Fasting Plasma Glucose Assessed by Continuous Glucose Monitoring

Axel Hedman

School of Electrical Engineering

Bachelor's thesis
Espoo 4.5.2023

Supervisor

PhD Markus Turunen

Advisors

D.Sc Lauri Palva

Mgr. Matej Králik

Aalto-yliopisto
Sähkötekniikan
korkeakoulu

Aalto University, P.O. BOX 11000, 00076 AALTO
www.aalto.fi
Abstract of the bachelor's thesis

Author Axel Hedman

Title Fasting Plasma Glucose Assessed by Continuous Glucose Monitoring

Degree programme Electrical engineering

Major Bioinformation technology **Code of major** ELEC3016

Teacher in charge PhD Markus Turunen

Advisors D.Sc Lauri Palva, Mgr. Matej Králik

Date 4.5.2023 **Number of pages** 28 **Language** English

Abstract

The prevalence of obesity and overweight is a growing health issue worldwide. Obesity increases the risk for metabolic complications including diabetes mellitus, cardiovascular disease, and various types of cancer. An unhealthy lifestyle is a leading cause of obesity. Lifestyle changes have been proven an effective approach to overcoming obesity and overweight. Fasting plasma glucose (FPG) is an established indicator of whether an individual is metabolically healthy. Traditionally an FPG test requires a medical appointment including a blood sample. Such a test requires the user to fast for at least 8 hours before measuring FPG levels from a blood sample. Newer research has challenged the need for an 8-hour fasting widow and suggests that FPG levels may be achieved by a shorter fasting period. Modern technology has brought alternative solutions to blood glucose monitoring. Today, continuous glucose monitoring (CGM) devices can be paired with smartphones and utilize mobile applications to streamline the glucose monitoring process. This thesis explores the possible usage of CGM data to approximate FPG. The continuous stream of glucose data provided by a CGM device and meal information allows for thorough glucose analysis. Regular FPG approximations can be utilized to optimize lifestyle for maintaining good metabolic health. The thesis investigates and demonstrates possible methods for approximating FPG. The demonstrations presented in this thesis are made possible by a collaboration with a company named Veri. The CGM data and event information used in this thesis is provided by Veri. The demonstrations are mainly visual and illustrate how FPG can be approximated from CGM data. The visual demonstrations compare an 8-hour fasting window with a shorter fasting window of 3 hours. This thesis's main contribution to the field is that FPG approximations based on CGM data are possible.

Keywords continuous glucose monitoring, metabolic health, fasting plasma glucose

Aalto-yliopisto
Sähkötekniikan
korkeakoulu

Aalto-universitetet, PB 11000, 00076 AALTO
www.aalto.fi
Sammandrag av kandidatarbetet

Författare Axel Hedman

Titel Fasteplasmaglukos fastställt av kontinuerlig glukosmonitorering

Utbildningsprogram Elektroteknik

Huvudämne Bioinformationsteknologi **Huvudämnets kod** ELEC3016

Ansvarslärare PhD Markus Turunen

Handledare TkD Lauri Palva, Mgr. Matej Králik

Datum 4.5.2023 **Sidantal** 28 **Språk** Engelska

Sammandrag

Förekomsten av fetma och övervikt är ett växande hälsoproblem världen över. Idag är närmare en tredjedel av världens befolkning antingen överviktiga eller diagnostiserade med fetma. Fetma ökar risken för en rad metabola komplikationer inklusive diabetes mellitus, kardiovaskulära sjukdomar och diverse cancerformer. En ohälsosam livsstil har visat sig vara en av de ledande orsakerna till fetma. Näringsintag, sömn, stress och träning påverkar alla kroppens blodsockernivåer. För att upprätthålla hälsosamma blodsockernivåer krävs gynnsam förvaltning av alla livsstilsrelaterade delområden. Fasteplasmaglukos är en etablerad indikator när det kommer till metabol hälsa. För att mäta fasteplasmaglukos krävs en fasteperiod av förbestämd varaktighet. Under fasteperioden bör patienten avstå från alla former av kaloriintag. Ett fasteplasmaglukostest har traditionellt krävt ett läkarbesök med ett tillhörande blodprov. Modern teknologi har tillfört alternativa metoder till blodsockermätning. Kontinuerlig glukosmonitorering har visat sig vara ett konkurrenskraftigt alternativ till blodsockermätning. Idag kan mobila applikationer kombineras med kontinuerlig glukosmonitorering för att förse användaren med kontinuerliga glukosdata direkt i smarttelefonen. Detta arbete utforskar möjligheten att approximera fasteplasmaglukos med hjälp av kontinuerlig glukosmonitorering. Approximering av fasteplasmaglukos kräver såväl glukosdata som information angående näringsintag. Den kontinuerliga dataströmmen tillhandahållen av kontinuerlig glukosmonitorering tillsammans med information angående näringsintag tillåter genomgående blodsockeranalys. Regelbundna approximationer av fasteplasmaglukos kan användas för att upprätthålla en hälsosam livsstil och förebygga metabol sjukdom. Förhöjda fasteplasmaglukosnivåer under en längre tidsperiod indikerar att åtgärder bör vidtas för att förhindra sjukdom. Med regelbundna approximationer av fasteplasmaglukos kan patienten själv följa med och reagera på onormala fasteplasmaglukostrender. Förändringar i livsstil kan sänka fasteplasmaglukos. Om livsstilsförändringar inte hjälper är den rekommenderade åtgärden att söka professionell hjälp. Arbetets slutsats är att approximation av fasteplasmaglukos med hjälp av kontinuerlig glukosmonitorering är möjlig. Fasteplasmaglukosapproximaitoner kräver information angående näringsintag. För att framgångsrikt approximera fasteplasmaglukos bör fasteperioden tas i beaktande. Ytterligare forskning krävs för att fastställa den mest exakta metoden för approximation av fasteplasmaglukos med hjälp av kontinuerlig glukosmonitorering.

Nyckelord metabol hälsa, kontinuerlig glukosmonitorering, fasteplasmaglukos

Contents

Abbreviations

Abbreviations

BMI	body mass index
CGM	continuous glucose monitoring
FPG	fasting plasma glucose
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
MARD	mean absolute relative difference
OGTT	oral glucose tolerance test

1 Introduction

A growing health issue worldwide is the prevalence of obesity and overweight. Since 1980, the number of patients diagnosed with obesity and overweight has doubled. Today, nearly a third of the world's population is considered obese or overweight [1]. As the prevalence of obesity and overweight increases, public health is at risk. Obesity affects nearly all physiological activity in the human body. It lowers life expectancy and increases the risk of multiple severe diseases including diabetes mellitus, cardiovascular disease, and various types of cancer[1][2]. There are several approaches on how to tackle obesity and overweight but the majority of them revolve around diet and lifestyle management. Medications and surgery may solve short-term complications but several studies have shown that lifestyle changes are necessary to ultimately overcome obesity[2][3][4].

Traditionally, glucose levels have been monitored with blood samples and finger pricks. When used correctly, glucose monitoring can be a useful tool when tracking changes in patients' lifestyles. Sleep, Diet, stress, and exercise affect blood glucose levels as well as overall health[5]. Studies have shown that correctly applied lifestyle changes not only lower blood glucose levels but they also result in a lower body mass index (BMI) and weight, improved cholesterol and triglyceride values, and lower blood pressure[5]. If not managed correctly, blood glucose levels can reach unusually high or low levels potentially causing acute and chronic conditions[6].

A combination of obesity and unnecessarily high glucose levels can lead to the onset of type 2 diabetes[7]. Type 2 diabetes patients are heavily dependent on glucose monitoring to correctly use medications and avoid critical conditions[8]. Nevertheless, studies have shown that with appropriate lifestyle changes, type 2 diabetes can be reversed with diet alone[9]. Such a reversal requires a fundamental understanding of how diet affects blood glucose. Hence, glucose management and monitoring is a vital part of alleviating and preventing obesity and type 2 diabetes.

Fasting plasma glucose (FPG) is an established indicator of whether an individual is metabolically healthy or not[10][11]. FPG is usually measured from a blood sample taken after a minimum of 8 hours of fasting[12]. An FPG test traditionally requires a medical appointment. Before attending the medical appointment, patients have to go through the 8-hour fasting window. A procedure that may be perceived as disruptive.

Modern technology has brought alternative glucose measurement methods. Continuous glucose monitoring (CGM) is an already introduced method to monitor blood glucose[13]. CGM has struggled to become a medically approved method due to large measurement errors - because in the year 2000, the mean absolute relative difference (MARD) of CGM was larger than $\pm 20\%$ which is the accepted average for regulatory approval. As technology is advancing the MARD of CGM has now reduced to under $\pm 10\%$ and the accuracy continues to improve[14][15].

CGM uses an invasive electrochemical biosensor to measure glucose levels in the interstitial fluid between cells. The biosensor utilizes a small filament inserted through the skin to measure glucose levels. The in vivo response to a needle-type biosensor has been one of the biggest challenges to accurate CGM measurements.

The infiltration of proteins, the release of cytokines and reactive oxygen species, and subsequent influx of inflammatory cells all contribute to the instability of implanted glucose sensors.[15]. Nevertheless, compared to blood samples and finger pricks, CGM provides a complete set of continuous glucose data for the user to analyze. A finger prick, for example, doesn't provide an overview of the long-term effects that lifestyle and diet have on glucose levels. Hence, CGM has established itself as a viable option when it comes to glycemic control and overall improvement of metabolic health.

This thesis is done in collaboration with Veri[16], a Finnish company focusing on improving metabolic health through CGM. Veri combines a mobile application with a CGM sensor providing continuous glucose data for the user to analyze. By tracking glucose levels with CGM, users are able to observe the metabolic impact of diet, sleep, stress, exercise, and other lifestyle factors on long-term health. To support the research and conclusions of this thesis, Veri has provided deidentified glucose data to help visualize trends in blood glucose. The provided data set includes meal, exercise, sensor, and demographic data.

This thesis aims to explore the possibility of using CGM data to approximate FPG by comparing a traditional 8-hour fasting window to a shorter fasting window of 3 hours. By utilizing the continuous data stream of a CGM device, FPG approximations can be made based on large portions of data compared to the momentary blood sample of a traditional FPG test[12].

The advantage of FPG approximations assessed by CGM is how they can be continuously acquired from day to day without having to schedule a doctor's appointment. Likewise, the approximation includes data acquired over a longer period of time compared to the momentary blood sample of a traditional FPG test. Earlier research on the topic and visual demonstrations using the data provided by Veri will be the supporting pillars when examining the possibility of approximating FPG from CGM data.

