean (mg/dL)	104±9	93±6†	82±10‡	82±8*	**<0.0001**	104±13	94±10	85±8‡	77±10* $_{\alpha}$	**<0.0001**
Min (mg/dL)	62±7	62±6	68±8	77±8$^{*\alpha\Omega}$	**<0.0001**	59±15	67±4	72±8	69±11	0.116
Time to peak (mins)	37±8	31±5	29±7	44±35	0.335	35±10	23±5	24±8	25±18	0.124
Time to minimum (mins)	98±20	71±25	72±18	70±40	0.076	98±34	85±28	102±20	89±36	0.853
ROC [rest-peak] (mg/dL/min)	+2.2±0.6	+1.9±0.5	+1.2±0.7‡	+0.1±0.3 $^{*\alpha\Omega}$	**0.007**	+2.3±0.8	+2.3±0.8	+1.3±0.7	+0.2±0.4 $^{*\alpha\Omega}$	**<0.0001**
ROC [peak to minimum] (mg/dL/min)	-1.8±0.8	-1.6±0.4	-1.2±0.8	-0.0±0.4	**<0.001*** $_{\alpha\Omega}$	-1.3±0.8	-1.3±0.4	-0.6±0.3$^{\infty}$ ‡	-0.4±0.3 $^{*\alpha}$	**<0.0001**

Table 3.2. Summary of glycaemic metric comparisons between each beverage for both interstitial glucose [iG] and blood glucose [BG] concentrations. * indicates a difference between **50g** and **PLAC** trial, † Indicates a difference between **50g** and **25g**, ‡ indicates differences between **50g** and **10g**. α indicates a difference between **25g** and **PLAC**. ∞ indicates a difference between **25g** and **10g**. Ω indicates a difference between **10g** and **PLAC** (P≤0.05). Data is displayed as mean±SD. Rate of change (ROC).

The concentration of carbohydrate solution

The glycaemic responses to differing concentrations (**20%**, **10%**, **5%** and a Placebo [**PLAC**]) of carbohydrate (25 g of dextrose) in different amounts (500, 250 and 125mls) of water are displayed for [iG] and [BG] in **Figures 3.3A** and **3.B** respectively. Detailed glycaemic metrics are displayed in **Table 3.3** with a comparison of [iG] and [BG] measurements displayed in **Table 3.5**.

Influence of different carbohydrate concentration solutions on interstitial glucose concentrations

At rest [iG] was similar with all beverages compared to the **PLAC.** From rest, the rate of change to peak was different with all beverages compared to **PLAC** (**5%** +1.9±0.5, **10%** +1.4±0.6 and **20%** +1.7±0.7 mg/dL/min, p<0.05). Peak [iG] was greater in all beverages when compared to **PLAC** (**5%** 137±17, **10%** 134±18, and **20%** 138±26 mg/dL, p<0.05). The time of the peak concentration was similar with all beverages, occurring between ~30-45mins. The rate of change from peak to minimum [iG] was different for all beverages compared to **PLAC** (**5%** -1.6±0.4, **10%** -1.4±0.4 and **20%** -1.6±0.7 mg/dL/min, p<0.05). The minimum [iG] was lower

in all beverages when compared to **PLAC** (**5%** 63±6, **10%** 64±5 and **20g** 60±3 mg/dL, p<0.05) but the timing was similar occurring between approximately 70 and 90mins). Finally, mean [iG] was greater for both **10%** and **20%** than it was for **PLAC.** (**10%** 94±11 and **20%** 94±13 mg/dL, p<0.05).

Influence of different carbohydrate concentration solutions on blood glucose concentrations

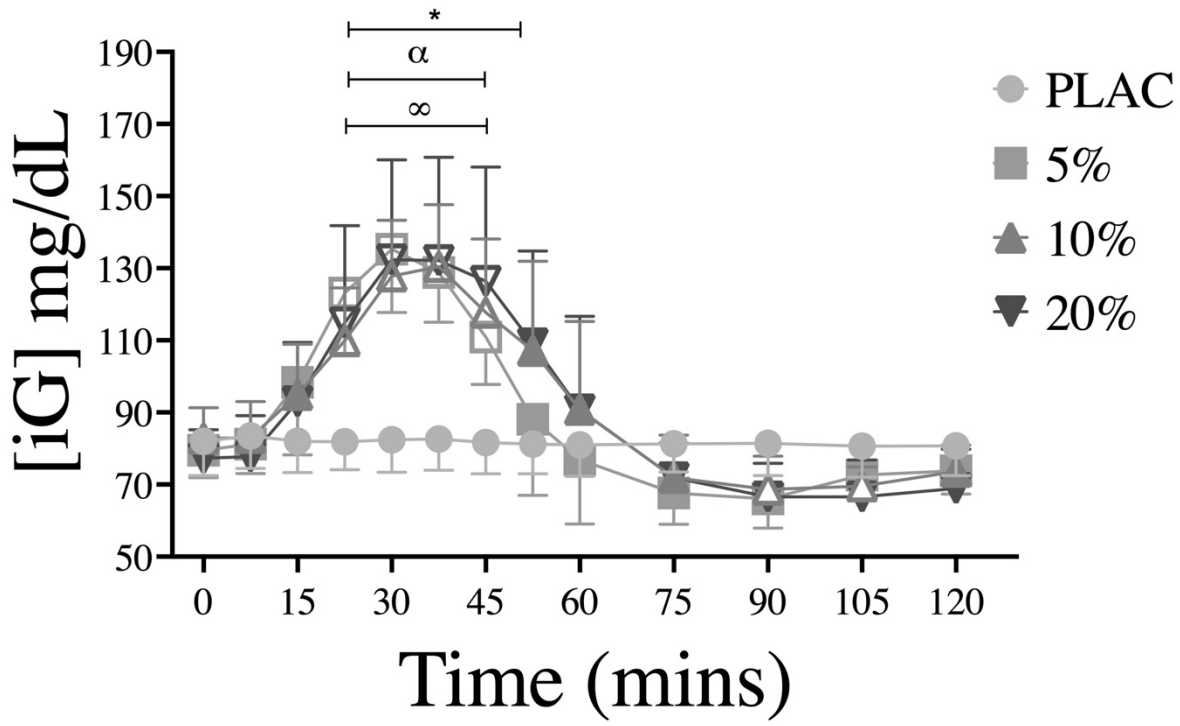
At rest [BG] was similar between all beverages. From rest, the rate of change to peak was different for all beverages when compared to **PLAC** (**5%** +2.3±0.1, **10%** +1.8±0.8 and **20%** +1.7±0.8 mg/dL/min, p<0.05). The peak [BG] was greater in all of the beverages when compared to **PLAC** (**5%** 133±17, **10%** 133±16, and **20%** 137±31 mg/dL, p<0.05), the time of peak came earlier in **5%** than **20%** (**5%** 23±5 vs. **20%** 35±9mins, p=0.023). The rate of change from peak to minimum [BG] was different for both **5%** and **10%** solutions compared to **PLAC** (**5%** -1.3±0.8, and **10%** -1.3±0.8 mg/dL/min, p<0.05). The minimum [BG] and its timings were similar with all beverages, occurring between ~84 and 94mins. Mean [BG] was greater with all beverages compared to **PLAC** (**5%** 94±10, **10%** 94±10, and **20%** 101±16 mg/dL, p<0.05).

Comparison of interstitial and blood glucose concentrations following consumption of carbohydrate solutions of different concentrations

The difference between [iG] and [BG] across the 2h period in the CHO-containing trials have been adjusted from the difference between [iG] and [BG] in the **PLAC** trial and displayed in **Figure 3.3C**.

During the **PLAC** trial [iG] and [BG] glycaemic metrics were similar apart from the higher [iG] minimum values (Δ+8.5±11.5 mg/dL, p=0.035). At rest [iG] and [BG] were similar for all of the beverages. The rate of change to peak was similar for both [iG] and [BG]. In both the **5%** and **10%** trials, the time of the peak came later for [iG] (**5g** Δ+8±5 and **10%** Δ+5±6mins, p=0.05). The rate of change from peak to minimum [iG] in the **20%** was slower than [BG] (Δ-0.6±0.5 mg/dL/min, p=0.007). In the **5% and 20%** trials, minimum [iG] was lower than [BG] (**5g** Δ-5±5 and **20%** Δ-8±5 mg/dL, p<0.05). Finally, the mean [iG] was lower than [BG] for the **20%** trial (Δ-6.1±7.4 mg/dL, p=0.03

A)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[iG] mg/dL
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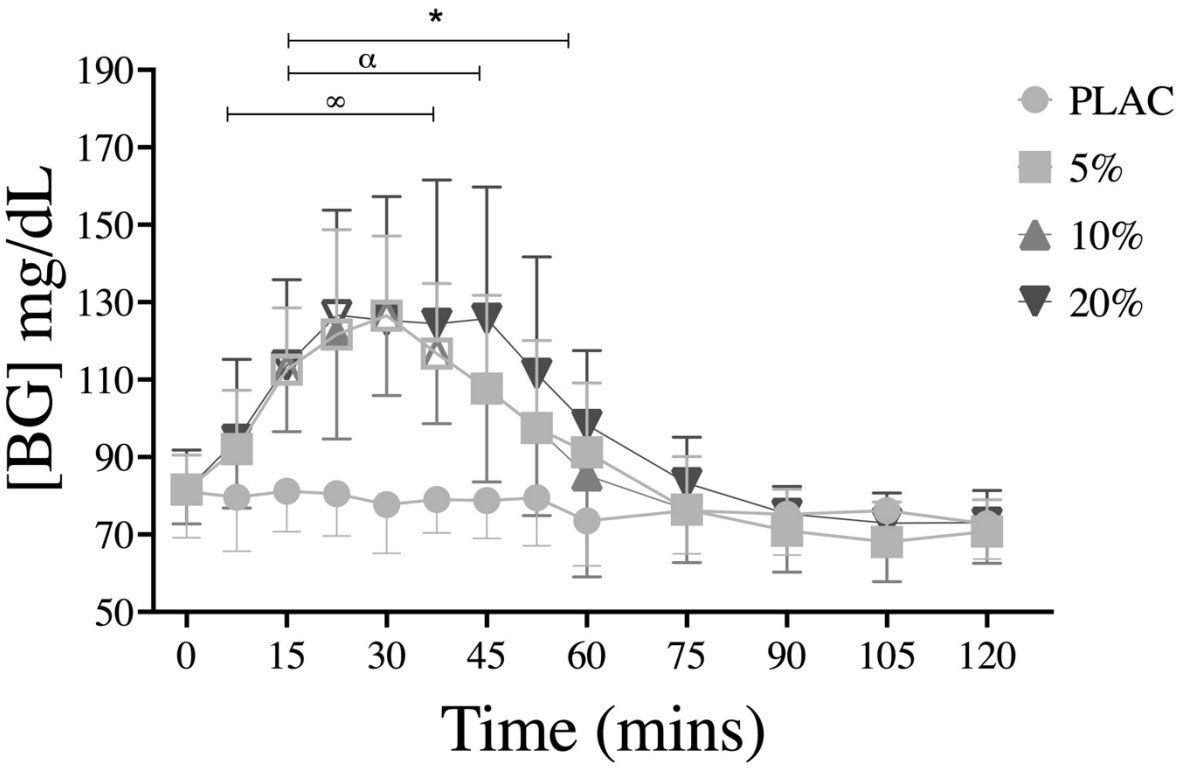
Time (mins)
PLAC
5%
10%
20%

B)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[BG] mg/dL
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Time (mins)
PLAC
5%
10%
20%

C)

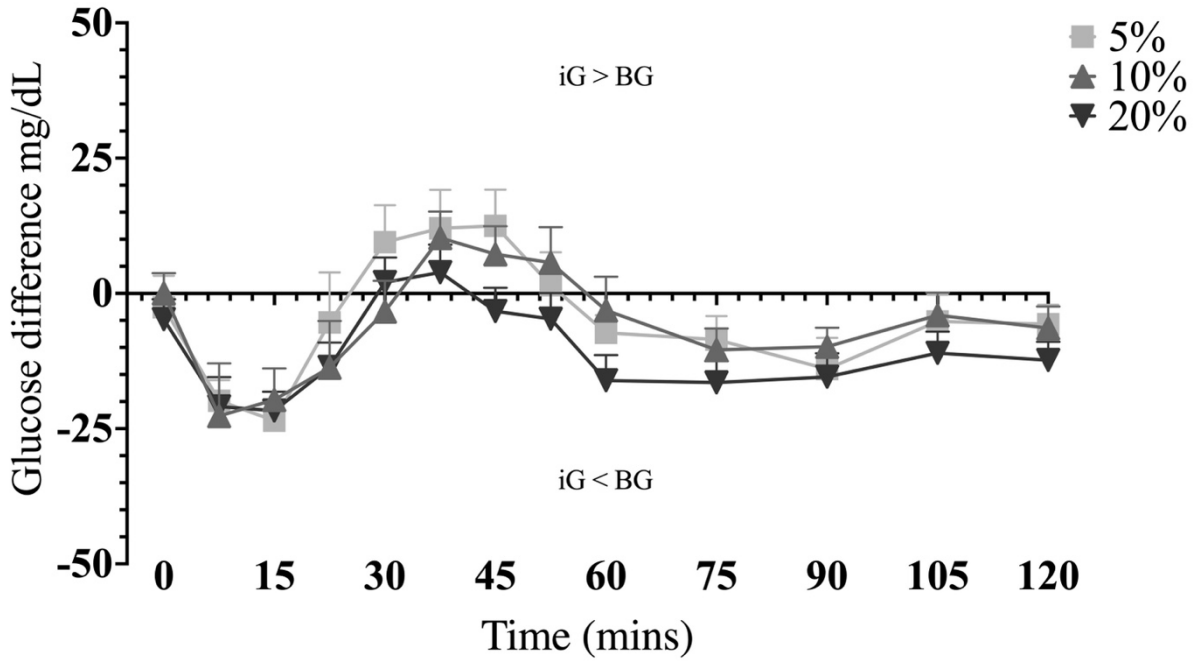


Figure 3.3. A) Interstitial glucose concentration [iG], B) Blood glucose concentrations [BG] and C) the difference between [iG] and [BG] values in carbohydrate-containing beverages adjusted from the differences between [iG] and [BG] in the **PLAC** values (C is displayed as Mean ± SEM) following a 2 h post ingestion of a **20%** solution of Dextrose (**20%**) (n=10), a **10%** solution (**10%**) (n=10), a **5%** solution (n=9) or Placebo (**PLAC**) (n=11). Negative values indicate [iG] was lower than [BG], while positive values indicate where it was greater. All carbohydrates were consumed in water with 20ml flavouring (**PLAC**). Hollow sample points indicate changes from rest within condition ($P \leq 0.05$). * indicates differences between **20%** and **PLAC**. α indicates a difference between **10%** and **PLAC**. ∞ indicates a difference between **5%** and **PLAC** ($P \leq 0.05$). Data is displayed as mean±SD.

Concentration of Solution	[iG]					[BG]				
	5% (25g 500ml)	**10%** (25g 250 ml)	**20%** (25g 125ml)	**PLAC** **500ml**	**p value**	**5%** (25g 500ml)	**10%** (25g 250 ml)	**20%** (25g 125ml)	**PLAC** **500ml**	**p value**
Peak (mg/dL)	137±17	134±18	138±26	86±8*α∞	**<0.0001**	133±17	133±16	137±31	84±12*α∞	**<0.0001**
Mean (mg/dL)	93±6	94±11	94±13	82±8α∞	**<0.0001**	94±10	94±10	101±16	77±10*α∞	**<0.0001**
Min (mg/dL)	63±6	64±5	60±3	77±8*α∞	**<0.0001**	68±4	64±13	69±8	69±11	0.701
Time to peak (mins)	30.9±5	38±7	36±7	44±35	0.516	23±5	33±11	35±9	25±18	0.104
Time to minimum (mins)	71±25	87±15	90±2	70±40	0.233	85±28	94±26	84±44	89±36	0.908
ROC [rest-peak] (mg/dL/min)	+1.9±0.5	+1.4±0.6	+1.7±0.7	+0.1±0.3 *α∞	**<0.0001**	+2.3±0.8	+1.8±0.8	+1.7±0.8	+0.2±0.4 *α∞	**<0.0001**
ROC [peak to minimum] (mg/dL/min)	-1.6±0.4	-1.4±0.4	-1.6±0.7	+0.0±0.4 *α∞	**<0.0001**	-1.3±0.8	-1.3±0.8	-1.0±0.6	+0.4±0.3 α∞	**0.005**

Table 3.3. Summary of glycaemic metric comparisons between each beverage solution for both interstitial [iG] and blood glucose [BG] concentrations. * indicates differences between **20%** and **PLAC**. α indicates a difference between **10%** and **PLAC**.∞ indicates a difference between **5%** and **PLAC**. ¥ indicates a difference between **5%** and **20%** (P≤0.05). Data is displayed as mean±SD. Rate of change (ROC).

Glycaemic index of Carbohydrates

The glycaemic responses to 50g of carbohydrates with different glycaemic indices (Dextrose **[DEX],** Isomaltulose **[ISO]** and a Placebo [**PLAC**]) in 500mls of water are displayed for [iG] and [BG] in **Figures 3.4A and 3.4B** respectively. Detailed glycaemic metrics are displayed in **Table 3.4** with a comparison of [BG] and [iG] measurements displayed in **Table 3.5**.

Influence of carbohydrate glycaemic index on interstitial glucose concentrations

At rest [iG] was similar with all beverages. From rest, the rate of change to peak was different for both **DEX** and **ISO** compared to **PLAC** (**ISO** +0.7±0.3 mg/dL/min, p<0.005) and faster for **DEX** than **ISO** (p=0.001). Peak [iG] was greater for both **DEX** and **ISO** compared to **PLAC** (**ISO** 113±11 mg/dL, p<0.05) but also greater in **DEX** than **ISO** (p<0.001). The time of peak was similar with all trial beverages (~37-44mins). The rate of change from peak to minimum was different for both **DEX** and **ISO** than it was for the **PLAC (ISO** -0.7±0.4 mg/dL/min, p<0.05**)**. The minimum [iG] was lower for **DEX** compared to **PLAC** (p<0.001) and also lower than **ISO (ISO** 76±7 mg/dL, p<0.05), while the time of the minimum was similar for all trial

beverages, occurring between ~70 and 98mins. Finally, the mean [iG] across the 2 h period was greater for both **DEX** and **ISO** compared to **PLAC** (**ISO** 93±6 mg/dL, p=0.05), and it was also greater in **DEX** compared to **ISO** (p=0.01).

Influence of carbohydrate glycaemic index on blood glucose concentrations

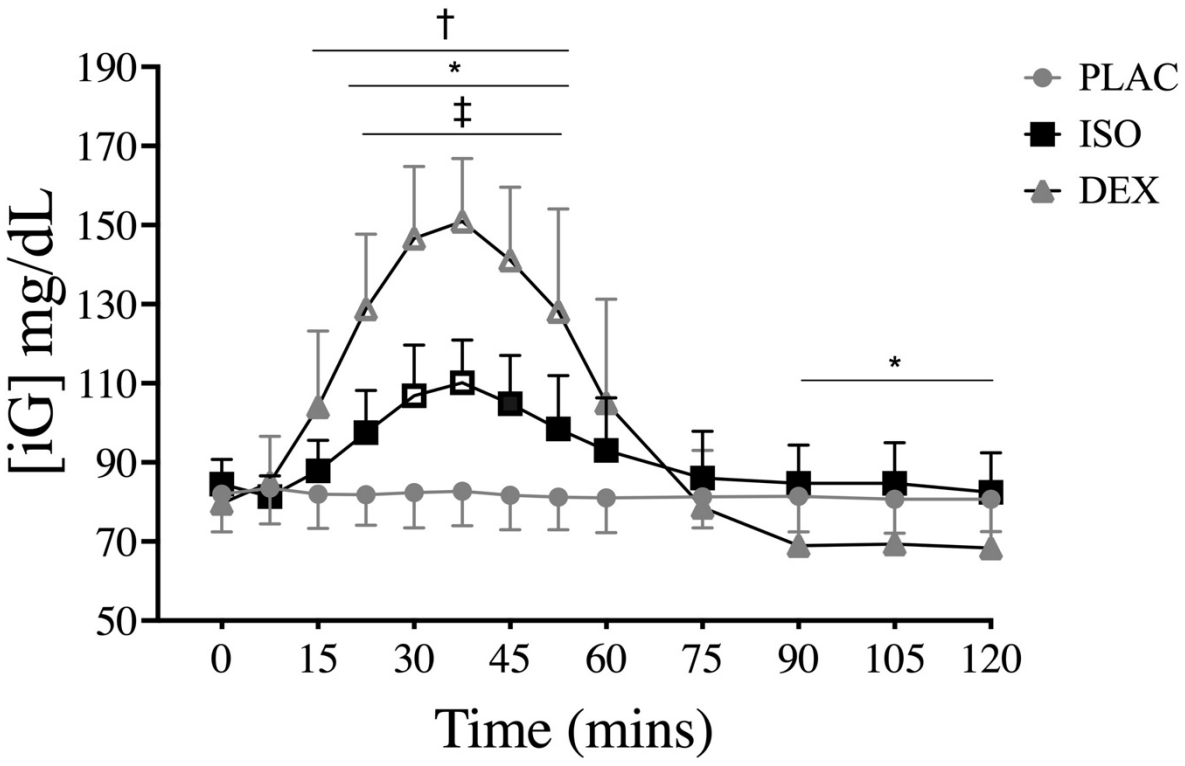
At rest [BG] was similar between all beverages. From rest, the rate of change to peak was different for **DEX** than **PLAC** (p<0.001), and it was faster than **ISO** (+0.8±0.1 mg/dL/min, p<0.001). Peak [BG] was greater with both carbohydrate types compared to **PLAC** (**ISO** 113±17 mg/dL, p<0.05), it was also greater in **DEX** than **ISO** (p<0.001). The time of peak appeared later with **ISO** than it appeared with **PLAC** (**ISO** 42±15mins, p=0.039). The rate of change from peak to minimum was different with **DEX** than it was for PLAC (p=0.001), it was also faster than ISO (0.6±0.4 mg/dL/min, p=0.015). Minimum concentration and the timing of the minimums were similar for both **DEX** and **ISO** when compared to **PLAC**. **DEX**, however, displayed a lower minimum [BG] than **ISO** (78±10 mg/dL, p=0.012). Finally, the mean [BG] across the 2 h period was greater for both **DEX** and **ISO** compared to **PLAC** (**ISO** 95±8 mg/dL, p<0.05).

Comparison of blood and interstitial glucose concentrations in response to consumption of carbohydrate differing in glycaemic index

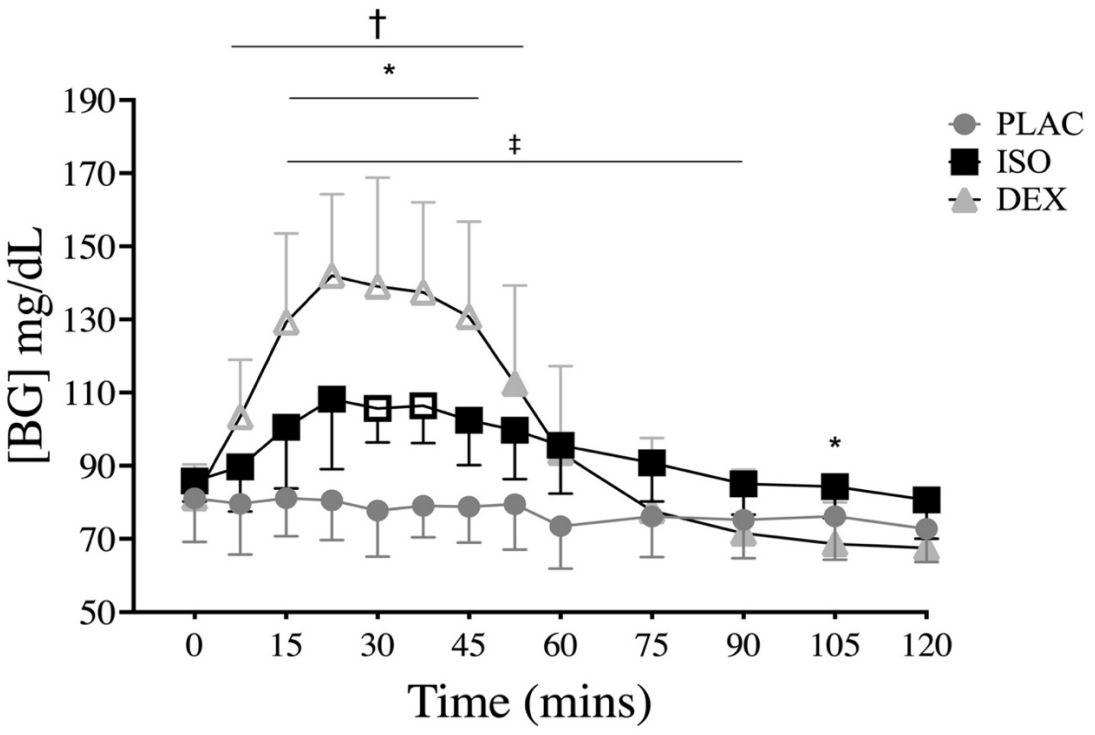
The difference between [BG] and [iG] in the carbohydrate-containing beverages have been adjusted from the differences between [iG] and **PLAC** trial and displayed in **Figure 3.4C**.

During the **PLAC** trial [iG] and [BG] metrics were similar with only minimum values being different (Δ8.5±11.5 mg/dL, p=0.035). At rest, [iG] and [BG] measurements were similar in both **DEX** and **ISO**. The rate of change to peak, the peaks and the timing of the peaks were similar in both [iG] and [BG]. The rate of change from peak to minimum, the minimum and its timing were all similar in both [iG] and [BG] in **DEX** and **ISO**. The mean [iG] and [BG] were also similar in both beverages.

A)


†
*
‡
*
PLAC
ISO
DEX
[iG] mg/dL
190
170
150
130
110
90
70
50
0
15
30
45
60
75
90
105
120
Time (mins)

B)


†
*
‡
*
PLAC
ISO
DEX
[BG] mg/dL
190
170
150
130
110
90
70
50
0
15
30
45
60
75
90
105
120
Time (mins)

C)

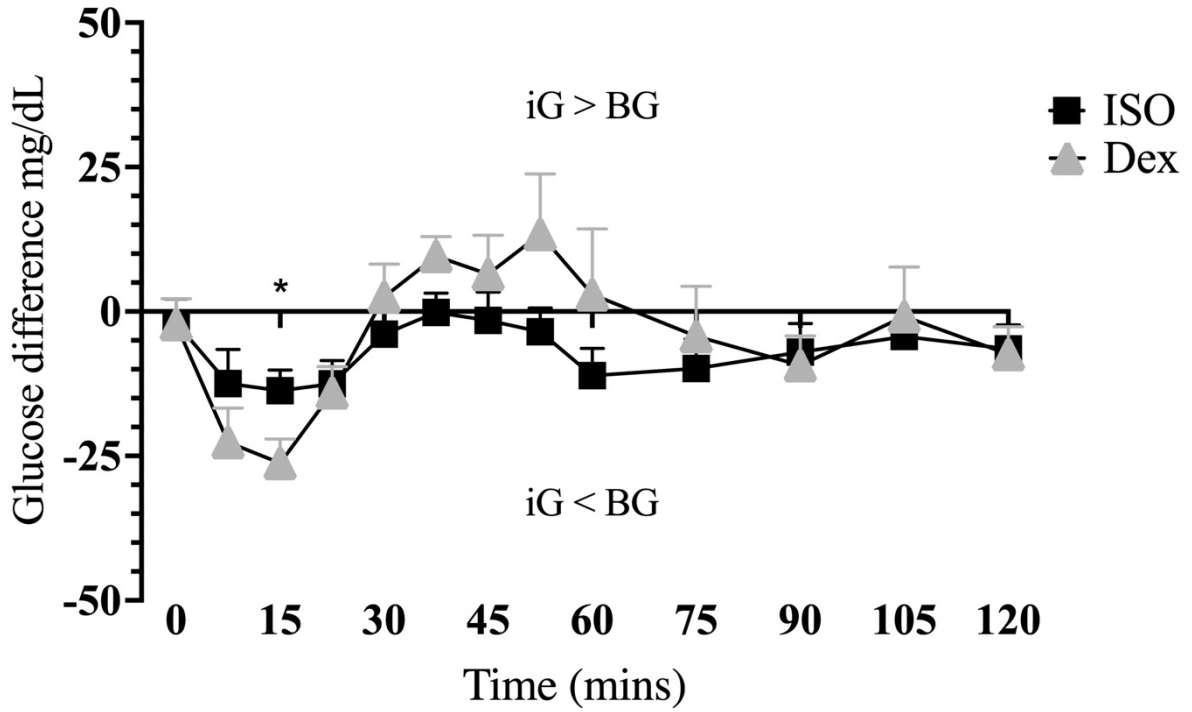


Figure 3.4. A) Interstitial glucose concentrations [iG], B) Blood glucose concentrations [BG] and C) the difference between [BG] and [iG] values in carbohydrate-containing beverages adjusted from the **PLAC** values (C is displayed as Mean ± SEM) following an overnight fasted and over a 2 h following ingestion of 50 g of Dextrose (**DEX**, n=10), Isomaltulose (**ISO**, n=10) or Placebo (**PLAC**, n=11). All carbohydrates were consumed in 480ml water with 20ml flavouring (**PLAC**). Negative values indicate [iG] was were lower than [BG], while positive values indicate where it was greater. Hollow sample points indicate changes from rest within condition. * indicates differences between **DEX** and **ISO**. † indicates differences between **DEX** and **PLAC**. ‡ indicates differences between **ISO** and **PLAC** (P≤0.05). Data is displayed as mean±SD.

Glycaemic Index	[iG]				[BG]			
	DEX (50g 500ml)	ISO (50g 500ml)	Placebo 500ml	p value	DEX (50g 500ml)	ISO (50g 500ml)	Placebo 500ml	p value
Peak (mg/dL)	158±17	113±11*	86±8†‡	**<0.0001**	154±23	113±17*	84±12†‡	**<0.0001**
Mean (mg/dL)	104±9	93±6*	82±8†‡	**<0.0001**	104±13	95±8	77±10†‡	**<0.0001**
Min (mg/dL)	62±7	76±7*	77±8†	**<0.0001**	62±13	78±10*	69±11	**0.016**
Time to peak (mins)	37±8	43±10	44±35	0.742	35±10	42±15‡	25±18	**0.042**
Time to minimum (mins)	98±20	72±47	70±40	0.194	98±34	92±36	89±36	0.844
ROC [rest-peak] (mg/dL/min)	2.2±0.6	0.7±0.3*	0.1±0.3†‡	**<0.001**	2.3±1.0	0.8±0.1*	0.2±0.4†	**<0.001**
ROC [peak to minimum] (mg/dL/min)	1.8±0.8	0.7±0.4*	-0.0±0.4†‡	**<0.001**	1.3±0.4	0.6±0.4*	0.4±0.3†	**<0.001**

Table 3.4. Summary of glycaemic metric comparisons between each beverage for both interstitial [iG] and blood glucose [BG] concentrations. * indicates differences between **DEX** and **ISO**. † indicates differences between **DEX** and **PLAC**. ‡ indicates differences between **ISO** and **PLAC** (P≤0.05). Data is displayed as mean±SD. Rate of change (ROC).

Amount of CHO	**50g**		**[BG] vs. [iG]**	**25g**		**[BG] vs. [iG]**	**10g**		**[BG] vs. [iG]**
	iG	**BG**		**iG**	**BG**		**iG**	**BG**	
Peak (mg/dL)	158±17	154±23	p=0.434	137±17	133±17	p=0.496	107±22	107±14	p=0.95
Mean (mg/dL)	104±9	104±13	p=0.997	93±6	94±10	p=0.690	82±10	85±8	p=0.384
Min (mg/dL)	62±7	59±15	p=0.633	62±6	67±4	**p=0.034***	68±8	72±8	p=0.129
Time to peak (mins)	37±8	35±10	p=0.343	31±5	23±5	**p=0.033***	29±7	24±8	**p=0.05***
Time to minimum (mins)	98±20	98 ±34	p=0.934	71±25	85±28	p=0.442	72±18	102±20	**p=0.01***
ROC [rest-peak] (mg/dL/min)	2.2±0.6	2.3±1.0	p=0.772	1.9±0.5	2.3±0.8	p=0.233	1.2±0.7	1.3±0.7	p=0.689
ROC [peak to minimum] (mg/dL/min)	1.8±0.4	1.3±0.4	p=0.063	1.6±0.4	1.3±0.8	p=0.325	1.2±0.8	0.6±0.3	**p=0.019***
Concentration of Solution	**5%** 720 ± 0 mOsm.kgH_20		**[BG] vs. [iG]**	**10%** 1270 ± 0 mOsm.kgH_20		**[BG] vs. [iG]**	**20%** 2540† ± 0 mOsm.kgH_20		**[BG] vs. [iG]**
	iG	**BG**		**iG**	**BG**		**iG**	**BG**	
Peak (mg/dL)	137±17	133±17	p=0.496	134±18	133±16	p=0.928	138±26	137±31	p=0.596
Mean (mg/dL)	93±6	94±10	p=0.690	94±11	94±10	p=0.913	94±13	101±16	**p=0.03***
Min (mg/dL)	63±6	68±4	**p=0.019***	64±5	64±13	p=0.983	60±3	69±8	**p=0.001***
Time to peak (mins)	31±5	23±5	**p=0.003***	38±7	33±11	**p=0.05***	36±7	35±9	p=0.78
Time to minimum (mins)	71±25	85±28	p=0.442	87±15	94±26	p=0.237	90±22	84±44	p=0.671
ROC [rest-peak] (mg/dL/min)	1.9±0.5	2.3±0.8	p=0.145	1.4±0.6	1.8±0.8	p=0.092	1.7±0.7	1.7±0.8	p=0.742

ROC [peak to minimum] (mg/dL/min)	1.6±0.4	1.3±0.8	p=0.325	1.4±0.4	1.3±0.8	p=0.607	1.6±0.7	1.0±0.6	**p=0.007***
High vs. Low GI	**DEX (High)**		**[BG] vs. [iG]**	**ISO (Low)**		**[BG] vs. [iG]**	**Placebo 500ml**		**[BG] vs. [iG]**
	iG	**BG**		**iG**	**BG**		**iG**	**BG**	
Peak	158±17	154±23	p=0.434	113±11	113±17	p=0.972	86±8	84±12	p=0.542
Mean	104±9	104±13	p=0.997	93±6	95±8	p=0.320	82±8	77±10	p=0.176
Min	62±7	59±15	p=0.633	76±7	78±10	p=0.539	77±8	69±11	**p=0.035***
Time to peak	37±8	35±10	p=0.343	43±10	42±15	p=0.780	44±35	25±18	p=0.070
Time to minimum	98±20	98 ±34	p=0.934	72±47	92±36	p=0.159	70±40	89±36	p=0.236
ROC [rest-peak] (mg/dL/min)	2.2±0.6	2.3±1.0	p=0.772	0.7±0.3	0.8±0.1	p=0.600	0.1±0.3	0.2±0.4	p=0.670
ROC [peak to minimum] (mg/dL/min)	1.8±0.4	1.3±0.4	p=0.063	0.7±0.4	0.6±0.4	p=0.432	-0.0±0.4	0.4±0.3	p=0.057

Table 3.5. Summary of interstitial [iG] and blood glucose [iG] measurements, and differences for all trials. * indicates a statistical difference between BG & iG p≤0.05. † indicates where measurements were estimated due to values exceeding the measurement range. This estimate was made based on expected osmolarity (2 times the 10% beverage osmolarity) All data are displayed as mean±SD (n=10).

3.3.2 CGM accuracy

Across all paired samples (n = 923), the mean absolute relative difference (MARD) was 13.5 ± 13.8%, with a Bland–Altman bias of 1.1 ± 15.8 mg·dL^{-1} and 95% limits of agreement (LOA) from −29.9 to +32.0 mg·dL^{-1}. During hyperglycaemia, bias increased to +15.8 ± 18.4 mg·dL^{-1} (LOA: −20.3 to +52.0 mg·dL^{-1}), while in hypoglycaemia, MARD was 18.5 ± 25% and the CGM underestimated blood glucose by −6.9 ± 14.6 mg·dL^{-1} (LOA: −35.5 to +21.8 mg·dL^{-1}). MARD was greater during hypoglycaemia than during euglycaemia ($p<0.001$) and vs. overall ($p<0.001$). Direction-specific patterns were also evident, with overestimation during rapid glucose rises (+12.9 ± 14.3 mg·dL^{-1}; LOA: −15.3 to +40.8 mg·dL^{-1}) and underestimation during rapid declines (−7.3 ± 27.1 mg·dL^{-1}; LOA: −40.4 to +45.9 mg·dL^{-1}). MARD values are displayed in Table 3.6 below.

	MARD % (95% CI)	**Bland Altman Bias mg/dL (95%LOA)**
Overall (n=923)	13.5±13.8% (12.6, 14.4%)	1.1±15.8 (-29.9, 32)
Hyperglycaemia	12.7±9.5% (9.7, 15.6%)	15.8±18.4 (-20.3, 52.0)
Euglycaemia	12.5±10.3% (11.8, 13.3%)	1.7±15.1 (-27.8, 31.2)
Hypoglycaemia	18.5±25% (14.3, 22.7%)	-6.9±14.6 (-35.5, 21.8)
Rising quickly (>2 mg/dL/min)	13.8±13.1% (11.8, 15.8%)	12.9±14.3 (-15.3,40.8)
Rising (1–2 mg/dL/min)	13.5±12.8% (10.7, 16.2%)	4.9±18.3 (-31.0, 40.7)
Stable (<1 mg/dL/min).	10.5±8.6% (9.5, 11.5%)	0.00±13 (25.4, 25.4)
Falling (1–2 mg/dL/min)	17.0±24.4% (13.5, 20.5%)	-6.3±18.8 (-43.1, 30.4)
Falling Quickly (>2 mg/dL/min)	20.4±27.4% (11.9, 28,9%)	-7.26±27.1 (-40.4, 45.9)

Table 3.6. Displays the percentage of Mean absolute relative difference (MARD), Bland Altman analysis and 95% Limits of agreement (95%LOA) between blood and interstitial glucose concentration in each glycaemic range and during different rates of change as concentration rises and falls. All data is displayed as Mean±SD (901 pairs).