Chapter 2 describes the background including central concepts connected to the topic. In Chapter 3, the data used to illustrate glucose trends is presented. Chapter 4 demonstrates the possibilities of how FPG can be approximated from CGM data and discusses possible use cases. Chapter 5 further discusses the possible methods presented in Chapter 4 and Chapter 6 concludes the thesis.

2 Background

This chapter defines fundamental concepts and methods closely related to the topic of this thesis. The physiology behind glucose absorption is explained as well as interstitial glucose and fasting plasma glucose (FPG). The chapter also discusses how lifestyle has an impact on blood glucose and how elevated FPG levels can lead to health-related complications. Continuous glucose monitoring (CGM) is described as it is the method used to obtain the glucose data used in this thesis.

2.1 Glucose absorption

Glucose is one of the primary energy sources of the human body. It is a monosaccharide composed of Carbon, Hydrogen, and Oxygen. During digestion, carbohydrates are broken down into monosaccharides including glucose. Glucose is absorbed into the bloodstream by the small intestine[17].

A family of G-protein coupled receptors, known as sweet taste receptors, located in the small intestine are responsible for glucose detection and absorption. Together with glucose transporters, including SGLT1 and GLUT2, the sweet taste receptors transport glucose from the small intestine into the bloodstream. After absorption glucose is either used as energy by the different tissues of the human body or stored in the liver for later use[17]. Figure 1 illustrates the different stages of the glucose absorption process.

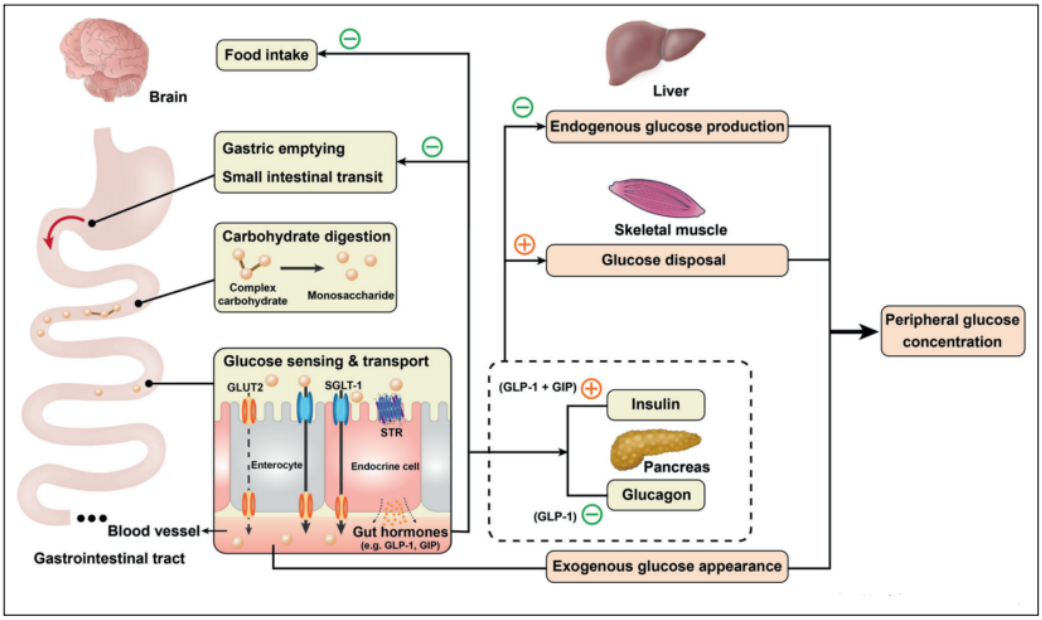

Figure 1: Illustrartion of the glucose absorption process in the human body[17].

2.2 Interstitial glucose

The bloodstream is not the only place where glucose is abundant. Interstitial glucose is a result of diffusion across the capillary barrier caused by a difference in glucose concentration between blood capillaries and the interstitial fluid between cells[18]. Interstitial glucose can be utilized directly by tissues including fat and muscle cells[19].

The time it takes for glucose to diffuse over the capillary barrier results in a lag time between changes in plasma glucose and interstitial glucose. Apart from the lag time interstitial glucose behaves almost exactly the same as plasma glucose[20]. Figure 2 illustrates the diffusion of glucose molecules over the capillary barrier between the blood plasma (C1) and the interstitial fluid (C2). A CGM sensor is able to utilize interstitial glucose to measure plasma glucose.

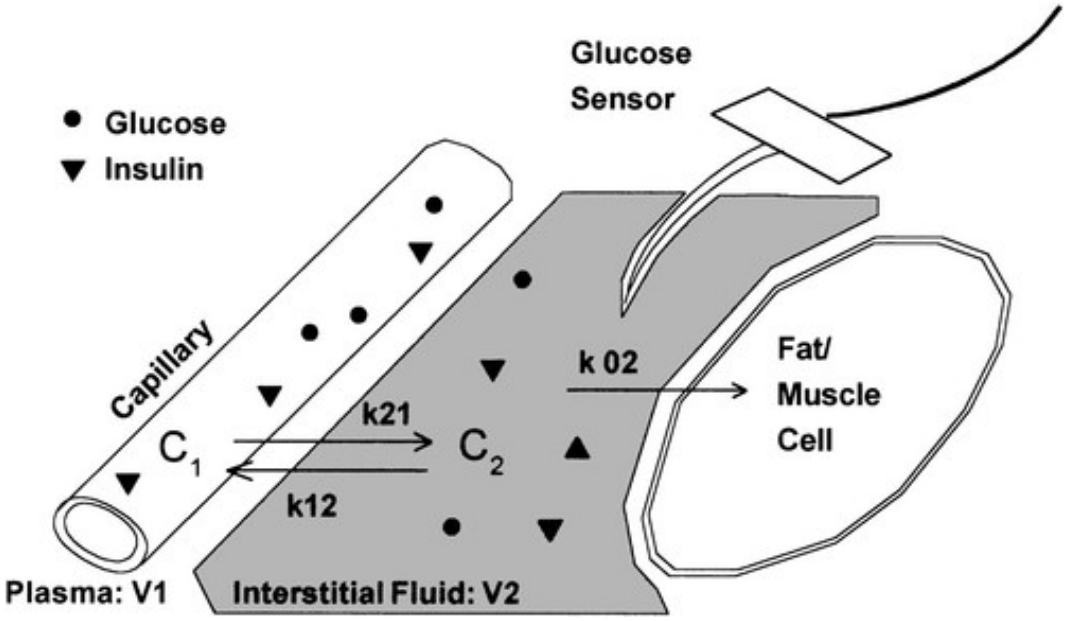

Figure 2: Interstitial glucose as a result of diffusion over the capillary barrier[19].

2.3 Fasting Plasma Glucose

Fasting plasma glucose (FPG) is a metric used when evaluating the metabolic health of an individual[12][21]. An FPG test is usually measured from a blood sample taken during a medical appointment. An FPG test measures the plasma glucose concentration in the bloodstream. FPG is measured in the units mmol/L or mg/dL. This thesis uses the unit mmol/L.

A clinical FPG test requires an 8-hour fasting window. Fasting is defined as no caloric intake during a certain time period[12]. During the fasting widow, the patient is not allowed to eat or drink anything except water. This is to ensure that blood glucose levels have time to settle and are not affected by earlier nutritional intake.

Every meal generates a corresponding spike in blood glucose. The size of the spike depends on the nutritional content of the meal[22]. Figure 3 illustrates how nutrition causes an elevation in blood glucose that settles over time as long as no

more food is ingested. The data presented in Figure 3 is acquired from the data set provided by Veri.

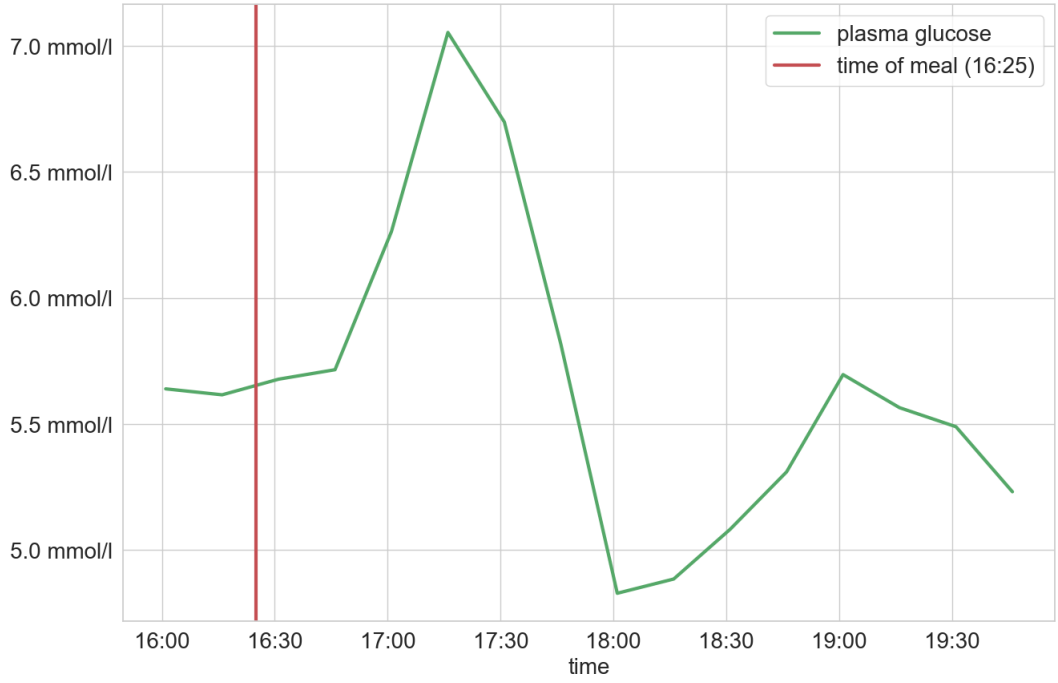

Figure 3: Elevation in blood glucose caused by nutritional intake. The data presented in this figure is acquired from the data set provided by Veri.

Studies have shown that the traditional 8-hour fasting window may not be necessary for the human body to reach FPG levels[10]. According to [10], a fasting window of 3 hours is enough to achieve a reliable fasting plasma glucose measurement. The data presented in [10] is enough to challenge the traditional approach of an 8-hour fasting window but further research is required to establish the 3-hour fasting window as a clinical method.

A shorter fasting window is highly relevant when considering CGM as a method for approximating FPG. CGM data doesn't always ensure that the patient has fasted for at least 8 hours. As a matter of fact, an 8-hour fasting window rarely happens during waking hours. With a shorter fasting window, a larger portion of the CGM data could be utilized without having to be restricted to longer fasting periods.