CHO amount	50g [iG]	50g [BG]	[BG] vs. [iG]	50g [iG] Offset	50g [BG] offset	[BG] vs. [iG]	25g [iG]	25g [BG]	[BG] vs. [iG]	25g [iG] offset	25g [iG] Offset	[BG] vs. [iG]	10g [iG]	10g [BG]	[BG] vs. [iG]	10g [iG]offset	10g [BG] offset	[BG] vs. [iG]
Area of Positive AUC	2732	2564	p=0.743	2590	2757	p=0.789	1561	1406	p=0.661	1466	1498	p=0.934	913	730	p=0.513	818	1084	p=458
Std. Error	339	383		415	442		227	271		216	319		234	152		215	286	
95% Confidence Interval	2067 to 3397	1812 to 3315		1777 to 3403	1891 to 3622		1117 to 2005	875 to 1937		1042 to 1890	873 to 2122		454 to 1372	432 to 1028		398 to 1239	524 to 1645	
Area of Negative AUC	408	468	p=0.875	387	204	p=0.598	549	529	p=0.938	606	187	p=0.267	0	277	p=0.081	0	0	NA
Std. Error	243	295		230	259		205	151		294	235		0	158		0	0	
95% Confidence Interval	0.0 to 884	0.0 to 1045		0.0 to 838	0.0 to 710		147 to 950	234 to 824		30 to 1182	0.0 to 647		0.0 to 0.0	0.0 to 587		0.0 to 0.0	0.0 to 0.0	
Total Area	3140	3032	p=0.743	2977	2960	p=0.981	2110	1935	p=0.688	2078	1685	p=0.468	947	1007	p=0.868	874	1084	p=0.587
Std. Error	417	483		474	512		305	310		368	396		285	219		247	286	
95% Confidence Interval	2322 to 3958	2084 to 3979		2048 to 3907	1957 to 3963		1511 to 2709	1327 to 2542		1356 to 2800	909 to 2461		390 to 1505	577 to 1436		389 to 1358	524 to 1645	
Concentration	**5% [iG]**	**5% [BG]**	**[BG] vs. [iG]**	**5% [iG] offset**	**5% [BG] Offset**	**[BG] vs. [iG]**	**10% [iG]**	**10% [BG]**	**[BG] vs. [iG]**	**10% [iG] offset**	**10% [BG] Offset**	**[BG] vs. [iG]**	**20% [iG]**	**20% [BG]**	**[BG] vs. [iG]**	**20% [iG] offset**	**20% [BG] Offset**	**[BG] vs. [iG]**
Area of Positive AUC	1561	1406	p=0.662	1466	1498	p=0.934	1491	1550	p=0.889	1455	1803	p=0.460	1955	2095	p=0.460	1915	2348	p=0.531
Std. Error	227	271		216	319		272	321		268	386		390	456		423	545	
95% Confidence Interval	1117 to 2005	875 to 1937		1042 to 1890	873 to 2122		959 to 2024	920 to 2181		929 to 1980	1047 to 2560		1189 to 2720	1202 to 2989		1085 to 2745	1281 to 3416	
Area of Negative AUC	549	529	p=0.938	606	187	p=0.267	608	505	p=0.696	662	221	p=0.228	437	272	p=0.816	415	0	**p=0.016***
Std. Error	205	151		294	235		162	207		231	282		184	123		171	0	
95% Confidence Interval	147 to 950	234 to 824		30 to 1182	0.0 to 647		291 to 924	100 to 911		210 to 1114	0.0 to 773		77 to 797	30 to 514		80 to 750	0.0 to 0.0	
Total Area	2110	1935	p=0.688	2078	1685	p=0.468	2099	2056	p=0.931	2117	2024	p=0.876	2392	2367	p=0.970	2336	2404	p=0.926
Std. Error	305	310		368	396		316	382		354	478		432	472		459	565	
95% Confidence Interval	1511 to 2709	1327 to 2542		1356 to 2800	909 to 2461		1479 to 2719	1306 to 2805		1423 to 2810	1087 to 2961		1546 to 3238	1441 to 3293		1436 to 3237	1296 to 3512	
Glycaemic Index	**DEX [iG]**	**DEX [BG]**	**[BG] vs. [iG]**	**DEX [iG] Offset**	**DEX [BG] offset**	**[BG] vs. [iG]**	**ISO [iG]**	**ISO [BG]**	**[BG] vs. [iG]**	**ISO [iG] offset**	**ISO [BG] offset**	**[BG] vs. [iG]**						

Area of Positive AUC	2732	2564	p=0.743	2590	2757	p=0.789	857	1019	p=0.649	837	1421	p=0.270
Std. Error	339	383		415	442		256	246		307	431	
95% Confidence Interval	2067 to 3397	1812 to 3315		1777 to 3403	1891 to 3622		355 to 1360	536 to 1501		235 to 1440	575 to 2266	
Area of Negative AUC	408	468	p=0.875	387	204	p=0.598	18	68	p=0.718	31	0	p=0.363
Std. Error	243	295		230	259		22	137		34	0	
95% Confidence Interval	0.0 to 884	0.0 to 1045		0.0 to 838	0.0 to 710		0.0 to 60	0.0 to 336		0.0 to 98	0.0 to 0.0	
Total Area	3140	3032	p=0.743	2977	2960	p=0.981	889	1087	p=0.610	874	1421	p=0.306
Std. Error	417	483		474	512		267	281		314	431	
95% Confidence Interval	2322 to 3958	2084 to 3979		2048 to 3907	1957 to 3963		366 to 1413	535 to 1638		259 to 1489	575 to 2266	

Table 3.7. Glucose responses (area under the curve, AUC) to beverages varying in carbohydrate amount, concentration, and glycaemic index, comparing interstitial glucose [iG] and blood glucose concentrations [BG]. Absolute AUC values and placebo-adjusted (offset). Positive AUC represents glucose excursions above baseline, while negative AUC reflects dips below baseline. Total AUC represents net glucose excursion. * indicates a statistical difference between iG & BG $p \leq 0.05$.

Area under the curve (AUC)

Absolute AUC and placebo-adjusted (offset) AUC values are presented in **Table 3.7**. Positive AUC refers to glucose excursions above baseline, while negative AUC reflects the area contained within the dips below baseline. The absolute AUC reflects overall glucose dynamics across the 2hr period while the offset values help to isolate the impacts of the individual beverage interventions. [iG] and [BG] in both absolute and offset values were similar only showing a difference in the 20% concentration values when offset against the Placebo trial.

Figure 3.5 below, displays a surveillance error grid of all measured glucose data from the CGM paired to the reference measurements (901 pairs). 72.4% (652 pairs) showed no risk of error, 22% (198) showed slight risk of lower measurement, 5.1% (46 pairs) showed slight risk of higher measurement, 0.04% (4 pairs) showed moderate risk of lower measurement and 0.01% (1 pair) showed a moderate risk of over measurement.

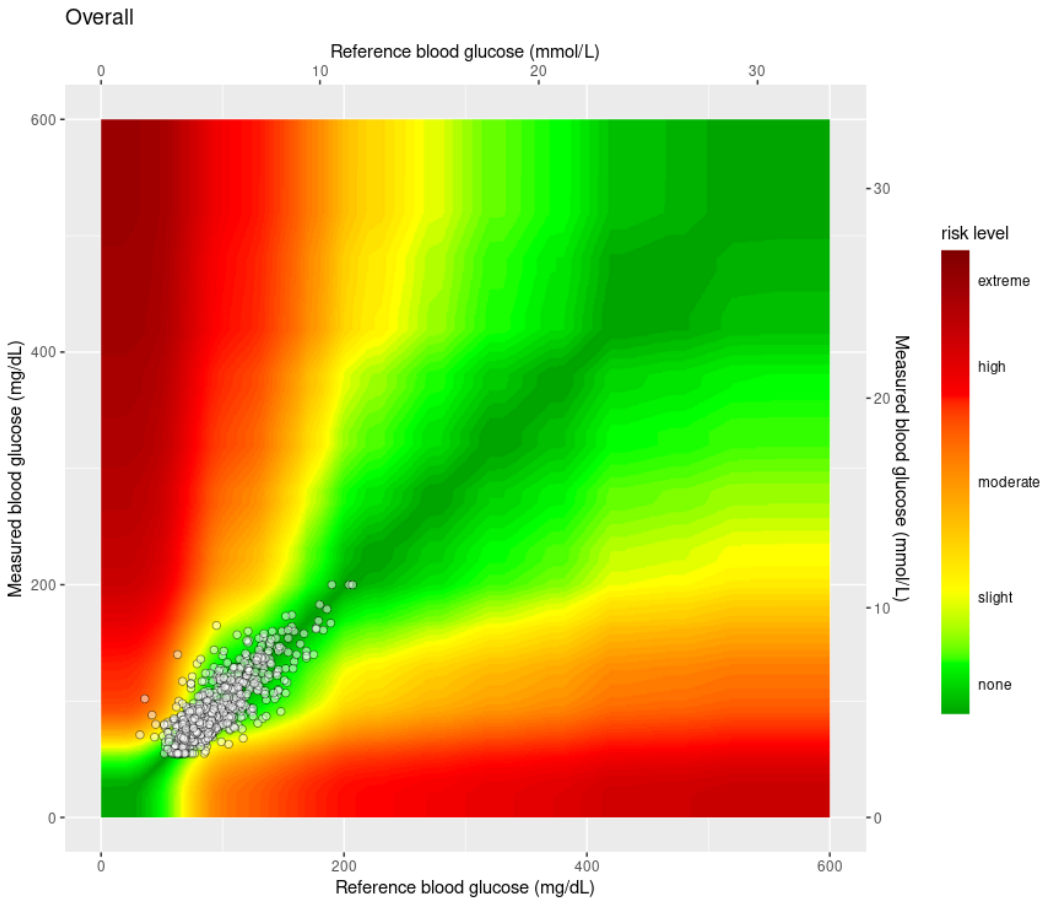


Figure 3.5. Colour-coded continuous surveillance error grid and key to colour-coded risk levels for all glucose measurements comparing the continuous glucose monitoring (CGM) device to the reference measurement (901 pairs). Colours indicate associated risk levels ranging from none (dark green) to extreme (brown).

Figure 3.6. below displays a surveillance error grid of all measured glucose data which was above the target range (>140 mg/dL) as defined by reference measures (42 pairs). 81% (34 pairs) showed no risk of error, and 19% (8 pairs) showed slight risk of lower measurement.

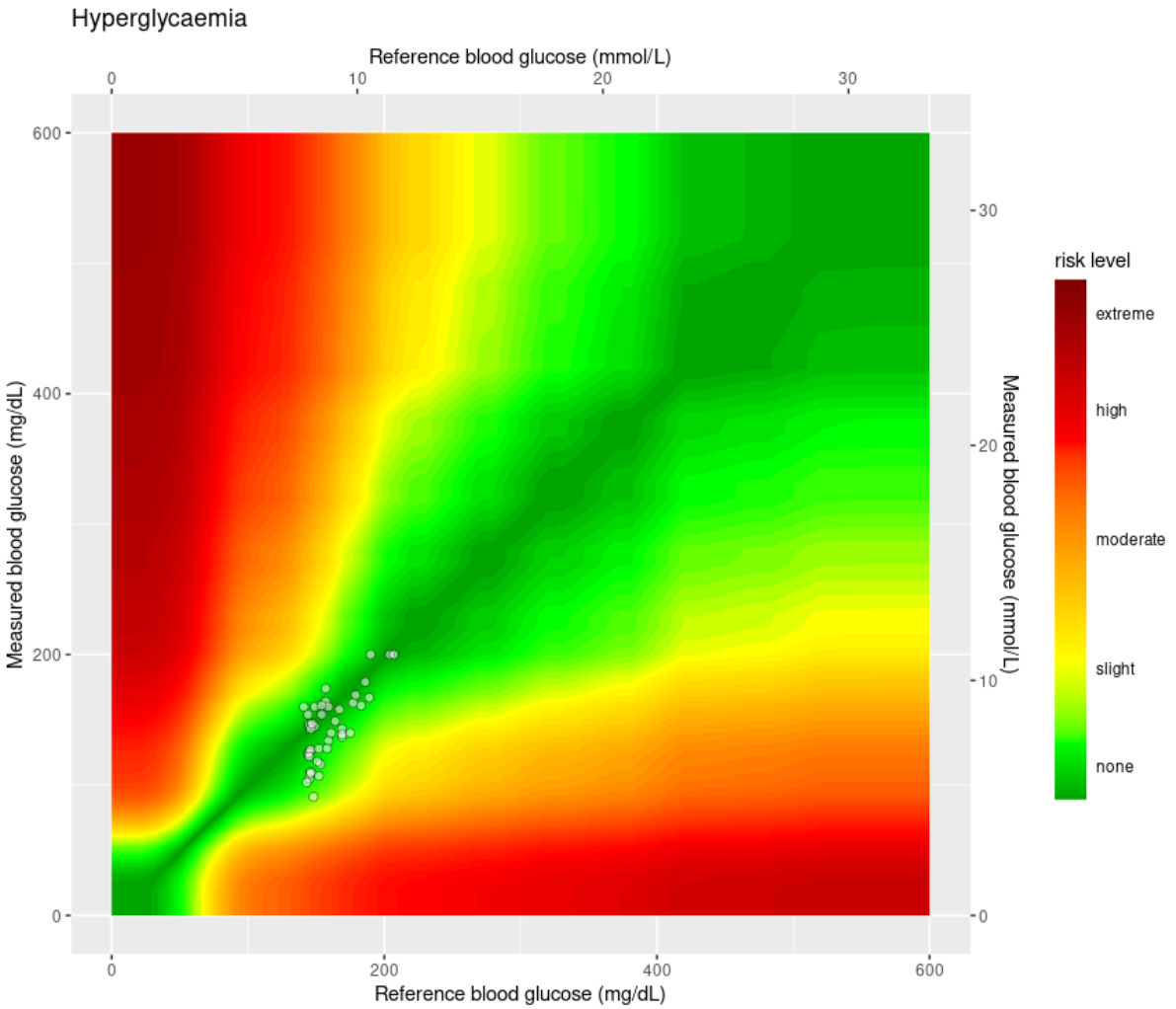


Figure 3.6. Colour-coded continuous surveillance error grid and key to colour-coded risk levels for all glucose measurements which were above the target range (>140 mg/dL) as defined by reference measures (42 pairs). Colours indicate associated risk levels ranging from none (dark green) to extreme (brown).

Figure 3.7 below, displays a surveillance error grid of all measured glucose data from the CGM paired to the reference measurements (726 pairs) falling within target range (71-140 mg/dL) as defined by reference measures. 75.3% (547 pairs) showed no risk of error, 20.9% (152) showed slight risk of lower measurement and 3.7% (27 pairs) showed slight risk of higher measurement.

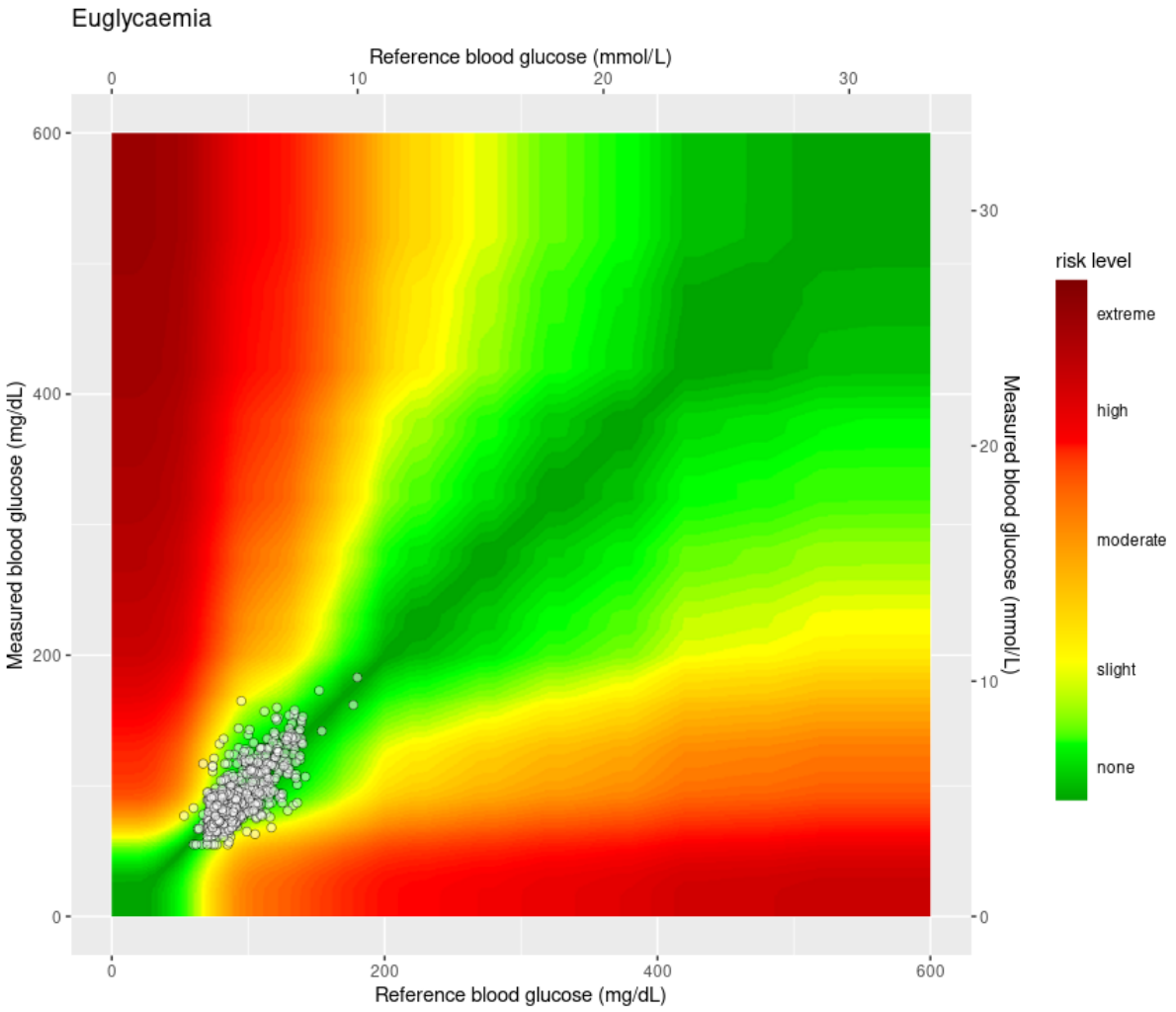


Figure 3.7. Colour-coded continuous surveillance error grid and key to colour-coded risk levels for all glucose measurements falling within target range (71-140 mg/dL) as defined by reference measures (726 pairs). Colours indicate associated risk levels ranging from none (dark green) to extreme (brown).

Figure 3.8 below displays a surveillance error grid of all measured glucose data from the CGM paired to the reference measurements (133 pairs), which fall below the target range (<71 mg/dL) as defined by reference measures. 53.4% (71 pairs) showed no risk of error, 28.6% (38) showed slight risk of lower measurement, 14.3% (19 pairs) showed slight risk of higher measurement, 3% (4 pairs) showed moderate risk of lower measurement and 0.8% (1 pair) showed a moderate risk of over measurement.

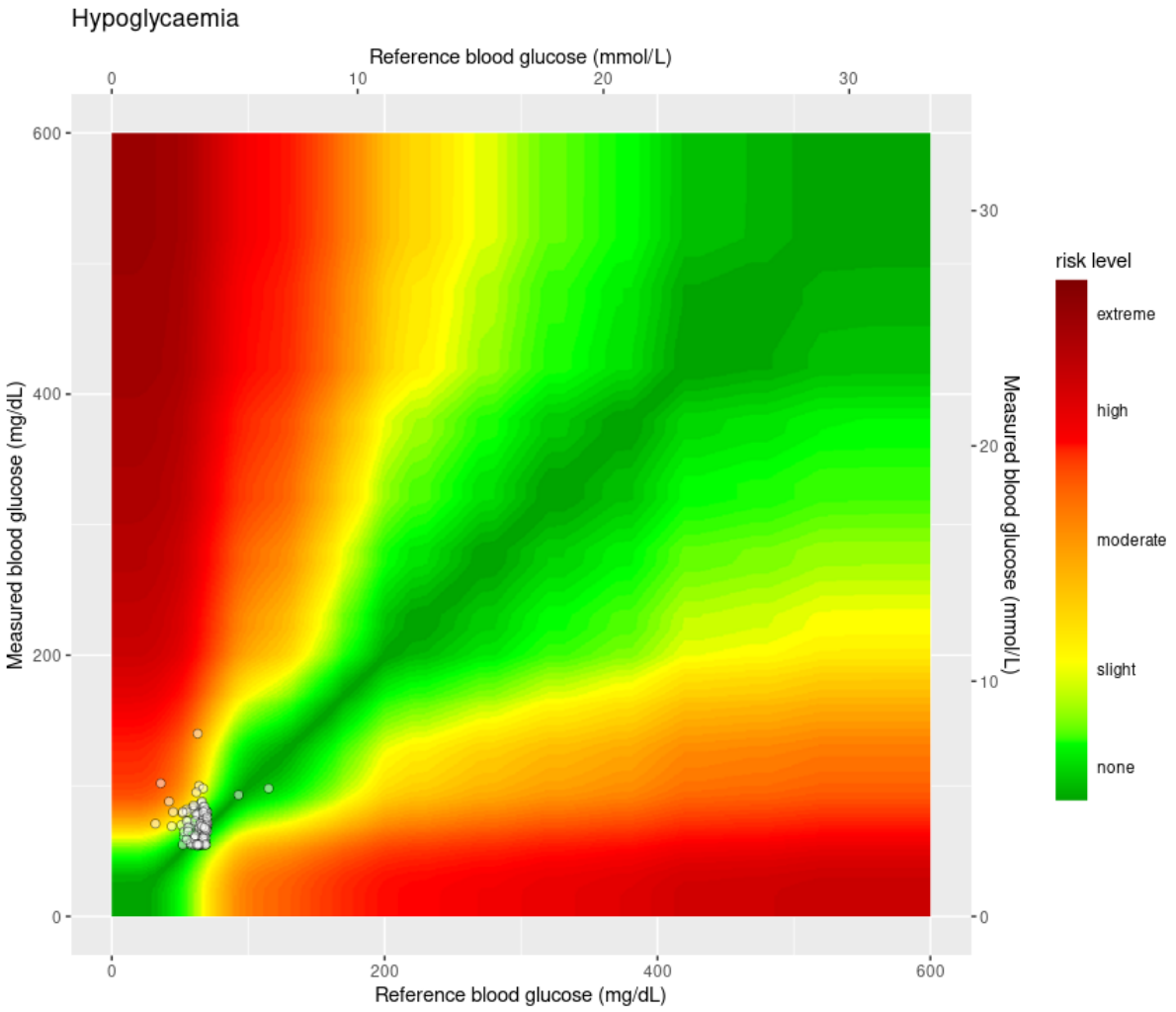


Figure 3.8. Colour-coded continuous surveillance error grid and key to colour-coded risk levels for all glucose measurements which fall below target range (<71 mg/dL) as defined by reference measures (133 pairs). Colours indicate associated risk levels ranging from none (dark green) to extreme (brown).

3.3.3 Plasma Volume Changes

Plasma volume changes from rest (baseline) were estimated using measures of haemoglobin and haematocrit at 30, 60, 90 and 120 min timepoints. Summary data for haemoglobin and haematocrit are displayed in **Table 3.8** while summary data for estimated plasma changes are displayed in **Table 3.9**.

Carbohydrate amount

After consuming a beverage with different amounts of dextrose (**50g, 25g and 10g**) and a Placebo (**PLAC**) in a fixed volume of water (500mls) no differences in haemoglobin changes

were detected between amounts (p=0.808). Differences were detected within the **25g** trial. Haemoglobin was different from baseline at 90 mins (p=0.05) and at 120 mins (p=0.023). Haematocrit was similar between carbohydrate amounts (p=0.963) and within each trial across all timepoints (p=0.999). Plasma volume changes were similar between amounts (p=0.101) and within each trial across all timepoints (p=0.925).

Concentration of solution

After consuming beverages containing a fixed amount of carbohydrate in differing fluid concentrations (**5%, 10% and 20%**) no changes in haemoglobin were detected between solutions(p=0.743). Differences were detected within the **10%** trial. Haemoglobin was different from baseline at 90 mins (p=0.05) and at 120 mins (p=0.023). Haematocrit was similar between all solutions (p=0.958). The timepoint of measurement affected haematocrit changes (p=0.001) however, post hoc analysis did not locate differences within any specific trial. Plasma volume changes were similar between solutions (p=0.262) and within each trial across all timepoints (p=0.358).

Glycaemic Index

After consuming 50g of carbohydrates differing in their glycaemic index (**DEX and ISO**), haemoglobin plasma volume changes were similar between each carbohydrate type (p=0.532) and within each trial across all timepoints (p=0.229). Haematocrit was similar between each carbohydrate type (p=0.825). Haematocrit changes were different between timepoints (p=0.040) but post hoc analysis did not located differences within either carbohydrate type. Plasma volume changes were similar between each carbohydrate type (p=0.277) and within each trial across all timepoints (p=0.852).

Carbohydrate amount								
	50g		25g		10g		PLAC	
Δ	**Hct**	**Hb**	**Hct**	**Hb**	**Hct**	**Hb**	**Hct**	**Hb**
Baseline	43±4	144±11	43±3	137±11	42±3	146±11	44±2	146±7
30min	43±3	140±7	43±3	144±9	43±2	146±8	44±3	148±9
60min	43±4	141±8	43±3	145±5	44±2	145±8	44±3	148±8
90min	44±4	148±6	43±3	**149±10**	43±3	146±7	44±2	148±10
120min	43±4	147±11	43±3	**151±7**	44±3	145±8	44±2	145±14
Concentration of solution								
	5%		**10%**		**20%**		**PLAC**	
Δ	**Hct**	**Hb**	**Hct**	**Hb**	**Hct**	**Hb**	**Hct**	**Hb**
Rest	43±3	137±11	42±3	141±8	43±3	143±8	44±2	146±7
30 mins	43±3	144±9	43±3	144±10	43±3	145±11	44±3	148±9
60 mins	43±3	145±5	43±3	141±9	43±3	144±8	44±3	148±8
90 mins	43±3	**149±10**	44±3	144±10	44±3	141±11	44±2	148±10
120 mins	43±3	**151±7**	44±3	148±7	44±3	147±12	44±2	145±14
Glycaemic index								
	DEX		**ISO**		**PLAC**			
Δ	**Hct**	**Hb**	**Hct**	**Hb**	**Hct**	**Hb**		
Rest	43±4	144±11	42±3	142±7	44±2	146±7		
30	43±3	140±7	43±2	144±6	44±3	148±9		
60	43±4	141±8	43±2	151±6	44±3	148±8		
90	44±4	148±6	44±2	144±8	44±2	148±10		
120	43±4	147±11	43±2	150±6	44±2	145±14		

Table 3.8. Haemoglobin (Hb) (g/L) and haematocrit (Hct) (%) changes from rest (baseline) and thereafter at 30, 60, 90 and 120 min timepoints after consuming a beverage with carbohydrates with different amounts of carbohydrate (**50g, 25g and 10g**), different concentrations (**5%, 10% and 20%**) and different glycaemic index (**DEX** and **ISO**) compared to a Placebo (**PLAC**) in a fixed volume of water (500mls). Values in bold indicate a difference from resting values. * indicates a difference between **DEX** and **ISO.** Data is displayed as mean±SD, $p \leq 0.05$.

Carbohydrate amount				
PV%Δ	**50g**	**25g**	**10g**	**PLAC**
Rest	-	-	-	-
30min	3.4±9.2	-4.8±6.7	-1.2±4.8	-1.2±7.3
60min	-0.2±9.3	-1.4±5.3	0.2±6.8	-0.4±8.1
90min	-5.8±3.2	-2.3±6.5	7.3±20.1	0.2±7.8
120min	2±7.7	-1.1±7.1	-4.5±14.6	2.2±9.1
Concentration of solution				
PV%Δ	**5%**	**10%**	**20%**	**PLAC**
Rest	-	-	-	-
30 mins	3.4±9.2	-8.0±15.3	-0.8±10.7	-1.2±7.3
60 mins	-0.2±9.3	2.4±6.5	1.4±7.2	-0.4±8.1
90 mins	-5.8±3.2	-2.8±7.5	1.3±9.0	0.2±7.8
120 mins	2±7.7	-2.8±8.8	-3.6±6.5	2.2±9.1
Glycaemic index				
PV%Δ	**DEX**	**ISO**	**PLAC**	
Baseline	-	-	-	
30	3.4±9.2	-2.1±8.4	-1.2±7.3	
60	-0.2±9.3	-4.1±6.9	-0.4±8.1	
90	-5.8±3.2	3.3±10	0.2±7.8	
120	2±7.7	-3.1±5.0	2.2±9.1	

Table 3.9. Plasma volume changes from rest (baseline) and thereafter at 30, 60, 90 and 120min timepoints after consuming a beverage with carbohydrates with different amounts of carbohydrate (**50g, 25g and 10g**), different concentrations (**5%, 10% and 20%**) and different glycaemic index (**DEX** and **ISO**) compared to a Placebo (**PLAC**) in a fixed volume of water (500mls). Data is displayed as mean±SD, $p \leq 0.05$.

3.4 Discussion

This study aimed to investigate the relationship between interstitial and blood glucose concentrations following ingestion of various carbohydrate-containing beverages. By assessing the agreement between glycaemic metrics derived from both compartments, some potential physiological and sensor-related measurement differences were identified. These findings highlight conditions that may compromise CGM accuracy and the susceptibility of certain metrics to divergence from blood-based measurement.

3.4.1 Glycaemic responses and sensor agreement

Overnight fasted, morning rested interstitial and blood glucose concentrations were similar at the start of all trials. Following ingestion of different carbohydrate containing beverages, both [iG] and [BG] rose. The rate of glucose rise from baseline to peak was delayed for [iG] in several trials (**Table 3.5**). MARD values varied depending on the speed and direction of glucose change. While peak concentrations were generally similar, bias and error increased at higher glucose levels and during more dynamic phases of the OGTT. In agreement with other work, higher glucose concentrations and faster rates of change were associated with greater bias and reduced accuracy (Jin et al., 2023; O. Moser, Eckstein, McCarthy, et al., 2019). Across all paired samples (n = 923), MARD was 13.5 ± 13.8%, with a Bland–Altman bias of 1.1 ± 15.8 $mg \cdot dL^{-1}$ and 95% limits of agreement ranging from −29.9 to +32.0 $mg \cdot dL^{-1}$, indicating moderate overall agreement but considerable individual variability. The ±30 $mg \cdot dL^{-1}$ limits suggest that although mean bias was small, individual readings could differ meaningfully between blood and interstitial compartments, particularly when glucose levels were changing rapidly.

During periods of rising glucose, particularly >2 $mg \cdot dL^{-1} \cdot min^{-1}$, MARD increased to 13.8 ± 13.1%, with [iG] showing a positive bias (+12.9 ± 14.3 $mg \cdot dL^{-1}$; LOA: −15.3 to +40.8 $mg \cdot dL^{-1}$). Slower rates of rise (1–2 $mg \cdot dL^{-1} \cdot min^{-1}$) yielded similar MARD values (13.5 ± 12.8%) but smaller bias (+4.9 ± 18.3 $mg \cdot dL^{-1}$). Accuracy was highest when glucose remained relatively stable (MARD: 10.5 ± 8.6%; bias: 0.0 ± 13.0 $mg \cdot dL^{-1}$; LOA: −25.4 to +25.4 $mg \cdot dL^{-1}$).

Both carbohydrate amount and glycaemic index were significant contributors to the peak post-ingestion, as expected from previous observations (Augustin et al., 2015; Brouns et al., 2005; Jenkins et al., 1981; Pasmans, Meex, van Loon, & Blaak, 2022). Fixed amounts of carbohydrate in varying fluid volumes (5%,10% and 20% solutions) appeared to produce similar peak glucose concentrations regardless of the carbohydrate concentration of the drink. MARD values were 12.5±9.5 %, 12.7±9.5%, with a bias of 15.8±18.4 mg/dL during hyperglycaemia (LOA: −20.3 to +52.0 mg·dL^{-1}). This widening of the limits of agreement at higher glucose concentrations indicates greater dispersion and reduced reliability at the upper end of the range, a pattern also observed in recent CGM validation studies (Hutchins et al., 2025).

Greater glycaemic differences between [iG] and [BG] were observed during glucose declines. When glucose was falling rapidly (>2 mg/dL/min), MARD reached 20.4±27.4%, and [iG] underestimated [BG] by -7.26±27.1 mg/dL (LOA: −40.4 to +45.9 mg·dL^{-1}). Even moderate declines (1–2 mg/dL/min) resulted in elevated MARD (17.0±24.4%) and negative bias (-6.3±18.8 mg/dL). Similarly, MARD in hypoglycaemia was elevated (18.5 ± 25%), with a consistent tendency for [iG] to underestimate [BG] (bias: −6.9 ± 14.6 mg·dL^{-1}; LOA: −35.5 to +21.8 mg·dL^{-1}).

The wider LOA observed during rapid changes and at glycaemic extremes suggests that transient physiological lag and sensor kinetics substantially influence the instantaneous alignment between compartments. Collectively, these data indicate that while overall bias remained relatively low, the limits of agreement were impacted substantially during rapid changes and at glycaemic extremes, suggesting that [iG] tracks directionality but cannot be considered interchangeable with [BG] on a point-by-point basis. The LOA observed in our study is similar to that observed in a number of others in similar cohorts. Fellinger et al. (2024) reported LOA ranging −20.7 to 42.8 mg/dL, while Jin et al. (2023) observed −25.9 to 67.0 mg/dL.

These findings in healthy individuals without diabetes confirm that differences between interstitial and blood glucose are most pronounced during fast-changing glycaemic states. CGM can misrepresent declines in glucose concentration. While this is unlikely to pose a substantial health risk in healthy populations, in a clinical context, this can be particularly hazardous for insulin-dependent individuals who rely on CGM for real-time decision-making (Brar et al., 2024). This is especially important for those utilising an automated insulin delivery

(AID) system, where insulin dosing decisions are made algorithmically based on interstitial glucose trends (Sherr et al., 2023). If a device underestimates [BG] during a declining phase, it may fail to alert users to an impending hypoglycaemic episode or prompt corrective carbohydrate ingestion based on a perceived low [iG] value, when blood glucose is not critically low. A confirmation via a self-monitoring blood glucose (SMBG) device might be advised for safety reasons under these circumstances, especially when symptoms do not match CGM trends (O. Moser et al., 2016).

For healthy or athletic populations, this inaccuracy has broader implications. In situations where athletes use CGM to guide fuelling during extended or high-intensity sessions, a false sense of urgency to consume carbohydrates, or a failure to respond to actual hypoglycaemia, could compromise performance or safety.

Together with prior findings, our data suggest CGM provides valuable trend information but should not be solely relied upon during rapid glucose changes or hypoglycaemia. Practitioners and users must interpret low [iG] values cautiously, considering glucose trajectory and context rather than absolute values alone.

3.4.2 Factors influencing CGM accuracy

Mean blood glucose is important in the clinical use of CGM as it is linked to HbA1c over prolonged periods (Makris & Spanou, 2011). While mean [iG] and [BG] were generally similar over two hours, this masked discrepancies during post-peak declines, for example, the 20% carbohydrate trial showed a greater drop in post-peak [iG], lowering overall mean [iG]. This highlights limitations of summary metrics in capturing acute glucose dynamics.

Glycaemia is generally considered to be relatively tightly controlled in healthy participants. The range of expected concentration deviations is much less than that experienced in type 1 diabetes. However, accuracy in our study was better than what was observed in other studies with healthy participants after feeding. Jin et al. (2023) reported much greater MARDs during all glycaemic states and rates of change; however, in their study, CGM was being compared to venous sampling as opposed to the capillary sampling in ours. O. Moser, Eckstein, McCarthy, et al. (2019) also examined the accuracy of CGM in relation to glycaemic states in individuals with type 1 diabetes. In comparison to our data accuracy (assessed by MARD) was slightly

worse overall (13.5±13.8 vs. 14.3%), during euglycaemia (12±10.3 vs. 16%) and during hypoglycaemia (18.5±25 vs. 31.6%), but it was slightly better during hyperglycaemia (12.7±9.5 vs. 9.4%). It is worth noting that the range of deviation for each measure in our study was relatively high. Glycaemic state, however, appears to have a correlative relationship with sensor accuracy.

Some of the differences observed may relate to the time required for glucose to move from blood into the interstitial space (Schmelzeisen-Redeker et al., 2015). Cellular uptake may also create another source of divergence from blood concentration (Richter et al., 2025). While CGM algorithms attempt to compensate for this delay, the observed errors show that such filtering is not always sufficient to preserve accuracy (Siegmund et al., 2017), especially during rapid declines (Davey, Low, Jones, & Fournier, 2010).

The lowest accuracy and largest discrepancies were observed during falling glucose, where [iG] often showed a greater decline than [BG]. Glucose uptake in surrounding tissues, combined with a delayed fall in interstitial concentrations, may account for this pattern (Richter et al., 2025). Falling glucose thus remains the most challenging condition for CGM accuracy, particularly in non-clinical settings where relative changes may be more informative than absolute thresholds.

3.4.3 Sensor design and algorithmic filtering

CGMs detect glucose chemically, producing a signal influenced by biological factors (contamination, hydration, temperature) and sensor interference (movement, pressure). Time lag between blood and interstitial glucose is inherent. Modern CGMs use filtering algorithms and predictive modelling to smooth data, improve accuracy, and reduce artefacts (Rebrin, Sheppard, & Steil, 2010). While these advances have lowered MARD over time, they highlight the limits of how precisely sensors can reflect blood glucose instantaneously.

3.4.4 Practical implications

This study demonstrates that CGM can reflect the general direction of blood glucose change in response to carbohydrate ingestion, but caution is required when interpreting values during rapidly changing or low glucose states (Brar et al., 2024). Researchers and practitioners using CGM in acute non-clinical settings should be aware that common metrics such as mean glucose

may not fully capture the dynamics of interest. Metrics based on the rate of change or relative trends may be more appropriate in these contexts. In addition, some caveats must be applied to the level of accuracy of displayed values. More chronic glycaemic investigations may also warrant the use of metrics which better reflect long-term glycaemia, such as time in range, given the limitations of short-term acute observations.

3.4.5 Strengths and limitations

A key strength of this study was its randomised, within person, controlled design, which enabled direct comparisons across different carbohydrate formulations. The inclusion of a placebo trial helped to isolate beverage effects from natural glycaemic variability. A limitation was the CGM measurement floor of 54 mg/dL, which may have prevented detection of true minimum values and influenced some post-peak metrics. However, [iG] still measured lower than [BG] in several instances, suggesting that this limitation did not affect the main findings.

3.5 Conclusion

This study aimed to assess the agreement between interstitial glucose [iG] and blood glucose [BG] responses following ingestion of carbohydrate-containing beverages differing in amount, concentration, and glycaemic index. While CGM-derived [iG] generally tracked the direction of [BG] changes, discrepancies emerged during periods of rapid glucose decline or hypoglycaemia. Overall, MARD (13.5±13.8%) aligns with prior healthy individual data (Nielsen et al., 2024). Accuracy was acceptable during stable or rising glucose but requires caution during declines to avoid underestimation and misinterpretation. In applied or research contexts, glucose trend direction and rate of change are essential complements to absolute [iG] values for meaningful interpretation. To understand how these measurement characteristics present over longer periods in real-world settings, Chapter 3 examined day-to-day glycaemic variability in professional athletes during a multi-day training camp.

CHAPTER FOUR

Continuous measurement of interstitial glycaemia in professional female UCI world tour cyclists undertaking a 9-day cycle training camp

4.1 Introduction

Historically, scientific understanding of the demands of professional cycling has been obtained from predominantly male riders with a clear under-representation of female cyclists in research and practice. Encouragingly, there has been an increase in the number of professional female cycling teams now competing in previously male-only events (Sanders, van Erp, & de Koning, 2018; The Cyclists' Alliance, 2022).

In the limited number of exercise science studies that have explored sex comparisons, many are performed in the controlled setting of the exercise laboratory (Clavel et al., 2022; Doering, Cox, Areta, & Coffet, 2019; Hawley, Bosch, Weltan, Dennis, & Noakes, 1994; Herrington et al., 2012; F. Thomas, Pretty, Signal, Shaw, & Chase, 2017). Whilst offering a greater degree of control, laboratory-based protocols and environmental conditions often fail to reflect the real-world scenarios that are habitually undertaken in the field and suffer from poor ecological validity. Thus, observations of cyclists in their habitual training or race environments are important in shedding new light on the demands of the female athlete.

Stores of carbohydrate and circulating glucose are the preferred fuels during intense exercise and it is well recognised that maintaining adequate supply is essential for optimising performance (A Coggan & Coyle, 1987; AR Coggan & Coyle, 1989; Jeukendrup, 2014a; Jeukendrup & Jentjens, 2000; Jeukendrup, Raben, et al., 1999; Jeukendrup, Wagenmakers, et al., 1999). The relatively recent development of continuous glucose monitoring (CGM) provides real-time feedback of interstitial glucose concentrations via subcutaneous sensors viewed by a mobile phone application or reader. Though originally developed for the therapeutic management of people with diabetes, these technologies have recently grown in popularity as a 'biofeedback tool' in athletes (Bowler *et al*., 2022; Holzer *et al*., 2022). Whilst studies have noted the potential utility of CGM in an exercising context, there is currently very little evidence of its utility in an applied sporting setting (Holzer *et al*., 2022; Kinrade & Galloway, 2021; Klonoff *et al*., 2022; Podlogar & Wallis, 2022). Although the use of CGM is prohibited in racing by the Union Cycliste Internationale (UCI), gathering information under training conditions might be valuable in progressing our understanding of the glycaemic demands of sports performance in elite level athletes. The potential to amalgamate data from physical activity wearables e.g., mobile power meters and heart rate monitors presents

opportunities to explore how glycaemia might be influenced by endurance exercise stress in competitive athletes.

With this in mind and given the inherent sex differences in physiological and metabolic responses to exercise (Cano et al., 2022; Elliot-Sale et al., 2021; Tarnopolsky, MacDougall, Atkinson, Tarnopolsky, & Sutton, 1990; Wismann & Willoughby, 2006), more female-focused research in professional cycling is warranted in an attempt to bridge current knowledge gaps.

This study aimed to characterise the day-to-day glycaemia of professional female UCI world tour cyclists using continuous interstitial glucose monitoring over a 9-day cycle training camp.

4.2 Methods

4.2.1 Study design

This was an observational, exploratory study involving nine professional female UCI tour riders. Ethical approval was granted by Supersapiens^{TM}. An in-house ethical review was conducted by the company's Medical Officer in accordance with internal governance procedures (Ref no. SS-001). The study was carried out in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice. Only data collected from cyclists that provided informed consent were included in the study.

4.2.2 Cycle training regimen

Data was collected over a nine-day training camp undertaken in January in Majorca, Spain. Throughout this period, riders performed daily exercise training sessions that were individualised and prescribed by the team's sports performance coaches. Some riders completed supplemental sessions aimed at addressing injury rehabilitation. The group took one rest day (day 4) and one reduced riding day (day 7), the latter of which was a sponsor-related online cycling event. A summary of the grouped mean training loads throughout the week is detailed in **Table 4.1**.

The riders were on a training camp in the early stage of the season, focusing mostly on low intensity training volume. This was the first group meet-up of the year and, for several riders, their first involvement with the team. All training data was collected via individual rider head units and power meters. Each rider's data was imported to the Training Peaks application (Training Peaks, Peaksware LLC, Louisville, USA), then downloaded and sent to the research team for retrospective analyses. For each session, the head units recorded distance (km), speed (km/hr), power (watts) and heart rate (beats per minute).

Although dietary information was initially intended to be collected in collaboration with the professional cycling team, data provision was voluntary and inconsistent. The resulting dietary logs were incomplete and lacked sufficient detail for analysis, and were therefore excluded.