FPG is a recommended screening method when evaluating the risk of developing type 2 diabetes[21]. Normal FPG levels range between 4.0 mmol/L and 5.6 mmol/L. An FPG value of 5.6 - 6.0 mmol/L indicates a risk of developing type 2 diabetes[6]. Here it is worth mentioning that a momentary elevated FPG value is not necessarily a problem. Nevertheless, elevated FPG levels over a longer period of time are a strong indicator of metabolic abnormalities.

Prediabetes is a state in which FPG levels exceed normal levels to reach values of 6.1 - 6.9 mmol/L. An FPG value of 7 mmol/L is diagnosed as diabetes[23]. If FPG levels stay in the abnormal range without exceeding 7 mmol/L the patient should

continue frequent screening and apply lifestyle changes to ensure that FPG levels are kept under control[21].

2.4 Impaired Fasting Glucose and Impaired Glucose Tolerance

Type 2 diabetes develops over a longer period of time. Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are both complications associated with the early stages of type 2 diabetes[24]. IFG is defined by the FPG value of a patient. A patient with an elevated FPG value of 5.6-7 mmol/L is diagnosed with IFG [25]. IGT is determined by an Oral glucose tolerance test (OGTT) together with an FPG test.

An OGTT usually involves consuming a 75g glucose load, usually in the form of a concentrated glucose solution. Plasma glucose is measured 2h after consuming the concentrated glucose solution to achieve an OGGT value. A patient with an OGTT value of 7.8-11.1 mmol/L and an FPG value of < 7 mmol/L is diagnosed with IGT[25]. Here, an FPG value of > 7 mmol/L and an OGTT value of > 11.1 mmol/L strongly indicate that the patient has developed type 2 diabetes[24][23].

The overlap in FPG shows that one can suffer from both IFG and IGT. Historical patterns show that among individuals diagnosed with either IGT or IFG, 25% progress to diabetes, 50% remain in the abnormal range without developing diabetes, and 25% reacquire normal glucose tolerance. Being diagnosed with both of these metabolic complications doubles the probability of developing diabetes[25].

2.5 Correlations between lifestyle and blood glucose

Diet, sleep, exercise, and stress all affect FPG. A healthy lifestyle includes favorable management of all four subcategories. Failing to control these may result in unhealthy fluctuations in FPG leading to metabolic disorders including IGT, IFG, and eventually, type 2 diabetes[5].

The earlier a patient detects FPG abnormalities, the better. Metabolic disorders usually develop over a longer period of time. A healthy lifestyle can not only prevent but also reverse metabolic complications, especially if caught in the early stages[9].

2.5.1 Sleep

The natural fasting window during sleeping hours allows for blood glucose to settle and reach FPG levels. A good night's sleep often results in a fasting window of at least 8 hours, fulfilling the traditional requirements of fasting plasma glucose.

A long night's sleep is not always favorable when it comes to FPG. Studies have shown an association between elevated FPG levels and sleep duration. A sleeping duration of under 6 hours or over 8 hours has been shown to cause elevated FPG levels[26].

2.5.2 Diet

Diet has a major impact on plasma glucose concentration[27]. Food is the main source of nutrition in the human body. During digestion, carbohydrates break down into glucose. Glucose is then absorbed into the bloodstream by the small intestine, as explained in Chapter 2.1, for the body to use as energy or store for later use.

Carbon hydrates can be divided into simple and complex carbohydrates[28]. A simple carbohydrate is either a monosaccharide or a disaccharide. The simple chemical structure of simple carbohydrates allows the body to quickly digest and utilize them for energy. As a result, simple carbon hydrates often cause a rapid elevation in plasma glucose concentration and insulin secretion[29]. Complex carbohydrates, on the other hand, are composed of three or more sugars chained together. Complex carbohydrates often contain fiber, vitamins, and minerals. As complex carbohydrates take longer to digest, they have less of an immediate impact on plasma glucose[29]. Most foods contain both simple and complex carbohydrates but one is usually more present[27].

Table 1 concertizes simple and complex carbon hydrates with examples of sugars that fall into the two categories. Examples of food sources from where the different sugars can be obtained are also included.

carbohydrate	**sugars**	**food sources**
simple	fructose lactose glucose	candy carbonated beverages fruit juice
complex	cellobiose rutinulose amylose	broccoli lentils brown rice

Table 1: Examples of simple and complex carbohydrates in food[30].

The glycemic index is a way of ranking carbon hydrates based on how they affect plasma glucose. On a scale of 0-100, foods rated >70 are considered high glycemic foods. Medium-level foods are rated 56-69 and low-glycemic 55 or less[31]. Glucose has a glycemic index of 100 and is considered a reference point for the top of the scale.

The higher the glycemic index the higher the fluctuations in plasma glucose[22]. Studies have shown that eating large quantities of high-glycemic foods over a longer period of time has a negative effect on fasting plasma glucose and increases the risk of obesity, type 2 diabetes, and heart disease[22]. Table 2 presents examples of foods and their corresponding glycemic index.

food	GI
apple, raw	36 ± 2
milk, full fat	39 ± 3
porridge	55 ± 2
potato, boiled	78 ± 4
white table sugar, glucose	100

Table 2: Average GI of common food sources[32].

2.5.3 Exercise

Exercise has been proven to cause both elevations and dips in plasma glucose depending on the type of workout. During high-intensity workouts such as heavy weightlifting and sprints, the body produces adrenaline. Adrenaline stimulates the liver to release glucose causing rapid elevation in plasma glucose[33]. Aerobic exercise on the other hand will lower your glucose levels during the workout. During moderate exercise, the muscles use more glucose than the body releases causing lower blood glucose levels. Studies have also shown that regular aerobic exercise can lower FPG and 2-h postprandial blood glucose levels in diabetic patients[34].

2.5.4 Stress

Stressful situations such as infections, serious illnesses, or significant emotional stress cause insulin levels to fall and the body to produce adrenaline. As a result, stress stimulates the liver to release glucose causing elevations in plasma glucose[35]. Studies have shown that stress has a negative impact on FPG and may lead to diabetes-related morbidities[36].

2.5.5 Obesity and type 2 diabetes

The prevalence of obesity is one of today's most eminent health problems across the globe[1]. Obesity is a result of an unhealthy lifestyle over a longer period of time. A patient with a BMI of 30 or higher is diagnosed with obesity [37]. If not treated correctly, obesity leads to elevations in FPG causing IGT, IFG, and eventually diabetes[7].

Studies have shown that correctly implemented lifestyle changes in obese individuals and patients diagnosed with prediabetes can lower FPG levels and reduce the risk for type 2 diabetes significantly[9][24]. Other studies have also shown how type 2 diabetes can be reversed by diet[9]. A strict low-calorie diet has been proven to bring FPG to normal levels among individuals diagnosed with type 2 diabetes[9].

2.6 Continuous Glucose Monitoring

The first CGM device was approved in 1999 by the U.S. Food and Drug Administration. Since then, technology has improved significantly and CGM has established

itself as a viable alternative to glucose monitoring and management[38].

Today, CGM is not only able to monitor glucose levels but it can also be paired with an insulin pump to automate insulin dosage in diabetes patients[39]. There are two components in a CGM device, an electrochemical sensor implanted in the subcutaneous tissue of the abdomen or the arm or the stomach, and a monitor displaying glucose data[39]. Today, the monitoring part of CGM is often handled by a mobile application. These mobile applications have developed to become useful tools for helping people with their glycemic control. Aboot's LibreLink application, for example, comes with additional features of an alarm that alerts the user when blood glucose reaches an unhealthy level[40].

All the data used in this thesis is obtained by a CGM form known as flash glucose monitoring. Flash glucose monitoring is based on CGM technology and offers lower daily costs and does not require regular calibration. A flash glucose monitoring device requires scanning the sensor at least every 8 hours to access full 24-hour data[41].

Veri utilizes flash glucose monitoring by pairing its application with the Freestyle Libre sensor by Abbot. Utilizing Abbot's LibreLink application Veri's users are able to scan their Freestyle Libre sensor to access 24-hour glucose data. Veri's application continuously fetches glucose data from LibreLink for analysis. The data set used in this thesis is obtained by the combination of the Freestyle Libre sensor, the LibreLink application, and Veri's own application.

2.6.1 Flash glucose monitoring sensor

CGM measures interstitial glucose, found in the interstitial fluid between cells. The in-vivo sensor, which utilizes a small filament to measure glucose, is inserted under the skin with the help of a needle. The filament of the CGM sensor contains an enzyme known as glucose oxidase and is made up of a three-electrode system[42].

When inserted through the skin, the enzyme reacts with the interstitial fluid resulting in the oxidation of hydrogen peroxide. This process generates an electrical current that is indicative of the glucose concentration[42]. Figure 4 presents a visual comparison of the physiological differences between the traditional approach to glucose monitoring and flash glucose monitoring.

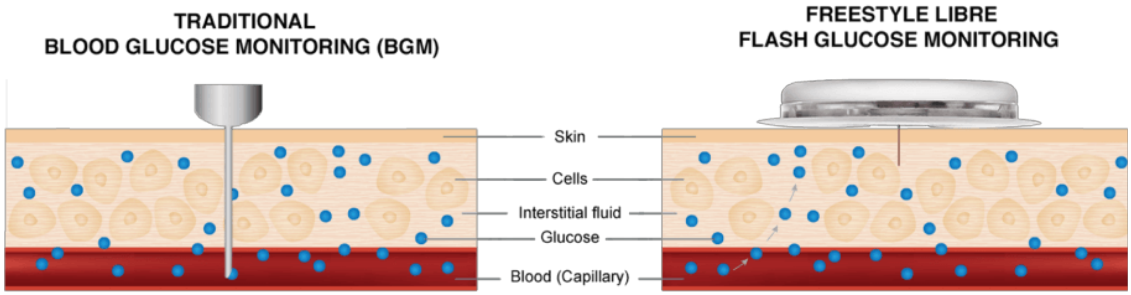

Figure 4: Visual comparison of the physiology behind the traditional approach to blood glucose monitoring and flash glucose monitoring[43]. Compared to a traditional blood sample, the CGM sensor utilizes a small filament containing an enzyme named glucose oxidase. Glucose oxidase reacts with the interstitial fluid producing an electrical current that is indicative of the glucose concentration.

2.6.2 Limitations

Despite its popularity, CGM has its limitations. The in vivo response to a needle-type biosensor has been one of the biggest challenges to accurate CGM measurements. The infiltration of proteins, the release of cytokines and reactive oxygen species, and subsequent influx of inflammatory cells all contribute to the instability of implanted glucose sensors[15].

When measuring interstitial glucose it is important to consider how it differs from blood glucose. As mentioned, interstitial glucose is the result of diffusion between blood capillaries and the interstitial fluid. The lag time caused by the time it takes for glucose to diffuse over the capillary barrier causes delay between interstitial glucose and plasma glucose. Studies have also shown that distortions may occur when comparing interstitial glucose measurements to plasma glucose[44].

Another drawback of the CGM device is its seemingly short lifetime. For hygienic reasons, the sensor of a CGM device has to be replaced every 10-14 days. A process that may be perceived as disruptive and unwieldy.

2.7 FPG monitoring as a preventive measure for disease

The prevalence of obesity and type 2 diabetes is closely related to FPG. Obesity is a result of an unhealthy lifestyle over a longer period of time, causing elevated FPG levels[7]. Elevated FPG levels over a long period of time lead to complications including IFG and IGT that ultimately may develop into type 2 diabetes. Patients diagnosed with IFG and IGT run a significant risk of developing type 2 diabetes[25].

As discussed in Chapter 2.2, IFG and IGT are both defined using FPG. With frequent FPG tests, patients are able to detect elevations in FPG and seek care before FPG reaches unhealthy levels. Optimally, FPG abnormalities are detected and remedied before they develop into IFG or IGT. Proactive lifestyle changes during the prediabetes stage can prevent IFG, IGT, and the development of type 2 diabetes[9].

3 Research material

This chapter summarizes the research material used in this thesis. In this thesis, the data set provided by Veri was used to illustrate trends in blood glucose. The graphical demonstrations presented in this thesis help the reader visualize how blood glucose is affected by lifestyle and how FPG can be approximated by CGM data.

3.1 Data set

The data set used in this thesis contains deidentified user health data obtained by Veri. The data set includes glucose data from roughly 6000 Veri users. Apart from glucose data, the data set also includes the users' sleep, exercise, and demographic information.

As Veri's data depends on user input the data set is incomplete to some extent. Non-logged events, absent profile information, and irregular glucose scans result in missing glucose data. Nevertheless, the data set provides an adequate overview of the glucose data among the users.

Figure 5 presents a graphical summary of the demographic data of the data set. The height distribution of the users is normally distributed between 140-200cm with a mean of 171.1cm. The weight distribution of the users follows a slightly skewed normal distribution between 40-150kg with a mean of 79.4kg. The height and length distributions result in an average BMI of just under 25kg/m^2. Among the users, 3400 identify as female, 2100 as male.

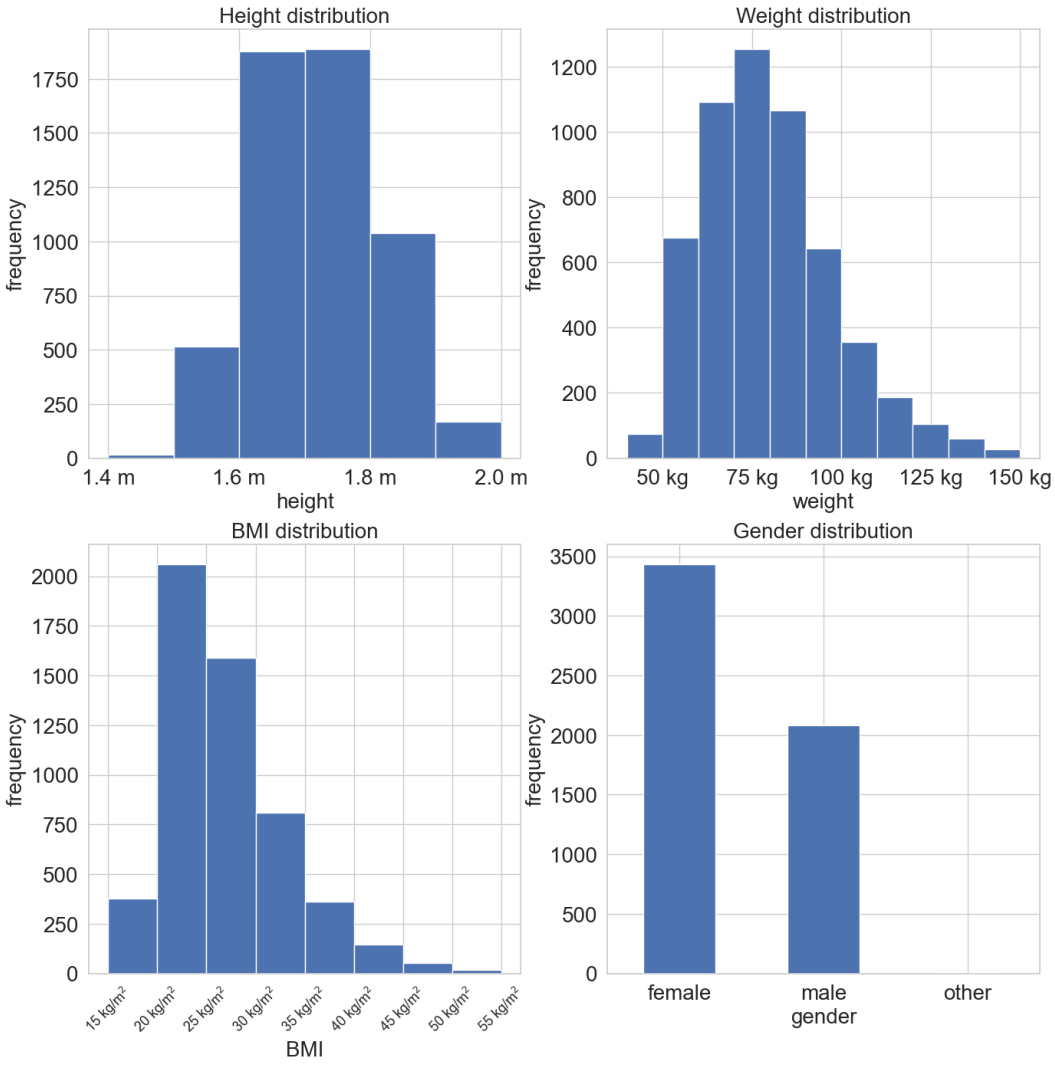

Figure 5: Graphical summary of the demographics of the data set used in this thesis to visually demonstrate how FPG can be approximated from CGM data.

The data set also contains user event data, including sleep, meal, and exercise information. The event data visualizes the habits of the users. Figure 6 shows a graphical summary of the sleep and meal information of the users.

The first histogram shows the users' preferred number of meals per day. The majority of the users prefer 3 meals a day. Studies have shown that the number of meals per day has an impact on blood glucose, where a larger number of meals result in augmented glucose levels throughout the day[45].

The second histogram visualizes the distribution of the duration of every recorded sleeping event in the data set. As shown in the histogram. Most users sleep between 7 and 9 hours. The sleeping patterns of the users are highly relevant to the topic of finding FPG through CGM. A good night's sleep of over 8 hours automatically fulfills the fasting window requirement of FPG. Unfortunately, this is not always the case as the histogram implies.

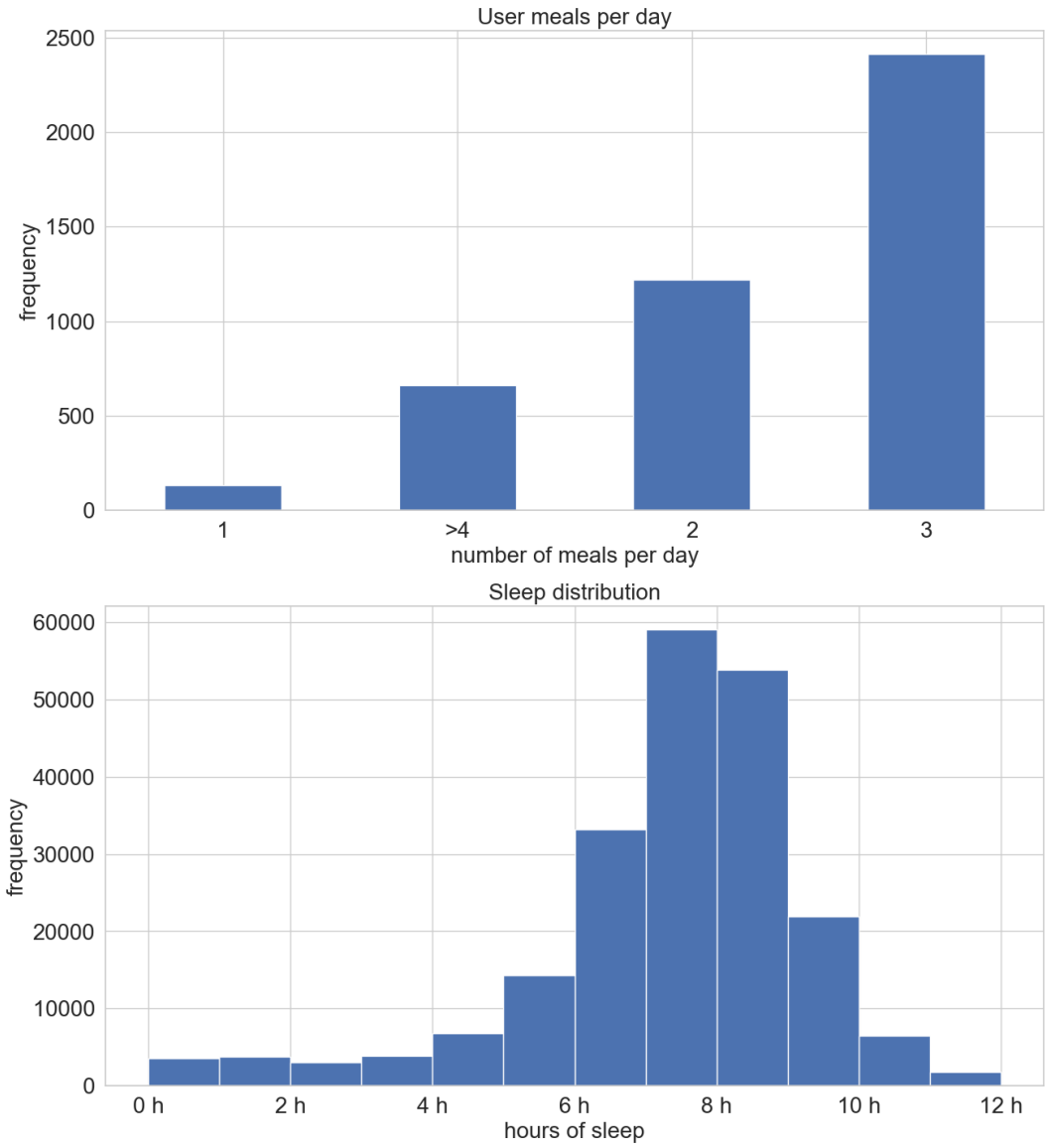

Figure 6: Graphical summary of user event data obtained from the data set provided by Veri.