This did not affect the primary study objective, which was to characterise glycaemia and observe trends.

4.2.3 Computation of glycaemic data

All interstitial glucose [iG] data were recorded via the Abbot Libre Sense Biosensor CGM (Abbot Laboratories, Chicago, IL, USA). The sensor was applied to the subcutaneous fat pad located over the triceps brachii as per manufacturer instructions (see additional procedure in **section 2.4.2**). The CGM device was paired to the Supersapiens™ Software application (TT1 Products Inc., Atlanta, GA, USA) which was installed on the participant's smart phone. Raw CGM data were exported and analysed via Excel 2019 (Microsoft Corp., Redmond, WA, USA). Daily [iG] data were retrospectively split into distinct time ranges i.e., Overall (24-hourly), day-time (06:00-23:59), night-time (00:00-05:59) and exercise; defined as the data points that fell within the in-ride time-frame provided from each rider's head unit.

Group means were calculated for [iG] concentrations (mg/dL) and indices of glycaemic variability i.e., the coefficient of variation (CV) and standard deviation (SD). [iG] data were also stratified into a percentage of time spent in specific glycaemic ranges pre-defined by the Supersapiens™ application: time below range ([TBR] <70 mg/dL), time in range ([TIR] 70-140 mg/dL) and time above range ([TAR] ≥141 mg/dL).

4.2.4 Statistical analyses

All statistical analyses were carried out using SPSS V 28.0 statistical software and GraphPad Prism V 9.5. All data were checked for normality. Data are presented as mean±SD. Differences between variables across the days of the camp were assessed using a repeated measures one-way ANOVA. A two-way ANOVA was used to discern differences between day- and night-time variables as the camp duration progressed. Pearson's product moment correlation of coefficient test was used to explore relationships between exercise variables. A p-value of ≤0.05 was accepted as a statistically significant difference or relationship. See further details and sample size justification in **section 2.12**.

4.3 Results

4.3.1 Participants

Nine female UCI World tour riders (age: 26±5 years, height: 168±5 cm, mass: 58.5±4.5 kg) took part in the study.

4.3.2 Exercise training data

Grouped mean daily exercise duration was 4:15:03±1:43:50 hours during the camp. Riders completed a mean of 7±2 rides over the nine-day period. During camp, riders had one complete rest day (day 4) and one day with a short session of active recovery (day 7). The mean distance covered per training session was 116.11±48.95 km. Mean heart rate during exercise was 138±4 bpm. Mean power output was 152±10 watts. Summary exercise training data is displayed in **Table 4.**

Day	Duration (hr:min:sec)	Distance (km)	Heart rate (bpm)	Power (watts)	Speed (km/hr)
1	03:47:25±0:03:36	115.5±0.4	144±8	159±19	32.0±0.4
2	03:03:57±1:14:59	109.4±9.9	143±7	164±16	33.7±1.3
3	05:46:48±0:09:49	158.6±12.3	134±9	147±19	28.9±1.9
4	Rest				
5	04:11:38±0:21:11	104.1±7.1	140±5	156±14	26.5 ±1.11
6	05:12:04±0:23:42	144.4±13.4	138±9	164±14	29.8±0.34
7	00:40:37±0:05:46	12.7±7.8	137±16	134±4	19.3±9.29
8	04:04:53±0:26:42	111.0±10.1	138±8	144±27	28.8±0.86
9	06:21:56±1:33:09	173.2±38.1	133±5	147±29	28.5±5.66
Mean±SD	**04:15:03±1:43:50**	**120.3±43.8**	**138±9**	**153±22**	**29.0±4.6**

Table 4.1. Summary exercise data for each day of the training camp (n=9 riders). Data are reported as mean±SD.

4.3.3 24-hour glucose

The group mean [iG] for the nine riders across the 9-day period was 93±2 mg/dL with SD of 17±1 mg/dL and CV of 18±1%. There were no [iG] differences between days (all p≥0.05, Table 2). Maximum [iG] values were 158±7 mg/dL and occurred during the day- rather than night-time hours. Minimum values were 61±2 mg/dL. Each 24-hour average [iG] was similar across 9 days (p=0.164, **Table 4.2**).

Figure 4.1 displays grouped mean [iG] concentrations across camp whilst **Table 4.2** provides information on each glycaemic parameter over a 24-hour period on a day-by-day basis.

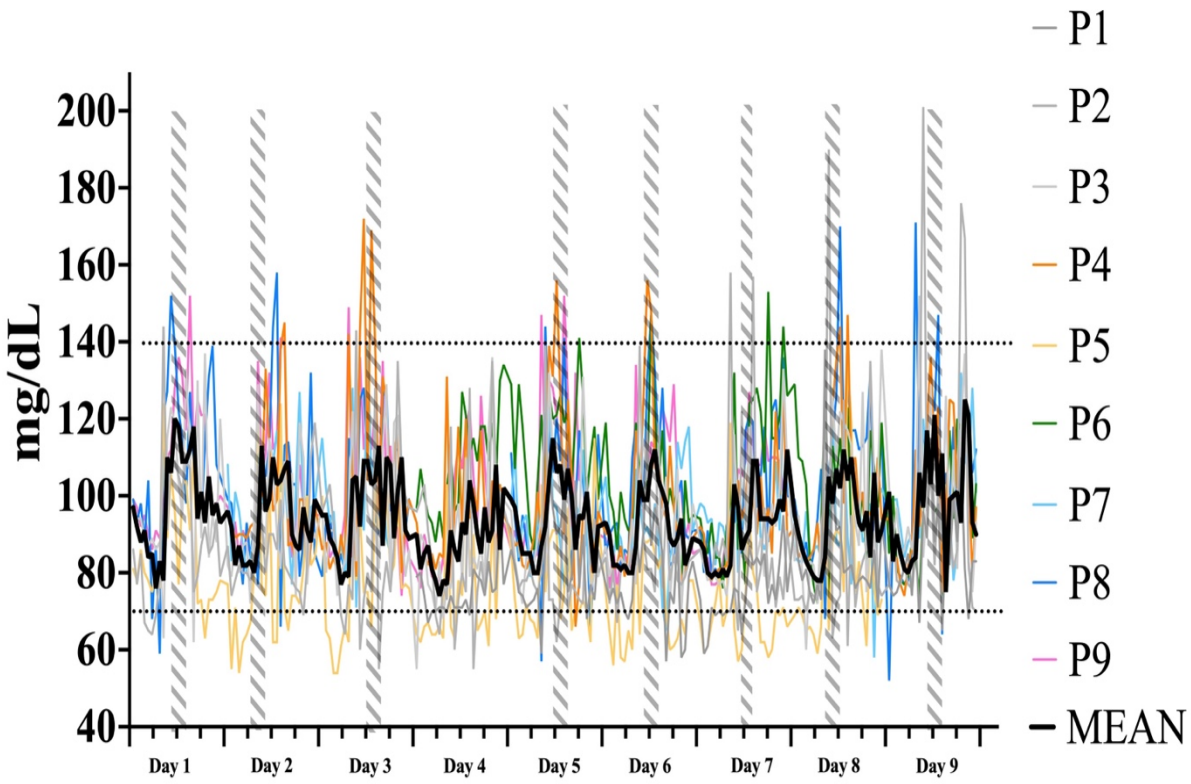


Figure 4.1. Grouped mean [iG] responses across each of the nine days of training camp. Data are displayed as the mean (black line) and individual traces (coloured lines) in daily [iG] concentrations across each day of camp. Minor ticks on the X-axis indicate 6 hour (quarterly) time periods. The timing of each exercise session is indicated via the vertical dashed lines. Day 4 was a rest day while day 7 had some short activity. The euglycaemic range (70-140 mg/dL) is indicated by the two parallel dashed lines running horizontally across the graph.

Glycaemic parameter	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	p-value
Overall (24 hours)										
Max (mg/dL)	164±9.	161±20	156±27	145±20	150±17	157±27	154±32	161±24	169±24	p=0.199
Mean (mg/dL)	96±9	93±9	91±8	90±10	93±11	92±11	91±12	92±11	96±7	p=0.165
Min (mg/dL)	61±8	63±8	58±5	60±8	61±8	63±7	64±8	59±6	61±3	p=0.289
SD (mg/dL)	18±3	16±3	18±4	15±4	15±3	16±3	16±6	18±4	19±5	p=0.168
CV (%)	19±2	17±3	20±4	17±4	16±3	17±2	18±5	19±4	20±5	P=0.211
TAR (%)	3±3	3±3	3±3	2±2	2±2	3±3	4±4	4±5	3±3	p=0.345
TIR (%)	89±6	96±2	92±6	92±10	95±5	95±5	93±8	93±3	95±3	p=0.192
TBR (%)	6±6	7±14	11±13	12±18	8±12	8±13	10±19	9±15	3±3	p=0.302
Day-time (06:00-11:59)										
Max (mg/dL)	164±9	161±20	156±27	145±20	150±17	157±27	154±32	161±24	169±24	p=0.144
Mean (mg/dL)	99±10	96±9	93±10	93±12	94±11	94±12	95±14	95±11	100±8	p=0.144
Min (mg/dL)	62±8	63±8	58±5	61±9	61±8	63±7	65±8	60±6	61±3	p=0.318
SD (mg/dL)	19±3	17±3	17±4	16±3	16±3	17±3	17±6	18±5	20±6	p=0.188
CV (%)	19±2	18±3	20±4	17±4	17±3	18±3	18±5	20±4	20±6	p=0.222
TAR (%)	4±5	3±3	3±4	1±2	2±2	3±4	3±5	2±3	3±4	p=0.429
TIR (%)	90±6	93±5	88±10	88±15	91±10	90±11	76±3	90±10	91±7	p=0.367
TBR (%)	6±6	4±6	9±10	11±15	7±11	7±12	10±11	8±11	6±8	p=0.172
Night-time (00:00-05:59)										
Max (mg/dL)	106±10	104±13	114±16.	106±19	111±22	104±11	99±13	107±17	120±21	p=0.345
Mean (mg/dL)	86±9	86±10	87±13	84±12	92±17	84±9	82±9	84±11	87±6	p=0.200
Min (mg/dL)	66±11	69±12	68±9	69±11	80±23	70±8	70±9	67±11	74±3	p=0.279
SD (mg/dL)	7±2	7±2	9±4	8±4	8±5	69±2	6±2	8±5	9±4	p=0.364
CV (%)	8±3	8±3	11±4	10±5	10±5	9±4	8±4	8±4	10±4	p=0.544
TAR (%)	0±0	0±0	0±0	0±0	1±3	0±0	0±0	0±0	0±0	p=0.408
TIR (%)	91±17	91±23	86±28	85±28	92±16	91±19	89±25	87±30	100±1	p=0.989
TBR (%)	9±17	9±23	13±28	15±28	6±16	9±19	11±25	13±30	0±1	p=0.535
Exercise										
Max (mg/dL)	162±18	149±29	123±17	Rest	138±19	159±30	127±14	145±35	152±31	p=0.304
Mean (mg/dL)	125±12	109±16	93±11	Rest	107±17	104±16	104±16	109±23	103±14	p=0.234
Min (mg/dL)	93±14	73±10	63±8	Rest	75±17	74±15	81±9*	72±14	61±2*	p=0.022

SD (mg/dL)	15±3	16±7	12±3	Rest	11±2	14±3	14±2	15±8	15±4	p=0.690
CV (%)	12±3	15±5	13±3	Rest	11±1	14±2	14±0	13±5	14±2	p=0.403
TAR (%)	21±15	8±9	0±1	Rest	5±10	6±10	0±0	15±20	3±4	p=0.120
TIR (%)	79±15	89±8	93±8	Rest	94±9	92±9	100±0	84±20	94±4	p=0.281
TBR (%)	0±0	2±5	7±9	Rest	4±9	3±4	0±0	3±4	2±4	p=0.698

Table 4.2. Summary of group mean glycaemic parameters from all nine riders throughout the entire 9-day training camp where data have been treated as an overall 24-hour period, a day-time period (06:00 to 23:59), a night-time period (00:00 to 05:59) and as an exercise period (in-ride data based on the duration of each individual cycling session). [iG]: interstitial glucose. Max: maximum. Min: Minimum. SD: Standard deviation CV: Coefficient of variation. TAR: The percentage of time spent with interstitial glucose levels above the target range (≥141 mg/dL). TIR: The percentage of time spent with interstitial glucose levels within the target range (70-140 mg/dL). TBR: The percentage of time spent with interstitial glucose levels below the target range (<70 mg/dL). Data displayed as mean±SD. * Indicates a statistical diffeence between days for the respective glycaemic parameter (P≤0.05)

4.3.4 Day-time glucose

Mean [iG] during day-time hours was 95±3 mg/dL, with mean SD of 18±1 mg/dL and mean CV 18±1%. Maximum [iG] values were 157±7 mg/dL and minimum 61±2 mg/dL. There were no significant differences in any [iG] metric between each 24 hour period (**Table 4.2**).

4.3.5 Night-time glucose

The mean [iG] during the night-time period was 86±3 mg/dL, with a SD of 8±1 mg/dL and CV of 9±1%. Mean maximum night-time [iG] value was 108±6 mg/dL whilst the mean minimum value during the night was 70±4 mg/dL. There were no significant differences in any [iG] metric between each 6 hour night-time period (**Table 4.2**).

4.3.6 Exercise glucose

The mean [iG] during exercise was 108±9 mg/dL with a SD of 14±2 mg/dL and CV of 13±2%. The mean maximum in-ride [iG] value was 144±14 mg/dL whilst the mean minimum value was 74±10 mg/dL. There were no significant differences in any [iG] metric between each exercise period (**Table 4.2**).

4.3.7 Day-time versus night-time glucose comparisons

When comparing day-time vs. night-time periods, a significant main effect was detected as the camp progressed ($p=0.037$). Mean [iG] was higher during the day-time hours (day: 95±3 vs. night: 86±3 mg/dL, $p<0.0001$). The SD (day: 18±1vs. night: 8±1 mg/dL, $p<0.0001$) and CV (day: 18±1 vs. night: 9±1%, $p<0.0001$) of [iG] were both higher during the day-time hours as was the TAR (day: 3±1 vs. night: 0±0%, $p<0.0001$). Both the TBR (day: 8±3 vs. night: 10±5%, $p=0.165$) and TIR (day: 89±5 vs. night: 90±5%, $p=0.364$) were similar between the day- and night-time periods.

4.3.8 Relationships between glycaemia and exercise performance metrics

Table 4.3 details relationships between exercise glycaemic variables with the exercise performance metric. No associations were observed between in-ride [iG] variables and exercise performance metrics on the same day. When observing the relationship between glycaemic

variables from the preceding night-time period to the subsequent day's exercise, there were no significant associations. There were also no associations found between exercise performance metrics each day and the [iG] metrics observed during the subsequent night-time periods.

Same day [iG]	[iG] Mean	TAR	TIR	TBR
Power	0.19	0.18	-0.10	-0.23
HR	0.04	-0.11	0.25	-0.21
Duration	-0.12	-0.11	0.04	0.13
Night-Day [iG]	[iG] Mean	TAR	TIR	TBR
Power	0.03	0.10	-0.01	-0.01
HR	0.23	-0.03	0.06	-0.06
Duration	0.12	0.10	0.002	-0.01
Day-Night [iG]	[iG] Mean	TAR	TIR	TBR
Power	0.08	0.15	0.11	-0.12
HR	0.28	0.01	0.19	-0.20
Duration	0.12	0.04	0.08	0.08

Table 4.3. Relationships between glycaemic variables and exercise performance metrics. Same day: in ride [iG] and in ride exercise performance metrics. Night to day: Preceding night [iG] with subsequent days' exercise performance metrics. Day-Night; daytime exercise performance metrics with subsequent nights' [iG]. HR; Heart rate. TBR; The percentage of time spent with interstitial glucose levels below the target range (<70 mg/dL). TIR; The percentage of time spent with interstitial glucose levels within the target range (70-140 mg/dL). TAR The percentage of time spent with interstitial glucose levels above the target range (≥141 mg/dL).

4.4 Discussion

This study sought to characterise the glycaemic demands of an intensive training camp in professional female UCI world tour riders using continuous glucose monitoring devices. These data provide novel insight into the daily glycaemic responses of female cyclists engaged in consecutive days' worth of heavy exercise training as part of a performance camp.

Overall, riders in the present study spent a proportionately high percentage of their time (93±2%) with [iG] levels in the 'clinically defined' target range i.e., 70-140 mg/dL with average euglycaemic values of 93±2 mg/dL and little evidence of pronounced glycaemic variability (CV ~18%). This carried over into the exercise period, with a mean iG concentration of 108±93 mg/dL and a CV of ~13%. Similar findings of tight glycaemic control during exercise have been observed in studies investigating mixed-sex ultrarunners competing in single-stage events (Hargreaves *et al*., 1984; Ishihara *et al*., 2020; Kulawiec *et al*., 2021; Sengoku *et al*., 2015). For example, Ishihara and colleagues (2020) noted normoglycemic iG concentrations in their cohort of runners throughout a 160 km ultramarathon event using an intermittent CGM device (All runners [n=10]: 134±19 mg/dL with a CV of 14.0%. Female only runners [n=3]: 124±18 mg/dL with a CV of 14.2%). Kinrade and Galloway (2021) also observed mean euglycaemic [iG] levels in mixed-sex ultra-endurance runners (n=14) undertaking a continuous 24 hour event (i.e., 124±1 mg/dL). Important caveats that prevent direct inter-study comparisons include differences in the use of CGM devices, glycaemic thresholds, time capture periods and exercise disciplines. Nevertheless, collectively they provide insight as to the seemingly tight level of glycaemic control that can be maintained under metabolically challenging circumstances. During exercise, both endogenous (glycogenolysis and gluconeogenesis) (Jeukendrup, Raben, *et al*., 1999; Kjaer *et al*., 1984) and exogenous (dietary carbohydrate intake) (Jeukendrup *et al*., 2006; Sengoku *et al*., 2015) inputs contribute significantly to the maintenance of glucose homeostasis at a time when skeletal muscle tissue fuel demands are increased exponentially. The exploratory, observational nature of this study precluded access to information around endogenous and exogenous fuel use during exercise. However, the integration of continuous CGM over consecutive days' worth of data capture including daily bouts of cycle training expands our current knowledge base of glycaemia in an all-female elite cycling cohort.

This study focused on collecting measures of glycaemic variability throughout a nine-day training camp. While others have also tracked some measures of variability (Francois, Cosgrove, Walker, Lucas, & Black, 2018; F. Thomas, C. Pretty, T. Desaive, & G. Chase, 2016), few have collected data during the recovery period post exercise in a free living, real life training camp environment. CGM allows for a constant stream of data which improves the ability to detect rapid fluctuations which might be missed if adopting a fixed timepoint collection schedule, which would be typical of finger prick sampling, the impracticability of which makes for difficulty in obtaining real-time information.

A difference in variability was identified between the day- and night-time periods. Both SD and CV were significantly different as well as the TAR. While [iG] was elevated during exercise, the maximum and minimum concentrations were experienced outside of exercise but within the day-time period. This is potentially an effect of increased variability often observed post exercise (Francois et al., 2018; Kulawiec et al., 2021; F. Thomas, C. Pretty, T. Desaive, & G. Chase, 2016). While dietary intake is known to influence glycaemic responses, assessing dietary factors was not an explicit aim of this study. Efforts to obtain dietary data were limited by voluntary participant reporting, resulting in insufficient information for analysis. However, it was standard practice for the riders in the present study to consume a meal soon after exercise. Ingestion of carbohydrate-rich meals inherently raise the concentration of glucose in circulation, a pattern that can be identified in our data in **Figure 4.1**. Indeed, in some riders, the ingestion of this meal resulted in transient hyperglycaemia (maximum [iG] data displayed in **Table. 4.2**). The post-prandial insulin response instigates a subsequent fall in [iG]. Exercise has been shown to increase glucose uptake through insulin-independent mechanisms and via increased insulin sensitivity for a number of hours post-exercise (Borghouts & Keizer, 1999; Kjaer et al., 1984; Maarbjerg et al., 2011; Mikines, Sonne, Farrell, Tronier, & Galbo, 1988). The decline in [iG] in this study appears to continue into the night-time hours until the early hours of the following morning. Fittingly, mean [iG] was significantly lower during the night-time period when compared against the designated day-time period. There was also a trend towards larger amounts of TBR (<70 mg/dL) during the night-time, although it did not reach statistical significance.

A number of studies have shown a tendency for lower [BG] during the night-time hours, perhaps as a reflection of a reduction in sympathetic activity and counter-regulatory hormone responses (Graveling & Frier, 2017; Iscoe, Corcoran, & Riddell, 2008; Jones et al., 1998; Merl

et al., 2004). It has also been suggested that the threshold for counter-regulation of [BG] is lower during sleep (Gais *et al*., 2003). While this information is of clinical importance regarding people living with metabolic dysregulation e.g., diabetes where nocturnal hypoglycaemia is a common and concerning issue, the health and/or performance implications for athletic populations is unknown. Hence caution in interpretation is clear given the lack of population-specific glycaemic ranges.

In this study, some hyperglycaemia was experienced and all TAR occurred during day-time hours. Mean TAR in our data during the overall 24hr period was 3±1%. Shah *et al* (2019) reported a similar proportion of TAR in healthy individuals at 2.1%, Birmingham *et al* (2023) observed even less with 0.3% TAR. At present, there is no established recommendation for TAR in a healthy population. The threshold for TAR in adults with Type 1 diabetes is >180mg/dL and consensus guidelines advise that less than 25% of total daily time should be spent exceeding target range (i.e., >140 mg/dL) (Battelino *et al*., 2019) Previous work has set a threshold of ≥140mg/dL to identify groups not currently diagnosed with diabetes but at a heightened risk of developing health complications (American Diabetes Association, 1997) These thresholds are based on risk factors for potential pathologies but not general health. In young and healthy individuals, it is unlikely that these thresholds would be markedly breached for a substantial time. Therefore, there is debate as to what is the upper threshold for optimal health, particularly in highly athletic individuals.

Worth noting was the proportionate amount of time the riders in this study spent in hypoglycaemia. The athletes displayed an average of 8±2% of time below target range on a daily basis. This is twice that recommended by the International consensus guidelines of 4% total per day (Battelino *et al*., 2019). As the CGM used in this study has an effective measurement floor of 55mg/dL it was unable to quantify any time spent in severe hypoglycaemia (<54 mg/dL). This study was observational and retrospective, no reactive interventional measurements such as finger stick sampling were employed to validate sensor concentrations. Hence, it is possible that some of our female riders may have experienced time within this range without us being able to quantify it. With the caveat of ambiguity in a clear definition for hypoglycaemia in those without diabetes, the implications of hypoglycaemia, when termed as <70 mg/dL, on general health and wellbeing outside of a sporting context are well documented (American Diabetes Association, 2021; Cox, Gonder-Frederick, Schroeder, Cryer, & Clarke, 1993; Graveling & Frier, 2009; Owens, Parker, & Benton, 1998). Yet,

transference of these findings to highly athletic, professional, sports people from both an exercise performance and recovery perspective is missing. Considering the demands of multi-day activity and the carbohydrate requirements for adequate glycogen replenishment, (American College of Sports and Exercise Medicine, 2000; LM Burke et al., 2001; Coyle, 2012; Jeukendrup, 2014a) the occurrence of hypoglycaemia identified by CGM may offer some warning of inadequate carbohydrate intake in the post-exercise period.

Some of the hypoglycaemic events observed in this study were abrupt, severe and somewhat unexpected. Not only did they fall below the physiological range for sustained periods of time, but their recovery to euglycemia appeared to be quite sudden. The events in question occurred during night-time hours and due to their unusual pattern warranted some further consideration. Sensors have also been shown to have poorer accuracy when concentrations fall to hypoglycaemic levels. Work by Moser (O. Moser, Eckstein, McCarthy, et al., 2019) detected a mean absolute relative difference (MARD) of 31.6% during hypoglycaemia in comparison to 16% during euglycaemia. "Compression lows" have also been documented as a potential sensor limitation (Helton *et al*., 2011; Mensh *et al*., 2013). As a result, sleeping position cannot be ruled out as a cause for some of the measured TBR during the night-time period. External factors such as sensor compression from body position or clothing, (Roder *et al*., 2016) skin temperature (Coates *et al*., 2023) and/or sensor location must therefore be considered when assessing the possible mechanisms underlying some of the changes that are captured by CGM. We found no relationship between glycaemic parameters and exercise performance outcomes. Nor were there any associations between glycaemic parameters obtained throughout the night-time period that preceded a day of training and the next-day's exercise outcomes. The lack of association between [iG] and exercise metrics is in agreement with Kinrade & Galloway (2021) who observed no association between [iG] and race distance during competition. An important caveat is that the session goal and/or prescribed intensity may have undermined any definitive association between glycaemia and performance outcomes. Studies have shown CGM accuracy to worsen during exercise (Bauhaus et al., 2023; Da Prato et al., 2022; Fabra et al., 2021; O. Moser, Eckstein, Mueller, et al., 2019) much of the discrepancy between iG and BG measurements can be explained by a lag in sensing (E. Moser et al., 2020; O. Moser et al., 2017). This lag may be heightened due to a number of factors many relating to the rapid changes which occur in the body during exercise. It is possible that such discrepancies may have prevented the identification of any association to exercise performance should they have existed. MARD values of up to 29.8% during exercise have been detected in past studies (O.

Moser, Eckstein, McCarthy, et al., 2019). Hence, further work investigating such relationships under race conditions may provide a better scenario in which to study the area.

Overall, the study identified some possibilities for when CGM may offer greater insight into the glycaemic demands of intensified training. The most obvious being an education tool for individuals and athletes to learn more about their own personal physiology. The impact of food types and meal timing can also be identified using the technology and has generated interest by others (Zignoli, Fontana, Lipman, et al., 2023). This might help guide nutrition strategies during exercise and in the post-exercise recovery period (Bowler *et al*., 2022; DuBose *et al*., 2020; Kinrade & Galloway, 2021; Podlogar & Wallis, 2022). Due to the considerable and continual high energetic demands of being a professional athlete, low energy availability is a concern for both female and male athletes (Bowler *et al*., 2022; Logue *et al*., 2020) (Saris, Erp-Baart, Brouns, Westerterp, & ten Hoor, 1989). Low energy availability has been associated with observed mild hypoglycaemia (Smith et al., 2016; F. Thomas, C. Pretty, T. Desaive, & G. Chase, 2016). Hence, CGM could act as a potential warning system for chronic inadequate carbohydrate intake if mapped against nutritional intake information.

4.4.2 Study strengths, limitations, and possible considerations for future research incentives

Strengths of this study are its inclusion of several consecutive days of glycaemic profiling (via CGM) in an all-female professional cycling team which has been stratified into distinct phases and mapped against a quantifiable background of exercise training. This provided valuable normative data describing glycaemic behaviour across multiple training days in an elite female cohort, a population that remains underrepresented in the literature.

However, in addition to the understandably small participant number, the absence of comprehensive dietary intake data and menstrual phase information are notable limitations. The omission of detailed nutritional data, in particular, restricts the interpretation of the observed glycaemic fluctuations. Carbohydrate availability, timing, and type are known to exert substantial effects on interstitial glucose dynamics, particularly in the hours surrounding exercise and recovery. Without corresponding dietary context, it is difficult to fully disentangle whether variations in glycaemia reflect physiological responses to training load, differences in fuelling practices, or sensor-related artefacts.

Given the highly individualised nutrition strategies often adopted by elite athletes, even within the same team, these differences may have contributed meaningfully to the day-to-day variability in glycaemic patterns observed. Therefore, future research would benefit from the integration of structured dietary monitoring, such as real-time logging applications or weighed food records, to more accurately characterise the relationship between carbohydrate intake and glycaemic regulation in high-performance environments. Combining these approaches with menstrual tracking and qualitative insights (e.g., individual case studies) could offer a richer understanding of how fuelling strategies, hormonal fluctuations, stress, and recovery interact to shape glycaemic trends in elite female athletes.

This limitation was directly addressed in the subsequent study presented in Chapter 5, where a more structured and supervised approach to dietary data collection was implemented. By employing a validated dietary tracking tool and maintaining closer communication with participants, it was possible to capture a more complete picture of dietary intake and its relationship to glycaemic patterns. Consequently, the findings of Chapter 5 extend those presented here, offering greater contextual understanding of the dietary influences on glycaemia that could not be explored in the present study.

CGM sensors have known limitations during exercise (Clavel *et al*., 2022; Fabra *et al*., 2021). Most of which have been reported on older generation sensors. Few studies have been completed on newer sensors which manufacturers claim have improved upon accuracy and reduced delays in sensing. Current CGM technologies are shown to be effective for improving clinical outcomes and they are approved for use in glycaemic management during exercise with those with Type 1 diabetes (E. Moser et al., 2020).

4.5 Conclusion

This observational study characterised interstitial glucose data in professional female cyclists during a 9-day training camp. Riders maintained a high percentage of time in the target range, yet exhibited periods of hypoglycaemia (<70 mg/dL), and average night-time glucose concentrations were lower than daytime values. Glycaemic variability was greater during daytime than night-time, reflecting the influence of training and daily nutritional intake. When considered alongside Study 1, which demonstrated that interstitial glucose generally tracks blood glucose but can diverge during rapid excursions, these results indicate that CGM

discrepancies are apparent under real-world training conditions and that athlete glycaemia is both highly dynamic and context-dependent. Collectively, these findings highlight the potential role of habitual dietary composition in shaping daily glycaemic patterns, providing the rationale for Study 3, which investigated the effects of prolonged low- versus high-glycaemic index diets on glucose regulation and exercise performance in trained athletes.

CHAPTER FIVE

Glycaemic Impact of Low- and High-Glycaemic Index Carbohydrate diets in Ultra-Endurance Athletes: Insights from Continuous Glucose Monitoring

5.1 Introduction

In recent years, there is a rise in the popularity of ultra-endurance athletic events. Ultra-endurance events can exceed 6 h and place large demands on body stores of energy for athletes to perform successfully. Recommendations for carbohydrate (CHO) consumption for endurance activities suggest dietary intake of >60% of total daily energy or between 8–12 $g \cdot kg^{-1} \cdot day^{-1}$ for competition (T. Thomas, Erdman, & Burke, 2016). Further, in training, ultra-endurance athletes complete large weekly volumes of exercise activities (Rüst, Knechtle, Kneachtle, Wirth, & Rosemann, 2012; Tanda & Knechtle, 2015)and to meet such high energetic demands, carbohydrates form the mainstay of daily energy intake (Stellingwerff, 2016). Exogenous carbohydrate intake substantially impacts blood glucose concentrations, and if large amounts and/or high glycaemic index (HGI) sources are consumed, dysglycaemia can occur despite endogenous gluco-regulatory mechanisms striving to maintain glucose homeostasis (Bazzano, Serdula, & Liu, 2005).

Recent technological developments have led to the emergence of continuous glucose monitors (CGMs) to manage glycaemia in metabolically dysregulated populations (Galindo & Aleppo, 2020). Continuous real-time recording and display provides a 24 h continuous trajectory of glucose around meals, physical activity and during sleep (Keshet et al., 2023; Shah et al., 2019). Thus, the use of CGM can provide detailed insights into glycaemic excursions, potentially identifying metrics that might clarify the impact of food, exercise, and/or chronic stress). Acute observation or intervention studies have revealed some insight into the influence of feeding and exercise in a number of conditions ranging from controlled laboratory based exercise trials to in-competition sensing (Clavel et al., 2022; Coates et al., 2023; Francois et al., 2018; Ishihara et al., 2020; Sengoku et al., 2015; Zignoli, Fontana, DJ, et al., 2023). During competition, maintaining stable interstitial glucose levels has been suggested to positively impact performance outcomes, such as sustaining running pace (Ishihara et al., 2020; Sengoku et al., 2015). However, the implications of day-to-day glucose variability on exercise performance is not currently well understood.

Longer studies, have profiled glycaemia over short periods (<19 days) of intensified training (Bowler et al., 2024; Francois et al., 2018; Hamilton, McCarthy, Bain, & Bracken, 2024; Skroce et al., 2024; Zignoli, Fontana, DJ, et al., 2023). These studies characterised glycaemia using a

variety of different metrics such as the percentage of time spent in different ranges (hyper-, eu- or hypo-glycaemia), albeit with varying threshold concentrations, and frequency and severity of hypo- and hyperglycaemia. These initial investigations have detailed observations of dysglycaemia in athletes (Flockhart & Larsen, 2023; Francois et al., 2018; Hamilton et al., 2024; Kulawiec et al., 2021; F. Thomas, C. Pretty, T. Desaive, & G. Chase, 2016) Furthermore, during periods of heavy training, Flockhart et al. (2021) reported significantly greater time spent above range in athletes compared to a healthy control group. Hamilton et al. (2024) observed elite female cyclists spending 3±1% TAR. Weijer et al. (2024) showed similar TAR in a group of para-cyclists (5.4%). Bowler et al. (2024) also witnessed 2.4±1.6% TAR with race walkers. Zignoli et al. (2024) observed even greater TAR in professional cyclists (13.0±10.2%). In addition, frequent periods of hypoglycaemia were also observed by Hamilton et al. (2024) (TBR 8 ± 2%), by Weijer et al. (2024) (TBR 2.1%) and Zignoli et al. (2024) (TBR 2.6 ± 9.2%, although specific to the night time-period). Interestingly, studies have also used mean (Bowler et al., 2024; Hamilton et al., 2024; Prins et al., 2023; Weijer et al., 2024; Zignoli et al., 2024), median, (Prins et al., 2023) standard deviation (Bowler et al., 2024; Hamilton et al., 2024; Prins et al., 2023; Weijer et al., 2024; Zignoli et al., 2024), coefficient of variation (Bowler et al., 2024; Hamilton et al., 2024; Prins et al., 2023; Weijer et al., 2024)and mean amplitude of glycaemic excursion (MAGE) (Bowler et al., 2024; Weijer et al., 2024) to explore glycaemic characteristics over time.

Few studies have observed glycaemia in athletic cohorts for more prolonged periods, with very few detailing glycaemia in response to chronic nutritional interventions. Longer periods of CGM utilization appear to have a greater benefit to glycaemic management (Anderson et al., 2011). Despite this, longer-term glycaemic patterns in athletes remain largely unknown, despite useful data and insights into some metrics in short-duration studies. Certain physiological adaptations, such as changes to metabolism, body composition shifts or muscle hypertrophy, take time to occur (Egan & Zierath, 2013). With that in mind, longer study durations may be necessary to investigate some physiological adaptations. Further investigation is warranted to explore the metabolic and health impacts associated with glycaemic management in response to different sports nutrition strategies. Prins et al. (2023)demonstrated that 5-weeks of a low carbohydrate high fat (LCHF) diet reduced 24 h mean glucose and resulted in greater fat oxidation during an exercise assessment at the end of the intervention, when compared to a high carbohydrate low fat diet. Other alternative strategies, such as isocaloric low glycaemic

diets, might also alter glycaemia and performance outcomes, but have not been explored in athletes.

Consumption of low glycaemic index (LGI) carbohydrates typically result in a slower rise and lower peak glucose response that can aid stable glucose concentrations (Jenkins et al., 1981). As such, they might help prevent hypoglycaemia around exercise (LM Burke, Collier, & Hargreaves, 1998; Ching-Lin, Nicholas, Williams, Took, & Hardy, 2003). Pre-exercise meals containing LGI carbohydrates are effective at maintaining exercise glycaemia, especially when exercise is prolonged and feeding opportunities are limited (D. Thomas, Brotherhood, & Brand, 1991; Wu & Williams, 2006). LGI carbohydrates incorporated into pre-exercise meals have shown improvements of 2.8-3.3% in time-trial performances when compared to meals comprised of HGI carbohydrate (Moore, Midgley, Thomas, Thurlow, & McNaughton, 2009; Moore et al., 2010; Wong et al., 2008) Overall, the literature demonstrates equivalent, or in some cases, small improvements in performance in comparison to consuming isocaloric amounts of moderate- or high GI carbohydrates (Burdon, Spronk, Cheng, & O'Connor, 2017). One such low glycaemic index carbohydrate is isomaltulose (Palatinose^{TM}) which is a disaccharide sucrose isomer of glucose and fructose, it has a hydrolysation rate 20–25% of that of sucrose (Gunther & Heymann, 1998; Lina et al., 2002), giving it a glycaemic index value of 32. As a result, meals and diets incorporating isomaltulose display lower glycaemic responses when compared to meals and diets incorporating higher GI carbohydrates (CJ Henry, Kaur, & Quek, 2017; Maresch, Petry, Theis, Bosy-Westphal, & Linn, 2017; Notbohm et al., 2021; van Can, Ijzerman, van Loon, Brouns, & Blaak, 2009). The consumption of LGI carbohydrates before exercise also appears to promote lipid oxidation (Chen et al., 2008; Stevenson et al., 2006; van Can et al., 2009; Wee, Williams, Gray, & Horabin, 1999; Wee et al., 2005; Wong et al., 2008; Wu & Williams, 2006)

Some research studies have effectively used simple dietary alterations to improve glycaemia, observed via CGM (Bergia et al., 2022; Chekima et al., 2022) in healthy but non-athletic cohorts. With such emphasis on carbohydrate intake and its importance for exercise performance, gaining better insights into how GI might impact the glycaemia of a highly active individual who consumes a carbohydrate-rich diet for their athletic endeavours is of great interest, especially in the context of exercise performance. Thus, we hypothesise that when matched for total carbohydrate intake, consuming a low or high glycaemic index diet for 28

days will have no effect on mean glucose concentration, glycaemic variability, or endurance capacity in trained athletes.

This randomised, repeated crossover study examined the glycaemic impact of adopting a 28-day carbohydrate-rich diet primarily consisting of either low- or high-GI carbohydrates on acute and chronic glycaemia using continuous glucose monitoring and explored the impact on endurance capacity in ultra-endurance athletes. Secondary biomarkers are included to screen for potential physiological stress or health impacts of the diets. These exploratory analytes cover lipid metabolism (ketones, triglycerides, glycerol), liver function (AST, ALT, GGT, bilirubin), inflammation and hormonal responses (TNF-α, interleukin-6, insulin, adrenaline, noradrenaline), and tissue stress (CK-MB, HFABP, IFABP).

5.2 Methods

5.2.1 Participants and ethical approval

Nine ultra-endurance trained athletes (8 male) took part in this randomised, cross-over study (participant characteristics in **Table 5.1**). Ethical approval was granted by the Swansea University Research Ethics Committee. The study was carried out in accordance with the Declaration of Helsinki and International Conference on Harmonisation of Good Clinical Practice. All volunteers provided written informed consent prior to study involvement.

AGE (years)	Height (cm)	Body mass (kg)	Est body fat (%)	Fat mass (kg)	Est LBM (%)	LBM (kg)	BMI (kg/m^2)	$\dot{V}O_2$ max ($ml.kg^{-1}.min^{-1}$)
41±7	176±9	79.8±16	21.3±5.4	17±7.1	78.6±5.4	62±9.8	25.5±3.3	56.9±3.9

Table 5.1. Participant characteristics. LBM is lean body mass. All data is displayed as mean±SD.

5.2.2 Screening visit

Before undertaking any experimental procedures, participants completed a screening visit during which eligibility for trial inclusion (see **section 2.7**) was assessed alongside a review of their medical history via the PAR-Q questionnaire. After confirmation of study suitability (based on inclusion criteria and providing sufficient evidence of active participation in ultra-endurance exercise), data on anthropometric characteristics (see **section 2.5**) were collected before participants completed a treadmill ramp test to volitional exhaustion to determine individualised intensity thresholds for subsequent experimental visits (see **section 2.4.4** for protocol). The treadmill gradient remained at 1%, and breath-by-breath data were recorded using a pulmonary gas analyser (MetaMax® 3B; Cortex Biophysik GmbH, Germany). Blood samples were analysed using the Biosen C-Line system (EKF Diagnostics). Participants were then familiarised to procedures by running a portion of the outdoor course, and treadmill test at their assigned velocity. They were also instructed on how to use physical activity logging apps and CGM sensors (and ecosystem) to allow them to familiarise themselves to its use over the 7 days preceding the commencement of the study.

5.2.3 Study design

As part of the randomisation (via computerised, randomised sequence), participants were allocated to start with either LGI or HGI carbohydrate-rich diets over a 28-day period before crossing over to the opposing dietary arm. After an initial 7-day regular habitual diet, the first 28 d diet arm began the day after the initial acute laboratory visit then ended on day 35 (the second acute laboratory day of the arm), and the athlete then returned to their regular diet for a 14-day washout period, athletes then began the second diet arm for another 28 days and finished on day 77. At the start and end of each dietary arm, participants attended four laboratory arm days that involved the evaluation of acute LGI (isomaltulose) or HGI (maltodextrin) carbohydrate responses to endurance exercise capacity tests. A study schematic is displayed in **Figure 5.1**. Participants maintained their routine exercise training regimes throughout the 28-day dietary periods, logging all exercise sessions via GPS sports watches uploading data to TrainingPeaks™ (Training Peaks, Peaksware LLC, Louisville, USA). This data was then accessible to the research team for retrospective analysis.

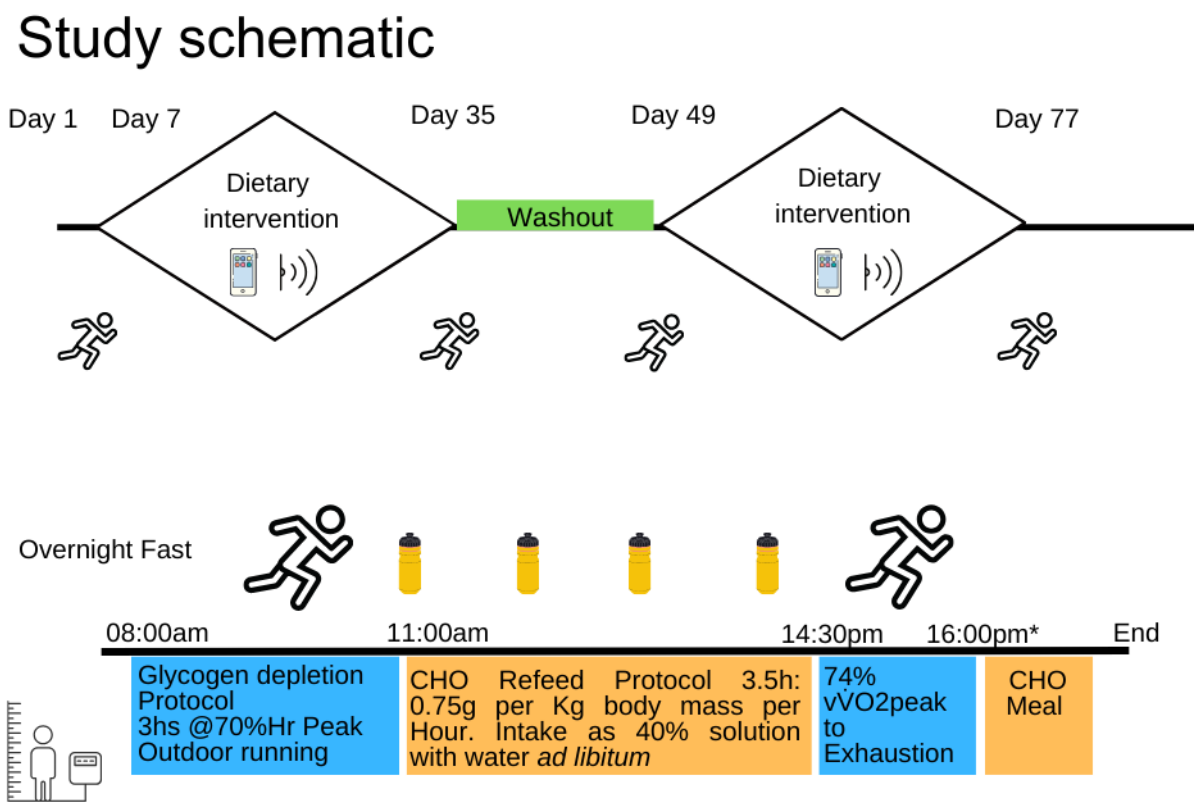


Figure 5.1. Study schematic. Study overview is displayed from day 1 to day 77. The laboratory exercise trials are indicated and continuous glucose monitor (CGM) collection with the phone and scanner symbol. The timeline of the acute laboratory days is also included in lower portion of figure providing indicative times for each stage of the trial. Anthropometry were recorded as soon as participants arrived (indicated by the figure and scale symbol) before they began their outdoor run at 71±2% Heart rate (HR) peak. They then completed the carbohydrate (CHO) refeed (0.75 grams [g] per kilogram [kg] body mass), indicated by bottle symbols. Both the 3-h outdoor run and treadmill test to exhaustion (at 74±1% $v\dot{V}O_{2peak}$) are indicated by running man symbols. * The exact finish time was dependent on the outcome of the run capacity test.

5.2.4 Experimental trial day procedures

Participants attended the laboratory after an overnight fast (≥10 hours) having avoided any physical activity in the preceding 24 h. After gathering anthropometric measures (height, body mass, estimated body fat and lean percentages via bioelectric impedance analysis (Bodystat Quadscan 4000, Bodystat Ltd, USA) (see **section 2.5**), a blood sample (4ml in a EDTA tube & another 2ml in a serum sedimentation tube SST tube) was collected via antecubital venepuncture which was carried out by a member of the research team trained in phlebotomy (see **section 2.8.2**). Additional samples were taken post-3 h run, post-refeed, upon cessation of run capacity test and a final sample at the end of the refeed period (see sampling procedures

and blood analysis in **chapter 2.6)**. Participants proceeded to run outdoors on a standardised pre-measured course for 3 h at an intensity equivalent to 70% $\dot{V}O_{2peak,}$ monitored via heart rate telemetry. HR was kept within ± 5 bpm of this pre-determined intensity with run data collected from their own GPS watch for later downloaded from TrainingPeaks™. Participants were encouraged to consume water with added electrolyte powder (Bulk, Chichester, United Kingdom) during this run.

Following the outdoor run, participants returned to the laboratory where they consumed a carbohydrate drink (0.75 $g.kg^{-1}$ BM h^{-1} as 40% fluid solution [approx. 2.7g/kg BM]) containing 1 g of electrolyte powder with either (i) the LGI carbohydrate; Isomaltulose (ISO; Palatinose™) (BENEO, Mannheim, Germany) or (ii) the HGI carbohydrate; Maltodextrin (MAL) (BENEO, Mannheim, Germany). Subsequent carbohydrate refeeding took place under rested conditions over 3.5 h. Thereafter, participants began an indoor treadmill test where they ran at an intensity equivalent to 74±1% $v\dot{V}O_{2peak}$ (11.65±0.60 $km.h^{-1}$) until volitional fatigue (see **section 2.8.4**). Continuous measures of cardiopulmonary data were collected for the first hour of this test.

5.2.5 Collection of glycaemic data

All interstitial glucose [iG] data were recorded via the Abbot Libre Sense Biosensor (Abbot Laboratories, Chicago, IL, USA). The CGM device was paired to the Supersapiens™ fuel band receiver and Software application (TT1 Products Inc., Atlanta, GA, USA) which was installed on the participant's smartphone. Raw CGM data were exported to a database and analysed via Excel 2019 (Microsoft Corp., Redmond, WA, USA).

Group means were calculated for [iG] concentrations (mg/dL) and indices of glycaemic variability i.e., the coefficient of variation (CV) and standard deviation (SD). [iG] data were also stratified into a percentage of time spent in specific glycaemic ranges: time below range ([TBR] <70 mg/dL), time in range ([TIR] 70-140 mg/dL) and time above range ([TAR] >140 mg/dL). Hypoglycaemia was further stratified into level 1 hypoglycaemia ([LVL1] 55-69 mg/dL) and level 2 hypoglycaemia ([LVL2] ≤54 mg/dL).

5.2.6 Collection of dietary information

After attending the screening visit, participants followed their regular diet for a period of 7 days, recording all dietary intake using the Nutritics™ smartphone application (Nutritics,

Dublin, Ireland) (see **section 2.9.2**). Based on this information, they were advised on suitable substitutions to ensure they were made aware of either LGI or HGI variations of their preferred carbohydrate foods e.g., for a low GI swap, a white potato was exchanged for sweet potato. They were provided with food list detailing suitable food options for each trial arm, based on their usual food choices (protocol in **section 2.8.3**).

In addition, over each 28 days and to further enhance the different glycaemic properties of each diet, participants supplemented their physically active lifestyle with low (isomaltulose) or high (maltodextrin) GI-carbohydrate drinks, respectively. Participants were encouraged to follow dietary recommendations of 7 $g.kg.d^{-1}$ of carbohydrates (T. Thomas et al., 2016). Around exercise activities, athletes were encouraged to consume each low or high GI carbohydrate in solution (e.g. 50 g of either ISO or MAL in 550 ml of water as a 9% solution 1-2 h before exercise as well as every hour during exercise). In the first 90 minutes of recovery from an exercise session, participants were encouraged to consume 0.75 $g.kg\ BM^{-1}$ of the low or high GI-carbohydrate with water. All dietary intake information was continuously analysed for verification of adherence by the research team and continuous guidance was provided to ensure appropriate dietary choices were appropriate.

5.2.7 Collection of training information

Participants followed their own physical training programmes throughout each of the 28-day diet arms. All training data was collected by the individual participant's GPS sports watches. Each participant's data was subsequently imported to the Training Peaks application then downloaded and sent to members of the research team for analysis.

For the retrospective classification of exercise intensities, a three-zone training model was utilised. Intensity zones were defined with HR using the first and second lactate threshold turning points as identified by the lactate curve from the graded incremental exercise test (Seiler, 2010). Assessment of overall duration and distribution of training intensity were retrospectively made after each diet.

5.2.8 Statistical analyses

Statistical analyses were carried out using Excel (Microsoft Office) and Graphpad Prism V 9.5. All data are presented as mean±standard deviation (SD). Data were tested for normal distribution (Shapiro–Wilk test) A one-way ANOVA was conducted to compare differences between (Anthropometrics, Exercise metrics, Glycaemic metrics [day to day] and metabolic data). When significant main effects were identified, Bonferroni post hoc adjustments were applied to correct for multiple comparisons and identify where the differences were observed. A two-way ANOVA was employed to assess the interaction effects between [Glycaemic metrics between trials and timepoints across the acute trial day]. If significant interactions were found, simple main effects were analysed using Bonferroni-corrected pairwise comparisons. Finally, for pairwise comparisons (LGI vs. HGI trail arm means) paired t-tests were used. Significant differences were reported if $p \leq 0.05$. For further information on statistics and sample size justification, (see **section 2.12)**.

5.3 Results

5.3.1 Anthropometric data

Anthropometric measures; Body mass, Est body fat, Fat mass, Est LBM, LBM and BMI remained similar across both trial arms ($p<0.05$) (**Table 5.2)**. There were no differences in any anthropometric variable within or between diet arms.

	ISO $_{\text{pre-diet}}$	**ISO** $_{\text{post-diet}}$	**MAL** $_{\text{pre-diet}}$	**MAL** $_{\text{post-diet}}$	***Overall p value***	**Δ LGI**	**Δ HGI**	***LGI vs. HGI***
Body mass (kg)	79.4±15.8	78.9±14.9	79.7±15.6	79.5±16.2	*p=0.972*	-0.5±1.3	-0.2±1.4	*p=0.720*
Est body fat (%)	21.4±5.5	20.7±5.5	21.5±4.9	21.7±6.5	*p=0.589*	-0.7±2.2	+0.2±2.5	*p=0.421*
Fat mass (kg)	17.3±7.4	16.7±7.3	17.4±6.9	17.6±8.1	*p=0.459*	-0.6±1.4	+0.2±2.0	*p=0.332*
Est LBM (%)	78.7±5.5	79.5±5.3	77.9±5.2	78.3±6.5	*p=0.234*	+0.8±2.2	+0.4±2	*p=0.745*
LBM (kg)	62.1±10.3	62.3±9.7	61.7±10.4	61.9±10.5	*p=0.714*	+0.2±2.1	+0.1±1.7	*p=0.920*
BMI (kg/m^2)	25.5±3.6	25.4±3.1	24.5±4.9	24.5±5.1	*p=0.443*	-0.2±0.5	-0.1±0.4	*p=0.642*

Table 5.2. Anthropometry of ultra-endurance athletes during each trial day arm under each carbohydrate (isomaltulose [ISO] or maltodextrin [MAL]) condition both before (pre) and after (post) each 28-day diet period. LBM is lean body mass. Δ denotes the change from start to end of each of the dietary arms. Data displayed as mean±SD (n=9).

5.3.2 28-day glycaemic data

24-hour [iG]

The 28-day glycaemic group 24 h mean [iG] variables are shown in **Table 5.3**.

	LGI carbohydrate diet	**HGI carbohydrate diet**	***95% CI***	***p value***
Max (mg/dL)	168.8±9.2	169.9±8.2	-3.528 to 5.732	*p=0.598*
Mean (mg/dL)	101.6±4.6	100.0±5.0	-6.289 to 2.921	*p=0.424*
Min (mg/dL)	63.6±2.8	61.2±1.6	-4.401 to -0.05152	***p=0.046***
SD (mg/dL)	16.7±1.7	18.3±1.7	0.3821 to 2.726	***p=0.016***
CV (%)	16±1%	18±1%	1.298 to 2.947	***p=0.0003***
TAR (%)	4±2%	4±2%	-0.8634 to 1.386	*p=0.607*
TIR (%)	93±4%	91±3%	-5.288 to 2.646	*p=0.465*
TBR (%)	2±1%	4±2%	0.8570 to 3.559	***p=0.006***
LVL1 (%)	1±1%	3±2%	0.6497 to 2.561	***p=0.005***
LVL2 (%)	0±0%	1±1%	-0.1011 to 1.357	*p=0.082*

Table 5.3. Mean interstitial glucose metrics for both 28-d low- (LGI) and high-glycaemic index (HGI) carbohydrate rich diet arms. Mean: average mean concentrations of participants over each 28-d arm. Max: maximum concentrations of participants over each 28-day period. Min: minimum concentrations of participants over each 28-day period. CI: Confidence limits. SD: Standard deviation. CV: Coefficient of variation. TAR: The percentage of time spent with interstitial glucose levels above the target range (>140 mg/dL). TIR: The percentage of time spent with interstitial glucose levels within a target range (70-140 mg/dL). TBR: The percentage of time spent with interstitial glucose levels below the target range (<70 mg/dL). LVL1: The percentage of time spent with interstitial glucose levels within a range (55-69 mg/dL). LVL2: The percentage of time spent with interstitial glucose levels below the target range (≤54 mg/dL). Data displayed as mean±SD (n=9). P values in bold italics indicate a significant difference (p≤0.05).

Time in glycaemic ranges

While the mean [iG] concentrations were similar during both 28-d diet arms, measures of variance i.e., SD and CV, were lower in the LGI- compared to the HGI-diet arms (p=0.016 and p=0.0001 respectively). TBR (LVL1) was higher, and [iG] minimum lower, in the HGI-diet arm (table 2).

5.3.3 28-day dietary intake

Carbohydrate intake was ~58% of total daily energy intake in both diets. The daily intake of supplemental carbohydrates using the pre-formulated carbohydrate powders to daily meals was equivalent between diet arms, accounting for ~30% of overall daily intake (LGI 32±9 vs. HGI 28±13%, p=0.402). There were no differences in overall energy intake (LGI 3044±452 vs. HGI 2961 ± 233 kcals, p=0.562) or the amounts of carbohydrate (LGI 443±41 vs. HGI 429±70 g, p=0.486 and fat (85±9 vs. HGI 83±7 g, p=0.283*)* consumed between dietary arms. However, more protein was consumed during the LGI diet arm (121±15 vs. 107±11g, p<0.001).

5.3.4 28-day physical activity data

The total exercise duration undertaken throughout the 28-d was similar between the low and high GI-arms (LGI 37.9±9.5 vs. HGI 34.5±7.5 h, p=0.165). Time spent in Z1 was similar (LGI 25.8±11.9 vs. HGI 22.7 ± 9.5 h, p=0.450), as was time spent in Z2 (LGI 6.4±3.6 vs. HGI 6.5 ± 2.0 h, p=0.997) and Z3 (LGI 1.4±2.0 vs. HGI 1.1±0.7 h, p=0.700). There was no difference in the distribution of training intensities between the dietary arms.

5.3.5 Trial day [iG]

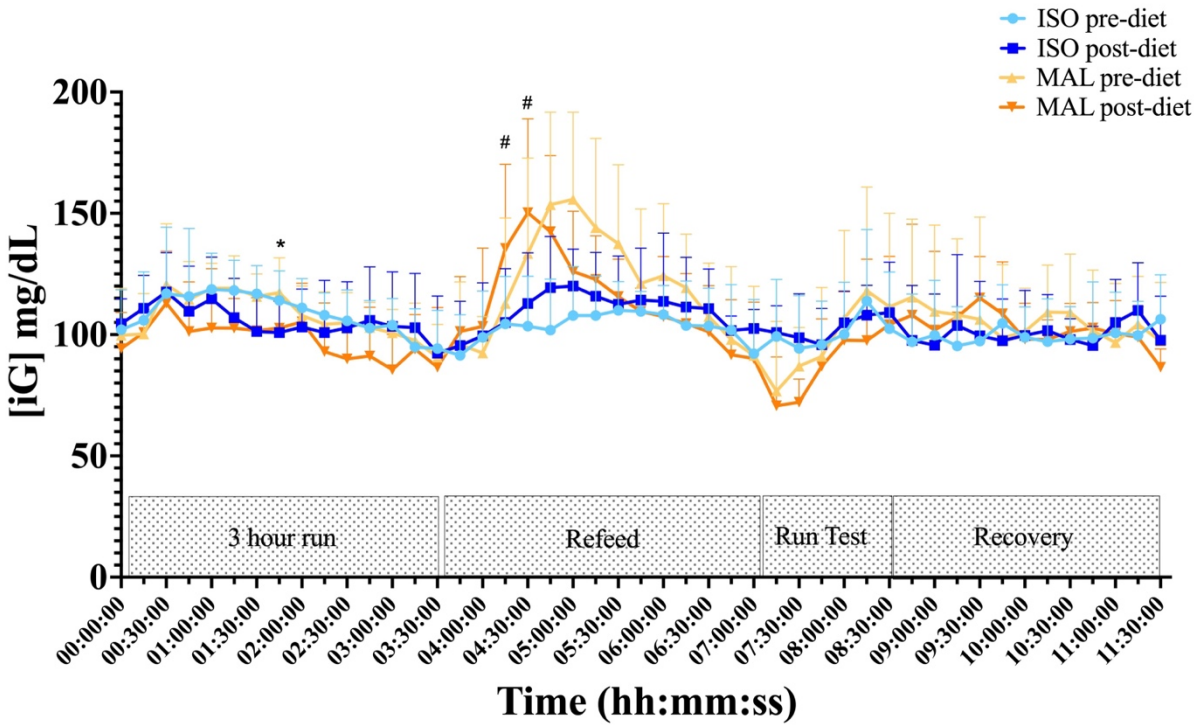


Figure 5.2. Mean interstitial glucose [iG] concentrations under each carbohydrate (isomaltulose [ISO] or maltodextrin [MAL]) condition before (pre) and after (post) each 28-day diet arm. Time-course of the laboratory trial day has been smoothed into 15-minute intervals. Run Test; run test to exhaustion. * indicates a difference in the respective point concentration of [iG] between ISO arms before and after the 28-d diet. # indicates a difference in the respective point concentration of [iG] between ISO and MAL arms after the 28-d diet arm ($p \leq 0.05$). Data are presented as mean±SD (n=9).

[iG] data during each acute trial day was predefined into time segments; 3 h run, refeed, run test and the recovery period. A continuous CGM trace for the acute trial day is displayed in **Figure 5.2** above. Summary time-segmented data is displayed in **Table 5.4**. Mean [iG] was similar before and after a run test to exhaustion whether at the start or end of a 28-day low or high GI carbohydrate diet. However, measures of variance, standard deviation (p=0.001) and coefficient of variation (p=0.002) were lower for both ISO arms compared to MAL during the carbohydrate refeeding period, in the performance run test to exhaustion (SD p=0.05, CV p=0.008) and in the subsequent recovery period (SD p=0.01, CV p=0.002).

		ISO PRE-DIET	ISO POST-DIET	MAL PRE-DIET	MAL POST-DIET	*P VALUE*	Δ LGI	Δ HGI
REST	Max (mg/dL)	101.0±23.7	113.3±15.8	115.2±23.2	103.8±10.6	*0.339*	+9.0±36.0	-10.5±26.8
	Mean (mg/dL)	93.1±20.2	104.9±11.6	97.0±18.7	94.6±9.3	*0.444*	+8.4±26.5	-2.5±22.0
	Min (mg/dL)	86.6±18.6	97.8±10.3	86.6±17.3	86.0±11.5	*0.331*	+7.3±22.4	-1.8±25.1
	SD (mg/dL)	4.8±3.4	5.0±2.4	7.3±3.8	5.8±2.5	*0.349*	+0.4±5.3	-0.4±4.0
	CV %	5.0±3.4	5±2	8±5	6±3	*0.241*	+0±4	+0±5
	TAR %	0±0	1±2	0±0	0±0	*0.349*	+1±2	+0±0
	TIR %	80±40	99±2	89±20	100±0	*0.223*	+12±33	+9±20
	TBR %	20±40	0±0	12±20	0±0	*0.209*	-13±36	-9±20
3H RUN	Max mg/dL	134.4±18.4	139.0±19.0	141.7±9.9	137.1±13.1	*0.787*	5.3±26.3	-7.3±12.2
	Mean (mg/dL)	111.2±12.3	107.6±13.8	109.9±12.2	106.9±10.0	*0.866*	-5.8±19.6	-4.1±17.0
	Min mg/dL	92.7±13.2	82.0±17.0	86.8±16.0	82.9±12.2	*0.425*	-14.5±17.8	+0.9±15.5
	SD (mg/dL)	10.8±6.3	11.6±3.0	12.6±3.7	12.3±7.6	*0.891*	**+1.8±4.1**	**-3.0±2.4**
	CV %	10±6	11±3	12±4	11.3±6.3	*0.845*	+2±3	-3±4
	TAR %	3±10	3±5	4±5	3±4	*0.985*	-1±13	-1±7
	TIR %	96±10	96±4	94±8	95±8	*0.925*	0±12	+4±8
	TBR %	1±3	1±2	3±8	3±7	*0.880*	+1±2	-3±8
REFEED PERIOD	Max mg/dL	132.9±15.6	142.8±13.4	171.0±27.8†	168.4±27.1	***0.002***	+10.4±17.4	+8.1±18.7
	Mean (mg/dL)	104.5±12.4	110.2±10.2	122.0±22.4	115.2±13.5	*0.131*	+3.1±11.1	-1.6±15.0
	Min mg/dL	74.6±10.6	72.8±13.3	73.9±14.1	64.9±9.1	*0.300*	-9.0±25.4	-8.8±17.9
	SD (mg/dL)	12.2±3.8	16.3±4.9	27.2±10.4†	23.7±8.0	***0.001***	+5.4±4.4	+0.8±9.7
	CV %	12±5	15±4	23±8†	20±6	***0.002***	**+5±4**	**0±10**
	TAR %	1±1	8±8	33±22	18±19	***0.001***	+8±7	-10±17
	TIR %	95±13	91±8	59±16	79±18	***<0.001***	**-9±7**	**+18±23**
	TBR %	5±13.3	1±1	8±18	4±8	*0.709*	+1±2	-8±20
PERFORMANCE TEST	Max mg/dL	111.6±25.3	122.0±18.3	116.6±32.1	114.9±16.1	*0.844*	+2.4±30.0	+11.6±32.4
	Mean (mg/dL)	94.6±19.7	104.1±14.1	88.4±21.7	82.8±10.4	*0.098*	+5.7±25.4	+3.4±24.8
	Min mg/dL	79.1±19.1	87.9±16.3	62.4±12.4	64.0±19.8	*0.767*	+21.7±34.9	+6.2±29.4
	SD (mg/dL)	10.2±6.3	10.4±7.1	17.8±10.2	18.4±5.0	***0.047***	-1.8±3.4	+1.5±10.0
	CV %	11±7	10±8	19±11	22±5#	***0.008***	-2±3	+6±8
	TAR %	0 ± 0	3±7	7±18	0±0	*0.382*	+3±7	-9±20
	TIR %	84 ± 35	93±12	60±32	69±20	*0.094*	-7±9	+14±52

	TBR %	16 ± 35	4±11	33±35	31±20	*0.146*	+3±6	-13±52
RECOVERY	Max mg/dL	132.9 ± 20.0	133.1±18.2	143.4±36.6	143.7±14.0	*0.683*	-3.6±23.8	+0.2±27.6
	Mean (mg/dL)	101.2 ± 16.6	102.3±8.2	100.7±23.2	103.4±8.7	*0.987*	-4.2±9.1	+2.6±21.2
	Min mg/dL	79.8 ± 12.0	74.4±9.0	70.3±17.6	67.1±7.7	*0.230*	-9.6±10.6	-2.0±17.0
	SD (mg/dL)	11.6 ± 1.9	14.7±5.4	18.0±5.6	19.5±4.3	***0.010***	+3.8±5.0	+0.1±4.9
	CV %	12 ± 3	14±5	18±3†	19±4	***0.002***	+4±4	+0±3
	TAR %	0 ± 1	4±8	10±12	5±9	*0.182*	+3±9	-6±9
	TIR %	91 ± 25	95±8	76±14	89±11	*0.148*	-6±10	+15±18
	TBR %	9 ± 25	1±3	14±20	6±9	*0.503*	+2±4	-8±20

Table 5.4. Summary of [iG] metrics during each pre-defined time-period: rest, 3 h run, refeed, performance test to exhaustion and recovery under each carbohydrate (isomaltulose [ISO] or maltodextrin [MAL]) condition both before (pre) and after (post) each 28-day period. Data expressed as mean ± SD (n=9). † indicates a difference between ISO and MAL arms before starting the 28-d diet. # indicates a difference between ISO and MAL arms after the 28-d diet ($p \leq 0.05$). Δ denotes the change within each of the dietary arms. Data expressed as mean ± SD (n=9). ($p \leq 0.05$).

5.3.5 3 h standardised run data

The total distance covered over the standardised 3 h run was similar between all acute trial arm days (ISO_{pre} 25.1±2.3, ISO_{post} 27.0±2.9, MAL_{pre} 25.3±2.7, MAL_{post} 26.5±2.7 km, p=0.352), as was mean HR (ISO_{pre} 126±6, ISO_{post} 126±6, MAL_{pre} 129±5, MAL_{post} 128±6 bpm, p=0.862) and speed (ISO_{pre} 8.4±0.9, ISO_{post} 9.01.0, MAL_{pre} 8.3±1.0, MAL_{post} 8.6±1.1 $km.h^{-1}$, p=0.445). Exercise intensity (expressed as percentage of HRmax) was also similar during the fasted morning run performed at the start of each trial day (ISO_{pre} 70±2, ISO_{post} 71±3 MAL_{pre} 70±3, MAL_{post} 70±4% HR_{max}, p=0.904).

5.3.6 Endurance capacity run test data

Endurance capacity run test data are displayed in **Table 5.5.**

	ISO $_{\text{pre-diet}}$	**ISO** $_{\text{post-diet}}$	**MAL** $_{\text{pre-diet}}$	**MAL** $_{\text{post-diet}}$	***Overall p value***	**Δ LGI**	**Δ HGI**	***LGI vs. HGI***
Mean time to failure (mins)	50±20	65±15	69±23	72±16	*p=0.104*	+15±17	+5±24	*p=0.414*
Heart Rate (bpm)	157±6	158±9	161±11	157±10	*p=0.140*	-2±6	-5±6	***p=0.014***
Percent of HR_{max} **(%)**	88±5	87±3	89±4	86±3	*p=0.533*	-1±3	-3±3	*p=0.270*
$\dot{V}O_2$ **(ml.kg^{-1}.min^{-1})**	42±4	42±3	41±4	41±5	*p=0.932*	+1±4	+5±11	*p=0.280*
RPE (Borg)	15±2	15±1	15±2	15±2	*p=0.772*	NA	NA	NA

Table 5.5. Summary data for each time to exhaustion treadmill test during each acute trial day visit under each carbohydrate (isomaltulose [ISO] or maltodextrin [MAL]) condition both before (pre) and after (post) each 28-day period, as well as the changes within. Time to exhaustion (min), heart (bpm), ratings perceived exertion and volume of oxygen uptake ($\dot{V}O_2$ ml.kg^{-1}.min^{-1}) are displayed. P values in bold italics indicate a significant difference ($p \leq 0.05$) in the corresponding variable between the two dietary arms. Δ denotes the change within each of the dietary arms. All data is displayed as mean ± SD (n=9).

5.3.7 Fuel oxidation data during the indoor treadmill run to exhaustion

Fuel oxidation data are displayed in **Figure 5.3**. There was a greater oxidation rate of lipids and lower oxidation of carbohydrates during the first hour of the indoor treadmill run to exhaustion with consumption of ISO compared to MAL both at the start and end of the 28-d diet arms.

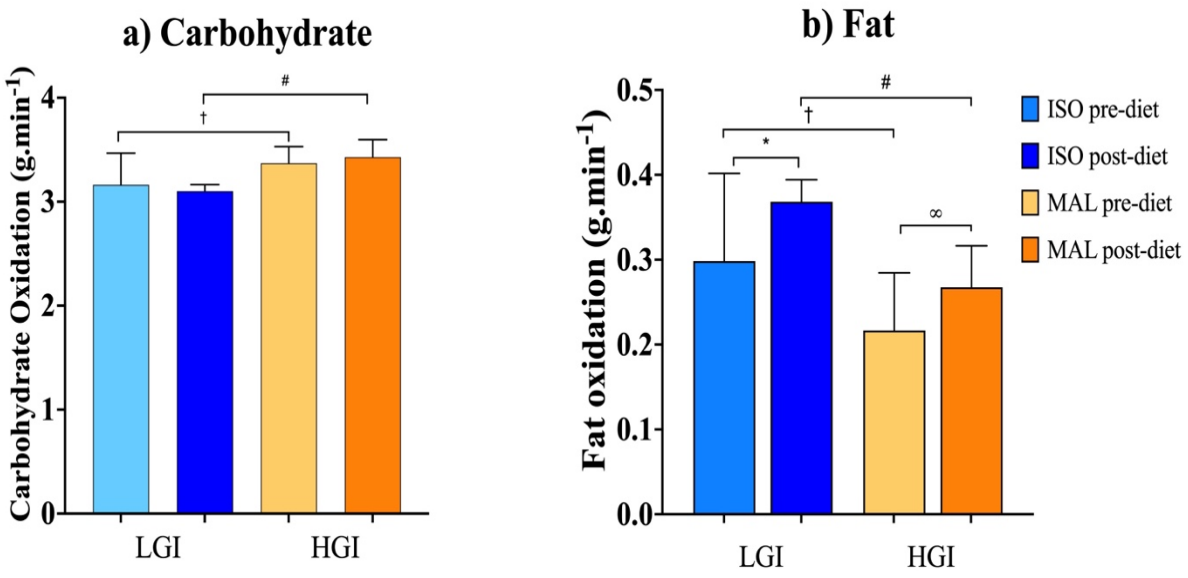


Figure 5.3. Summary of fuel oxidation rates for a) carbohydrate and b) fat in the first hour of the endurance capacity run test under both carbohydrate (isomaltulose [ISO] or maltodextrin [MAL]) conditions, both before (pre) and after (post) each 28-d low-glycaemic index (LGI) and high-glycaemic index (HGI) diet arms, as well as the changes within. * indicates a difference between ISO pre and post 28-days. ∞ indicates a difference between MAL pre and post. † indicates a difference between ISO and MAL before the 28-day diet. # indicates a difference between ISO and MAL after each 28-day diet ($p \leq 0.05$). All data are displayed as mean±SD (n=9).

5.3.8 Blood analytes

Lipid metabolism: Plasma concentrations of triglycerides, glycerol, and ketones were similar before and after the performance run regardless of refeeding carbohydrate type (isomaltulose or maltodextrin) or glycaemic index (GI) diet phase.

Liver function: ALT, AST, GGT, and total bilirubin showed no consistent differences between carbohydrate types. However, elevated recovery AST was observed following the low-GI diet, independent of refeeding condition.

Hormonal and inflammatory markers: Insulin concentrations were generally lower following isomaltulose compared to maltodextrin. Adrenaline and noradrenaline remained unchanged across conditions. IL-6 was transiently elevated after isomaltulose feeding pre-diet, but tended to be lower following the 28-day low-GI diet. TNF-α concentrations were unaffected.

Tissue stress markers: CK-MB and HFABP concentrations were unaffected by carbohydrate type or diet. IFABP levels were similar between feeding conditions following the low-GI diet.

Blood glucose and lactate: Blood glucose and lactate responses were similar before and after the performance run across all diet and refeeding conditions.

5.4 Discussion

This study demonstrated that the adoption of a carbohydrate-rich diet consisting of low-glycaemic index carbohydrates by ultra-endurance athletes over 28 d reduced glycaemic variability and time spent below target range compared to the high GI-carbohydrate diet. Furthermore, low GI-carbohydrate diets reduced carbohydrate oxidation during submaximal exercise, but had no impact on run capacity to exhaustion compared to the isoenergetic HGI-carbohydrate diet.

5.4.1 Glycaemia

The average lowest interstitial glucose concentrations were higher by 3±4% under the low GI-carbohydrate-rich diet compared to the high GI-carbohydrate diet over the 28 days. In addition, in the LGI-carbohydrate diet arm we found a lower standard deviation (Δ LGI -1.55±1.52 mg/dL, $p=0.016$) and coefficient of variation (Δ LGI -2±1%, $p<0.001$) in interstitial glucose concentrations. These findings demonstrate a lower variation around the mean values and suggest daily rises and falls of circulating glucose were less in the LGI-carbohydrate arm compared with the HGI-carbohydrate arm. Other studies have also reported other lower measures of variance with LGI-carbohydrate diets compared to high glycaemic alternatives, e.g. mean amplitude of glycaemic excursion (MAGE) (CJ Henry et al., 2017; Kaur, Quek, Camps, & Henry, 2016). MAGE measures glucose variability by averaging differences between peaks and nadirs, considering only excursions exceeding one standard deviation. Its accuracy relies on consistent, frequent data recording. Irregular intervals, data gaps, and multiple CGM inputs can skew estimates. In our study, we obtained raw data from files, not app-generated findings, so some signal breaks introduced gaps and variability, and therefore, MAGE was not able to be assessed.

Though it might be surmised that the HGI-carbohydrate-rich diet raises circulating glucose more than an LGI-carbohydrate diet, we did not see this in our data of maximum values. Participants displayed similar average daily and mean interstitial glucose concentrations over each 28-d arm whilst on the LGI- or HGI-carbohydrate diets. A “time in tight range” (TITR) principle was applied to assess glycaemia in this study. TITR is a relatively recent progression from the standard TIR and it is the model utilised by the Supersapiens^{TM} software package. TITR sets a tighter band of concentration (70-140 mg/dL [3.9 to 7.8 mmol/L^{-1}]) than current

clinical recommendations (70-180 mg/dL [3.9 to mmol/L^{-1}]). The time spent above, in or below standardised glucose range in people without diabetes provides a useful way of detailing the percentage of time spent in the 'extremes' of high or low glucose concentrations. Our data showed that when participants were on the LGI-carbohydrate-rich diet the average time spent below 70 mg/dL each day over 28-days was half of that observed in the HGI-carbohydrate diet arm. Our data suggests that LGI-carbohydrate diets that incorporate isomaltulose may result in less time spent in hypoglycaemia (TBR) in ultra-endurance athletes.

The clinical significance of level 1 hypoglycaemia in healthy individuals is somewhat debatable, with the suggestion that values below 70 mg/dL (3.9 mmol/L^{-1}) are more an indication of low glucose rather than of clinical concern (Danne et al., 2017). These values are somewhat arbitrarily set, as symptoms of hypoglycaemia can begin to occur at a wider range of lowered blood glucose concentration and are highly individualised (Jeukendrup & Killer, 2010; Simpson et al., 2008). However, level 1 hypoglycaemia marks an alert value for corrective intervention for those with type 1 diabetes for obvious reasons. Exposure to glucose at this lowered level may not induce overt physiological symptoms but falls below it may initiate milder symptoms such as sweating, shaking, and hunger in some individuals (E. Cryer, 2007). Further decline of glucose concentration to level 2 hypoglycaemia may bring more severe symptoms such as confusion, drowsiness, speech difficulty and issues with coordination (Graveling & Frier, 2009). Repeated hypoglycaemia (antecedent hypoglycaemia) blunts counter-regulatory mechanisms. This leads to impaired awareness of hypoglycaemia, making symptoms less noticeable, and a reduced ability to raise blood glucose levels. For athletes, this potentially increases the risk of impaired cognitive and physical performance (Brun, Dumortier, & Mercier, 2001). In this study, TBR was spent in level 1 hypoglycaemia although some level 2 was experienced under both diets (~1%), however the lower limit set on recording in the biosensor precludes further definitive understanding. The Abbott biosensor CGM used in this study has a lower detection limit of 54 mg/dL, making it unable to capture the full extent of LVL2 hypoglycaemia. However, estimations of the time spent below 55 mg/dL [3.1 mmol/L^{-1}] were possible. Moreover, CGM accuracy tends to decrease during hypoglycaemia. In a study by O. Moser, Eckstein, McCarthy, et al. (2019), the mean absolute relative difference (MARD) during the trial day was found to be 31.6% in hypoglycaemic conditions, compared to 16% during euglycaemia. Another potential influence is the occurrence of "compression lows," where pressure on the sensor causes falsely low readings (Mensh et al., 2013). Consequently,

night time TBR readings should be interpreted with caution as readings could partly be due to body position during sleep.

Time in range was somewhat different in our study compared to others which appear to report greater TIR or lesser TBR and TAR. Shah et al. (2019) used similar threshold limits over a 10 d period reporting 24 h glycaemia as: TBR 1.1%, TIR 96% and TAR 2.1%. Bowler et al. (2024) applied slightly different ranges: time below range <72 mg/dL), time in range (72-144 mg/dL) and time above range (>144 mg/dL). They observed race walkers over a 4 d period and reported 24 h glycaemia as: TBR 0.5%, TIR 96.3% and TAR 2.4%. Skroce et al. (2024) retrospectively analysed the Supersapiens^{TM} user database which included 12,504 physically active individuals. They reported more similar time in ranges as: TBR 3.4%, TAR 3.6% and the remainder within target euglycaemic range (~93%). Hamilton et al. (2024) observed 9 professional female cyclists during a 9-day training camp and reported greater TBR with mean 24 h glycaemia as: TBR 8%, TIR 93% and TAR 3%. Weijer et al. (2024) reported 24 h glycaemia as: TBR 2.1, TIR 90.8% and TAR 5.4%. Taken together, along with our data and accepting there is currently no accepted threshold for hyperglycaemia, it would appear glycaemia is generally well controlled in healthy athletic individuals. Interestingly, in the study by F. Thomas, C. Pretty, T. Desaive, and J. Chase (2016) the researchers utilized an upper threshold of 126 mg/dL, which is lower than those used in the previously mentioned studies. This resulted in a higher proportion of time spent above range (TAR). Their findings highlight a need for the harmonisation of glycaemic thresholds for athletic individuals.

5.4.2 28-day nutrition and training data

Diet logging by athletes was recorded as 97% for both low and high GI-carbohydrate diet arms, indicating a high adherence by study participants even though inaccurate reporting is a recognised limitation of the collection of diet logs (LM Burke et al., 2001). Daily energy intakes were isocaloric during both 28-day diet arms. It is recognised that protein and fat content of foods can influence a foods glycaemic index (Jenkins et al., 1981) and, low GI foods can contain more protein and/or fat in comparison to high GI versions. There was a ~14g.d^{-1} greater consumption of protein in the LGI-carbohydrate diet than in the HGI-carbohydrate arm. The mean CHO intake per day in our cohort was 5.4 and 5.6 g.kg^{-1}.d^{-1} for LGI- and HGI-carbohydrate diets respectively. These are lower than our initial suggestions. However, given the overall volume and intensity of the recorded training, these intakes do fall within an

appropriate range for fuelling general endurance training (5-7 $g.kg^{-1}.d^{-1}$) (T. Thomas et al., 2016). CHO intake as a percentage of daily energy intake was slightly lower in the LGI- than in the HGI-diet arm (LGI 56±3 vs. HGI 60±3%, $p<0.001$). This is likely to be explained by the slightly greater daily intake of fat (not statistically significant) and higher protein in the LGI diet. Nonetheless, the carbohydrate intakes meet the minimum recommendation of ~ 45% of daily intake for active individuals (Manore, 2005). It is worth noting that assigning strict ratio-based intakes, have been criticised for leading to unrealistic and unnecessary recommendations in some cases (LM Burke et al., 2001). Thus, an absolute and relativised gram-to-body mass approach is deemed more appropriate and less problematic when supporting highly active individuals (LM Burke et al., 2001; Manore, 2005).

Training volumes were similar in both LGI and HGI-carbohydrate diet arms and typical of competitive ultra-runners. Volume may depend on the background of the athlete and the specific event. A weekly volume of ~9 h is the reported average in the typical ultra-marathoner completing multi-day events (Rüst, Knechtle, Knechtle, & Rosemann, 2012). The weekly training volume in this study was ~9.5 h and ~8.8 h for low or high GI-diet arms respectively a value that is lower in volume than might be observed in other ultra-endurance sports such as Ironman triathlon and ultra-endurance cycling but might speak to the periodised training phase of the year. For comparison, reported training volumes for amateur Ironman triathletes are ~14 h and ~12 h per week for ultra-endurance cycling (Rüst, Knechtle, Kneachtle, et al., 2012).