Every user has their own set of glucose values fetched by a CGM device. Each glucose value is paired with a timestamp. Below is a histogram illustrating the mean glucose values of Veri's users. The average mean glucose of the users is 5.45 mmol/L with a standard deviation of 0.57 mmol/L. As [6] states, normal FPG levels range between 4.0 mmol/L and 5.6 mmol/L. The average glucose value of a user will be higher compared to the FPG value of the user as the average glucose value includes meals and other events affecting blood glucose. Figure 7 shows the distribution of user mean glucose.

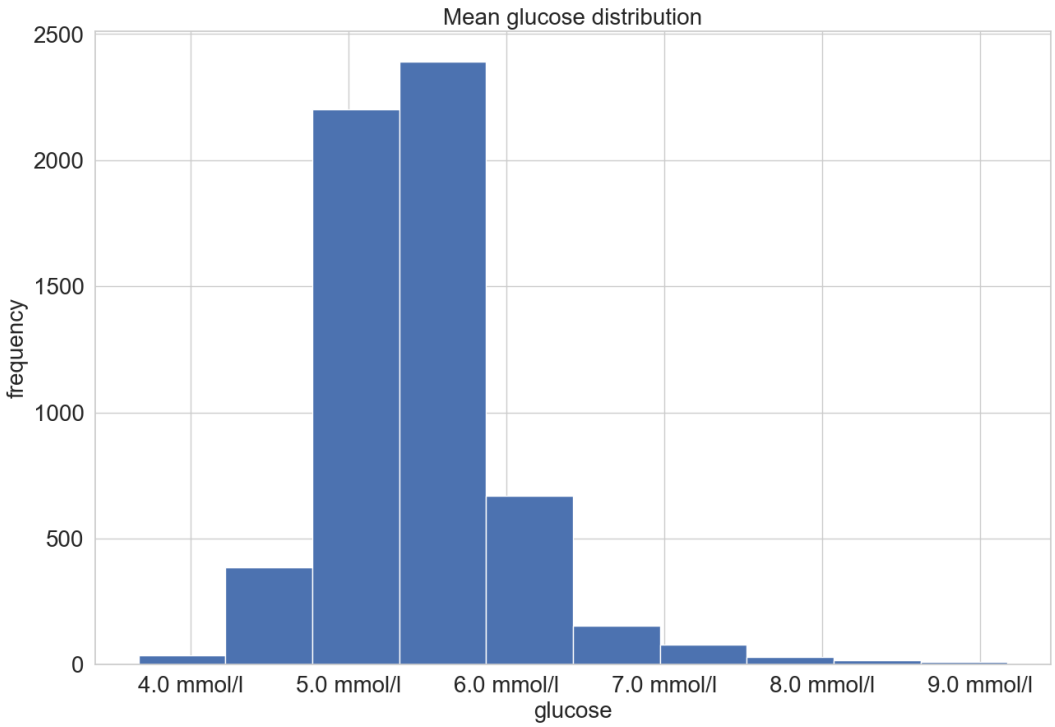

Figure 7: Histogram visualizing user mean glucose distribution of the data set provided by Veri.

When looking at the glucose data on an individual level, lifestyle's impact on glucose is evident. Figure 8 shows a graphical visualization of the glucose data of a single user over a period of two days. The glucose data used to visualize glucose trends is obtained from the data set presented in this chapter. During the daytime variation in blood glucose is high due to meals and other lifestyle-related events[5]. During nighttime blood glucose has time to settle and reaches a more steady state due to the natural fasting window occurring[46].

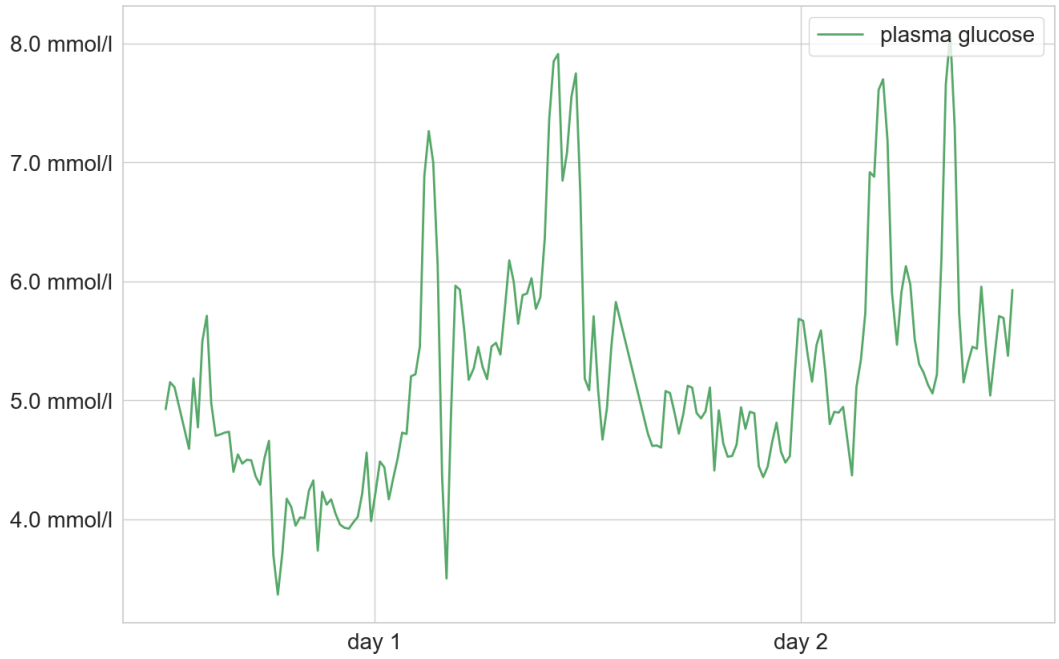

Figure 8: Glucose curve of a single user obtained from the data set provided by Veri.

The glucose data alone provides an incomplete picture of lifestyle's impact on blood glucose. Figure 9 shows the same glucose data as in Figure 8 but with added overlays of the events occurring during the same time interval. The blue areas represent sleep and the red lines represent meals.

The glucose data and the added events provide a more complete picture and explain the daily fluctuations in blood glucose. As the graph shows, the fluctuations in blood glucose during sleeping are much lower compared to the daytime. As mentioned, during sleeping hours, blood glucose usually has time to reach FPG levels due to the natural fasting window occurring. FPG levels may vary from night to night. As [26] states, sleeping duration has an impact on FPG levels. Elevations in nightly FPG may be caused by many different factors, and duration of sleep is one of them.

Studies have shown that late evening meals result in elevated nocturnal blood glucose levels[46]. Glucose tolerance decreases during the night. Late evening meals not only affect nocturnal glucose levels but may also generate larger glucose spikes than a normal evening meal[46].

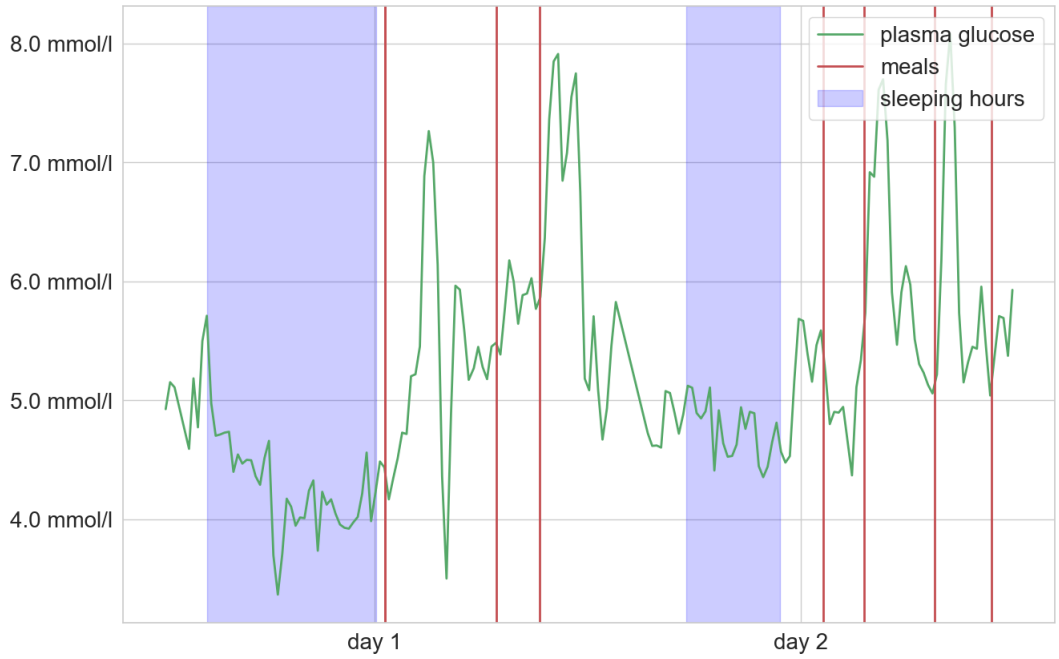

Figure 9: Glucose data of a single user with additional events obtained from the data set provided by Veri.

4 FPG approximations based on CGM data

This chapter includes four visual demonstrations of FPG approximations assessed from CGM data. The data presented in this chapter is obtained from the data set provided by Veri. When approximating FPG from CGM data, a choice has to be made on whether to stick with the traditional approach of an 8-hour fasting window[6] or utilize a shorter fasting window[10]. A major flaw of the traditional 8-hour fasting window is that it limits the data by excluding a larger portion of the data. 8-hour fasting windows rarely occur outside sleeping hours.

A 3-hour fasting window occurs more frequently, usually several times per day. Hence, a shorter fasting window could be utilized to obtain several FPG measures per day. This allows for a comparison of meals and how they affect FPG. The major drawback of a 3-hour fasting window approach is that it currently lacks research supporting it. The data presented in [10] challenges the 8-hour fasting window but further research has to be made to establish the 3-hour fasting window as a clinical method for measuring FPG.