5.4.3 Run capacity

Before and after embarking on a 28-day period of following a LGI- or HGI-carbohydrate diet, participants completed an acute laboratory run capacity trial to exhaustion (74±1% $v\dot{V}O_{2peak}$) following a 3 h standardised run. There were no differences across all carbohydrate trials in endurance performance variables (Table 3) when refeeding with either isomaltulose or maltodextrin, nor was there a difference before or after 28-days on either LGI- or HGI-carbohydrate-rich diets. Endurance running duration to volitional exhaustion was similar across trials with similar improvements after both periods. Physiological measures were similar before and after 28-days following both diet arms, although there was a small significant difference in the change in mean HR after each diet. This difference was greater in the HGI diet arm. As the CHO quantity was matched both CHO sources were both likely to provide sufficient glucose to the working muscle, although through different pathways (J. Fuchs et al.,

2019b; Jeukendrup, 2010).Adopting a low glycaemic index carbohydrate fuelling strategy pre-exercise has been shown to help maintain glucose stability (Ching-Lin et al., 2003; D. Thomas, Brotherhood, & Brand Miller, 1994). However, improved glucose stability has not consistently been linked to improved performance outcomes (Burdon et al., 2017).

Carbohydrate oxidation with isomaltulose was less than that of maltodextrin before the 28-day diets began. After 28-days of a LGI diet, carbohydrate oxidation was significantly lower under the isomaltulose arms when compared to the maltodextrin arm values. The lipid oxidation rate before engaging in a 28-day diet was greater under isomaltulose than maltodextrin, and increased to a greater extent after following a 28-day LGI-carbohydrate diet. This study reveals that the reduction in lipid oxidation typically seen after consuming carbohydrate was less pronounced with isomaltulose than with maltodextrin, both acutely and over a 28-day period following a LGI diet. These results suggest that the benefit of minimized lipid oxidation suppression with isomaltulose persists with regular, prolonged consumption. This is often seen as a favourable adaptation due to the potential fuel stores in adipose tissue compared to relatively limited glycogen stores (Hawley, Brouns, & Jeuekendrup, 1998). While there is limited evidence to support increased fat oxidation improving endurance performance, some studies indicate it is beneficial, particularly in longer-duration endurance events (Frandsen, Dahl Vest, Larsen, Dela, & Helge, 2017; Rowlands & Hopkins, 2002).

5.4.4 Additional stress biomarkers

Although a comprehensive panel of exploratory biomarkers was included to assess potential systemic stress or adverse effects associated with the dietary interventions, these secondary analytes did not reveal any consistent or meaningful changes. Markers of liver function, inflammation, hormonal status, lipid metabolism, and tissue stress (e.g., AST, ALT, TNF-α, insulin, HFABP) remained largely unchanged across conditions. While their inclusion broadened the physiological scope of the study, the lack of clear effects suggests that the dietary interventions were well tolerated, or that these markers were not sufficiently sensitive to detect subtle changes within this population or timeframe.

5.4.5 Future considerations

In this study adopting a low glycaemic index diet reduced glycaemic variability and improved time spent in the euglycaemic range. The reduced time spent in hypoglycaemia may suggest that low glycaemic index carbohydrate sources may help maintain better glucose stability over longer periods than high GI-carbohydrate diets. The long-term downstream impact of this is less well-known, although LGI diets have been linked with improved ratings of wellbeing, mood and cognitive function in some studies (Phillippou & Constantinou, 2014; Sünram-Lea & Owen, 2017), the proposed mechanism being more stable glycaemia throughout the course of a day. Cognitive performance and decision-making are integral factors for an athlete to perform at their best. LGI diets appear to offer a supportive role in multiple facets to support athletes both in daily life and competition.

In addition to glycaemic control, improved lipid oxidation during exercise is a much-desired adaptation for both athletes and coaches. Commonly applied methods often involve some form of carbohydrate restriction or manipulation, which runs the risk of hindering high-intensity performance (LM Burke & Whitfield, 2023; LM Burke et al., 2020; Impey et al., 2018). This can also quickly contribute to health issues like inadequate energy intake and Relative Energy Deficiency in Sport (RED-S) (LM Burke, 2010; LM Burke et al., 2001; Stellingwerff et al., 2021). The metabolic benefits observed in this study, while maintaining endurance capacity, may offer a more appealing strategy.

5.4.6 Strengths and limitations

A key strength of this study was the reasonably long randomized observation period, which included two trial arms that collected glycaemic data, dietary information, and physical activity data with strong adherence to logging under controlled conditions. This design also allowed for the assessment of adaptive responses, supported by controlled laboratory trials. However, the study was limited by a relatively small sample size, although appropriate for the scope of the observations. Additionally, there was less female representation than desired, preventing the assessment of biological sex as a potential variable (Cowley, Olenick, McNulty, & Ross, 2021). In terms of the performance assessment, tests to exhaustion are associated with some limitations concerning reliability (Laursen, Francis, Abbiss, Newton, & Nosaka, 2007).

However, our findings were in line with other similar studies in the available literature (Burdon et al., 2017).

5.7 Conclusion

This study investigated the influence of a 28 d low- and high-glycaemic index carbohydrate diet on glycaemic control and the impact on endurance capacity in ultra-endurance athletes. Continuous glucose monitoring revealed that a low-glycaemic diet, incorporating Isomaltulose, improved glycaemic stability, reduced time in hypoglycaemia, promoted lipid oxidation with similar endurance run capacity.

CHAPTER SIX

General Discussion

6.1 Summary of aims and findings

The overall aim of this thesis was to gain a better understanding of the role of continuous glucose monitoring (CGM) in the glycaemic management of healthy athletic cohorts. The effectiveness and practicality of CGM in individuals with dysglycaemia has been well established over recent decades. The insights and feedback provided by CGM can be beneficial in guiding individuals' glycaemic management. Certain metrics have enabled users and clinicians to make timely, data-driven decisions, often leading to improved downstream clinical outcomes. As glucose sensor technology continues to improve, attention has turned to whether CGM might also offer value in populations without metabolic disorders. Initially, it is not obvious how an individual with a fully functioning pancreas might make use of CGM, let alone derive any performance or health benefit. The first question, therefore, is how CGM reflects glycaemia in healthy individuals, and what insights, if any, can be gained.

The first experimental study (Chapter 3) investigated how healthy individuals respond to the ingestion of carbohydrates differing in amount, concentration, and type, factors known to influence the magnitude and shape of the glycaemic response. By comparing blood-based and interstitial glucose responses, this study assessed the agreement between compartments. In doing so, it clarified which metrics offer the most accurate and insightful information in acute scenarios where rapid changes in glycaemia are of interest. CGM generally tracked the direction of blood glucose changes through timing and observing peaks and nadirs as well as the rates of change. At rest, when glucose was stable [iG] and [BG] were similar but as glucose concentration began to change, discrepancies emerged. While [iG] peak was often delayed in comparison to [BG], the absolute peak concentrations were similar. When glucose fell, however, the differences between the two compartments became greater. When glucose was falling rapidly (>2 mg/dL/min), MARD reached 20.4±27.4%, and [iG] underestimated [BG] by -7.26±27.1 mg/dL. These findings raise concerns about the reliability of CGM in acute settings, particularly where short-term, discrete changes in glycaemia are critical to performance and fuelling strategies. The ability to detect and act on the influence of carbohydrate intake in real time has been a major early selling point for CGM in athletic contexts, but this study highlights limitations in that use case.

Given the observed limitations of CGM in acute scenarios, a more chronic application was deemed necessary. The second experimental study (Chapter 4) aimed to characterise the glycaemic variability of elite-level endurance athletes over a 24 h period across multiple days of heavy training. At the time, normative glycaemic data for healthy athletic populations was lacking, especially for female athletes. This study addressed that gap by providing 24 h glycaemic metrics from nine professional UCI cyclists during a nine-day training camp. In addition to detailing glucose concentrations across the day, night, and exercise periods, associations between training load and glycaemic variability were examined. A notable portion of time (8±2%) was spent below the target range, double of what is recommended (Battelino et al., 2019). This prompted further investigation to explore glycaemic variability during intense training and to what extent it might be mitigated.

In light of the concerns regarding glycaemia, the third experimental study (Chapter 5) explored the glycaemic impact of a 28-day isocaloric diet consisting primarily of either low- or high-glycaemic index (GI) carbohydrates, with a focus on both acute and chronic glycaemia as well as endurance performance. Few studies have observed glycaemic responses in athletes over extended periods, particularly beyond 14 days. While chronic dietary interventions paired with CGM have shown clinical benefits in dysglycaemic populations (Bergia et al., 2022; Chekima et al., 2022), their impact on athletes remains unclear. This study successfully characterised glycaemic patterns across two 28-day dietary periods. Importantly, the type of carbohydrate ingested influenced overall glycaemic control, with low GI sources reducing time below range (LGI 2±1 vs. HGI 4.2%), SD (LGI 16.7±1.7 vs. HG 18.3±1.7 mg/dL) and CV (LGI 16±1 vs. HGI 18±1%), without negatively affecting endurance capacity or body composition. Total carbohydrate intake remained similar, suggesting that carbohydrate type, not just quantity, can influence glycaemic outcomes in training athletes.

In summary, this thesis provides novel insights into the application of CGM in healthy athletic individuals. It highlights limitations in CGM accuracy under specific physiological conditions while also contributing data to establishing normative values in elite female athletes, and it demonstrates the capacity of dietary modification to influence glycaemia. These findings help direct future investigations and inform more effective use of CGM in both research and applied settings.

6.2 Glycaemic dynamics in healthy, active populations

CGM technologies were originally developed for clinical use, particularly in diabetes management. Their growing popularity in healthy, active populations raises important questions about the appropriateness of interpreting glycaemic data with a clinical perspective. Clinical frameworks, such as time-in-range targets or hypoglycaemia thresholds, are grounded in the need to manage impaired glucose regulation (Battelino et al., 2019). However, these standards do not necessarily reflect normal counterregulatory responses in individuals without metabolic dysfunction.

Across all three study chapters in this thesis, data consistently indicated that fluctuations in glucose were typically transient and corrected without intervention. In Chapter 3, high postprandial peaks were observed following ingestion of carbohydrate-containing beverages. These peaks occurred between 30 and 40 minutes and varied in magnitude depending on the amount and type of carbohydrate. These peaks, while elevated, remained far below levels associated with diabetes (Amercian Diabetes Association, 2023). In otherwise healthy individuals, raised glucose concentrations rapidly evoke a pancreatic insulin release. The consequent blood glucose clearance can sometimes lead to rebound hypoglycaemia before hormonal counter-regulation ensues (Flockhart & Larsen, 2023; Zignoli, Fontana, Lipman, et al., 2023). Interstitial glucose sensing in these instances may also lag behind the physiological recovery in the blood. In Chapter 3, minimum concentrations appeared lower for [iG] in some trials (PLAC, 25 g, 5%, and 20% trials), and MARD during hypoglycaemia was elevated (18.5±25%), indicating more severe hypoglycaemia than was observed in blood. These findings highlight the need for caution when interpreting low or declining [iG] as CGM feedback, in such situations, may incorrectly suggest the need for additional carbohydrate.

In Chapter 4, hypoglycaemia was observed in highly trained athletes undergoing substantial training loads. As in Chapter 3, dips below 70 mg/dL occurred but resolved without intervention, reinforcing the effectiveness of the counterregulatory system in maintaining glucose homeostasis (Roder et al., 2016). Group 24 h minimum was 61±2 mg/dL on a daily basis with some substantial time below range during night time periods (10±5%). There was some variance in the group, but the trend for night-time hypoglycaemia has been observed elsewhere (Flockhart et al., 2021; Weijer et al., 2024; Zignoli et al., 2024). The impact of these episodes on either health or performance, if any, is worthy of future investigation. Zignoli et

al. (2024) suggested that these fluctuations may reflect metabolic disturbances induced by high training loads, rather than factors related to energy intake. The potential for compression-induced artefacts during sleep further complicates interpretation (Mensh et al., 2013).

These factors raise concerns about the risk of "false alerts" when clinical hypoglycaemia thresholds are applied to healthy individuals, particularly in acute contexts such as post-exercise or postprandial periods, when athletes are most likely to rely on CGM data to inform behavioural decisions. The potential for increased anxiety or over-interpretation of CGM readings, especially false or transient alerts, may lead to unnecessary behavioural changes or stress, which could ultimately be detrimental rather than beneficial for healthy, active individuals (Bowler et al., 2022).

In Chapter 5, the effect of glycaemic index on longer-term glycaemic stability was assessed through time in range profiling and glycaemic variability metrics (SD &CV). Overall, both dietary conditions resulted in glucose levels that were largely within the target range (TIR: LGI 93±4 vs. HGI 91±3%). The low-GI diet produced lower SD and CV than the high-GI diet. Time below range was also half that of the HGI diet. Similar to Bergia et al. (2022) low-GI carbohydrates appear to reduce variability although it had no impact on 24 h mean glucose concentration. It is also noteworthy that the high-GI group experienced slightly lower minimum glucose compared to the low-GI group.

These thesis findings suggest that clinical glycaemic thresholds when applied to healthy populations may lead to unnecessary concern or misdirected responses. Thresholds such as <70 mg/dL for hypoglycaemia, while valid in diabetes management, do not adequately reflect the robust counterregulatory responses observed throughout all three study chapters. CGM interpretation in healthy cohorts should account for the context, timing, and dynamics of glucose changes, with recognition of intact counterregulatory mechanisms. CGM may be better utilised as a tool to better understand responses to influences such as training and fuelling, where the emphasis is on feedback rather than control (Flockhart & Larsen, 2023).

6. 3 Refining glycaemic metrics and thresholds for healthy, active Individuals

From the observations made throughout the thesis chapters, it would appear that a different perspective may offer more appropriate insights. Traditional summary metrics such as mean,

maximum, and minimum glucose values remain valuable for characterising overall glycaemic ranges and establishing normative baselines in healthy, active individuals. They lack the sensitivity to capture the nuanced fluctuations occurring within these ranges. These conventional measures effectively define the boundaries of glucose concentrations and provide a foundational understanding of glycaemic control, serving as important reference points in both clinical and athletic contexts. However, they do not fully reflect the dynamic nature of glucose regulation, which is influenced by acute factors such as meals, exercise, and sleep.

This limitation highlights the added utility of variability metrics (Hjort et al., 2024), such as coefficient of variation (CV) and standard deviation (SD), which offer enhanced insight by capturing the direction, rate, and magnitude of glucose changes even when glucose remains within clinically normal ranges. Such measures provide greater resolution and practical relevance for healthy populations, allowing for a more sensitive detection of subtle glycaemic shifts that may inform personalised lifestyle or nutritional adjustments without overemphasising isolated high or low values (Berry et al., 2020).

For example, the commonly used hypoglycaemia threshold of 70 mg/dL may not adequately reflect what constitutes 'low' glucose in this population (Boyle et al., 1988). Chapters 3 and 4 revealed frequent transient dips, which were naturally corrected without intervention, suggesting that 70 mg/dL may be too high to flag hypoglycaemia in healthy contexts. Similarly, defining an upper glucose threshold remains challenging; while clinical hyperglycaemia thresholds (>180 mg/dL) are unlikely to be reached, postprandial peaks were directly observed in both Chapters 3 and 5, often exceeding 140 mg/dL, but they rarely exceed 180 mg/dL. TAR in Chapter 5, however, was well within recommended limits (Battelino et al., 2019).

These observations emphasise a need for adjusted or context-specific thresholds that better reflect healthy, active individuals. More recent research has suggested that in healthy individuals, exhibiting glucose levels at or above 130 mg/dL for over 10 % of the time over at least two monitoring days shows a higher risk of developing type 2 diabetes (Pazos-Couselo et al., 2025). Others have suggested an upper limit of 101 mg/dL to be more appropriate (Bermingham et al., 2023). If such thresholds were applied to our studies, the in-exercise glucose concentrations alone would raise concern. In both Chapters 4 and 5, maximum glucose concentration regularly exceeded these, albeit for short periods. Other studies have also observed in-exercise glucose concentrations that would be flagged if these thresholds were applied (Ishihara et al., 2020; Weijer et al., 2024; Zignoli et al., 2024). While tighter thresholds

may be appropriate, particularly during resting conditions, the context in which they are applied is critically important. Future recommendations might look to incorporate some flexibility in these ranges to reflect situations which may experience either elevated or reduced glucose concentrations, such as during exercise or during sleep, respectively.

6.4 CGM in the pursuit of health and wellbeing

While continuous glucose monitoring (CGM) has a well-established utility in diabetes management, its application as a health promotion tool in otherwise healthy populations is less clearly defined. At present, there is little direct evidence that the use of CGM improves long-term health outcomes in healthy individuals. However, several studies have reported elevated blood glucose levels in athletes (Weijer et al., 2024), sometimes reaching thresholds consistent with impaired glucose tolerance or even prediabetes (e.g., elevated fasting or postprandial glucose) (Prins et al., 2023; F. Thomas, C. Pretty, T. Desaive, & G. Chase, 2016). Although such findings have raised concern, they often lack context. For example, the nature of recent dietary intake, the timing of exercise, or the acute recovery status. Importantly, exercise can acutely elevate glucose levels, particularly during and immediately following high-intensity or prolonged efforts (Flockhart et al., 2021; Flockhart et al., 2022; Kulawiec et al., 2021). This can contribute to a modestly elevated 24-hour mean glucose despite normal glycaemic control overall, which was observed in Chapter 4, where the day with the lowest mean 24 h glucose was the rest day. This suggests that some considerations should be made for those who are highly active for large periods of the day.

Continuous glucose monitoring (CGM) is increasingly explored as a tool for early identification of glycaemic dysregulation, particularly in individuals at risk of type 2 diabetes. The real-time visibility of glucose patterns can reveal fluctuations not captured by traditional markers like fasting glucose or HbA1c, potentially prompting earlier lifestyle or dietary interventions in at-risk populations (Battelino et al., 2025; Pazos-Couselo et al., 2025).

Beyond preventive applications, CGM may also support general health by helping individuals understand how daily behaviours influence glycaemic variability (Berry et al., 2020). In healthy, active populations, especially athletes, this can inform personalised decisions around fuelling, recovery, and training, aligning behaviour with individual glucose responses to support performance and overall wellbeing (Bowler et al., 2022; Flockhart & Larsen, 2023).

6.5 Practical use of CGM and relevant metrics in active populations

Across all three studies, it is clear that conventional metrics like mean glucose, maximum and minimum values, and even time in range offer limited practical value for healthy, active individuals. These metrics help establish broad glycaemic profiles and confirm that, generally, this population spends most time within clinically acceptable ranges, typically >90% in the thesis chapters, and similar in other studies with healthy groups (Bowler et al., 2024; Kashiwagi et al., 2023; Shah et al., 2019; Sofizadeh et al., 2022; Weijer et al., 2024). However, they often fail to detect short-term changes driven by feeding, exercise, or recovery behaviours, and they lack the resolution required to inform meaningful adjustments. Data from all three studies consistently showed that variability metrics revealed meaningful glucose dynamics that were not evident when relying solely on mean, maximum, or minimum values. This was particularly evident in Chapter 3, where significant peaks and dips would have gone undetected if only mean values had been reported. Chapter 4 further emphasised how mean glucose also fell well within target range despite a regular and somewhat concerning proportion of hypoglycaemia. Similar patterns are observed in other comparable studies (Weijer et al., 2024; Zignoli et al., 2024). Mean glucose in Chapter 5 also failed to show the differences in variability between diets that were captured by time in range, standard deviation and the coefficient of variation.

Building on this, narrower range metrics like TITR are a more appropriate baseline for healthy users (Zhang, Wang, Lu, & Zhou, 2024), particularly when tracking subtle dietary or longer-term lifestyle changes. However, even this approach remains grounded in time-based thresholds. What may be more impactful is a transition away from static thresholds and towards metrics that describe the shape, direction and velocity of glucose changes**.**

The thesis chapters highlighted some metrics and insights that offer practical feedback. In most cases, these did not differ massively from those already utilised by commercially available systems. However, the app-based feedback tools available place emphasis on metrics which are limited and often neglect information which may be quite important for interpretation. **Figure 6.1** below is an example of how a streamlined display with a subtle shift in perspective might be quite practical for healthy, active users.

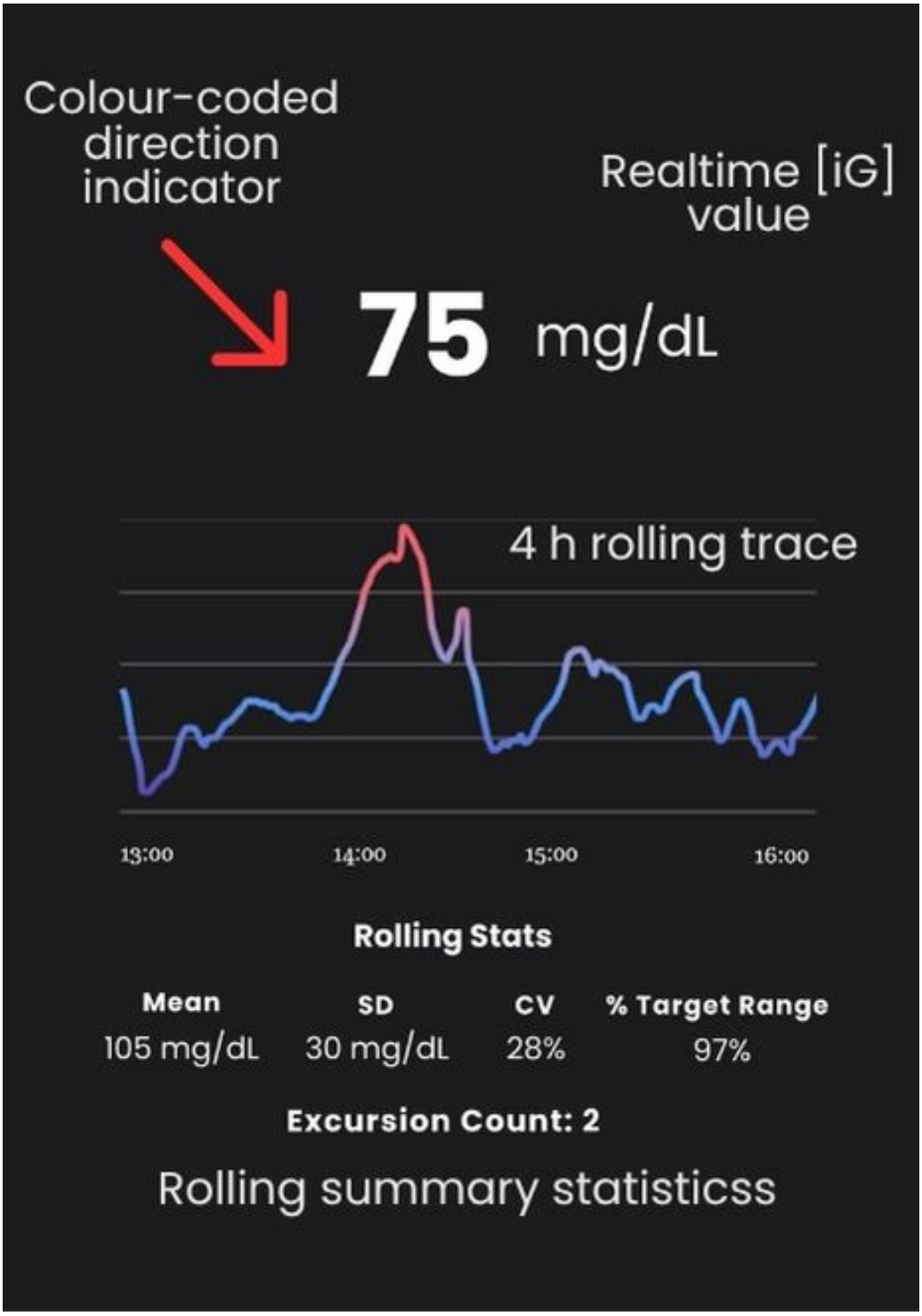


Figure 6.1. A proposed app display aimed at healthy, active users providing interstitial glucose concentrations [iG] in real-time.

While summary 24 h metrics are useful, they cover a wide range of time, which may not necessarily indicate where in the day the variability occurred. All thesis chapters have indicated that interpretation of data is contextual, and so breaking the glycaemic profile into more

specific time segments might help achieve this. For example, post-prandial, in exercise or night-time periods could be selected. In **Figure 6.1** an arbitrary 4 h time window is applied.

At the forefront of this display, there is a ***colour-coded directional arrow***. Red would indicate the detection of rapidly changing glucose, orange for moderate rates and green for stable concentration (as defined in Chapter 3). The arrow direction would indicate whether glucose is rising or falling. The directional arrow is already present in many systems, but the colours often indicate a breach of a threshold (TAR or TBR). Informed by the findings of Chapter 3, the colour coding would highlight periods where interpretation must be made with caution, as accuracy is likely to be affected by the detected rate of change.

Real-time interstitial glucose concentration should be included as a numerical measure, as it does provide a reference to the scale of changes. It should be observed taking into account the directional arrow display and colour.

A real-time interstitial glucose trace also provides some visual reference similar to the real-time value. However, this provides the added benefit of providing some feedback on the general trajectory and shape of glycaemia over the past few hours. This can be used to identify disturbances and potentially help with managing periods of instability.

Summary metrics of the rolling time period could also be useful. Mean concentration offers some general oversight, but the addition of SD and CV provide feedback on one's ability to stabilise their glucose over a more immediate period. In addition, custom ranges would allow an individual to set their own targets, specific to their personal needs. When combined with a more defined time period, it may also be useful for applying different ranges for different times of the day. For example, during exercise or during night-time periods.

A simple ***excursion count*** feature could benefit individuals seeking a straightforward indication of the frequency of sudden glucose changes, without the need to classify these against typical clinical thresholds. For example, an excursion could be defined by a deviation of ‘X’ mg/dL from a rolling mean. In the context of glycaemic stability, this trigger point could be customised, widened or tightened, based on an individual’s level of glycaemic control. This would offer intuitive feedback for those implementing lifestyle strategies aimed at preventing or reducing large fluctuations, which have been linked to negative health outcomes (Ceriello et al., 2008; Siegelaar, Holleman, Hoekstra, & DeVries, 2010). This feature might also serve a

purpose in scenarios similar to the investigations made in Chapter 5, where the comparison of dietary manipulations may be assessed.

Overall, while this display is similar to many offered on the market, it provides informed, streamlined and practical features which are more appropriate to healthy and active users.

6.6 Applications of CGM in personalised nutrition, product testing, and athlete support

Although the present observations do not undermine the utility of CGM in applied sport science, they do highlight the limitations of relying solely on absolute glucose values in real-time without additional contextual information, such as recent food intake, exercise intensity, and individual physiological responses. Rather than using CGM as a direct "fuel gauge," a more effective approach may involve analysing glucose trends over time, particularly when these are interpreted alongside an athlete's training phases, nutritional strategies, and recovery demands (Coates et al., 2024; Flockhart & Larsen, 2023).

As Chapter 5 effectively displayed, CGM technology has potential as a tool for observing nutritional influence, enabling athletes and practitioners to better understand how specific dietary choices can mitigate glycaemic responses during and outside of exercise. This feedback loop may facilitate more personalised fuelling strategies and promote learning opportunities that help athletes optimise performance and recovery (Berry et al., 2020). For example, by observing how different carbohydrate types, amounts, and timings impact interstitial glucose, users can refine their nutrition plans in a data-informed manner.

In addition to tracking glycaemia, there is potential for CGM to offer insight into the glycaemic impact of sports nutrition products, particularly those designed with different carbohydrate types, glycaemic indices, or functional purposes (e.g., rapid fuelling vs. sustained energy). Chapter 3 offered some insight into the delivery of glucose in response to different carbohydrate-containing beverages. Traditional blood sampling approaches may limit the frequency and practicality of real-time data collection during training or competition. In contrast, CGM enables continuous tracking of interstitial glucose, providing insight into the onset, magnitude, and duration of glycaemic responses to specific products. However, it is important to recognise that some CGM-derived metrics may be less effective for capturing

rapid or short-term glycaemic changes due to the physiological lag between blood and interstitial glucose, as well as device-specific limitations in resolution and sampling frequency (Davey et al., 2010; Schmelzeisen-Redeker et al., 2015; Siegmund et al., 2017). Despite these constraints, CGM remains a useful tool for profiling broader glycaemic patterns in response to nutritional interventions (Bergia et al., 2022; Prins et al., 2023), especially when integrated with context-specific interpretation and, where appropriate, complementary blood measurements. Expanding this understanding will support the development of evidence-based guidelines for CGM use in sport, ensuring that its application maximises benefits while accounting for inherent physiological and technological constraints.

6.7 Thesis strengths and limitations

This thesis provides a novel and multifaceted contribution to the field of applied glucose monitoring in healthy, active individuals by addressing current gaps in our understanding of glycaemic dynamics, CGM validity, and the contextual factors that influence interstitial glucose readings in non-clinical populations. A key strength of the work lies in its diversity of methodological approaches: the integration of tightly controlled experimental trials such as Chapters 3 and 5, measurements taken in applied, real-life sporting contexts, and longer-term dietary intervention allow for a more comprehensive understanding of the strengths and limitations of CGM in applied sport science contexts.

CGM was consistently used throughout all studies, generating a large volume of data in populations that have been underrepresented in CGM research to date. This includes healthy, active individuals and elite athletes, with specific attention given to female athletes in Chapter 4. The inclusion of both laboratory and field-based assessments in Chapter 5 also allows for a meaningful comparison between controlled and uncontrolled environments, highlighting where CGM use may be most and least reliable.

Several limitations should be acknowledged. The work was somewhat constrained by small sample sizes, especially where elite athlete populations were involved. The small sample sizes, though typical in elite sport research, limited opportunities to explore between-group differences or individual response patterns. In particular, it was not possible to examine sex-based differences or to characterise the extent of inter-individual variability in glycaemic responses, both of which would require larger, more diverse participant cohorts. The collection

of dietary information was originally planned in Chapter 4. However, as this study was conducted in collaboration with a professional cycling team and relied entirely on voluntary individual participation, the quality of the dietary data was insufficient for meaningful analysis. Many diet logs were incomplete or lacked essential detail, and in some cases, athletes who submitted logs did not go on to wear the CGM sensor, rendering their data unusable. To address these limitations, a more structured dietary data collection strategy was implemented in Chapter 5. This included the use of a dedicated dietary tracking tool (see Section 2.9.2) and more frequent communication between participants and the research team. These measures led to substantially improved data quality, enabling a more detailed examination of dietary influences on glycaemia in Chapter 5.While the thesis incorporated both training load and dietary data in Chapter 5, the absence or limited control in others restricts the ability to fully account for the nature of glycaemic responses.

Although newer-generation CGM devices were used, issues were highlighted in Chapter 3 regarding sensor lag and reduced accuracy during rapid glucose flux. These technological limitations enforce the need for cautious interpretation, especially when CGM data is used in decision-making contexts such as training, fuelling, or recovery strategies.

A notable limitation inherent in this thesis overall, relates to the technical constraints of the continuous glucose monitoring devices used. The CGM sensors employed had a measurement floor of 54 mg/dL, which limited the detection of lower glucose values and may have influenced certain post-peak metrics. Additionally, the sampling intervals were somewhat irregular due to the asynchronous data collection from the sensor itself, the associated phone application, and the fuel band sensor. This variability in sampling frequency complicated data processing and precluded the use of some glycaemic variability metrics, such as Mean Amplitude of Glycaemic Excursions (MAGE). To ensure data quality, a coverage threshold of 70% was applied to all datasets, but the nature of sport-related activities led to technical failures and occasional accidental removal of devices, further reducing usable data. These factors necessitated extensive data filtering and careful handling to produce robust analyses. It is possible that alternative CGM models with more consistent sampling rates and improved sensor reliability might have mitigated some of these challenges. Alternative sensor models with more consistent sampling protocols and accompanying software may allow for more comprehensive analysis in future research.

The studies within this thesis also raised broader challenges associated with the use of CGM in athletic populations, namely, the need for context-rich data collection to interpret glycaemic patterns meaningfully. Without concurrent measurement of factors such as diet, menstrual cycle, or sleep, interpreting CGM data remains challenging and may risk oversimplification.

6.8 Thesis conclusions

This thesis highlights the glycaemia of healthy, active individuals and reinforces the need to tailor CGM interpretation accordingly. While metrics such as time in range (TIR) provide valuable context by summarising the proportion of glucose readings within standard thresholds, they do not capture the nuanced fluctuations that variability metrics like coefficient of variation and standard deviation reveal. These variability measures offer greater insight into the subtle, yet meaningful, glycaemic changes driven by factors such as diet, exercise, and recovery. Importantly, the interstitial fluid-based nature of CGM introduces a subtle measurement difference when compared to blood glucose, which must be carefully considered when interpreting rapid glucose excursions or hypoglycaemic episodes in this population. Overall, the findings support a more context-specific approach to CGM use in healthy, active individuals, one that combines traditional metrics with variability-focused analysis and acknowledges the characteristics of interstitial glucose measurement. This approach promises more practical, sensitive, and meaningful insights for optimising health, performance, and lifestyle decisions in this group.

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APPENDICES

APPENDIX A1:
PARTICIPANT INFORMATION SHEET (Chapter 3)
(Version 1.1, Date: 28/10/21)

Project Title: An investigation of the factors pertaining to the maintenance of glycaemia in humans.

Contact Details:

Ross Hamilton (PhD student)
Applied Sports, Technology, Exercise and Medicine (A-STEM) Research Centre
Swansea University
Email: [redacted]

Study Location:
A-STEM Research Laboratory (B108)
Engineering East
Bay Campus
Swansea University
SA1 8EN

1. Invitation Paragraph

You are invited to take part in this research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information, please do not hesitate to ask us.

2. What is the purpose of the study?

This study will investigate the glycaemic response to beverages containing different types, volumes and concentrations of carbohydrate. The study will look at the time course and magnitude of any glycaemic changes post ingestion of a beverage. This might provide valuable insight into the dynamics of glycaemia and the response to different beverages.

3. Why have I been chosen?

We are inviting healthy males and females, aged between 18-55 years, to take part in this study. The full inclusion/exclusion criteria for participation in the study are listed in the table below. During the initial visit, we will perform a pre-exercise health screening in case you are unsure if any of the exclusion criteria apply to you. This will include questionnaires on your health history and physical activity readiness, in addition to measures of body mass index (BMI), resting heart rate and blood pressure.

Inclusion Criteria

- Aged between 18 and 55 years
- Apparently healthy (i.e., No indications of acute or chronic illness) according to a self-report health history questionnaire administered during the pre-screening visit

Exclusion Criteria

- A history of cardiovascular, metabolic, pulmonary or immune-related disease
- Sucrase-isomaltase deficiency
- Smokers
- BMI $\geq$ 35 kg/m^{-2}
- Hypertension (SBP $\geq$ 140 and/or DBP $\geq$ 90 mmHg)
- Resting heart rate > 100 bpm
- 'Yes', to any questions on a standard physical activity readiness questionnaire (PAR-Q) (Appendix 6)
- Known or current acute infection or illness within 7 days prior to testing – to include COVID-19
- Pregnant

If you think any of these exclusion criteria apply to you, please inform the researchers as this may influence whether you are able and safe to participate in the study.

4. What will happen to me if I take part?

After a screen visit, the study will involve you making 2-4 visits to the A-STEM Laboratory at Swansea University, with a total time commitment of 6-12 hours.

Pre-Screening

After receiving this information sheet, you will be given at least 48 hours to consider your participation in the study. If you decide to take part, prior to the first visit you will be asked to sign a consent form and complete some questionnaires on your health history and physical activity readiness to check your eligibility to take part. We will also ask you to complete a questionnaire to characterize your current physical activity levels. In addition, you will be asked to complete a COVID-19 symptom screening and recent exposure history questionnaire to ensure that you and your household are asymptomatic before attending the laboratory.

Visit 1: Screening and familiarization session

During the first visit to the laboratory, we will measure your height, weight, BMI, resting heart rate and blood pressure as the final part of the screening. You will also return your consent form and health questionnaires. This will be an opportunity to ask any remaining questions you might have before taking part in the study. You will also get a chance to familiarize yourself with the protocol that will be used during the trial sessions.

Visits 2 to 7: Rested trials

You will be asked to arrive to each trial well rested and in good health. After some rested baseline measurements you will be asked to consume no more than 500ml of a beverage containing a particular type and amount of carbohydrate. You will then be asked to remain seated and at rest for a 2 hour period during which a number of pinprick blood samples will be taken from your finger. A Continuous Glucose Monitoring sensor (CGM) will also be applied to your upper arm which will continuously collect data on interstitial glucose. A sensor will last for 14 days during which you can record interstitial glucose data to your smart phone. Once the session is complete you are free to go.

5. What are the possible disadvantages of taking part?

The exclusion criteria and pre-screening mentioned above are in place to reduce any risks. You will be closely supervised by a researcher trained in first aid at all times, and an automated external defibrillator (AED) will also be readily available. If you experience any unusual or unexpected symptoms or a change in health status at any time during the study, please inform one of the researchers immediately.

The risks of complications from having blood collected via capillary sampling are rare but may include some temporary discomfort at the site of puncture, possible bruising around the puncture site and uncommonly, infection or faintness. However, good clinical practice by a researcher will minimize these risks.

After ingesting the beverages there is some *a* small risk of experiencing a temporary high or lowered glucose. This is normal and the body is effective and realigning blood glucose levels to normal values. These beverages may contain high GI carbohydrate which can in some cases result in one of the above-mentioned events. Normally the side effects are mild and pass quickly. Side effects may include shakiness, dizziness, sweating, irritability, headache and nausea. The volumes used in this study are unlikely to cause any significant side effects as they are within what is considered tolerable.

In light of the recent COVID-19 pandemic, there may be a risk of contracting COVID-19 infection. However, universal precautions will be taken to minimise the risk of COVID-19 transmission to participants. This includes adhering to government guidelines on social distancing with the researcher remaining at least 2 m away from the participant during exercise testing. Where social distancing is not possible e.g. for the collection of blood samples, PPE comprising of face masks, gloves, lab coat, apron and visor will be worn by the researcher. Participants will be required to wear a face covering in the lab. Hand washing and/or use of alcohol gel will be required upon entering and leaving the laboratory, as well as at regular intervals throughout the session. All shared equipment will be cleaned with detergent and disinfected thoroughly with appropriate solutions after each use. To minimise contact with other people, only one participant will be present in the laboratory at any one time, and testing sessions between participants will be separated by at least one hour to fully ventilate the laboratory to help dilute and disperse any aerosols safely. Before attending any laboratory session, the researcher, participant and both of their households will be asymptomatic as determined by a COVID-19 symptom screening questionnaire. If you experience any symptoms of COVID-19 (e.g. high temperature, cough, loss or change to sense of taste or smell) at any time during the study, even if these are mild, please inform a member of the research team as soon as possible.

6. What are the possible benefits of taking part?

By contributing to this research, you will be helping us better understand how certain carbohydrate beverages may influence Glycaemia. This is particularly beneficial for understanding the dynamics and physiology of how we process what we ingest. Those participating in sport will gain a unique insight into how their fueling and hydration strategies may be influenced to become more effective and efficient. In addition, you will receive accurate anthropometric measurements taken by a trained exercise scientist. You will also get the opportunity to use the CGM sensor for a two-week period. This will allow you to trace your own interstitial glucose levels throughout your day and during exercise. This novel application of established technology may provide some great insight into how you respond to certain food types.

7. Will my taking part in the study be kept confidential?

Your data will be processed in accordance with the Data Protection Act 2018 and the General Data Protection Regulation 2016 (GDPR). All the information gathered about you throughout the duration of the study will be kept completely confidential. The only record of your name and details will be made on the initial visit to the laboratory, to be able to contact you regarding the study (e.g., arranging visit times). If you agree to participate, we will also retain your consent form and pre-screening health questionnaires to ensure that you are willing and able to take part in this study. However, this identifiable information will be immediately separated from all other data sheets and stored in a locked filing cabinet, in a locked office. From there on you will be assigned a participant-code, which will be used in all proceeding data collections so that no one can identify you. An electronic record linking your name to the participant-code will be kept in a password protected file on a secure university computer. Personal data will be kept for one year after study completion. This allows reasonable time for you to request further feedback on the study outcomes and data that was collected from you during the study. After one year, the password-protected spreadsheet linking the participant-codes to the participant's name will be deleted; however, all other data will be kept, but will be anonymous. Data will be archived for at least 10 years. Whole blood samples will not be stored, and all plasma and serum samples will be anonymised by labelling with your unique participant study code, trial number and date only. No other identifying information will be on the samples. The samples collected will be used solely for this study and will not be used for any future projects. All processes will be in accordance with the university guidelines.

Data Protection and Confidentiality
Your data will be processed in accordance with the Data Protection Act 2018 and the General Data Protection Regulation 2016 (GDPR). All information collected about you will be kept strictly confidential. Your data will only be viewed by the researcher/research team.

All electronic data will be stored on a password-protected computer file on the PI's laptop. All paper records will be stored in a locked filing cabinet within the department laboratory. Your consent information will be kept separately from your responses to minimise risk in the event of a data breach.

Please note that the data we will collect for our study will be made anonymous; an ID code will be applied to all data once the initial screening has taken place. No data collected from this point on will be identified by any personal details, thus it will not be possible to identify and remove your data at a later date, should you decide to withdraw from the study. Therefore, if at the end of this research you decide to have your data withdrawn, please let us know before you leave.

The lead researcher will take responsibility for data destruction and all collected identifiable data will be destroyed on or before April 2023. Anonymised data will be held for a period of 10 years in a secure archive.

Data Protection Privacy Notice
The data controller for this project will be Swansea University. The University Data Protection Officer provides oversight of university activities involving the processing of personal data, and can be contacted at the Vice Chancellors Office.

Your personal data will be processed for the purposes outlined in this information sheet.
Standard ethical procedures will involve you providing your consent to participate in this study by completing the consent form that has been provided to you.

The legal basis that we will rely on to process your personal data will be that processing is necessary for the performance of a task carried out in the public interest. This public interest justification is approved by the College of Engineering Research Ethics Committee, Swansea University.

The legal basis that we will rely on to process special categories of data will be that processing is necessary for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes.

How long will your information be held?
We will hold any personal data and special categories of data for a period of one year should you want feedback from your data. After this point all personal data will be destroyed and only anonymized data will be kept. This data will not be identifiable to you and will be held in the University archive for a period of up to 10 years.

What are your rights?
You have a right to access your personal information, to object to the processing of your personal information, to rectify, to erase, to restrict and to port your personal information. Please visit the University Data Protection webpages for further information in relation to your rights.

Any requests or objections should be made in writing to the University Data Protection Officer:-

University Compliance Officer (FOI/DP)
Vice-Chancellor's Office
Swansea University
Singleton Park
Swansea
SA2 8PP
Email: dataprotection@swansea.ac.uk

How to make a complaint
If you are unhappy with the way in which your personal data has been processed you may in the first instance contact the University Data Protection Officer using the contact details above.

If you remain dissatisfied then you have the right to apply directly to the Information Commissioner for a decision. The Information Commissioner can be contacted at: -

Information Commissioner's Office,
Wycliffe House,
Water Lane,
Wilmslow,
Cheshire,
SK9 5AF
www.ico.org.uk

8. What if I have any questions?

If you require any further information about the study, please contact the researcher Ross Hamilton at the details stated at the top of this information sheet.

Thank you for taking the time to read this information sheet. If you choose to participate in the study, you will be given a printed copy of the information sheet to keep

This project has been approved by the College of Engineering Research Ethics Committee at Swansea University. If you have any questions regarding this, any complaint, or concerns about the ethics and governance of this research please contact the Chair of the College of Engineering Research Ethics Committee, Swansea University: coe-researchethics@swansea.ac.uk. The institutional contact for reporting cases of research conduct is Registrar & Chief Operating Officer Mr Andrew Rhodes. Email: researchmisconduct@swansea.ac.uk. Further details are available at the Swansea University webpages for Research Integrity. http://www.swansea.ac.uk/research/researchintegrity/.

APPENDIX A2:

PARTICIPANT CONSENT FORM (Chapter 3)
(Version 1.1, Date: 28/10/2021)

Project Title:

An investigation of the factors pertaining to the maintenance of glycaemia in humans.

Contact Details:

Ross Hamilton Email: [redacted] Tel: [redacted]

	Please initial box
1. I confirm that I have read and understood the information sheet dated 28/10/2021 (version number 1.1) for the above study and have had the opportunity to ask questions.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that sections of any of data obtained may be looked at by responsible individuals from the Swansea University or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access these records.	☐
4. I understand that data I provide may be used in reports and academic publications in anonymous fashion	☐
5. I agree to take part in the above study.	☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature
_____	_____	_____
Researcher	Date	

APPENDIX A3: (Chapter 3)

An investigation of the factors pertaining to the maintenance of glycaemia in humans.

STRICTLY CONFIDENTIAL

Pre-Test Health Questionnaire

NAME: ……..…..

Please answer these questions truthfully, as the purpose of these questions is to ensure that you are in a healthy state to complete the tests involved in the study. The questionnaire is confidential to the study investigators and the information will only be used to assess any risk associated with the study protocol.

1. Do you consider yourself to be in good physical and mental health? ❑ YES ❑ NO

If no, please explain

……
.

2. Have you had any acute illness or health problem over the last two weeks?

❑YES ❑ NO

If yes, provide details (type, severity)

……

……

……..……

3. Are you currently (**or** in the last 2 weeks) taking any medication (incl. Inhalers)?

❑YES ❑ NO

If yes, provide details (type)

……

4. Do you have a tendency to faint? ❑YES ❑ NO

If yes, under what circumstance(s)?:

……..

5. Do you suffer, or have you ever suffered from:

a) Chest problems (incl. Asthma) ❑ YES ❑ NO

b) Diabetes ❑ YES ❑ NO

c) Epilepsy ❑ YES ❑ NO

d) Leg circulation problems ❑ YES ❑ NO

e) Kidney trouble ❑ YES ❑ NO

f) Thyroid trouble ❑ YES ❑ NO

g) Nervous disorder ❑ YES ❑ NO

h) High blood pressure ❑ YES ❑ NO

6. Do you suffer, or have you ever suffered from any form of heart or heart rate complaint?

❑ YES ❑ NO

7. Is there any family history of the illnesses/conditions in Q 5 & 6?

❑YES ❑ NO

If yes, provide details:

……..

……

……

8. Do you have any form of muscle or joint injury or complaint?

❑YES ❑ NO

If yes, provide details (type, severity):

……

……

……

9. Have you had to suspend exercise in the last two weeks ❑YES ❑ NO
for any reason?

10. Is there any reason why you should not be able to successfully ❑YES ❑ NO
complete exercise tests that require maximal efforts?

If yes, please give brief details

.....

.....
.....

11. Are you taking part in any other experimental trial/study? ❑YES ❑ NO

Have you in the past 3 months? ❑YES ❑ NO

Do you intend to in the next 3 months? ❑YES ❑ NO

Signature: .....

Date: .....

APPENDIX A4: (Chapter 3)

Physical Activity Readiness Questionnaire (PAR-Q)

For most people physical activity should not pose any problem or hazard. PAR-Q has been designed to identify the small number of adults for whom physical activity might be inappropriate or those who should have medical advice before performing the type of exercise used in the current experiment.

Yes	No	1) Has a physician ever said you have a heart condition and you should only do physical activity recommended by a physician?
Yes	No	2) When you do physical activity, do you feel pain in your chest?
Yes	No	3) When you were not doing physical activity, have you had chest pain in the past month?
Yes	No	4) Do you ever lose consciousness or do you lose your balance because of dizziness?
Yes	No	5) Do you have a joint or bone problem that may be made worse by a change in your physical activity?
Yes	No	6) Is a physician currently prescribing medications for your blood pressure or heart condition?
Yes	No	7) Are you pregnant?
Yes	No	8) Do you have insulin dependent diabetes?
Yes	No	9) Do you know of any other reason you should not exercise?

If you answered YES to one or more questions:
If you have not recently done so, consult with your personal physician by telephone or in person before taking part in this exercise test.

If you answered NO to all questions:
If you answered PAR-Q accurately, you have reasonable assurance of your present suitability for this exercise test.

Name:
Date:
Signature:

APPENDIX A5: (Chapter 3)

HEALTH SCREENING PRIOR TO BLOOD SAMPLING

Please read through these questions and sign the form if none of these situations apply. In case the answer to one or more questions is 'yes' or if you are unsure about the answer, please inform the experimenter (note that in this case you DO NOT have to provide anyone with information as to which answer is confirmative!)

- Are you HIV positive or do you think you may be HIV positive?
- Have you ever had hepatitis B or hepatitis C or do you think you may have hepatitis now?
- Have you been told by a doctor you should never give blood?
- Are you currently on anticoagulation therapy? (e.g. warfarin)
- Do you have a history of fits?
- Do you have a bleeding disorder? (e.g. haemophilia, low platelets, etc.)
- Do you know of any other reason you should not have your blood taken?

If you answered 'No' to all questions we have reasonable assurance of your suitability to provide blood samples.
I confirm that to the best of my knowledge none of the situations above apply to me.

Participants name:	
Participant signature:	**Date:**

If you have a tendency to faint when seeing blood, please notify the experimenter.

APPENDIX A6: Risk assessment (Chapter 3)

Risk Assessment			
An investigation of the factors pertaining to the maintenance of glycaemia in humans.			
College/ PSU	College of Engineering	Assessment Date	28/10/21
Location	SPEX labs	Assessor	Ross Hamilton
Activity	Research	Review Date (if applicable)	
Associated documents	• SOP 101 General Cleaning and Disinfecting of Non-Clinical Laboratories		

Appendix 6:

Part 1: Risk Assessment

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
Risk Item 1: Catching or spreading Covid-19 through normal every-day contact with other laboratory users	Researchers, lab technicians, academic staff, cleaners, demonstrators, visitors, test participants, service engineers, UG + PG students, first aiders.	Exposure to COVID-19	• All University return to work inductions, check lists, research risk assessments, access requests and permits must be completed, read, and signed by each researcher before using the laboratories. • All University research involving human participants procedures will be followed and requests must be completed and approved by CoE REC prior to any test participants attending the laboratory that are not already on campus for work (e.g. undergraduate students, members of the public). • When in place, we will follow Welsh Government Level 4 restrictions and only travel to campus for work which cannot be done from home. • During the level 4 lockdown restrictions, only staff/students who are already traveling to campus for work are permitted to use the lab / or act as a test participant, i.e. no	3	2	6	No				

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
			members of the general public to travel to campus for the purpose of being a test participant. • Staff/students who are acting as participants will be treated with the same level of care and infection control measures as would any other member of the public volunteering for research. • We will follow local (Swansea University and Public Health Wales) social distancing rules as much as feasible, washing hands and use hand sanitiser before touching equipment/door handles and using good personal hygiene such as coughing in to elbows/tissues and disposing of appropriately, wearing face coverings around campus and in laboratories when social distancing becomes difficult, pre-booking labs with lab techs and not exceeding lab capacities. • Only come into the laboratories to do work that cannot be done from at home or in your own office and use the laboratories for the minimum amount of time that you need to. • No staff or PGR member will come into the laboratories if they feel unwell								

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
			and have any signs or symptoms of Covid-19. • The University Safe Operating procedures for reporting and isolating (available at: https://staff.swansea.ac.uk/healthsafety/covid-19/#covid-19-reporting-and-isolation-arrangements=is-expanded) will be followed should any staff member or PGR develop signs or symptoms of COVID-19 and the affected member will return home immediately. • Time spent in the laboratories must be booked in advance with Laboratory Technicians. This ensures lab and building capacities will not be exceeded. These covid risk reduction measures cover all previous project risk assessments and standard operating procedures.								
Risk Item 2: Catching or spreading Covid-19 through contact with contaminated	Researchers, lab technicians, academic staff, cleaners, demonstrators, visitors, test	Exposure to COVID-19	• Any waste will be disposed of immediately and in appropriate waste bins. Used PPE will be disposed of in biohazard bins that are present in all laboratories. • All researchers will be made aware of basic hygiene measures to prevent	3	2	6	No				

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
surfaces in the laboratory	participants, service engineers, UG + PG students, first aiders.		transmission of COVID-19, including: trying not to touch your face, using PPE such as appropriate gloves, keyboard covers, clinical mice and keyboards, disposable aprons, lab coats if you need to touch equipment or surfaces. Wash your hands before and after using the labs, as well as regularly during work. Wash hands prior to touching shared equipment and surfaces and all shared equipment and surfaces will be disinfected (using University approved cleaning products effective against COVID-19) before leaving the laboratory. • The SOP for cleaning procedures are to be read and understood by the researcher before commencing work (**document SOP101 Appendix 8**). These covid risk reduction procedures cover all previous project risk assessments and standard operating procedures.								
Risk Item 3: Risk of exposure and spread of COVID-19 due	Staff working in lab, including researcher and participant	Exposure to COVID-19.	• If the participant at any point before, during or after the trial experiences COVID-19 symptoms they will immediately self isolate and all their contacts will be tracked and traced	3	2	6	No				

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
to participating in the study.			following the Swansea University procedure (available at: https://staff.swansea.ac.uk/healthsafety/covid-19/#covid-19-reporting-and-isolation-arrangements=is-expanded). • Participants will be contacted by phone on the evening prior to, and on the morning of, each experimental trial, and a standardized set of questions to check for signs and symptoms of COVID-19 will be asked (these are outlined in **document Appendix 7**). If they answer "yes" to any question, the appointment will be cancelled and the appropriate track and trace notification procedures followed (as per above). • During Tier 4 restrictions, participants will strictly be staff and PGRs who work onsite and therefore are not unnecessarily travelling to the university for the purpose of being a participant. • Participants will enter the laboratory through a specifically labeled door and will be wearing a face covering throughout testing, with the exception of exercise. • Participants will wear a cloth mask the entire procedure except for the fitting of								

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
			face mask for gas exchange measurements. • Only the researchers and participant will be allowed in the lab during the trial (although another member of staff will be in the vicinity of the labs for first aid reasons). • The lab will be fully sanitised and set-up before the participant arrives to minimise the time they are required to be there and all equipment will be ready for the participant to self-fit. • A 2 m distance between the researcher and participant will be maintained throughout the trial where possible. The researcher will be wearing a face covering throughout, also wearing appropriate PPE for parts of the trial where social distancing cannot be maintained (risk item number) and for aerosol generating procedures (risk item number 5). • They will wait 1 hour after aerosol generating procedures before returning to clean to allow for aerosols to drop to the floor for cleaning. They will dispose of or clean/sanitise the equipment and the entire laboratory using the Universities cleaning and sanitising procedures (Document								

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
			SOP101 Appendix 8). • Equipment, such as the gas analysis mask and turbine and heart rate monitor will be soaked in Milton sterilising fluid for the recommended time. These covid risk reduction measures cover all previous project risk assessments and standard operating procedures.								
Risk Item 4: Catching or spreading Covid-19 when carrying out project procedures that do not allow for social distancing, e.g blood sampling, fitting face mask for gas analysis, measuring blood pressure, any other tests that require the	Staff working in lab, including researcher and participant	Exposure to COVID-19.	• PPE is to be worn and after hand washing: Nitrile gloves, lab coats-sleeves rolled down, disposable aprons. • Laboratory is to be ventilated with windows open at all times during the trial. • Once all testing is complete the lab will be thoroughly cleaned entire laboratory using the Universities cleaning and sanitising procedures (document SOP101 APPENDIX 8). • The researcher will a change their clothes at the end of the experimental period and they will be bagged, taken home, and washed immediately. These covid risk reduction measures cover all previous project risk assessments and standard operating procedures.	3	3	9	No				

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
researcher to come close or touch the test participant.											
Risk Item 6: Catching or spreading COVID-19 when carrying out blood handling/analysis procedures after testing	Researcher, participant, lab technicians	Exposure to COVID-19	• Where possible, blood handling, separation and analysis will take place in a separate room to the exercise bout to reduce exposure to aerosols (gloves and lab coats worn). • Where this is not possible, Level 2 PPE is to be worn after hand washing: Nitrile gloves (double gloves), lab coats, disposable aprons, eye protection (goggles and visors BSEN166 compliant). • A surgical mask will be worn during work requiring close proximity to the participant. • Participants to wear face coverings when in the lab and only remove when putting on face mask for gas exchange measurements. • Social distancing rules will be followed at all times other than when blood samples are being collected.	3	3	9	No				

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
			• Collected blood samples will be spun in a sealed centrifuge with lid. • Samples will be labelled detailing anonymous participant code, trial, date in permanent marker • All surfaces will cleaned and disinfected after use (document SOP101 Appendix 8). • Wash hands on entering and leaving. These covid risk reduction measures cover all previous project risk assessments and standard operating procedures. • Blood samples being spun or analysed will be done inside a category 2 safety cabinet to reduce exposure to any aerosols that may be produced.								
Risk Item 8: Side effects of wearing PPE such as discomfort, overheating, allergies, emotional discomfort.	Researchers, participants	Fatigue, discomfort, overheating, allergies, emotional discomfort	• All PPE is to be tested before use, all users trained for correct don/doff/disposal procedures by supervisors and/or lab technicians. • Masks should be worn only if comfortable (and testing therefore not be conducted if they are removed), and most models can be worn for a max of 3 hours. The time spent in the labs should be	2	3	6	No				

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
			kept to a minimum. • Wearers are to be encouraged to wear the appropriate level of PPE for the minimum time required and to report any adverse side effects such as allergies or discomfort immediately. • Researches should ensure that participants can hear/see them, that they feel comfortable at all times and they report any side effects to PPE. • Participants are free to withdraw from the study at any point. These covid risk reduction measures cover all previous project risk assessments and standard operating procedures.								
Risk Item 10: Catching or spreading Covid-19 when giving or receiving first aid	First Aider, Researcher, Participant	Exposure to COVID-19	• A first aid trained researcher will be present during all testing sessions. • At least one other person will be in the proximity of the lab where the testing is taking place. The researcher will confirm locality and contact methods for the other individual prior to their testing. • The first aider will have had Covid-19 additional PPE training and PPE	3	2	6	No				

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
			supplies will be located beside the first aid box in the laboratory. • The resuscitation council UK guidelines on delivering first aid and CPR during Covid-19 will be followed (available at https://www.resus.org.uk/covid-19-resources/covid-19-resources-general-public/resuscitation-council-uk-statement-covid-19). • Report all incidents to supervisors/ lab technicians/ line managers and on the Health and Safety Report It webpage. • If, during an emergency incident, the previously identified first aider cannot be immediately located, then 333 will be dialled from the phone present in the lab. These covid risk reduction measures cover all previous project risk assessments and standard operating procedures.								
Risk Item 13: Confidentiality of participant	The participants	A possibility that others might be able to see or gain access to their data.	All participants will be given a numerical identifier. Personal information will be stored on a password protected computer in a password protected file. All data will be destroyed in accordance with the Data	1	2	4	No				

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
			Protection Act (2018).								
Risk Item 14: Confidentiality of data	The participants	A possibility that others might be able to see or gain access to their data.	• The data will be stored on a password protected computer in a password protected file. Due care and attention will be taken transporting the data to the password protected file. Any data stored temporarily on a portable electronic device will be deleted immediately once stored on the password protected computer. The data will be destroyed in accordance with the Data Protection Act (2018). Withdrawal procedures are in place if the participant wants to withdraw from the study at any time up to publication.	1	2	2	No				
Risk Item 15: Contamination of trial beverage	The participants	There is a possibility of consuming a harmful substance	• Any beverages will be prepared in advance of the trial in a designated food/drink preparation area. • Hygiene and cleanliness will be a high priority ensuring all containers are clean and sterilized. • Hands will be washed and adequate PPE, Gloves and lab coats worn when preparing the solutions. • All ingredients will be adequately	1	2		No				

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
			stored and handled appropriately to ensure that contamination with any unwanted substances is avoided.								
Risk Item 16: Emergency procedure for spills	The researcher and participant.	Exposure to infectious material (Blood)	• Blood spill kits are present in the laboratory • Researcher is trained in the procedure for spills within the laboratory	1	2	2					
Risk Item 17: Waste disposal	The researcher	Exposure to sharps and other hazardous waste.	• Sharps bins and hazardous waste bins are present in the laboratory. • The researcher is trained in Safety & Sustainability within the lab • Lab technicians remove waste through appropriate waste disposal procedures on a regular schedule.	1	2	2					
			•								
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			•								

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
			•								

Part 2: Actions arising from risk assessment

Actions	Lead	Target Date	Done Yes/No

Actions	Lead	Target Date	Done Yes/No

Appendix 1. Risk Matrix

		Consequences				
		1 **Insignificant** No injuries/ minimal financial loss	**2** **Minor** First aid treatment/ medium financial loss	**3** **Moderate** Medical treatment/high financial loss	**4** **Major** Hospitalised/ large financial loss	**5** **Catastrophic** Death/ Massive Finanical Loss
Likelihood	**5** **Almost Certain** Often occurs/ once a week	5 Moderate	10 High	15 High	20 Catastrophic	25 Catastrophic
	4 **Likely** Could easily happen/ once a week	4 Moderate	8 Moderate	12 High	16 Catastrophic	20 Catastrophic
	3 **Possible** Could happen/ happen once a year	3 Low	6 Moderate	9 Moderate	12 High	15 High
	2 **Unlikely** Hasn't' yet happened but could happen	2 Low	4 Moderate	6 Moderate	8 High	10 High

	1 **Rare** Concievable but 1/100 year event	1 Low	2 Low	3 Low	4 Moderate	5 Moderate

Appendix A7:

Standard Operating Procedure

SOP Number *ISOP101*

SOP Title ***General Cleaning and Disinfecting of Non-Clinical Laboratories***

	NAME	TITLE	SIGNATURE	DATE
Author	**Wendy Clark**	**Senior Laboratory Technician**	***Wendy Clark***	**30/05/2020**
Reviewer				
Authoriser	**Adrian Jenkins**	**Technical manager**	***A.Jenkins***	**1/06/2020**

Effective Date:	**01/06/2020**
Review Date:	**01/06/2022**

Purpose

General procedure for carrying out systematic cleaning and disinfection non-clinical laboratories. The aim of these procedures is to help prevent the spread of viruses and bacteria- including Covid-19, on potentially contaminated surfaces within laboratories. Recommendations for these procedures have been taken from UK NHS websites, Welsh Ambulance advice and current Uk Government advice on how to stop the spread of Covid-19

Introduction

The current outbreak of the Covid-19 and the Duty of Care we need to demonstrate to our colleagues, students and families, means that we all now need to pay more attention to cleaning and disinfection of our specific work/laboratory areas. This document provides a simple procedure that can help prevent the spread of viruses when followed correctly.

Scope

Work and equipment surfaces in non-clinical laboratories in College of Engineering, Bay Campus, Swansea University.

Definitions

Cleaning*- Cleaning is a process that removes contaminants including dust, soil, microorganisms and the organic matter that shields them, such as bodily fluids.*

Disinfection*- Disinfection is a process that reduces the number of microorganisms to a level at which they are not harmful, and is only effective if the equipment or surface is thoroughly cleaned with a detergent beforehand.*

PPE*- Personal Protection Equipment such as gloves, safety goggles, aprons, laboratory coats and work-wear, and masks, designed to protect the wearer's body from infection or injury.*

FFP3*- Filtering Face-piece masks that protect against solid and liquid toxic aerosols*
Virus*- Virus is microscopic parasitic organism that can infect living organisms and cause diseases.*
MSDS*- Material Safety Data Sheet- Document prepared by manufacturers of chemicals describing the chemical and physical properties and safety considerations of that product. These help users create Risk Assessments as required by Control of Substances Hazardous to Health Regulations (COSHH).*

Responsibilities

Laboratory Technicians with responsibilities for cleaning their own designated laboratory areas.

SPECIFIC PROCEDURE

Cleaning -To ensure effective cleaning, the equipment used and the item to be cleaned should be in a good state of repair. Ensure sufficient contact time between surfaces and cloths when cleaning and disinfecting. Always work from clean to dirty areas, and use a method such as clockwise from entry. Make sure you have time to complete the job fully. Electrical items can be cleaned with a designated clean microfiber cloth that can be laundered afterwards. Cleaning materials / equipment are to be stored in a designated clean area and an appropriate cleaning schedule administered. Chemicals are to be used and stored according to MSDS and COSHH Risk Assessment.

- ***Some chemicals cause respiratory problems, especially when atomised- so use appropriate chemical for the surface and the user***
- ***Things must be dried properly after use – wet surfaces attract dust and actually provide better conditions for viruses and bacteria to thrive- eg Legionella and Covid-19***
- ***Dispose of/launder the cleaning materials appropriately***

Disinfection-The use of disinfectants, e.g.Milton, Clinell, Azo wipes - are recommended when dealing with blood/body fluid spillages or where an outbreak of infection has occurred. Dual acting products, e.g., Uni9, will complete the cleaning and disinfecting process in one action. Disposable alcohol wipes (such as Azo wipes) are useful for disinfecting electrical items –check suitable for surfaces first. Dilute chemicals according to instructions to avoid increase in microbial resistance and damage to surfaces.
Procedure:
Wash your hands
Wear appropriate PPE- inspect gloves and check they are certified for chemical resistance, wear disposable aprons over lab coats/ work-wear, eye protection and FFP3 mask if required
Cordon area, open windows or improve ventilation
Dilute detergent according to instructions

- *Remove excess dust/ waste by sweeping, wiping or pre-rinsing.*
- *Main clean – loosen surface waste and grease using a detergent.*
- *Rinse – remove loose waste, grease and detergent, then dry.*
- *Disinfection – kill the bacteria/ viruses with correct disinfectant or heat.*
- *Final rinse – remove the disinfectant if necessary.*
- *Drying – remove all moisture.*

Use detergent to wipe down all hard surfaces, electrical equipment (with rung-dry microfiber cloth / alcohol wipe)
Pay attention to 'grip' areas-under bench and chair edges, under equipment, buttons and handles. Wipe equipment from top to bottom.
Dispose of unused detergent, clean gloves and equipment, dispose of cloths and disposable PPE according to University policy or store for laundry

***Wash your hands* and record on cleaning schedule**

Forms/Templates to be used

Cleaning Schedule bespoke to each laboratory cleaned.

References

SOP000- Writing SOPs- Adrian Jenkins, College of Engineering, Swansea University.
https://assets.publishing.service.gov.uk/media/5eb9752086650c2799a57ac5/working-safely-during-covid-19-labs-research-facilities-240520.pdf
https://www.physoc.org/covid19/returning-to-the-lab/
https://www.england.nhs.uk/coronavirus/primary-care/infection-control/
https://phw.nhs.wales/topics/latest-information-on-novel-coronavirus-covid-19/

Change History

SOP no.	Effective Date	Significant Changes	Previous SOP no.
SOP101	**01/06/2020**	**Initial Version**	**N/A**
SOP101	**01/06/2021**	**review**	**N/A**

APPENDIX:B1 (Study Chapter 3)
PARTICIPANT INFORMATION SHEET
(Version 1.1, Date: 15 /07/22)

Project Title:

The metabolic stress of acute and chronic ultra-endurance exercise under low or high glycaemic index-carbohydrate diets incorporating Isomaltulose consumption.

Contact Details:

Ross Hamilton PhD researcher Swansea University ross.hamilton@swansea.ac.uk
Tel: 07427648416

1. Invitation Paragraph

You are invited to take part in this research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information, please do not hesitate to ask us. A member of the research team will go through the entire process and what is involved before you start.

2. What is the purpose of the study?

Carbohydrate intake has a profound impact on endurance performance. Carbohydrate is a particularly important energy source for prolonged moderate- to high- intensity exercise. Stores of energy in the body include liver and skeletal muscle glycogen, which can provide sufficient energy to sustain 45–60 mins of high- intensity exercise. However, at longer exercise durations (>60 mins) these stores may become significantly reduced and contribute to early fatigue.

The rate of liver and skeletal muscle glycogen repletion is an important factor determining the time needed to fully recover from exhaustive endurance exercise. This is particularly relevant when consecutive bouts of exercise are performed within 24 h, for example during multistage races or multiday activities like ultra-endurance events.

Muscle glycogen repletion rates can reach maximal values when sugar mixtures like dextrose or maltodextrins are ingested in an amount of 1.2 g per kg of bodyweight per hour. It has been speculated that post-exercise muscle glycogen replenishment might be further increased when ingesting multiple transportable carbohydrates (i.e., mix of glucose and fructose) by a liver storage mechanism.

Isomaltulose (Palatinose^{TM}) is a complex sugar comprised of glucose and fructose which has a 20-25% slower release into the blood than sucrose. This may have a benefit to endurance activity where glycogen can be spared, placing less demand on carbohydrate intake via race nutrition.

Research supports the role of Isomaltulose as an important carbohydrate for endurance activities. The purpose of this study is to examine the impacts of Isomaltulose as a low glycaemic- index, high carbohydrate fuel for acute exercise as well as when incorporated into a low glycaemic-index diet plan in ultra-endurance athletes.

3. Why have I been chosen?

You have been invited because you are:

- Generally healthy
- Aged between 18 and 65 years
- Participating in regular training (>10hrs Per week)
- Involved or regularly participating in Ultra endurance events.
- Have a VO_2max > 55ml.kg^{-1}.min^{-1}

Because you do not have:

- An abnormal electrocardiogram (ECG) - irregular heart function
- A current or history of substance abuse and/or excess alcohol intake
- Type 1 or 2 Diabetes
- Heart disease
- Cancer
- Gastrointestinal disease e.g. inflammatory bowel disease or irritable bowel syndrome
- Kidney disease
- Liver disease
- Pancreatitis
- Receipt of any investigational medicinal products within 1 month prior to screening
- Blood pressure outside the range of 90-140 mmHg for systolic or 50-90 mmHg for diastolic
- Any allergy or food intolerance e.g fructose intolerance
- Receipt of any hormonal therapies or medications.

And are not:

- A current smoker
- On hormone therapy for <6 months
- Prescribed anti-hypertensive or beta-blocker medication

However, the results of the screening may indicate that you will not be invited to take part. We aim to recruit a minimum of 10 participants in total.

4. What will happen to me if I take part?

If you agree to take part, you will then be asked to complete the consent form. A health screening will then be conducted to assess your eligibility. This involves having your body measurements taken (height, weight, body mass).

This study will last 77 days from your first screening session to completion. You will visit the laboratory at Swansea University Bay Campus a total of 5 times. The first visit will be a screening and familiarization session, where you will get an introduction to the processes involved and a baseline fitness test. The remaining 4 visits will include an exercise trial aimed at depleting your energy stores (glycogen) a re-feed period, followed by another exercise trial to exhaustion.

Between your 2nd and 3rd visit you will be assigned to either a high or low GI diet group. This will require you to supplement your diet with either Maltodextrin or Isomaltulose using a specific and tailored plan. In addition, you will substitute some of your regular carbohydrate sources for either high or low GI variations of the food type. You will log this using a simple food logging App on your phone (My FitnessPal). You will complete your regular training throughout the course of the study logging your activity to an online training log (TrainingPeaks) for the research team to access. You will also be given a Continuous Glucose monitor and shown how to install and use and directed to resources you may find useful. You will use this sensor for the entire study duration. Between your 3rd and 4th visit to the lab you will return to your normal diet to allow for a washout period. Then you will move to the opposite diet group and repeat another 4-week block of training logging information as you did before

Screening Visit (Week 0)

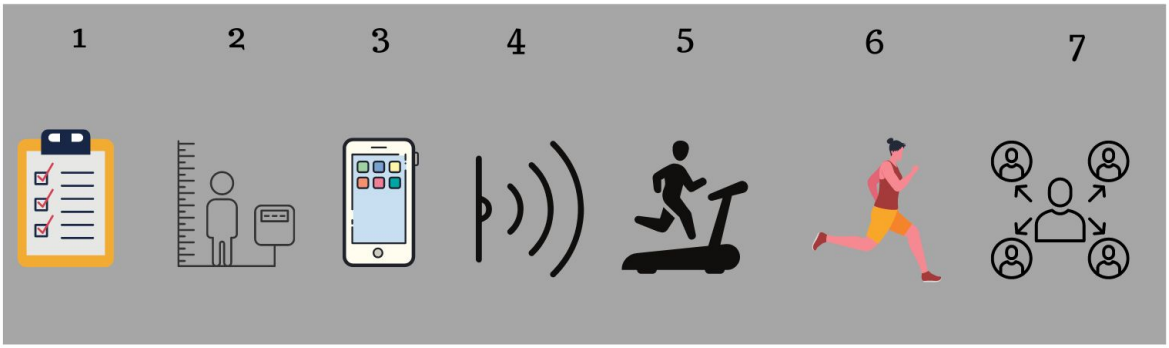
You will be invited to attend a screening visit at Swansea University where you will be interviewed by one of the researchers. You will be asked not to eat or drink anything (except water) from 8pm the night before your visit. If you wish to participate, you will be asked to sign a consent form. You will then be asked to fill out an; Body composition and body measurements will be taken. This involves your height, weight, and bioelectrical body composition analysis. This will allow us to establish your lean mass and bodyfat. It is a non-invasive test using a machine called the bio-electrical impedance analysis (BIA) which will send a low-level, painless, electric current throughout your body. You will also have your blood pressure taken.

You will also have to complete what is known as a Cardiopulmonary exercise test (CPET). This is to evaluate your fitness. This involves running on a treadmill at progressively faster speeds. You will be wearing a breathing mask to allow for breath-to-breath analysis. This will allow us to establish your VO_{2peak}. In addition, we will measure Heart rate and pace to establish your intensity zones.

If you are eligible to participate in the study, the researcher will disclose which group you will be first assigned to. The allocation sequence of which you will be assigned to is at random

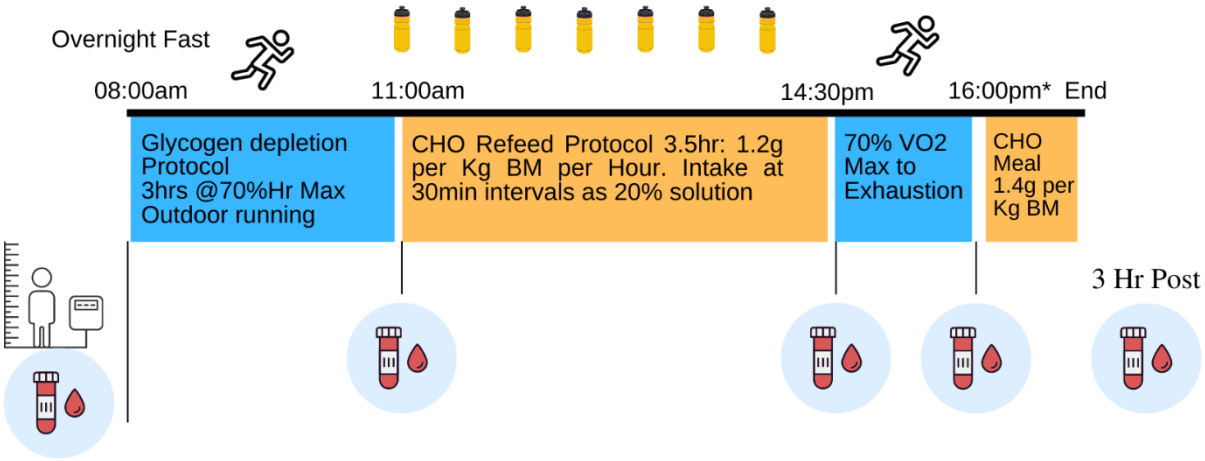
(generated through computerised random sequence) and pre-defined. Please note that you are unable to change groups once assigned as this will create a bias within the study.

The health screening should last no longer than 2 hours. Below is a schematic of the screening visit at Week 0. For the following 7 days you will be asked to record your normal diet using the phone app.



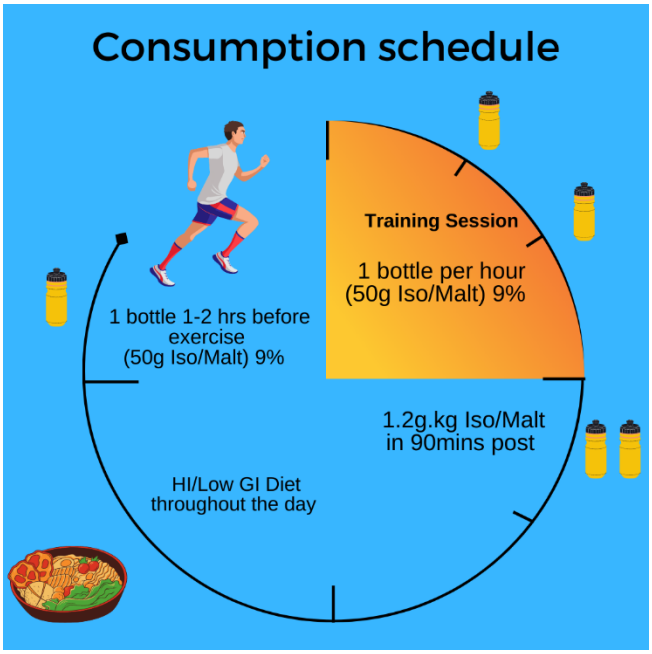
Study Visits – Week 1 and 8

You will be invited to attend 4 sessions at Swansea University: at the start (day 7) you will arrive to the ASTEM Laboratory on Bay Campus at 8am. You will refrain from eating anything from 8pm onwards the previous night. When you arrive your body measurements will be taken again in the same fashion as your screening session. A venous blood sample (approx. 1 tablespoon per sample) will be taken from your arm at rest before commencing your initial exercise protocol. This protocol will be completed outdoors on a mapped course in the natural reserve adjacent to the University building. You will run for 180mins at an intensity equal to 70% HRmax as defined by your fitness (CPET) test during your screening day. As soon as you finish you will return to the lab where another blood sample will be taken. You will then begin your re-feed. This will involve consuming a flavoured carbohydrate beverage. You will consume 1.2g per Kg of your bodyweight each hour. For example a 70kg individual will consume 84g an hour in approx. 400ml of fluid (20% Solution). The re-feed will last 410mins and you will consume 1.4L in this time. Throughout this period you will be asked to rate feelings of gut distress via a basic questionnaire. Once the re-feed period is finished another blood sample will be taken before your exhaustive trial. This exhaustive trial will take place using a treadmill in the lab. You will run as long as you possibly can at an intensity representing 70% of VO_{2max}. Once you finish another blood sample will be taken. You will then receive a carbohydrate meal as you recover from the session. Another blood sample will be taken 3 hrs post exercise and then you will be finished for the day. Below is schedule of the acute exercise protocol.



Dietary Intervention

Between visits 2 & 3 and again between 4 & 5 you will complete your dietary intervention. Once you finish your screening session you will be allocated to either the High or Low GI group. Both groups will supplement their diet with either Maltodextrin or Isomaltulose drinks. The schedule for supplementation can be seen in the diagram below.



You will also be advised on suitable alternatives for the regular carbohydrate foods in your diet. For example the Low GI alternative for white rice may be brown rice, white potato may be swapped with sweet potato. Every effort will be made to ensure that your diet remains achievable with alterations made only to alter the Glycaemic index of the carbohydrate food choices. You will be provided with food scale to weigh the quantities of the food you eat so that you can record your dietary intake using the phone app. Your training may continue as normal, but you must record your sessions and activity levels using a Garmin smart watch. This data must be regularly uploaded to the TrainingPeaks platform where it can be accessed by the research team.

You will complete this dietary intervention block twice separated with a two-week washout phase where you may return to your regular diet.

5. What are the possible disadvantages of taking part?

The exclusion criteria and pre-screening mentioned above are in place to reduce any risks. You will be closely supervised by a researcher trained in first aid at all times, and an automated external defibrillator (AED) will also be readily available. If you experience any unusual or unexpected symptoms or a change in health status at any time during the study, please inform one of the researchers immediately.

You will will be required to perform maximal exercise and as a result may experience some transient muscle soreness, fatigue, cardiorespiratory stress (elevated heart rate, blood pressure, and breathing) or possible nausea during and immediately following the exercise. There is also a small inherent risk of physical injury or an adverse cardiovascular event (e.g. heart attack), however, risks of cardiac origin are very low (approximately 0.5 events per 100,000 individuals each year). Furthermore, we will perform extensive pre-screening to exclude anyone with conditions or symptoms which suggest they may be at higher risk. In addition, you will be asked to inform the investigator immediately of any change in health status during the course of the study. A first aid and defibrillator trained adult will be present in the laboratory during all testing sessions. The laboratory is fitted with a defibrillator and emergency telephone as standard. You will be observed for 60 mins post steady state exercise to ensure they are ok prior to leaving.

The potential risks of having blood collected via venepuncture or cannulation are rare but may include temporary discomfort at the site of puncture, possible bruising around the puncture site and, uncommonly, infection or faintness. A standard operating procedure is in place for performing venepuncture and a risk assessment has been completed. Only researchers trained in phlebotomy will perform this procedure during this study and good clinical practice guidelines will be followed, thus minimizing any potential risk. There is also a low risk of infection to the collection site which will be mitigated using best practice for hygiene and cleanliness to reduce any possible contamination.

You will be asked to consume beverages with high GI carbohydrates there is some possibility for them to experience a hyper- or hypo-glycaemic response. These may bring on some common but mild side effects such as dizziness, shakiness, sweating, irritability, tingling sensations, nausea and headache. These are usually mild and very brief in those that may experience them. The PI will be monitoring the participants for any of these side effects throughout the trial session.

The study will require a considerable time commitment and multiple visits to the laboratory. You will receive an inconvenience allowance to reflect this. On completion of the study each participant will receive a £100 payment for each of the four lab visits attended, payable on completion of the study.

6. What are the possible benefits of taking part?

The direct benefit from taking part in this study will be a complete physiological and metabolic assessment which you can discuss with a member of the research team. It will also allow you to test, under tight conditions, what dietary interventions have a positive impact on your performance and health.

You will also get the opportunity to use the CGM sensor for a two-week period. This will allow you to trace your own interstitial glucose levels throughout your day and during exercise. This novel application of established technology may provide some great insight into how you respond to certain food types.

7. Will my taking part in the study be kept confidential?

Your data will be processed in accordance with the Data Protection Act 2018 and the General Data Protection Regulation 2016 (GDPR). All the information gathered about you throughout the duration of the study will be kept completely confidential. The only record of your name and details will be made on the initial visit to the laboratory, to be able to contact you regarding the study (e.g., arranging visit times). If you agree to participate, we will also retain your consent form and pre-screening health questionnaires to ensure that you are willing and able to take part in this study. However, this identifiable information will be immediately separated from all other data sheets and stored in a locked filing cabinet, in a locked office. From there on you will be assigned a participant-code, which will be used in all proceeding data collections so that no one can identify you. An electronic record linking your name to the participant-code will be kept in a password protected file on a secure university computer. Personal data will be kept for one year after study completion. This allows reasonable time for you to request further feedback on the study outcomes and data that was collected from you during the study. After one year, the password-protected spreadsheet linking the participant-codes to the participant's name will be deleted; however, all other data will be kept, but will be anonymous. Data will be archived for at least 10 years. Whole blood samples will not be stored, and all plasma and serum samples will be anonymised by labelling with your unique participant study code, trial number and date only. No other identifying information will be on the samples. The samples collected will be used solely for this study and will not be used for any future projects. All processes will be in accordance with the university guidelines.