The baseline for determining FPG from CGM data would be to take a single glucose sample at the end of the determined fasting window. Let's start by considering a minimum fasting window of 8 hours[6]. Figure 10 shows the same graph of glucose values and events as in Figure 9 with additional FPG measurements marked with black dotted lines. The FPG samples are taken after a fasting window of at least 8 hours. This momentary sample approach is equal to the traditional way of measuring FPG from a blood sample taken after an 8-hour fasting window, disregarding the

MARD of the CGM device.

Figure 10 depicts how this approach leads to identifying two FPG values - 4.01 mmol/L and 4.89 mmol/L. These measurements are already adequate approximations of FPG based on the requirements of a traditional FPG test[6]. However, the momentary samples fail to utilize the continuous stream of data provided by the CGM device.

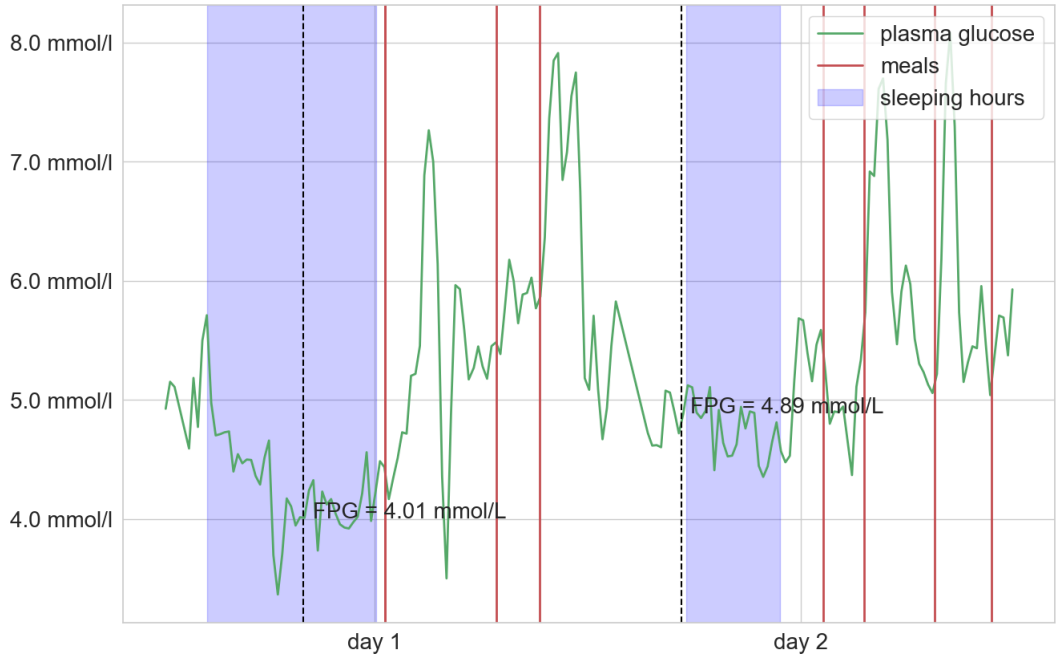

Figure 10: Individual FPG samples obtained after an 8-hour fasting window.

To fully utilize the continuous data stream of a CGM device an alternative would be to include all glucose data between the point of fulfilling the fasting window requirement and the next meal. FPG requires a fasting window of a certain duration. Hence, every glucose measurement between the end of said fasting window and the next nutritional intake cloud be considered an FPG value.

In Figure 11, the FPG approximation is achieved by calculating the mean value of the glucose data within the defined window. In this case, the green area represents the glucose data used to calculate the mean FPG value between fulfilling the 8-hour fasting window requirement and the next meal. This approach generated two mean FPG values of 4.14 mmol/L and 4.89 mmol/L.

Compared to the momentary sample approach shown in Figure 10, the mean FPG approach generates an approximation that relies on a larger portion of the data provided. As the glucose curve implies, fluctuations in blood glucose are evident even during longer fasting windows. A momentary measurement is heavily dependent on fluctuations in plasma glucose and the MARD of the CGM device. By calculating the mean blood glucose value over a longer fasting period, the impact of momentary fluctuations is excluded. Further research has to be made on whether the mean value is the best way of approximating FPG based on the data included. Nevertheless,

the mean value succeeds to deliver an approximation independent of momentary fluctuations among the FPG values included.

When comparing the mean FPG values in Figure 11 to the momentary FPG samples in Figure 10, the results are similar. Nevertheless, the mean FPG values in Figure 11 are based on a larger portion of data, arguably providing a more complete picture of FPG levels during corresponding fasting periods.

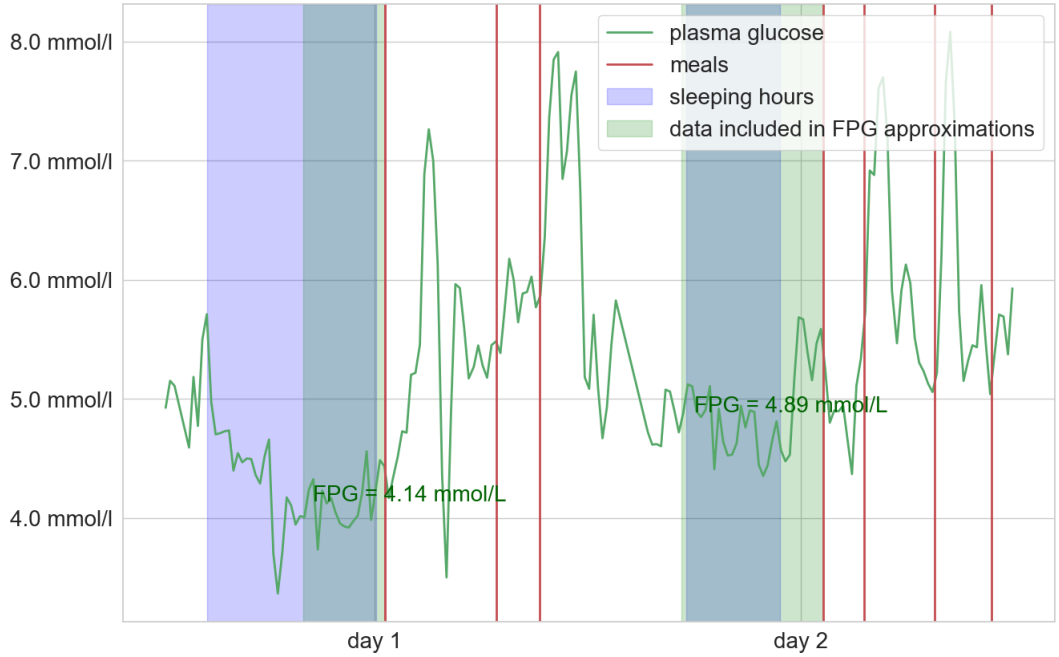

Figure 11: Mean FPG measurements with 8-hour fasting windows.

To include an even larger portion of the provided CGM data, a shorter fasting window of 3 hours can be utilized when approximating FPG[10]. Firstly, the momentary sample approach is applied with a 3-hour fasting window. Figure 12 shows the glucose curve of the same individual with additional events and FPG measurements with a 3-hour fasting window. Compared to an 8-hour fasting window, a 3-hour fasting window allows for 4 measurements instead of two in this particular case. The momentary values measured were 4.70 mmol/L, 6.14 mmol/L, 5.70 mmol/L, and 5.31 mmol/L. A shorter fasting window usually generates a larger number of FPG measurements.

As stated in Chapter 3.1, the majority of the users included in the data set eat 3 meals per day. 3 meals per day usually allow for multiple 3-hour fasting windows during the day. Nevertheless, there are also cases where a 3-hour fasting window generates an equal amount of FPG measurements as an 8-hour fasting window.

In this particular case, when comparing the momentary samples of a 3-hour fasting window to the momentary FPG samples of an 8-hour fasting window, the 3-hour fasting window has a tendency of generating slightly higher values than an 8-hour fasting window. The difference is especially visible when looking at the second measurement in Figure 12. The momentary sample of 6.14 mmol/L is taken during

the daytime between meals and is noticeably higher than both measurements in Figure 10.

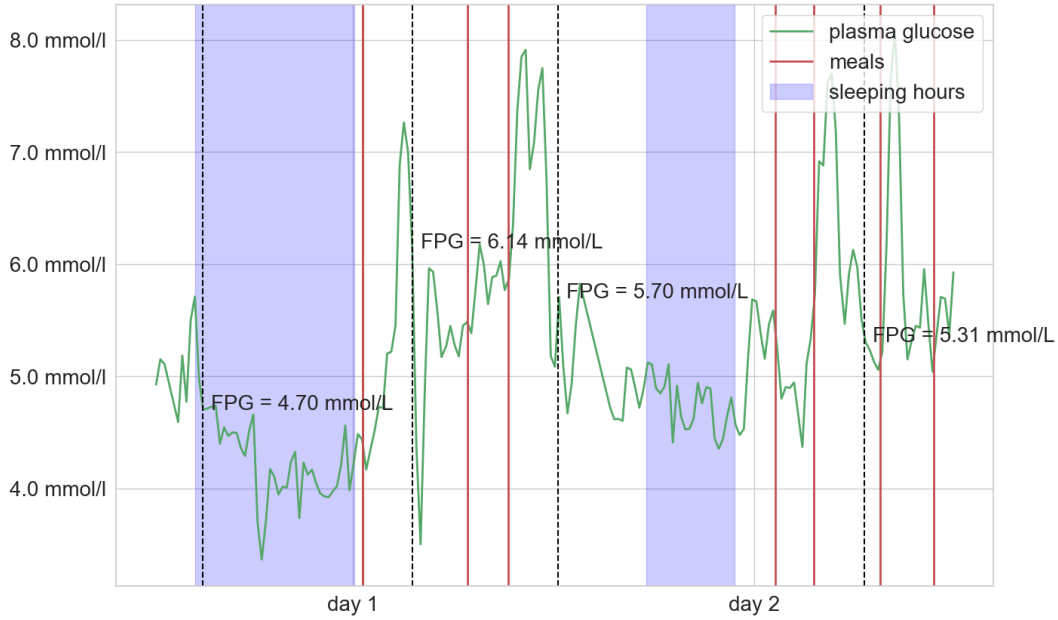

Figure 12: Individual FPG samples obtained after a 3-hour fasting window.

When applying the mean FPG approach to a 3-hour fasting window, the results in this particular case are noticeably lower. Figure 13 illustrates the data included between the end of the 3-hour fasting windows and their next corresponding meal. The mean FPG values measured in Figure 13 were 4.22 mmol/L, 5.17 mmol/L, 4.92 mmol/L, and 5.18 mmol/L. When comparing the values in Figure 13 to the values in Figure 12, the values in Figure 13 are noticeably lower.