Data Protection and Confidentiality

Your data will be processed in accordance with the Data Protection Act 2018 and the General Data Protection Regulation 2016 (GDPR). All information collected about you will be kept strictly confidential. Your data will only be viewed by the researcher/research team. Data may be made available to study sponsor once analysed and anonymised. No personal information will be shared.

All electronic data will be stored on a password-protected computer file on the PI's laptop. All paper records will be stored in a locked filing cabinet in the Supervisors office. Your consent information will be kept separately from your responses to minimise risk in the event of a data breach.

Please note that the data we will collect for our study will be made anonymous, you will be assigned a code once screening is complete which will be used to record your data, thus it will be possible to identify and remove your data at a later date, should you decide to withdraw from the study. Therefore, if at the end of this research you decide to have your data withdrawn, please let us know before you leave.

Please note that data collected online, once the data has been submitted online you will be unable to withdraw your information.

Data Protection Privacy Notice
The data controller for this project will be Swansea University. The University Data Protection Officer provides oversight of university activities involving the processing of personal data, and can be contacted at the Vice Chancellors Office.

Your personal data will be processed for the purposes outlined in this information sheet.
Standard ethical procedures will involve you providing your consent to participate in this study by completing the consent form that has been provided to you.

The legal basis that we will rely on to process your personal data will be processing is necessary for the performance of a task carried out in the public interest. This public interest justification is approved by the College of Engineering Research Ethics Committee, Swansea University.

The legal basis that we will rely on to process special categories of data will be processing is necessary for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes.

How long will your information be held?
Personal data will be kept for 12 months after study completion. This allows a reasonable time for any participant to request further feedback on the study outcomes and data that was collected from them during the study. After six months, the password-protected spreadsheet linking the participant-codes and the participant name will be deleted; however, all other data will be kept, but will be anonymous. Data will be archived for at least 10 years.

What are your rights?
You have a right to access your personal information, to object to the processing of your personal information, to rectify, to erase, to restrict and to port your personal information. Please visit the University Data Protection webpages for further information in relation to your rights.

Any requests or objections should be made in writing to the University Data Protection Officer:-

University Compliance Officer (FOI/DP)

Vice-Chancellor's Office
Swansea University
Singleton Park
Swansea
SA2 8PP
Email: dataprotection@swansea.ac.uk

How to make a complaint
If you are unhappy with the way in which your personal data has been processed you may in the first instance contact the University Data Protection Officer using the contact details above.

If you remain dissatisfied then you have the right to apply directly to the Information Commissioner for a decision. The Information Commissioner can be contacted at: -

Information Commissioner's Office,
Wycliffe House,
Water Lane,
Wilmslow,
Cheshire,
SK9 5AF
www.ico.org.uk

8. What if I have any questions?
Further information can be obtained from the researcher contact stated above. The project has been approved by the College of Engineering Research Ethics Committee at Swansea University. If you have any questions regarding this, any complaint, or concerns about the ethics and governance of this research please contact the Chair of the College of Engineering Research Ethics Committee, Swansea University: coe-researchethics@swansea.ac.uk. The institutional contact for reporting cases of research conduct is the University Head of Research Prof Helen Griffiths. Email: researchmisconduct@swansea.ac.uk. Further details are available at the Swansea University webpages for Research Integrity. http://www.swansea.ac.uk/research/researchintegrity/."

Project ID: U1111-1281-5048
Visit ID: _____
Participant ID: _____

APPENDIX: B2

CRF Screening & CPET Visit

(Version 4)

The metabolic effects of ultra-endurance exercise and training under low or high glycaemic index-carbohydrate diets.

Principal Investigator:
Name: Ross Hamilton MSc.

Co-investigators:
Name: Prof. Richard Bracken, PhD
Name: Dr. Rachel Churm PhD
Name: Dr. Olivia McCarthy, PhD
Name: Ruiyang Xia

Project ID: U1111-1281-5048
Visit ID: _____
Participant ID: _____

Visit Date:_____

09:00 (15mins)

INCLUSION CRITERIA

Has the participant met the following inclusion criteria?	Yes	No
1. Informed consent obtained (Appendix 1)	☐	☐
2. Male or female aged 18-65 years (both inclusive)	☐	☐
3. Has completed pre-medical questionnaire (Appendix 2)	☐	☐
4. Has completed International Physical Activity Questionnaire (IPAQ) and is deemed eligible for study participation. (Appendix 3)	☐	☐

All inclusion criteria must be answered YES (or N/A if not applicable). If any questions are answered NO the participant is not eligible to continue.

EXCLUSION CRITERIA

Has the participant met any of the following exclusion criteria?	Yes	No
1. Known or suspected hypersensitivity to trial product(s) or related products (any known sucrase-isomaltase deficiency)	☐	☐
2. Receipt of any investigational medicinal product within 1 month prior to screening in this trial	☐	☐
3. Known haemoglobin <8.0 mmol/L male) or < 7.0 mmol/L (female)	☐	☐
4. Suffer from or history of a life-threatening disease (i.e. cancer judged not to be in full remission except basal cell skin cancer or squamous cell skin cancer), or clinically severe diseases that directly influence the study results, as judged by the Investigator. This does not prohibit the participation of patients taking medications that influences the metabolism (e.g. statin) or cardio-respiratory system (e.g. asthma spray) as long as the therapy is stable and is not adapted throughout the run of the trial. Furthermore, it does not exclude patients who have celiac disease (or similar diseases or allergies), as long as the disease is stable, and patients are able to stay on their specific (e.g.) gluten-free diet.	☐	☐
5. Cardiac problems defined as decompensated heart failure (New York Heart Association (NYHA) class III and IV)10 at any time and/or angina pectoris within the last 12 months and/or acute myocardial infarction at any time	☐	☐
6. Blood pressure at screening outside the range of 90-140 mmHg for systolic or 50-90 mmHg for diastolic (excluding white-coat hypertension; therefore, if a repeated measurement on a second screening visit shows values within	☐	☐

the range, the participant can be included in the trial). This exclusion criterion also pertains to participants being on antihypertensives (as long as the blood pressure is within the range, participants on hypertensives can be included)		
7. Known ECG abnormalities	☐	☐
8. Proliferative retinopathy or maculopathy and/or severe neuropathy, in particular autonomic neuropathy, as judged by the Investigator	☐	☐
9. Any chronic disorder or severe disease which, in the opinion of the Investigator might jeopardize participant's safety or compliance with the protocol	☐	☐
10. Participant known to be positive for Hepatitis B surface antigen (HBsAg) or Hepatitis C antibodies (or diagnosed with active hepatitis), for HIV-1 antibodies, HIV-2 antibodies or HIV-1 antigen	☐	☐
11. History of multiple and/or severe allergies to drugs or foods or a history of severe anaphylactic reaction (except celiac disease – patient must exclude foods that contain gluten from the diet) _____ _____ _____	☐	☐
12. Surgery or trauma with significant blood loss (more than 500 mL) within the last 3 months prior to screening	☐	☐
13. Current treatment with systemic (oral or i.v.) corticosteroids, monoamine oxidase (MAO) inhibitors, non-selective or selective beta-blockers, growth hormone. Furthermore, thyroid hormones are not allowed unless the use of these has been stable during the past 3 months	☐	☐
14. Significant history of alcoholism or drug/chemical abuse as per Investigator's judgement.	☐	☐
15. Smoker (defined as a participant who is smoking more than 5 cigarettes or the equivalent per day)	☐	☐
16. Not able or willing to refrain from smoking, or use of nicotine substitute products during the inpatient period	☐	☐
17. Participant with mental incapacity or language barriers precluding adequate understanding or cooperation or who, in the opinion of their general practitioner or the Investigator, should not participate in the trial	☐	☐
18. Potentially non-compliant or uncooperative during the trial, as judged by the Investigator.	☐	☐
19. Any condition that would interfere with trial participation or evaluation of results, as judged by the Investigator	☐	☐

Project ID: U1111-1281-5048 **Visit ID: _____** **Participant ID: _____**

20. Any known history of diabetes mellitus, or the use of any anti-hyperglycaemic drug or insulin to treat diabetes and related conditions.	☐	☐

To qualify for trial participation all exclusion criteria must be answered NO (or N/A if not applicable). If any questions are answered YES the patient is not eligible to continue.

ABSOLUTE CONTRAINDICATIONS TO CPET

Has the patient met the following exclusion criteria for CPET	Yes	No
1. Acute myocardial infarction within 2 days	☐	☐
2. Ongoing unstable angina	☐	☐
3. Uncontrolled cardiac arrhythmia with hemodynamic compromise	☐	☐
4. Active endocarditis	☐	☐
5. Symptomatic severe aortic stenosis	☐	☐
6. Decompensated heart failure	☐	☐
7. Acute pulmonary embolism, pulmonary infarction, or deep venous thrombosis	☐	☐
8. Acute myocarditis or pericarditis	☐	☐
9. Acute aortic dissection	☐	☐
10. Physical disability that precludes safe and adequate testing	☐	☐

To qualify for CPET participation all inclusion criteria must be answered NO (or N/A if not applicable). If any questions are answered YES the patient is not eligible to continue.

Project ID: U1111-1281-5048 **Visit ID: _____** **Participant ID: _____**

PRE-CPET PREPARATORY PROCEDURES.

Has the patient has met the following preparatory criteria?	Yes	No
1. 24 hrs pre-exercise avoidance of strenuous exercise.	☐	☐
2. 24 hrs pre-exercise avoidance of alcohol	☐	☐
3. 12 hrs pre-exercise avoidance of caffeine	☐	☐

If any questions are answered NO the participant is still eligible to continue as the discretion of the investigator. If answered NO, please provide specification below;

Comments:

_____

_____

_____

_____

9:15 (10mins)

Treadmill GXT report form

Name Event Age (yr) Date of Birth / /

Test date / /2022 Hb $g.dL^{-1}$ T_C ºC

Blood pressure / mmHg Resting pulse $beats.min^{-1}$

Skinfold
Biceps mm
Triceps mm
Subscap mm
Suprailiac mm
Total mm
% Body fat (from tables) = %

Height _____ m Body mass _____ kg BMI _____ $kg.m^{-2}$ LBM _____ kg

Project ID: U1111-1281-5048
Visit ID: _____
Participant ID: _____

9:25 (50mins)

Incremental treadmill test

Sample ID	Stopwatch time (hh:mm)	Velocity $Km.h^{-1}$	HR $Beats.min^{-1}$	VO_2 $mL.kg^{-1}.min^{-1}$	RER	RPE (Borg)	Lactate
1	00:05 Rest						
2	00:08	9					
3	00:12	10					
4	00:16	11					
5	00:20	12					
6	00:24	13					
7	00:28	14					
8	00:32	15					
9	00:36	16					
10	00:40	17					
11	00:44	18					
12	00:48	19					
13	00:52	20					

File Saved
File Code:.....

Investigator name (in print): _____

Investigator signature: _____

10:30 (5mins)

CGM Application

Application check list?	Yes	No
1. Has the participant downloaded the Supersapiens™ App successfully	☐	☐
2. Has the participant registered a Supersapiens™ account	☐	☐
3. Has the participant been issued with a Supersapiens™ Biosensor	☐	☐
4. Has the participant been instructed on safe preparation for sensor application	☐	☐

Project ID: U1111-1281-5048 **Visit ID: _____** **Participant ID: _____**

5. Has the participant successfully applied the Biosensor	☐	☐
6. Has the participant been informed of Supersapiens™ online resources	☐	☐
7. Has the participant been briefed on what to do if sensor fails	☐	☐

10:35 (10mins)

Nutritics Setup

Application check list?	Yes	No
8. Has the participant downloaded the Nutritics App successfully	☐	☐
9. Has the participant registered a Nutritics account	☐	☐
10. Has the participant been issued with a diet sheet	☐	☐
11. Has the participant been issued with a food scales	☐	☐
12. Has the participant been instructed on how to record food log	☐	☐

10:40 (5mins)

Diet allocation

Application check list?	Yes	No
13. Has the participant been assigned and informed of their group	☐	☐
14. Has the participant been issued diet guide	☐	☐
15. Has the participant been briefed on the lead in week diet log	☐	☐

Project ID: U1111-1281-5048
Visit ID: _____
Participant ID: _____

10:45 Glycogen Depletion Familiarization

Application check list?	Yes	No
16. Has the participant been briefed on their exercise intensity zones	☐	☐
17. Has the participant been shown run course map	☐	☐
18. Has the participant been briefed on protocol	☐	☐
19. Has the participant become familiar with the course	☐	☐
20. Has the participant been made familiar with the TTF protocol	☐	☐

VISIT FAILURE FORM

Date patient left the trial: _____(dd/mm/yyyy)

It is hereby confirmed the patient has failed to qualify for further participation in the trial.

The reason for failure is:

Non-fulfilment of any of the inclusion criteria (enter number(s) below;

Inclusion criteria no. (s): _____

Fulfilment of any of the exclusion criteria (enter number(s) below;

Exclusion criteria no. (s): _____

Or

Other ☐

If 'Other', please specify:

_____
_____
_____

Project ID: U1111-1281-5048
Visit ID: _____
Participant ID: _____

PARTICIPANT CONSENT FORM
(Version 1.1, Date: 10/10/2022)

Project Title:

The metabolic effects of ultra-endurance exercise and training under low or high glycaemic index-carbohydrate diets.

Contact Details:

Ross Hamilton Email ross.hamilton@swansea.ac.uk Tel: 07427648416

Please initial box

6. I confirm that I have read and understood the information sheet dated 10/10/2022 (version number 1.1) for the above study and have had the opportunity to ask questions. ☐
7. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
8. I understand that sections of any of data obtained may be looked at by responsible individuals from the Swansea University or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access these records. ☐
9. I understand that data I provide may be used in reports and academic publications in anonymous fashion ☐
10. I agree to take part in the above study. ☐

_____	_____	
Name of Participant	Date	Signature
_____	_____	
Name of Person taking consent	Date	Signature
_____	_____	
Researcher	Date	

Project ID: U1111-1281-5048
Visit ID: _____
Participant ID: _____

STRICTLY CONFIDENTIAL

Pre-Test Health Questionnaire

The metabolic effects of ultra-endurance exercise and training under low or high glycaemic index-carbohydrate diets

NAME: .....

Please answer these questions truthfully, as the purpose of these questions is to ensure that you are in a healthy state to complete the tests involved in the study. The questionnaire is confidential to the study investigators and the information will only be used to assess any risk associated with the study protocol.

1. Do you consider yourself to be in good physical and mental health? ❑ YES ❑ NO

If no, please explain

.....

2. Have you had any acute illness or health problem over the last two weeks? ❑YES ❑ NO

If yes, provide details (type, severity)

.....

.....

3. Are you currently (**or** in the last 2 weeks) taking any medication (incl. Inhalers)? ❑YES ❑ NO

If yes, provide details (type)

.....

4. Do you have a tendency to faint? ❑YES ❑ NO

If yes, under what circumstance(s)?: .....

5. Do you suffer, or have you ever suffered from:

a) Chest problems (incl. Asthma)	❑ YES	❑ NO
b) Diabetes	❑ YES	❑ NO
c) Epilepsy	❑ YES	❑ NO
d) Leg circulation problems	❑ YES	❑ NO
e) Kidney trouble	❑ YES	❑ NO
f) Thyroid trouble	❑ YES	❑ NO
g) Nervous disorder	❑ YES	❑ NO
h) High blood pressure	❑ YES	❑ NO

6. Do you suffer, or have you ever suffered from any form of heart or heart rate complaint?

❑ YES ❑ NO

Project ID: U1111-1281-5048
Visit ID: _____
Participant ID: _____

7. Is there any family history of the illnesses/conditions in Q 5 & 6? ❑YES ❑ NO

If yes, provide details: ……..

……

8. Do you have any form of muscle or joint injury or complaint? ❑YES ❑ NO

If yes, provide details (type, severity):

……

……

9. Have you had to suspend exercise in the last two weeks for any reason? ❑YES ❑ NO

10. Is there any reason why you should not be able to successfully complete exercise tests that require maximal efforts? ❑YES ❑ NO

If yes, please give brief details

……..

……

11. Are you taking part in any other experimental trial/study? ❑YES ❑ NO
Have you in the past 3 months? ❑YES ❑ NO
Do you intend to in the next 3 months? ❑YES ❑ NO

Signature: **……**

Date: **……**

Project ID: U1111-1281-5048
Visit ID: _____
Participant ID: _____

Physical Activity Readiness Questionnaire (PAR-Q)

For most people physical activity should not pose any problem or hazard. PAR-Q has been designed to identify the small number of adults for whom physical activity might be inappropriate or those who should have medical advice before performing the type of exercise used in the current experiment.

Yes	No	1) Has a physician ever said you have a heart condition and you should only do physical activity recommended by a physician?
Yes	No	2) When you do physical activity, do you feel pain in your chest?
Yes	No	3) When you were not doing physical activity, have you had chest pain in the past month?
Yes	No	4) Do you ever lose consciousness or do you lose your balance because of dizziness?
Yes	No	5) Do you have a joint or bone problem that may be made worse by a change in your physical activity?
Yes	No	6) Is a physician currently prescribing medications for your blood pressure or heart condition?
Yes	No	7) Are you pregnant?
Yes	No	8) Do you have insulin dependent diabetes?
Yes	No	9) Do you know of any other reason you should not exercise?

If you answered YES to one or more questions:
If you have not recently done so, consult with your personal physician by telephone or in person before taking part in this exercise test.

If you answered NO to all questions:
If you answered PAR-Q accurately, you have reasonable assurance of your present suitability for this exercise test.

Name:
Date:
Signature:

Project ID: U1111-1281-5048
VISIT ID
Participant Code: _____

APPENDIX B3
Acute Trial Visit (V.3)

The metabolic effects of ultra-endurance exercise and training under low or high glycaemic index-carbohydrate diets.

Principal Investigator:
Name: Ross Hamilton MSc.

Co-investigators:
Name: Prof. Richard Bracken, PhD
Name: Dr. Rachel Churm PhD
Name: Dr. Olivia McCarthy, PhD
Name: Ruiyang Xia

Visit Date:	_____ d d m m y y y y

INFORMED CONSENT

Date Informed Consent obtained ..... _____
d d m m y y y y

TESTING DAY INCLUSION CRITERIA

Has the patient met the following inclusion criteria?	Yes	No
2. 24h before testing no alcohol	☐	☐
3. 24h before testing exercise avoided	☐	☐

TESTING DAY EXCLUSION CRITERIA

Has the patient met any of the following exclusion criteria?	Yes	No
1. Illness on and/or before testing day. If Yes please specify: _____ _____ _____	☐	☐
3. Mental incapacity or unwillingness to partake in trial	☐	☐
4. Any condition that the investigator feels would interfere with the trial participation or evaluation of data. If Yes please specify: _____ _____ _____	☐	☐

To qualify for trial participation all exclusion criteria must be answered NO (or N/A if not applicable). If any questions are answered YES the patient is not eligible to continue.

07:30 AM -30mins to start

All samples to be labelled in following format (Participant No./ Trial no./Timepoint number ie 1.1.4)

BODY MEASUREMENTS

Blood pressure:

After 5 min. rest _____/_____mmHg
Systolic Diastolic

Height.....m
(without shoes)
Body weight.....kg
(without shoes and coat)
Body Mass Index (BMI).....kg/m^2

Bioelectric Impedance Analysis Result BF:…….LBM……

Hip……cm

Waist…….cm

Skin Folds

Bicep……mm

Tricep……...mm

Subscap……mm

Suprailiac……...mm

Sum of skinfolds……..mm

Skinfold %.....

- Glucose from at arrival at the lab:
  - Blood glucose from EDTA: _____ mmol/L
  - Lactate from EDTA _____ mmol/L

  Venepuncture Sample
  - 4ml EDTA Collected Pink ☐
  - 2ml SST Collected Yellow ☐

BLOOD COLLECTION AND STORAGE PROCEDURE FOR ALL TIMEPOINTS.

SST To sit at room temp 15mins to fully clot then spun

Centrifuge for 5 mins 4000rpm

Serum divided into

500mL (randox)

1000mL

SPARE

EDTA Tube

Mix and centrifuge for 10 mins 1500rpm

Plasma divided into

500mL

500mL

T3 Assays 800mL

EDTA Spare

Stored in Freezer

0 mins (8:00am Estimated) (Start time_____)

- **BEGIN Outdoor Trial 70% Vo2 Hr (see table) .....**
  - **Clock start time record to group wattsapp**
  - **Ensure water is available**
  - **Ensure participant check in approx. 25-30min intervals**
- **Baseline bloods to be separated and stored (20mins)**
  - CHO bottle to be prepared ☐

Bottle refeed schedule. 1g/kg BM per hour at 30min intervals (See Table)
First bottle to include 1serving of electrolyte powder.

PARTICIPANT TARGET per hour .....mls

+3:00hrs (11:00 Estimated)(Actual: _____)

- **Finish Outdoor trial and return to lab**
  - Blood glucose from EDTA: _____mmol/L
  - Blood lactate: _____mmol/L
  - Cannula Inserted (To be assessed on the day ☐
  - 4ml EDTA Collected Pink ☐
  - 2ml SST Collected Yellow ☐

Restart Clock (Time _____)

Bottle refeed ASAP ☐

- **Post Depletion bloods to be separated and stored**
- **Participant may shower after beginning CHO consumption**

Bottle refeed	**+30mins**	☐
Bottle refeed	**+1hr**	☐
Bottle refeed	**+1:30**	☐
Bottle refeed	**+2:00**	☐
Bottle refeed	**+2:30**	☐
Bottle refeed	**+3:00**	☐
	Begin treadmill prep and metamax	
Bottle refeed	**+3:30**	☐

14:00

- Begin Metamax calibration and treadmill setup
- **Complete GI Questionnaire.**

Project ID: U1111-1281-5048

Gastrointestinal Distress Record

Please rate the following from 0-10. 0 being no discomfort or symptoms 10 being unbearable discomfort and severe symptoms.

1. ***Nausea***: A feeling of sickness in the stomach marked by an urge to vomit.

0 1 2 3 4 5 6 7 8 9 10

2. ***Regurgitation/reflux***: Sensation of food or fluid returning from the stomach to the oesophagus or mouth.

0 1 2 3 4 5 6 7 8 9 10

3. ***Belching***: Emit wind noisily from the stomach through the mouth

0 1 2 3 4 5 6 7 8 9 10

4. ***Heartburn:*** burning sensation in the chest, caused by acid regurgitation into the oesophagus.

0 1 2 3 4 5 6 7 8 9 10

5. ***Bloating:*** a feeling of tightness, pressure or fullness in your belly

0 1 2 3 4 5 6 7 8 9 10

6. ***Stomach fullness***: A sensation of fullness or abdomi- nal pressure in the upper abdomen.

0 1 2 3 4 5 6 7 8 9 10

7. ***Abdominal cramps***: Pain or cramping sensation, often experienced in the mid- or lower-portion of the abdomen.

0 1 2 3 4 5 6 7 8 9 10

8. ***Gas/flatulence***: Gas or flatus expelled through the anus.

0 1 2 3 4 5 6 7 8 9 10

9. ***Urge to defecate***: Sensation of needing to pass a bowel movement.

0 1 2 3 4 5 6 7 8 9 10

Comments:

14:30

- **Bottle refeed** ☐
  - Blood glucose from EDTA: _____mmol/L
  - Blood lactate from EDTA: _____mmol/L
  - 4ml EDTA Collected (Pink top) ☐
  - 2ml SST Collected (yellow top) ☐

14:45

- Fit Respiratory mask
- Begin Time to Exhaustion test @70% Vo2max Velocity 1% Incline ☐
- **Pre TTF bloods to be separated and stored**

START TIME:

FINISH TIME:

Project ID: U1111-1281-5048

HR Every 5mins (Backup)		RPE Every 15 mins
00:05	.....	
00:10	.....	
00:15	.....	.....
00:20	.....	
00:25	.....	
00:30	.....	.....
00:35	.....	
00:40	.....	
00:45	.....	.....
00:50	.....	
00:55	.....	
01:00	.....	.....
01:05	.....	
01:10	.....	
01:15	.....	.....
01:20	.....	
01:25	.....	
01:30	.....	.....
01:35	.....	
01:40	.....	
01:45	.....	.....
01:50	.....	
01:55	.....	
02:00	.....	.....
02:05	.....	
02:10	.....	
02:15	.....	.....
02:20	.....	
02:25	.....	
02:30	.....	.....
02:35	.....	

Grounds for completion:

Restart Clock ……. (16:00 Estimated)

- **TTE Finish**
  - Blood glucose from EDTA: _____mmol/L
  - Blood lactate from EDTA: _____mmol/L
  - 4ml EDTA Collected ☐
  - 2ml SST Collected ☐

16:15 estimated

Carbohydrate meal to be provided ASAP See nutrition Plan

- **Post TTF bloods to be separated and stored**

19:00 Estimated

  - Blood glucose from EDTA: _____mmol/L
  - Blood lactate from EDTA: _____mmol/L
  - 4ml EDTA Collected (pink) ☐
  - 2ml SST Collected (yellow) ☐

Participant leaves

- **Finishing bloods to be separated and stored**

FINISH

Date patient left the trial ……_____
dd mm yyyy

It is hereby confirmed the patient has failed to qualify for further participation in the trial.
The reason for failure is:
Unable to complete trial Reason …… ……☐
Inclusion criteria no. (s): _____
Other……☐
If Other, specify at the Investigator`s discretion:_____
_____
_____

VISIT REMINDER

- Make an appointment for next Visit
- Remind the participant to maintain logging and follow diet

_____(Signature)

_____Name (Investigator)

Project ID: U1111-1281-5048

APPENDIX: B4

The metabolic effects of ultra-endurance exercise and training under low or high glycaemic index-carbohydrate diets.

Participant Guide

Swansea University
Prifysgol Abertawe

Principal Investigator:
Name: Ross Hamilton MSc. RSCC

Co-investigators:
Name: Prof. Richard Bracken, PhD
Name: Dr. Rachel Churm PhD
Name: Dr. Olivia McCarthy, PhD
Name: Ruiyang Xia

Contents

Introduction:

The main focus of this study is the influence of Glycaemic index (GI) on Health and performance during and surrounding ultra-endurance sport. In order to investigate this you will undertake two separate dietary interventions. One predominantly comprised of Low GI carbohydrates and one comprised of High GI carbohydrate. In order to achieve a significant split in the GI of each diet you will make alternations to what is your typical diet. In most cases this will involve switching carbohydrate sources to their High or Low type.

In addition to switching some of your carbohydrate sources you will also supplement with a carbohydrate beverage. The Low GI diet will supplement with a flavoured beverage which contains Isomaltulose as it's main carbohydrate source. The High GI diet will supplement with a flavoured beverage containing Maltodextrin. Both of these products are very common in many commercial sports drinks. These have been formulated to quite exact standards so we ask that you do not alter them. These are in place to make it easier and convenient for you to consume carbohydrates and ensure they are the appropriate GI for the intervention arm you are completing. Each intervention will last 28 days with a 14 day washout period in between each.

In addition to these alternations and additions to your diet you will be asked to carefully log your food intake. This needs to be done on a daily basis.

Should you experience any difficulties with meeting the requirements please report them to a member of the research team. We are there to help you complete the study effectively and will work with you to try and find solutions to any problems you encounter.

One of the novel aspects of this study is the use of a continuous glucose monitor (CGM). We will be using Supersapiens™ technology which is supported by Abbott's Libre Sense CGM. The installation of this device will be shown to you at your screening session. Should you need help with reapplying the sensor you can see user guides for both the Supersapiens™ Sensor and app here.

https://supersapiens.zendesk.com/hc/en-us

Why have I been chosen?

You have been invited because you are:

- Generally healthy
- Aged between 18 and 65 years
- Participating in regular training (>10hrs Per week)
- Involved or regularly participating in Ultra endurance events.
- Have a VO_2max > 55ml.kg^{-1}.min^{-1}

Because you do not have:

- An abnormal electrocardiogram (ECG) - irregular heart function
- A current or history of substance abuse and/or excess alcohol intake
- Type 1 or 2 Diabetes
- Heart disease
- Cancer
- Gastrointestinal disease e.g. inflammatory bowel disease or irritable bowel syndrome
- Kidney disease
- Liver disease
- Pancreatitis
- Receipt of any investigational medicinal products within 1 month prior to screening
- Blood pressure outside the range of 90-140 mmHg for systolic or 50-90 mmHg for diastolic
- Any allergy or food intolerance e.g fructose intolerance
- Receipt of any hormonal therapies or medications.

And are not:

- A current smoker
- On hormone therapy for <6 months
- Prescribed anti-hypertensive or beta-blocker medication

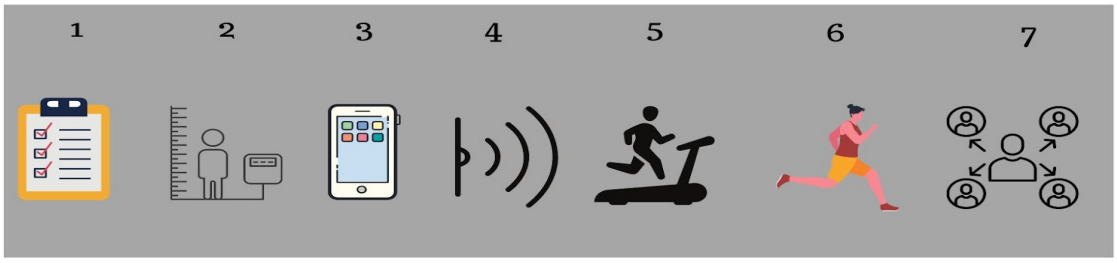
Screening day

You will be invited to attend a screening visit at Swansea University where you will be interviewed by one of the researchers. If you wish to participate, you will be asked to sign a consent form. You will then be asked to fill out a Health Questionnaire. Then, body composition and body measurements will be taken. This involves your height, weight, and bioelectrical body composition analysis. This will allow us to establish your lean mass and bodyfat. It is a non-invasive test using a machine called the bio-electrical impedance analysis (BIA) which will send a low-level, painless, electric current throughout your body. You will also have your blood pressure taken.

You will also have to complete what is known as a Cardiopulmonary exercise test (CPET). This is to evaluate your fitness. This involves running on a treadmill at progressively faster speeds (1km/hr per stage). Each stage will last 3mins with one minute breaks between stages. You will be wearing a breathing mask to allow for breath to breath analysis. This will allow us to establish your VO_{2peak}. In addition, we will measure Heart rate and pace to establish your intensity zones.

If you are eligible to participate in the study, the researcher will disclose which group you will be first assigned to. The allocation sequence of which you will be assigned to is at random (generated through computerised random sequence) and pre-defined. Please note that you are unable to change groups once assigned as this will create a bias within the study.

The health screening should last about 2 hours depending if you meet criteria and on the questions you might have. Below is a schematic of the screening visit at Week 0. For the following 5 days you will be asked to record your normal diet using the phone app. Following these 5 days you will have a zoom call with a member of the research team to discuss and issues you are experiencing, as well as receiving guidance on how best to implement your dietary changes.



Formulation of Drink Beverages.

You will be provided with an adequate supply of the designated beverage formula after your first Laboratory trial. These beverages will be in a powdered form which you must prepare yourself. You will be provided with serving scoops, Mixing bottle and weighing scales to ensure you formulate appropriately. You can see the dosing guide below.

You will have the choice of different flavours so that you are able to change to suit your preference on any given day. Should you at any point run out or have any issue with your supply of drink powder please contact a member of the research team to arrange a restock.

In addition to the powdered drinks will be provided with some plain Carbohydrate sources which may be used as a substitute for any sugar in your diet. This can be used in baking and cooking or in Tea/coffee as a sweetener etc..

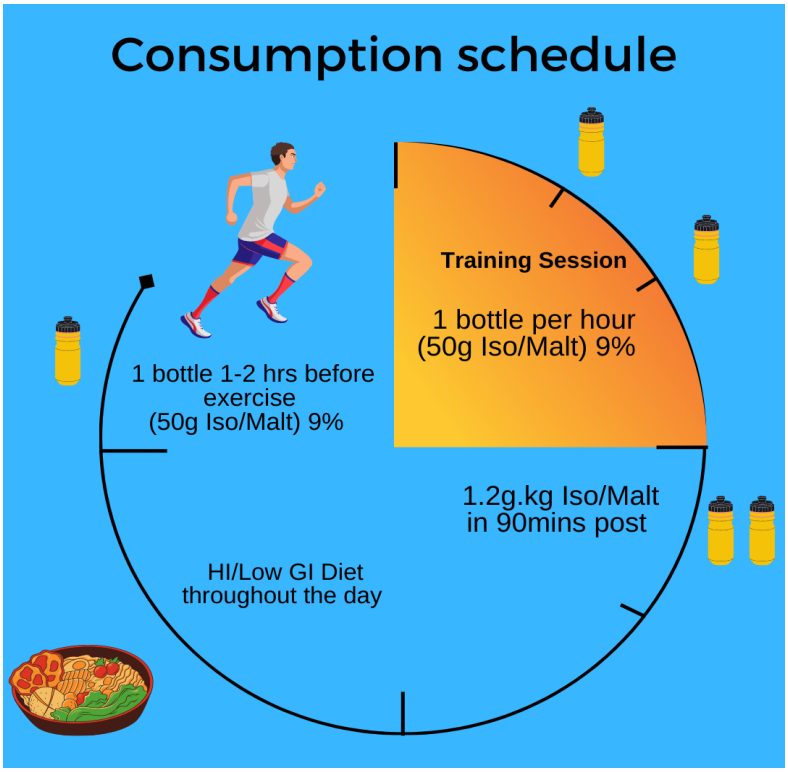
During the normal course of the day you will consume the supplement around your exercise. In the 120mins prior to your training you will consume 50g of CHO in 9%. You will aim to consume 50g CHO per hour during exercise in a 9% solution (This is similar to most commercial sports drinks) In the 90mins immediately post exercise you will consume 1.2g of CHO per Kilogram of body weight. This may require some quick calculations to ensure you have the right amount. Each level scoop contains about 20g.

As a rough formulation guide you will need just under 10g for every 100mls of fluid except the post workout drink which you may prefer a 20% solution (20g per 100mls).

These drinks may require vigorous mixing and to aid with the formulation you will be issued with a shaker bottle to help the process. In some case you might want to shake, let settle for a minute and shake again to ensure the powder is well dissolved.

This drink consumption must also be added to your food log.

You can see this schedule below.



These quantities are in line with recommended intakes of energy during exercise. While fatigued you may find these challenging targets to meet. Rest assured that the gut can be trained and tolerance to consuming fluid and fuel during exercise can adapt over time.

** If you wish to use any other forms of nutrition around your training sessions please consult with a member of the research team beforehand as we can best advise on the options suitable to the study ie. Electrolytes, energy bars etc.

Dietary Changes.

In the lead up to commencing the study you will be asked to start logging your food intake. Please follow the diet you normally would. We want to ensure your diet is altered minimally and the changes that are made are as minimal as possible. We will endeavour to make the intervention as least invasive on your lifestyle as possible and achievable.

When we assess your diet we will make recommendations of where food types may be switched to meet the aims of the study. In most cases this may be a simple switch to a different form of the same food. In other cases you may want to make a larger change. It is important to discuss these with a member of the research team. If you have any difficulties or cravings we may be able to offer suitable suggestions to help keep you on track.

If you are unsure of what category a certain food falls under you can consult below for guidance. On the low GI diet your aim is to eat foods from the Green list as much as possible and a moderate amount from the yellow list. You should avoid foods from the red list as much as possible while assigned to the low GI arm.

Here are some resources which you may find useful for making alterations that suit you.

https://glycemicindex.com https://www.the-gi-diet.org/recipes/

	Low	Med	High			Low	Med	High
Breakfast cereals	All Bran	Weetabix	Coco Pops		Legumes	Lentils		
	Muesli	Shredded wheat	Cornflakes			Baked beans		
	Porridge	Oatibix	Frosties			Pinto Beans		
	Oat Bran	Instant Porridge	Rice Krispies			Black Beans		
			Cheerios			Chick Peas		
			Crunchy Nut					
Fruits					Drinks	Milk (Full Fat)	Fanta	Gatorade
	Raspberries	Banana	Watermelon			Soy Milk	Coke	Lucozade
	Apples	Grapes	Dates			Almond Milk		Rice Milk
	Pears	Pineapple	Overripe Banana			Apple Juice		Chocolate Milk

	Blueberries	Plums				Coconut Water		
	Strawberries	Mango						
	Oranges	Raisins			Dairy	Yoghurt		
	Melon					Greek Yoghurt		
						our Cream		
Breads	Multi grain	Pitta	Bagel					
	Sourdough Rye	Sourdough	Wholemeal		Snakes	Hummus	Popcorn	Donuts
	Pumpernickel	Hamburger Bun	White			Nuts	Biscuits	Waffles
	Whole Wheat	Bran Muffin	Baguette			Nutella	Muffins	Confectionary
		Croissant	Ciabatta			Nut butters	Pancakes	Rice cakes
			Naan			Chocolate		Pretzels
								Scones
Pasta/Rice/Grains	Spaghetti	Wild Rice	Brown Rice					Cakes
	Macaroni	Basmati Rice	White Rice					Icing
	Brown Rice	Couscous	Jasmine Rice					
	Buckwheat	Gnocchi	Tapioca					
	Rice Noodles	Cornmeal						
	Quinoa							
Vegetables	Sweet Potato	Beetroot	Potato					
	Squash	Carrot	Pumpkin					
	Cauliflower		Parsnips					
	Broccoli							
	Lettuce							
	Mushrooms							
	Onions							

	Spinach							
	Tomatoes							
	Peas							

Logging your nutritional intake.

In order to log your nutrition you will use the Nutritics app.

You will be emailed an invite which will prompt you to download from the app store. Once you have downloaded you can update your account profile with your own password etc.

If you are experiencing difficulties with the app you can find many user guides here https://www.nutritics.com/en/support/category/libro

Your target macro nutrient per day can be seen below. This is based on a typical training day of 2-3hrs exercise. These are averages so you may be somewhat above or below on any given day depending on the amount of training you do. This is based off a day with

approx. 90mins moderate exercise.

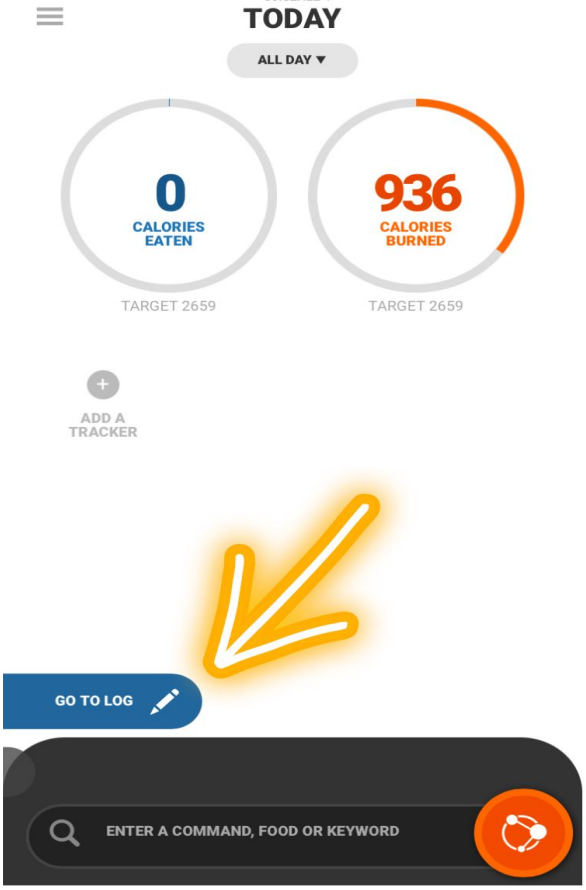
Daily Requirements							
BM (kg)	Kcals.d	CHO.g.d	%Intake.d	PRO.g.d	%Intake.d	FAT.g.d	%Intake.d
45	2020	317	62.8	62	12.2	56	25.0
50	2245	353	62.8	68	12.2	62	25.0
55	2469	388	62.8	75	12.2	69	25.0
60	2694	423	62.8	82	12.2	75	25.0
65	2918	459	62.8	89	12.2	81	25.0
70	3143	494	62.8	96	12.2	87	25.0
75	3367	529	62.8	103	12.2	93	25.0
80	3592	564	62.8	109	12.2	100	25.0
90	4041	635	62.8	123	12.2	112	25.0
100	4490	705	62.8	137	12.2	125	25.0
110	4939	776	62.8	150	12.2	137	25.0

Below is a step by step of how to log your daily food intake.

When you complete your trial day you will be given a pack of everything you will need during the trial. Included in this will be a digital food scales. Initially you will need these scales to correctly record your food. After a while you will need to measure less as you become familiar with quantities. We do ask that you be as accurate as possible.