When comparing the mean FPG values generated by a 3-hour fasting window to the mean FPG value generated by an 8-hour fasting window, the trend is similar to the comparison of the momentary FPG samples. The mean FPG values of 4.14 mmol/L and 4.89 mmol/L in Figure 11 correspond to the values of 4.22 mmol/l and 4.92 mmol/L in Figure 13. The 3-hour fasting window generates slightly higher mean FPG values than the 8-hour fasting window, indicating the need for further research to establish the 3-hour fasting window as a clinical method when measuring FPG[10].

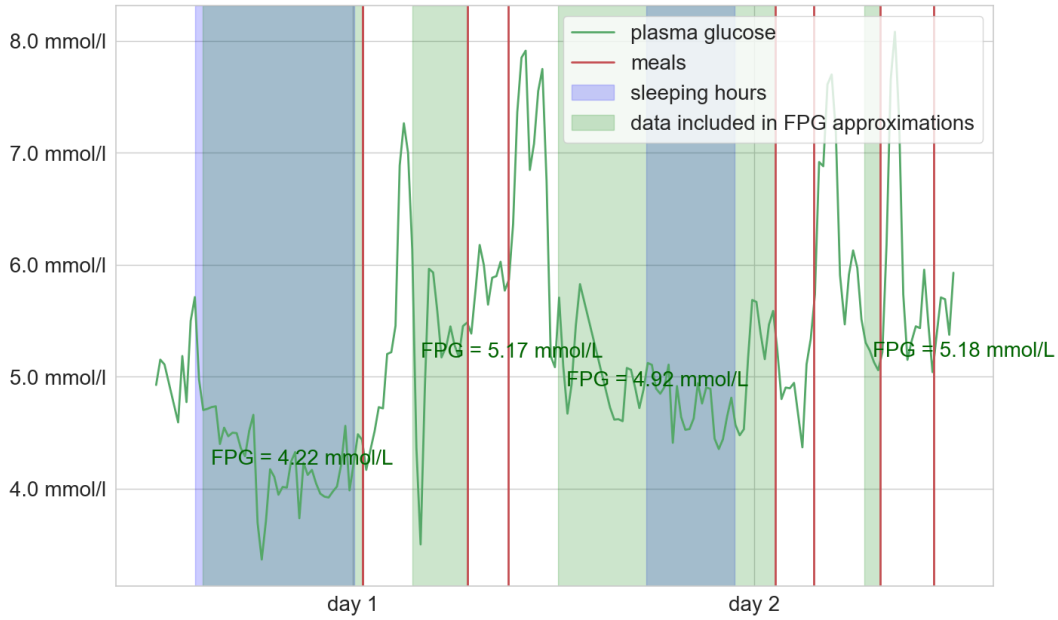

Figure 13: Mean FPG measurements with 3-hour fasting windows.

To determine how the four methods of approximation presented in this chapter perform in general, further analysis would have to be performed on the data set. The data set includes glucose-related data from roughly 6000 users and allows for further research regarding the approximation of FPG from CGM data.

5 Discussion

An FPG measurement requires a fasting window of a debatable size. Traditionally, an 8-hour fasting window has been the clinical standard when measuring FPG[12]. Newer research has challenged the traditional approach, stating that 8 hours of fasting may not be necessary to measure FPG[10]. A shorter fasting window of 3 hours favors CGM-generated FPG approximations by allowing larger portions of the CGM data to be included in the approximation. Further research has to be done to establish the 3-hour fasting window as a clinical method.

Possible methods for approximating FPG with CGM were illustrated in Chapter 4. Two different fasting window durations were applied. The duration of the fasting windows applied were 8 hours[12] and 3 hours[10]. Firstly, similarly to the traditional approach of measuring FPG, momentary samples were taken from the CGM data at the end of each corresponding fasting window. The major flaw of the momentary sample approach is that it fails to utilize the continuous stream of data that a CGM device provides. Nevertheless, it corresponds to the traditional way of testing FPG through a single blood sample.

To include a larger portion of the data set, a mean FPG value was calculated using glucose data between the end of the previous fasting window and the next meal. The mean FPG approach allows approximations based on a much larger portion of the CGM data provided compared to the momentary sample approach. As FPG measurements require a certain fasting window, every glucose value obtained after the fasting window and before the next nutritional intake is classified as FPG.

When comparing the different methods in the particular case presented in Chapter 4, the 3-hour fasting window had a tendency to generate a slightly higher FPG value. The data presented in [10] indicates that a fasting window under 8 hours generally generates a slightly higher FPG value than a fasting window over 8 hours. These results imply that further research still has to be made for a 3-hour fasting window to be clinically approved[10]. The data presented in [10] is still enough to challenge the traditional approach of an 8-hour fasting window when approximating FPG from CGM data.

Compared to the momentary sample approach, the mean FPG approach succeeds to utilize the full potential of the CGM device. A momentary sample is similar to the traditional approach where FPG is measured from a blood sample. The major difference between a traditional FPG test and an FPG approximation obtained by a CGM device is the MARD of the CGM device[14]. Today, the MARD of CGM is low enough to consider CGM as a valid method when approximating FPG[14].

When trying to achieve an FPG approximation based on a larger portion of the CGM data, the average FPG approach is the more favorable method. Depending on the duration of the previous fasting window, the average FPG approach generates an approximation based on all glucose data between the end of the fasting window and the next meal. To include the maximum amount of data in the approximation, a 3-hour fasting window would be the favored approach. The 8-hour fasting window is the safer approach to ensure that the approximation is based on clinical research[6].

6 Conclusion

FPG approximations from CGM data are made possible by obtaining meal-related information from the patient. Without knowing the time since the last nutritional intake of the patient it is hard to obtain a reliable FPG value. Wrongly approximated FPG values may lead to unnecessary worry and faulty diagnoses.

This thesis aimed to explore the possibility of using CGM data to approximate FPG by comparing the traditional 8-hour fasting window to a shorter fasting window of three hours. The result was obtained by combining earlier research with visual demonstrations of FPG approximations. The results still favor a longer fasting window of eight hours. Both earlier research and the visual demonstrations indicated that a shorter fasting window of 3 hours has a tendency of generating slightly higher FPG approximations than a longer fasting window of at least 8 hours. Despite the difference being relatively small, further research still has to be made to establish a shorter fasting window as a clinical approach when approximating FPG from CGM data.

Regular FPG approximations obtained by a CGM device do not require a medical appointment. By regularly monitoring FPG values, patients are able to react to elevations and apply lifestyle changes proactively to avoid further complications. Used correctly, FPG assessed by CGM favors metabolic health development.

References

[1] Y. C. Chooi, C. Ding, and F. Magkos, "The epidemiology of obesity," *Metabolism*, vol. 92, pp. 6–10, 2019. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S002604951830194X

[2] S. Nammi, S. Koka, K. M. Chinnala, and K. M. Boini, "Obesity: An overview on its current perspectives and treatment options," *Nutrition Journal*, vol. 3, no. 1, p. 3, 2004. [Online]. Available: https://doi.org/10.1186/1475-2891-3-3

[3] M. Mauro, V. Taylor, S. Wharton, and A. M. Sharma, "Barriers to obesity treatment," *European Journal of Internal Medicine*, vol. 19, no. 3, pp. 173–180, 2008. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0953620507002701

[4] L. H. Powell, J. E. Calvin III, and J. E. Calvin Jr., "Effective obesity treatments," *American Psychologist*, vol. 62, pp. 234–246, 2007, place: US Publisher: American Psychological Association. [Online]. Available: https://psycnet.apa.org/doiLanding?doi=10.1037%2F0003-066X.62.3.234

[5] K. Yamaoka and T. Tango, "Effects of lifestyle modification on metabolic syndrome: a systematic review and meta-analysis," *BMC Medicine*, vol. 10, no. 1, p. 138, 2012. [Online]. Available: https://doi.org/10.1186/1741-7015-10-138

[6] T. K. Mathew and P. Tadi, "Blood glucose monitoring," in *StatPearls*. StatPearls Publishing, 2022. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK555976/

[7] A. J. Garber, "Obesity and type 2 diabetes: which patients are at risk?" *Diabetes, Obesity and Metabolism*, vol. 14, no. 5, pp. 399–408, 2012, publisher: John Wiley & Sons, Ltd. [Online]. Available: https://dom-pubs-onlinelibrary-wiley-com.libproxy.aalto.fi/doi/full/10.1111/j.1463-1326.2011.01536.x

[8] C. M. Ripsin, H. Kang, and R. J. Urban, "Management of blood glucose in type 2 diabetes mellitus," *American Family Physician*, vol. 79, no. 1, pp. 29–36, 2009. [Online]. Available: https://www.aafp.org/pubs/afp/issues/2009/0101/p29.html

[9] R. Taylor, "Type 2 diabetes: Etiology and reversibility," *Diabetes Care*, vol. 36, no. 4, pp. 1047–1055, 2013. [Online]. Available: https://doi.org/10.2337/dc12-1805

[10] S. Moebus, L. Göres, C. Lösch, and K.-H. Jöckel, "Impact of time since last caloric intake on blood glucose levels," *European Journal of Epidemiology*, vol. 26, no. 9, pp. 719–728, 2011. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3186886/

[11] G. Danaei, M. M. Finucane, Y. Lu, G. M. Singh, M. J. Cowan, C. J. Paciorek, J. K. Lin, F. Farzadfar, Y.-H. Khang, G. A. Stevens, M. Rao, M. K. Ali, L. M. Riley, C. A. Robinson, and M. Ezzati, "National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants," *The Lancet*, vol. 378, no. 9785, pp. 31–40, 2011, num Pages: 10 Place: London, United Kingdom Publisher: Elsevier Limited Section: Articles. [Online]. Available: https://www.proquest.com/docview/874571417/abstract/3D54F177B1B24637PQ/1

[12] The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, "Report of the expert committee on the diagnosis and classification of diabetes mellitus," *Diabetes Care*, vol. 20, no. 7, pp. 1183–1197, 1997. [Online]. Available: https://doi.org/10.2337/diacare.20.7.1183

[13] T. Danne, R. Nimri, T. Battelino, R. M. Bergenstal, K. L. Close, J. H. DeVries, S. Garg, L. Heinemann, I. Hirsch, S. A. Amiel, R. Beck, E. Bosi, B. Buckingham, C. Cobelli, E. Dassau, F. J. Doyle, S. Heller, R. Hovorka, W. Jia, T. Jones, O. Kordonouri, B. Kovatchev, A. Kowalski, L. Laffel, D. Maahs, H. R. Murphy, K. NÃÿrgaard, C. G. Parkin, E. Renard, B. Saboo, M. Scharf, W. V. Tamborlane, S. A. Weinzimer, and M. Phillip, "International consensus on use of continuous glucose monitoring," *Diabetes Care*, vol. 40, no. 12, pp. 1631–1640, 2017. [Online]. Available: https://diabetesjournals.org/care/article/40/12/1631/37000/International-Consensus-on-Use-of-Continuous