1. When you open the app your home screen should look like this.

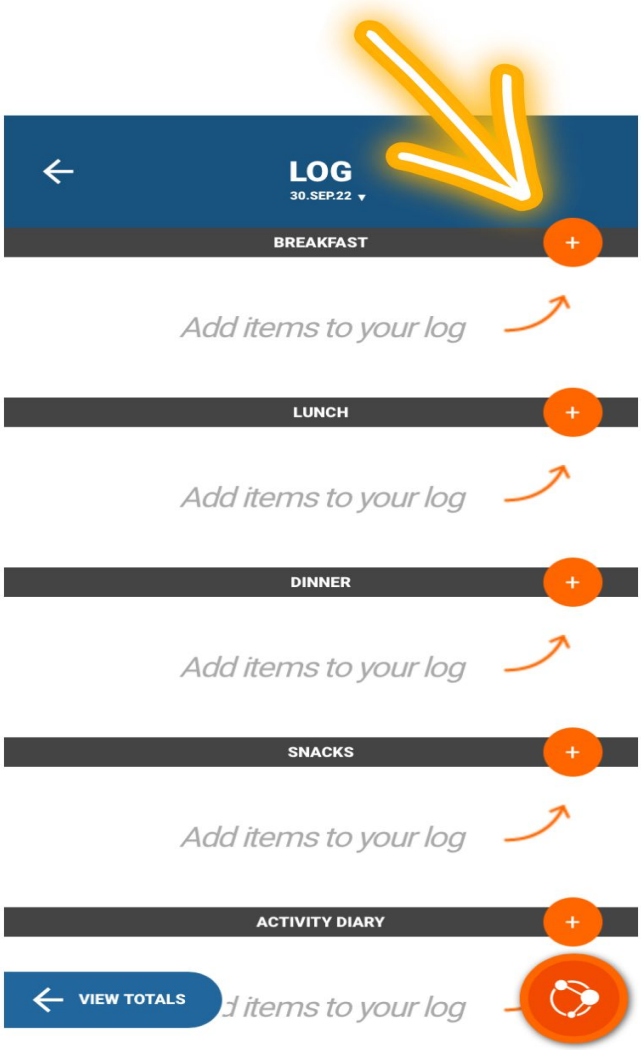
It displays your non active calories expenditure so far for the day and your calorie intake.



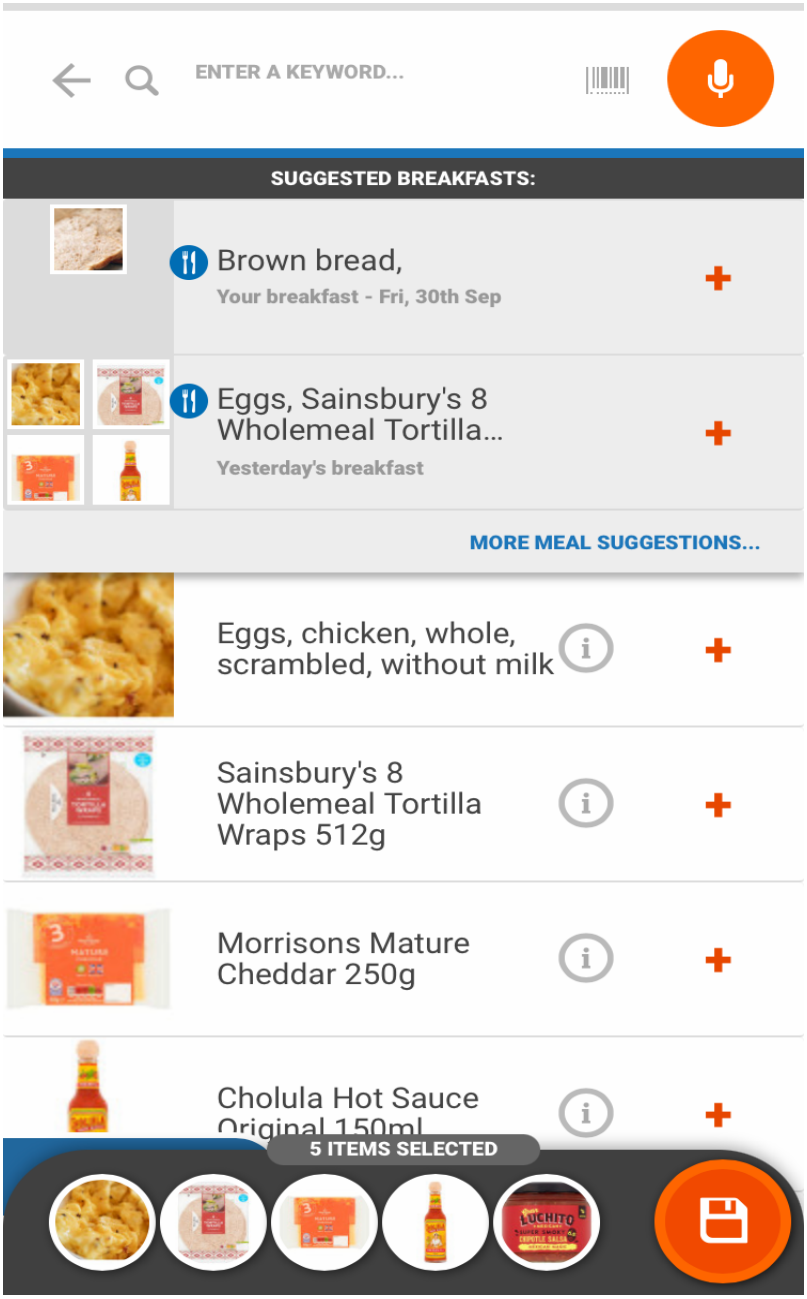
2. To log you must click the go to log button.

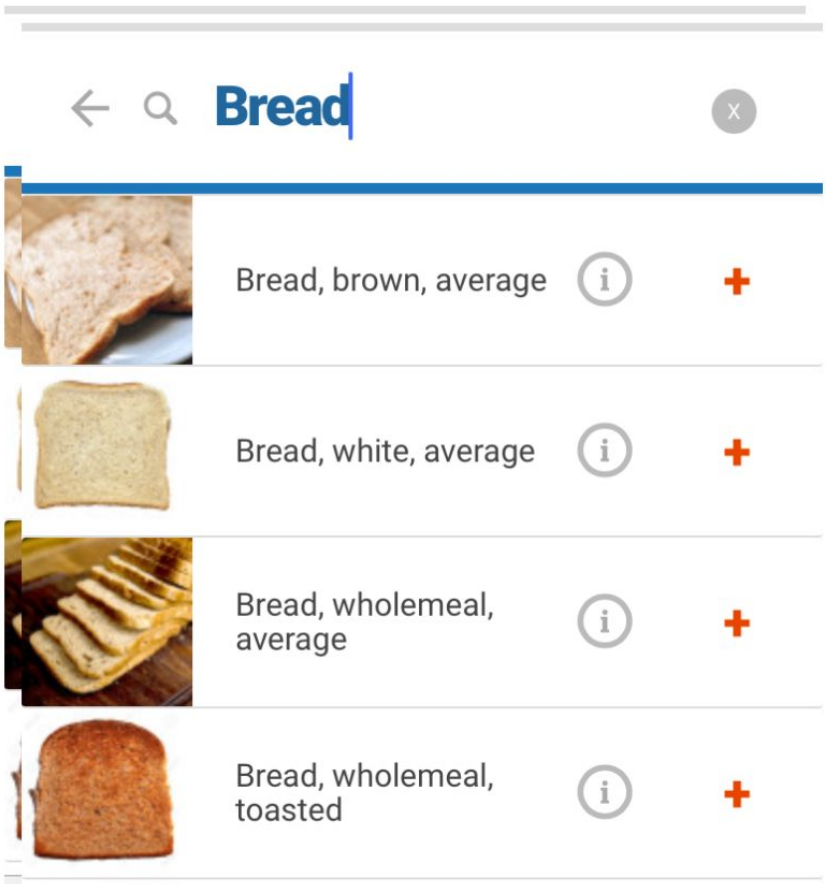
3. You should now be on the log page

This will display opportunities to log each meal of the day and any snacks you consume. You can also log activity but there is no need to do this as your watch is already measuring this.



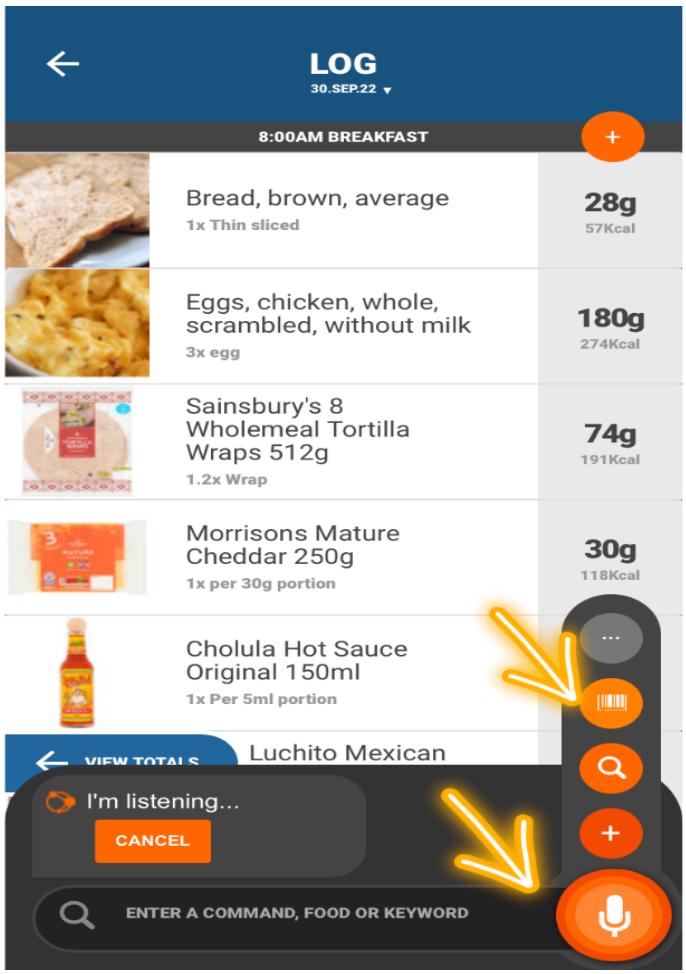
4. To log breakfast click the plus button beside breakfast
5. This will bring you to the food selection page. On the page you will have a search bar but also suggested meals. These are meals you have logged previously which if you are having again you can select in order to save you time searching everything again, just make sure quantities are correct.


ENTER A KEYWORD...
SUGGESTED BREAKFASTS:
Brown bread,
Your breakfast - Fri, 30th Sep
Eggs, Sainsbury's 8 Wholemeal Tortilla...
Yesterday's breakfast
MORE MEAL SUGGESTIONS...
Eggs, chicken, whole, scrambled, without milk
Sainsbury's 8 Wholemeal Tortilla Wraps 512g
Morrisons Mature Cheddar 250g
Cholula Hot Sauce
5 ITEMS SELECTED

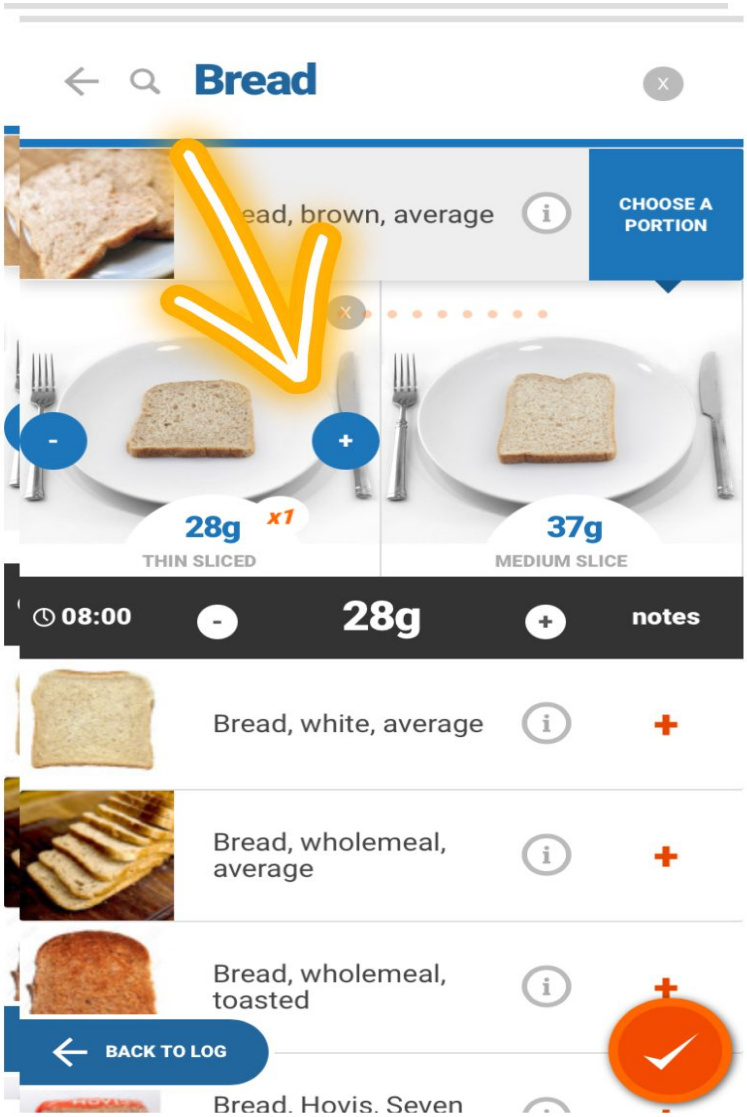


In this case we have typed bread and these are the options we have to choose from. You will also have the option to scan the barcode of the food item you wish to log. This is often the quickest option as the serving size will be pre saved.

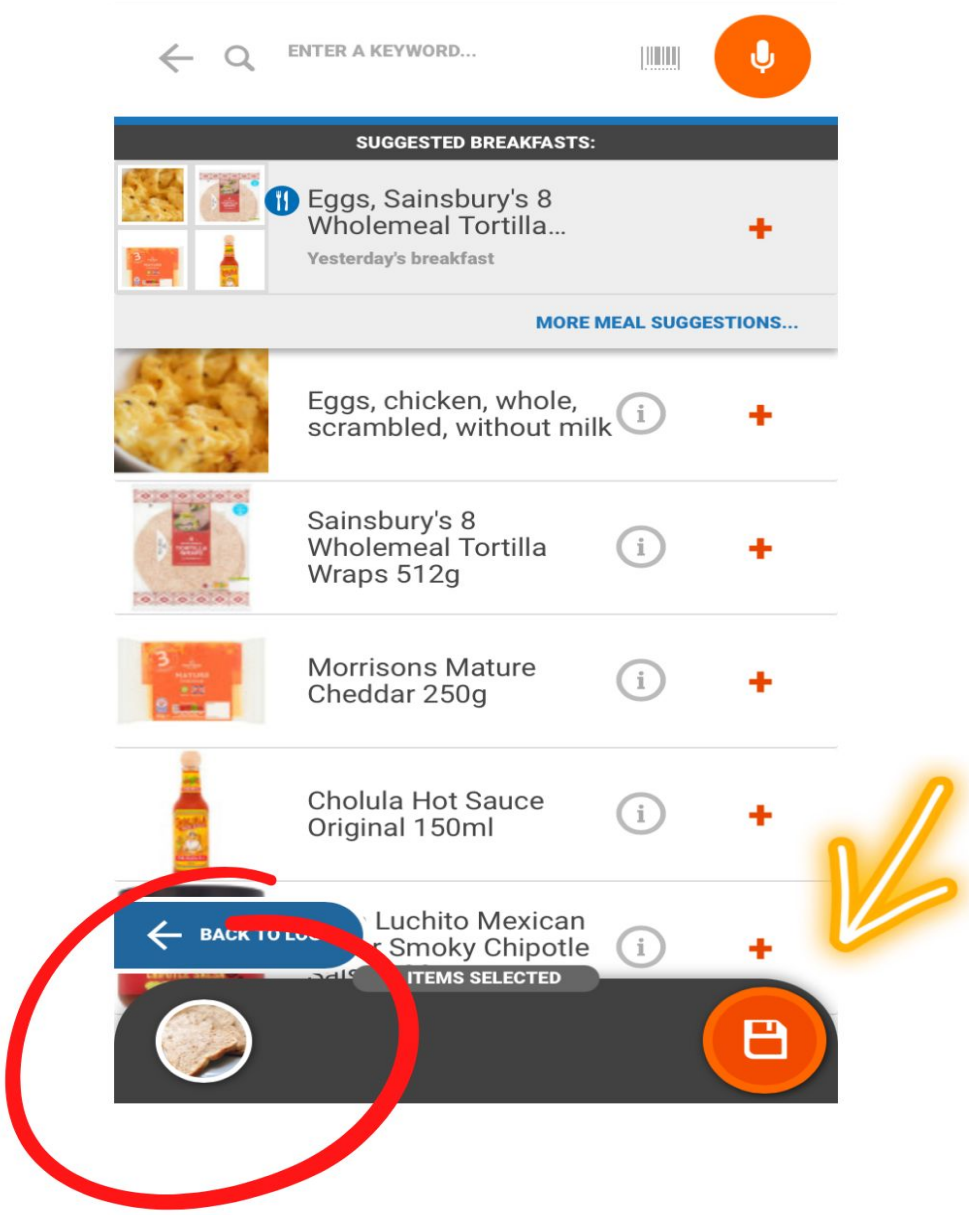
To scan you must click the option symbol and then the barcode scan. This will open your phones camera which can scan the barcoded item for uploading.



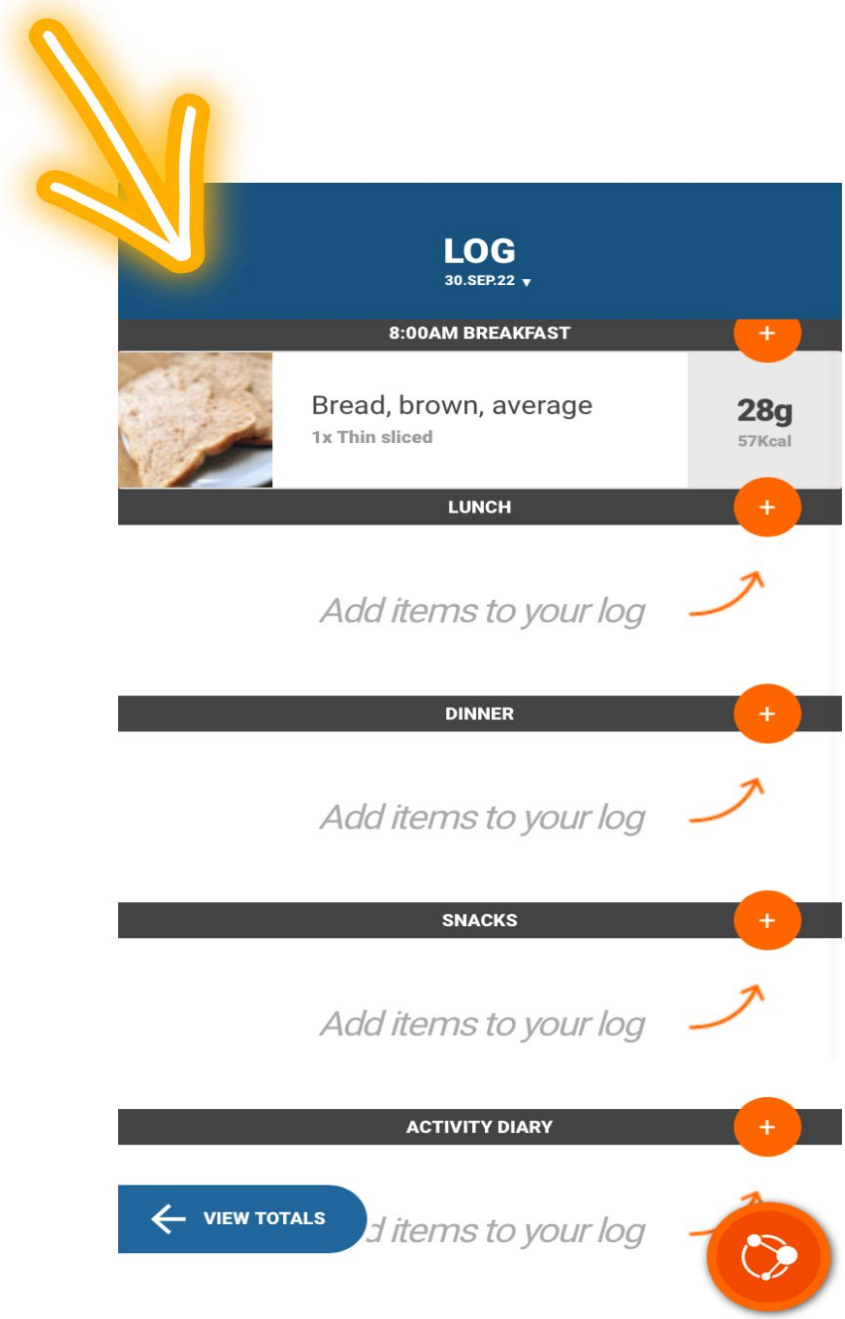
6. Once you have the item you want you can now select serving quantity.



Once selected hit the tick button.



7. You will see your item is now in the list to be saved to your log. You can now hit the save button.
8. This will return you to the log screen where you can double check it has been logged for the day.



Once you see the food logged you have successfully logged that meal item!

There are some other features to the app which you are welcome to use at your will. The logging feature is the only one we ask that you diligently use for the study period.

CGM Logging

During the study you will be using a continuous glucose sensor. Please refer to Supersapiens™ user guides for Installation guides and FAQs. The APP is available for both iOS and Android.

Normally once you apply the sensor and sync to the APP logging will occur continuously. When the phone is within range it will record at 60sec intervals. When out of range it will record at 15min intervals. Sometimes during the night and during exercise the connection may be lost with the phone. The sensor has up to 8 hours memory. It is important every so often and particularly when waking to scan the sensor with the phone to collect any data points saved via memory.

In addition to the sensor you will be provided with a Fuel Band. This is a recorder for the sensor which is a great option during exercise when you may not want to carry a phone. It is generally more consistent with collecting data so its use is encouraged. It has a limited battery life so regular charging is recommended. It is suggested that you prioritize the use of the band during exercise but use as much the battery allows otherwise.

The band should sync to the phone when you open the app. We recommend you check in on the app every few hours to ensure there haven't been any data blackouts.

You will notice a slight reduction in battery life when using the app as it is operating in the background.

CGM Care

Generally any connectivity issues can be resolved by simply restarting your phone.

The sensor has a battery life that lasts 14days. Often it will not quite last this length and you will be provided a spare sensor should you need it. If you are planning on swimming or using in wet conditions it is worth using a protector cover which we can provide if needed. Otherwise it can be prone to coming loose in water.

When you remove the sensor you may find there is some skin irritation. This is the result of the moist conditions that may occur through sweating or swimming etc. In some cases you might find you benefit from some antiseptic cream to help heal the underlying area. You should position the sensor an inch or so away from this sight so you can allow it to heal. Such issues are very mild but its still worth addressing.

If the CGM becomes damaged or dislodged please install the spare sensor and let one of the research team know and they can supply you with a replacement.

APPENDIX B5: Risk Assessment (Study Chapter 3)
(Or attached, if an alternative format)

Part 1: Risk Assessment

The metabolic stress of acute and chronic ultra-endurance exercise under low or high glycaemic index-carbohydrate diets incorporating Isomaltulose consumption.			
College/ PSU	College of Engineering	Assessment Date	9/7/22
Location	SPEX labs	Assessor	Ross Hamilton
Activity	Research	Review Date (if applicable)	
Associated documents	• VO_2max SOP • SOP101 Cleaning Procedures • Exercise Testing With Expired Gas Analysis Risk Assessment	• Venepuncture SOP	

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
Risk Item 1: Catching or spreading Covid-19 through normal every-day contact with other laboratory users	Researchers, lab technicians, academic staff, cleaners, demonstrators, visitors, test participants, service engineers, UG + PG students, first aiders.	Exposure to COVID-19	• Staff/students who are acting as participants will be treated with the same level of care and infection control measures as would any other member of the public volunteering for research. • We will follow local (Swansea University and Public Health Wales) social distancing rules as much as feasible, washing hands and use hand sanitiser before touching equipment/door handles and using good personal hygiene such as coughing in to elbows/tissues and disposing of appropriately, wearing face coverings around campus and in laboratories when social distancing becomes difficult, pre-booking labs with lab techs and not exceeding lab capacities. • No staff or PGR member will come into the laboratories if they feel unwell and have any signs or symptoms of Covid-19. • The University Safe Operating procedures for reporting and isolating (available at: https://staff.swansea.ac.uk/healthsafety/covid-19/#covid-19-reporting-and-isolation-arrangements=is-expanded) will be followed should any staff member or PGR develop	3	1	3	No				

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (SxL)	Do you need to do anything else to manage this risk?	S	L	Risk (SxL)	Additional Action Required
			signs or symptoms of COVID-19 and the affected member will return home immediately. • Time spent in the laboratories must be booked in advance with Laboratory Technicians. This ensures lab and building capacities will not be exceeded. These covid risk reduction measures cover all previous project risk assessments and standard operating procedures.								
Risk Item 2: Catching or spreading Covid-19 through contact with contaminated surfaces in the laboratory	Researchers, lab technicians, academic staff, cleaners, demonstrators, visitors, test participants, service engineers, UG + PG students, first aiders.	Exposure to COVID-19	• Any waste will be disposed of immediately and in appropriate waste bins. Used PPE will be disposed of in biohazard bins that are present in all laboratories. • All researchers will be made aware of basic hygiene measures to prevent transmission of COVID-19, including: trying not to touch your face, using PPE such as appropriate gloves, keyboard covers, clinical mice and keyboards, disposable aprons, lab coats if you need to touch equipment or surfaces. Wash your hands before and after using the labs, as well as regularly during work. Wash hands prior to touching shared equipment and surfaces and all shared equipment and surfaces	3	1	3	No				

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
			will be disinfected (using University approved cleaning products effective against COVID-19) before leaving the laboratory. • The SOP for cleaning procedures are to be read and understood by the researcher before commencing work (**document SOP101 Appendix 8**). These covid risk reduction procedures cover all previous project risk assessments and standard operating procedures.								
Risk Item 3: Risk of exposure and spread of COVID-19 due to participating in the study.	Staff working in lab, including researcher and participant	Exposure to COVID-19.	• If the participant at any point before, during or after the trial experiences COVID-19 symptoms they will immediately self isolate and all their contacts will be tracked and traced following the Swansea University procedure (available at: https://staff.swansea.ac.uk/healthsafety/covid-19/#covid-19-reporting-and-isolation-arrangements=is-expanded). • The lab will be fully sanitised and set-up before the participant arrives to minimise the time they are required to be there and all equipment will be ready for the participant to self-fit. • Equipment, such as the gas analysis mask and turbine and heart rate monitor will be soaked in Milton	3	1	3	No				

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
			sterilising fluid for the recommended time. These covid risk reduction measures cover all previous project risk assessments and standard operating procedures.								
Risk Item 4: Catching or spreading Covid-19 when carrying out project procedures that do not allow for social distancing, e.g blood sampling, fitting face mask for gas analysis, measuring blood pressure, any other tests that require the researcher to come close or touch the test participant.	Staff working in lab, including researcher and participant	Exposure to COVID-19.	• Laboratory is to be ventilated with windows open at all times during the trial. • Once all testing is complete the lab will be thoroughly cleaned entire laboratory using the Universities cleaning and sanitising procedures (https://staff.swansea.ac.uk/media/risk-assessment-cleaning-and-provision-of-sanitising-supplies-during-covid-19.pdf; document SOP101). These covid risk reduction measures cover all previous project risk assessments and standard operating procedures.	3	1	3	No				
Risk Item 5: Catching or spreading COVID-19 or other blood borne virus when carrying out blood handling/analysis procedures after testing	Researcher, participant, lab technicians	Exposure to COVID-19	• Where possible, blood handling, separation and analysis will take place in a separate room to the exercise bout to reduce exposure to aerosols (gloves and lab coats worn). • Where this is not possible, Level 2 PPE is to be worn after hand	3	1	3	No				

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (SxL)	Do you need to do anything else to manage this risk?	S	L	Risk (SxL)	Additional Action Required
			washing: Nitrile gloves (double gloves), lab coats, disposable aprons, eye protection (goggles and visors BSEN166 compliant). • Samples will be labelled detailing anonymous participant code, trial, date in permanent marker • All surfaces will cleaned and disinfected after use (document SOP101). • Wash hands on entering and leaving.								
Risk Item 6: Adverse cardiovascular response during exercise	Research Participants	Adverse cardiovascular event	• Risk deemed unlikely as all participants undergo extensive pre-screening in line with American College of Sports Medicine procedures (screening for health history, family health history, blood pressure, anthropometrics). • Participants are not able to take part if they have any health-related issue which places them at risk by taking part in the study. • Participants will be asked to let the research team know if they experience any change in health status. Furthermore, they will be	5	1	5					

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
			asked not to perform exercise during any period of acute illness. There will be a first aider and first aid kit in the laboratory and access to an emergency telephone if required.								
Risk Item 7: Participants may feel faint/nauseas during or after exercise	Research Participants	Fainting / Sickness	• Appropriate warm-up and cool down is integrated into the exercise protocol. There will be a first aider and first aid kit in the laboratory and access to an emergency telephone if required.	2	2	4					
Risk Item 8: Risk of hazards during outdoor exercise trial	The Participants	Accident or injury	• Course will be mapped and clearly communicated to participant. • Course will be inspected each trial day prior to trial taking place to ensure warnings are given to participant about any potential hazards. • There will be a first aider on hand. • The course will be in close proximity to the laboratory where first aid kit is located a member of the research team will have mobile telephone for emergencies if required.	2	1	2					
Risk Item 13: Confidentiality of participant	The participants	A possibility that others might be able to see or gain access to their data.	All participants will be given a numerical identifier. Personal information will be stored on a password protected computer in a password protected file. All data will be destroyed in accordance with the Data Protection Act (2018).	1	2	4	No				

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
Risk Item 14: Confidentiality of data	The participants	A possibility that others might be able to see or gain access to their data.	• The data will be stored on a password protected computer in a password protected file. Due care and attention will be taken transporting the data to the password protected file. Any data stored temporarily on a portable electronic device will be deleted immediately once stored on the password protected computer. The data will be destroyed in accordance with the Data Protection Act (2018). Withdrawal procedures are in place if the participant wants to withdraw from the study at any time up to publication.	1	2	2	No				
Risk Item 15: Contamination of trial beverage	The participants	There is a possibility of consuming a harmful substance	• Any beverages will be prepared in advance of the trial in a designated food/drink preparation area. • Hygiene and cleanliness will be a high priority ensuring all containers are clean and sterilized. • Hands will be washed and adequate PPE, Gloves and lab coats worn when preparing the solutions. • All ingredients will be adequately stored and handled appropriately to ensure that contamination with any unwanted substances is avoided.	1	2		No				

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
Risk Item 16: Emergency procedure for spills	The researcher and participant.	Exposure to infectious material (Blood)	• Blood spill kits are present in the laboratory • Researcher is trained in the procedure for spills within the laboratory	1	2	2					
Risk Item 17: Waste disposal	The researcher	Exposure to sharps and other hazardous waste.	• Sharps bins and hazardous waste bins are present in the laboratory. • The researcher is trained in Safety & Sustainability within the lab • Lab technicians remove waste through appropriate waste disposal procedures on a regular schedule.	1	2	2					
Risk Item 18: Infection from venepuncture.	The participant	Infection to site of venipuncture	• All researchers must comply with the A-STEM SOP for withdrawing blood by venipuncture.	2	4	8					

What are the hazards?	Who might be harmed?	How could they be harmed?	What are you already doing?	S	L	Risk (Sx L)	Do you need to do anything else to manage this risk?	S	L	Risk (Sx L)	Additional Action Required
Risk Item 19: Discomfort / Injury caused by incorrect use of Tourniquet	Research Participants, volunteer (practice) participants	Injury or discomfort	• Tourniquet is undone between finding the site and preparing to take the sample. Once flashback is observed the tourniquet is loosened/undone unless the vein is difficult.	2	2 4	4					
Risk Item 20: Nerve damage/pain from venepuncture	Research Participants, volunteer (practice) participants		• All researchers must comply with the A-STEM SOP for withdrawing blood by venipuncture.	2	3	6					
			•								
			•								
			•								
			•								
			•								
			•								

Part 2: Actions arising from risk assessment

Actions	Lead	Target Date	Done Yes/No

		Consequences				
		1 **Insignificant** No injuries/ minimal financial loss	**2** **Minor** First aid treatment/ medium financial loss	**3** **Moderate** Medical treatment/high financial loss	**4** **Major** Hospitalised/ large financial loss	**5** **Catastrophic** Death/ Massive Finanical Loss
Likelihood	**5** **Almost Certain** Often occurs/ once a	5 Moderate	10 High	15 High	20 Catastrophic	25 Catastrophic

	week					
	4 **Likely** Could easily happen/ once a week	4 Moderate	8 Moderate	12 High	16 Catastrophic	20 Catastrophic
	3 **Possible** Could happen/ happen once a year	3 Low	6 Moderate	9 Moderate	12 High	15 High
	2 **Unlikely** Hasn't' yet happened but could happen	2 Low	4 Moderate	6 Moderate	8 High	10 High
	1 **Rare** Concievable but 1/100 year event	1 Low	2 Low	3 Low	4 Moderate	5 Moderate

PARTICIPANT DISTRESS

Procedures to follow in the event of participant distress during Interviews/Focus Groups

Prior to the interview:

Prior to conducting interviews, pilot interviews will be conducted in liaison with the supervisor. These interviews will provide the researcher with an opportunity to identify any questions that might lead to distress and where appropriate, take steps to rephrase or change these questions.

Before conducting the first formal interview, the student will meet with their supervisor to discuss to procedures that are in place in case a participant becomes distressed during an interview. The supervisor will also ensure the student feels prepared for the interview. The supervisor must be satisfied that the researcher is competent in conducting interviews before giving approval for the commencement of data collection.

Students will inform their supervisor where and when they are completing all interviews and in turn the supervisor will ensure the student has a means of contacting them

when they are conducting interviews.

During the interview:
At the beginning of the interview the student will remind the participant that they can stop the interview at any time, that they can choose not to answer questions, and that there are no right or wrong answers to questions (so there is no fear of 'saying the wrong thing').

Once the interview begins, the researcher will be required to be aware of any potential indications of distress (e.g., withdrawing, visible upset, declining to answer numerous questions, shifting in seat, looking away from the interviewer, asking for the interview to end) and should air on the side of caution in all instances. If there is even the slightest indication that participants might be distressed students must immediately follow the procedure below:

1. The recording will be immediately stopped and the participant will be asked if they are ok. At this point the participant will be asked if they want to take a break/end the interview/continue talking – the participant's decision will be final. If the participant decides to take a break and continue with the interview, confirmation will be sought that the participant is actually comfortable continuing and they will be reminded there is no penalty for withdrawing.

2. If the participant wishes to continue but remains distressed, the interviewer will make the decision to drawn the interview to an end. At this point, the interviewer will commit to providing the participant with an opportunity to talk and ensure the participant is not visibly distressed when leaving the interview.

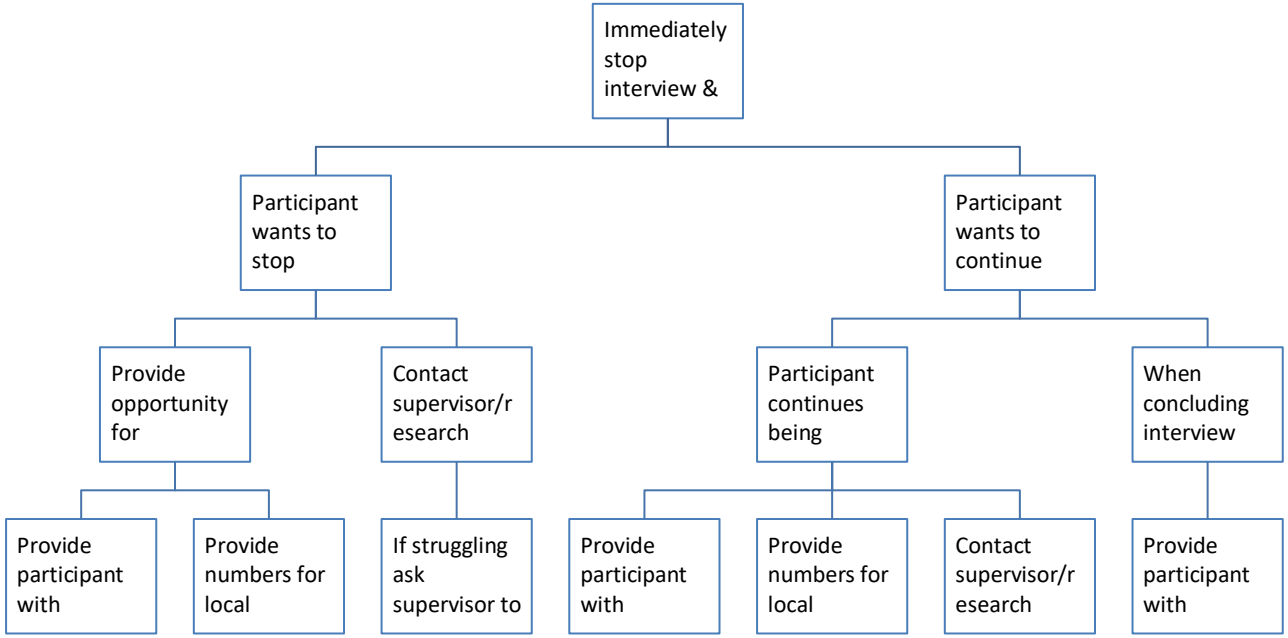
3. If the participant remains distressed and the researcher does not feel capable of managing the situation they will contact their respective supervisor who will be available at all times during interviews by phone contact. Depending on the situation, the supervisor will either provide guidance to the student, speak directly to the participant over the phone, or make attempts to go and meet with the researcher and the participant.

4. If the participant has become distressed at any point in the interview, the student will ensure the participant has the contact details of the rest of the research team and remind them that they are free to contact any member of the research team if there is anything further they would like to discuss.

5. The interviewer will also offer to provide the participants with a list of local contacts (e.g., counselling services, sport psychology services) if they would like them.

6. Following the interview, the student will debrief the interview with their supervisor and (if necessary) other senior members of the research team. A written record of the incident and the procedures followed will be made.

Management of Distressed Participants During Interviews



If participant has become distressed at any point you must debrief with supervisor and write up the steps that were taken throughout to manage the situation.

APPENDIX B6: Participant recruitment poster

Study title: The metabolic stress of acute and chronic ultra-endurance exercise under low or high glycaemic index-carbohydrate diets.

What is the Study about?

The purpose of this study is to examine the impacts of a low or high glycaemic- index, high carbohydrate fuel for acute exercise as well as when incorporated into a low or high glycaemic-index diet plan in ultra-endurance athletes.

Who is eligible?

- Healthy Males & Females aged between 18 and 65 years
- Participating in regular training (>10hrs per week)
- Involved or regularly participating in Ultra endurance events.

What do I have to do?

You will visit the lab at Swansea University 5 times over the course of 2 and a half months during which you will complete a specific exercise trial. You will follow two four week dietary interventions during which you will train as normal. Throughout the course of the entire study period you will log your diet and training for the research team to collect for analysis.

What do I get in return?

You will be given a complete physiological profile including a VO2max test and hormonal stress markers. In addition you will be given a continuous glucose monitor allowing you to gain valuable insight into your fuelling strategy.

If interested please contact Ross [redacted]

Project ID: U1111-1281-5048
Version 1. 5/7/22

Appendix C1: Form CS001: Biosen C-Line: Calibration Record Sheet

	Sensor test Solution		Linearity Std 1 (Blue)		Linearity Std 2 (Green)		Linearity Std 3 (Orange)		Ready Con Norm		Ready Con Pat		
	Glucose (mmol/L-1)	**Lactate** (mmol/L-1)	**Glucose** (mmol/L-1)	**Lactate** (mmol/L-1)	**Glucose** (mmol/L-1)	**Lactate** (mmol/L-1)	**Glucose** (mmol/L-1)	**Lactate** (mmol/L-1)	**Glucose** (mmol/L-1)	**Lactate** (mmol/L-1)	**Glucose** (mmol/L-1)	**Lactate** (mmol/L-1)	
	Target Value: **5.0**; Range: **4.8-6.4**)	Target Value: **5.0**; Range: **4.8-6.4**)	Target Value: **2.00**; Range: **1.80-2.20**)	Target Value: **2.00**; Range: **1.80-2.20**)	Target Value: **7.00**; Range: **6.75-7.25**)	Target Value: **7.00**; Range: **6.75-7.25**)	Target Value: **18.00**; Range: **17.5-18.5**)	Target Value: **18.00**; Range: **17.5-18.5**)	Target Value: **6.06**; Range: **5.39-6.72**)	Target Value: **3.00**; Range: **2.67-3.33**)	Target Value: **15.99**; Range: **14.24-17.75**)	Target Value: **15.00**; Range: **13.35-16.65**)	**Comments**

Form CS001: Biosen C-Line: Calibration Record Sheet