[14] D. Rodbard, "Continuous glucose monitoring: A review of successes, challenges, and opportunities," *Diabetes Technology & Therapeutics*, vol. 18, pp. S2–3, 2016, num Pages: S2-13 Publisher: Mary Ann Liebert, Inc., publishers. [Online]. Available: https://www.liebertpub.com/doi/full/10.1089/dia.2015.0417

[15] R. Gifford, "Continuous glucose monitoring: 40 years, what we've learned and what's next," *Chemphyschem.*, vol. 14, no. 10, 2013-07-22. [Online]. Available: https://chemistry-europe.onlinelibrary.wiley.com/doi/abs/10.1002/cphc.201300172

[16] Veri - discover better metabolic health. [Online]. Available: https://www.veri.co/

[17] T. Wu, C. K. Rayner, K. L. Jones, C. Xie, C. Marathe, and M. Horowitz, "Role of intestinal glucose absorption in glucose tolerance," *Current opinion in pharmacology.*, vol. 55, 2020-12. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S147148922030120X

[18] K. Rebrin and G. M. Steil, "Can interstitial glucose assessment replace blood glucose measurements?" *Diabetes Technology & Therapeutics*, vol. 2, no. 3, pp. 461–472, 2000, pMID: 11467349. [Online]. Available: https://doi.org/10.1089/15209150050194332

[19] K. Rebrin, G. M. Steil, W. P. van Antwerp, and J. J. Mastrototaro, "Subcutaneous glucose predicts plasma glucose independent of insulin: implications for continuous monitoring," *American Journal of Physiology-Endocrinology and Metabolism*, vol. 277, no. 3, pp. E561–E571, 1999, publisher: American Physiological Society. [Online]. Available: https://journals.physiology.org/doi/full/10.1152/ajpendo.1999.277.3.E561

[20] E. Cengiz and W. V. Tamborlane. A tale of two compartments: Interstitial versus blood glucose monitoring. Archive Location: 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA Publisher: Mary Ann Liebert, Inc. 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA. [Online]. Available: https://www.liebertpub.com/doi/10.1089/dia.2009.0002

[21] J.-M. Ekoe, R. Goldenberg, and P. Katz, "Screening for diabetes in adults," *Canadian Journal of Diabetes*, vol. 42, pp. S16–S19, 2018. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1499267117308146

[22] F. X. Pi-Sunyer, "Glycemic index and disease," *The American Journal of Clinical Nutrition*, vol. 76, no. 1, pp. S290–S299, 2002. [Online]. Available: https://linkinghub.elsevier.com/retrieve/pii/S0002916523058768

[23] M. E. Cox and D. Edelman, "Tests for Screening and Diagnosis of Type 2 Diabetes," *Clinical Diabetes*, vol. 27, no. 4, pp. 132–138, 01 2009. [Online]. Available: https://doi.org/10.2337/diaclin.27.4.132

[24] K. Z. Walker, K. O'Dea, M. Gomez, S. Girgis, and R. Colagiuri, "Diet and exercise in the prevention of diabetes," *Journal of Human Nutrition and Dietetics*, vol. 23, no. 4, pp. 344–352, 2010, _eprint: https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1365-277X.2010.01061.x. [Online]. Available: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-277X.2010.01061.x

[25] D. M. Nathan, M. B. Davidson, R. A. DeFronzo, R. J. Heine, R. R. Henry, R. Pratley, and B. Zinman, "Impaired fasting glucose and impaired glucose tolerance: Implications for care," *Diabetes Care*, vol. 30, no. 3, pp. 753–759, 2007. [Online]. Available: https://doi.org/10.2337/dc07-9920

[26] H. Nakajima, Y. Kaneita, E. Yokoyama, S. Harano, T. Tamaki, E. Ibuka, A. Kaneko, I. Takahashi, T. Umeda, S. Nakaji, and T. Ohida, "Association between sleep duration and hemoglobin a1c level," *Sleep Medicine*, vol. 9, no. 7, pp. 745–752, 2008. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1389945707002985

[27] W. R. Russell, A. Baka, I. Björck, N. Delzenne, D. Gao, H. R. Griffiths, E. Hadjilucas, K. Juvonen, S. Lahtinen, M. Lansink, L. V. Loon, H. MykkÃd̄nen, E. Ã̋ustman, G. Riccardi, S. Vinoy, and M. O. Weickert, "Impact of diet composition on blood glucose regulation," *Critical Reviews in Food Science and Nutrition*, vol. 56, no. 4, pp. 541–590, 2016, publisher: Taylor & Francis

_eprint: https://doi.org/10.1080/10408398.2013.792772. [Online]. Available: https://doi.org/10.1080/10408398.2013.792772

[28] A. E. Griel, E. H. Ruder, and P. M. Kris-Etherton, "The changing roles of dietary carbohydrates," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 26, no. 9, pp. 1958–1965, 2006, publisher: American Heart Association. [Online]. Available: https://www.ahajournals.org/doi/full/10.1161/01.ATV.0000233384.97125.bd

[29] J. E. Holesh, *Physiology, Carbohydrates*. StatPearls Publishing, Treasure Island (FL), 2022. [Online]. Available: http://europepmc.org/books/NBK459280

[30] J. E. Holesh, S. Aslam, and A. Martin, *Physiology, Carbohydrates*. StatPearls Publishing, Treasure Island (FL), 2022. [Online]. Available: http://europepmc.org/books/NBK459280

[31] F. S. Atkinson, K. Foster-Powell, and J. C. Brand-Miller, "International Tables of Glycemic Index and Glycemic Load Values: 2008," *Diabetes Care*, vol. 31, no. 12, pp. 2281–2283, 12 2008. [Online]. Available: https://doi.org/10.2337/dc08-1239

[32] F. Atkinson, K. Foster-Powell, and J. Brand-Miller, "International Tables of Glycemic Index and Glycemic Load Values: 2008," *Diabetes Care*, vol. 31, no. 12, pp. 2281–2283, 12 2008. [Online]. Available: https://doi.org/10.2337/dc08-1239

[33] Exercise can raise blood glucose (blood sugar) | ADA. [Online]. Available: https://diabetes.org/healthy-living/fitness/why-does-exercise-sometimes-raise-blood-sugar

[34] N. Shahgholian, O. KarimiFard, and S. Shahidi, "Effects of aerobic exercise on blood glucose in continuous ambulatory peritoneal dialysis patients," *Iranian Journal of Nursing and Midwifery Research*, vol. 20, no. 2, pp. 165–170, 2015. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4387637/

[35] Blood sugar & stress :: Diabetes education online. [Online]. Available: https://dtc.ucsf.edu/types-of-diabetes/type2/understanding-type-2-diabetes/how-the-body-processes-sugar/blood-sugar-stress/

[36] M. Yitshak-Sade, N. Mendelson, V. Novack, S. Codish, and I. F. Liberty, "The association between an increase in glucose levels and armed conflict-related stress: A population-based study," *Scientific Reports*, vol. 10, p. 1710, 2020. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6997375/

[37] E. Jéquier, "Pathways to obesity," *International journal of obesity.*, vol. 26, no. 2, 2002-9. [Online]. Available: https://www.nature.com/articles/0802123

[38] S. K. Garg and H. K. Akturk, "A new era in continuous glucose monitoring: Food and drug administration creates a new category of factory-calibrated nonadjunctive, interoperable class II medical devices,"

Diabetes Technology & Therapeutics, vol. 20, no. 6, pp. 391–394, 2018, publisher: Mary Ann Liebert, Inc., publishers. [Online]. Available: https://www-liebertpub-com.libproxy.aalto.fi/doi/full/10.1089/dia.2018.0142

[39] M. Vettoretti and A. Facchinetti, "Combining continuous glucose monitoring and insulin pumps to automatically tune the basal insulin infusion in diabetes therapy: a review," *BioMedical Engineering OnLine*, vol. 18, no. 1, p. 37, 2019. [Online]. Available: https://doi.org/10.1186/s12938-019-0658-x

[40] The FreeStyle LibreLink app. [Online]. Available: https://www.freestyle.abbott/sa-en/discover-freestyle-libre/Getting-Started-with-FreeStyle-Libre/the-freestyle-librelink-app.html

[41] J. R. Petrie, A. L. Peters, R. M. Bergenstal, R. W. Holl, G. A. Fleming, and L. Heinemann, "Improving the clinical value and utility of CGM systems: Issues and recommendations: A joint statement of the european association for the study of diabetes and the american diabetes association diabetes technology working group," *Diabetes Care*, vol. 40, no. 12, pp. 1614–1621, 2017. [Online]. Available: https://doi.org/10.2337/dci17-0043

[42] G. Schmelzeisen-Redeker, A. Staib, M. Strasser, U. Müller, and M. Schoemaker, "Overview of a novel sensor for continuous glucose monitoring," *Journal of Diabetes Science and Technology*, vol. 7, no. 4, pp. 808–814, 2013. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3879744/

[43] How FreeStyle works - FreeStyle libre | abbott. [Online]. Available: https://www.freestyle.abbott/ph-en/how-freestyle-works.html

[44] C. Cobelli, M. Schiavon, C. Dalla Man, A. Basu, and R. Basu, "Interstitial fluid glucose is not just a shifted-in-time but a distorted mirror of blood glucose: Insight from an in silico study," *Diabetes Technology & Therapeutics*, vol. 18, no. 8, pp. 505–511, 2016, publisher: Mary Ann Liebert, Inc., publishers. [Online]. Available: https://www-liebertpub-com.libproxy.aalto.fi/doi/full/10.1089/dia.2016.0112

[45] M. E. Holmstrup, C. M. Owens, T. J. Fairchild, and J. A. Kanaley, "Effect of meal frequency on glucose and insulin excursions over the course of a day," *e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism*, vol. 5, no. 6, pp. e277–e280, 2010. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1751499110000545

[46] M. Sato, K. Nakamura, H. Ogata, A. Miyashita, S. Nagasaka, N. Omi, S. Yamaguchi, M. Hibi, T. Umeda, S. Nakaji, and K. Tokuyama, "Acute effect of late evening meal on diurnal variation of blood glucose and energy metabolism," *Obesity Research & Clinical Practice*, vol. 5, no. 3, pp. e220–e228, 2011. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1871403X1100007X