



Review

Continuous glucose monitoring in a healthy population: understanding the post-prandial glycemic response in individuals without diabetes mellitus

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ABSTRACT

Continuous glucose monitoring has become a common adjunct in the management of Diabetes Mellitus. However, there has been a recent trend among individuals without diabetes using these devices as a means of monitoring their health. The increased visibility of glucose data has allowed users to study the effect lifestyle has upon post-prandial glucose levels. Although post-prandial hyperglycemia is well understood in the setting of diabetes, its impact in individuals without diabetes is less well defined. This article reviews the factors which contribute to post-prandial hyperglycemia in individuals without diabetes and how the data obtained from continuous glucose monitoring can be used to improve an individual's metabolic health.

1. Introduction

Continuous glucose monitoring (CGM) has become a common adjunct in the management of Diabetes Mellitus (DM). Modern CGMs most commonly combine a system of wearable biosensor paired with a handheld monitor or smartphone application (app). Continuous wear of the glucose biosensor provides the user with detailed information about real-time glucose levels, glucose fluctuations, and other glucose-specific metrics. The introduction of these devices has allowed the management of DM to become individualized as users are offered increased visibility to how their lifestyle choices and habits inherently impact their glucose levels. Individuals become equipped to link food intake, exercise habits, and other behaviors with glucose response and see the real-time impact of adjusting choices accordingly, with the goal of better long-term health outcomes [1].

Increased visibility of glucose data has resulted in a recent trend of individuals without DM using CGM as a means of monitoring their health [2]. One area of interest is the effect of post-prandial hyperglycemia (PPHG) upon the health of individuals with and without DM. Through dietary and lifestyle changes, individuals attempt to minimize PPHG to aid weight loss, optimize mental health, suppress hunger and food cravings, improve sleep, as well as avoid glycemic fluctuations which could lead to chronic disease including cardiovascular disease.

The aim of this review is to examine the topic of PPHG in individuals without DM and how the data obtained from continuous glucose monitoring can be used to improve an individual's metabolic health.

2. Post-prandial hyperglycemia

PPHG is defined as a sharp rise in plasma glucose concentrations following food intake and is influenced by many factors including the timing, quantity and composition of a consumed meal [3]. The state of post-prandial hyperglycemia begins when plasma glucose rises above the level of 140 mg/dL (7.8 mmol/L) 1 to 2 h after ingestion of food in individuals without DM, and >180 mg/dL (10.0 mmol/L) in individuals with DM [4,5]. A degree of fluctuation in blood glucose is common after food intake, especially with meals containing carbohydrate, but broadly speaking, in individuals without DM, glucose levels peak approximately 1 h after the start of a meal and return to baseline within 2 to 3 h [6]. Most meals peak below 140 mg/dL. Comparatively, in individuals with DM, glucose levels frequently exceed 180 mg/dL following food ingestion, and the time to return to pre-meal baseline is dependent upon the subject's diabetic control and treatment regime [6].

In a study of healthy, overweight adults without DM, Chandler-Laney et al. [2014] found individuals who consumed a high-carbohydrate, low-fat diet exhibited more marked PPHG than individuals who

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consumed a low-carbohydrate, high-fat diet. The low-carbohydrate, high-fat diet was associated with a flatter post-prandial glucose curve (i.e. a lower and later nadir in glucose levels following a meal) than the glucose response observed in those individuals partaking in a high-carbohydrate, low-fat diet [7].

Jenkins et al. [1981] described the concept of a 'glycemic index' to provide a numeric classification of carbohydrate-containing foods according to the effect a food has on blood glucose levels after consumption [8]. The higher the glycemic index of a particular food, the greater the rate glucose enters the blood stream. High-glycemic index foods are characterized by higher blood glucose responses of short duration, whereas low-glycemic index foods typically induce a smaller blood glucose response, providing a more even and sustained level of glucose in the post-prandial period. However, the glycemic index is not the only factor which determines PPHG, as the overall glycemic load and the availability of glucose in a food also influences the size and duration of a post-prandial glucose rise. High-glycemic index diets have been associated with an increased likelihood of developing Metabolic Syndrome, a complex constellation of metabolic factors including abdominal obesity, high blood pressure, impaired fasting glucose, high triglyceride levels, and low high-density lipoprotein cholesterol levels [9]. Observational studies suggest that diets with a high glycemic load are independently associated with increased risk of type 2 DM and cardiovascular disease [10–12]. The consumption of reduced glycemic response diets are associated with favorable changes in insulin resistance and hyperinsulinemia, particularly in those individuals with poor fasting blood glucose control [13].

A study where participants consumed standardized meals showed glucose metabolism is highly variable between individuals [14]. Glucose variability was reduced by decreasing the carbohydrate content of the participant's food, the consumption of more complex carbohydrates, and including protein in meals [14].

Meal timing also appears to affect post-prandial glucose levels. A study by Leung et al. in which ten healthy participants were provided with a low-glycemic index meal at 8 AM, 8 PM, and midnight suggested that even when meals were comprised of low-glycemic ingredients, higher glucose and insulin levels were seen at 8 PM and midnight than at 8 AM [15]. Additionally, glucose levels remained elevated for a longer duration during the evening hours compared to the 8 AM feeding. Similarly, Takahashi et al. described the effect of meal timing on 19 subjects' post-prandial glucose levels. In controlled conditions, evening meals and morning meals of identical composition were presented to the subjects. After 10–15 min, 30 min, 60 min and 120 min, intravenous blood was collected and assessed for blood glucose and insulin levels. Post-prandial glucose was observed to be elevated in the evening meals in comparison to the morning meals [16]. These studies suggest that insulin sensitivity is tied to circadian rhythms, being greater in the morning and lower in the evening.

The hypothalamus plays a critical role in blood glucose homeostasis [17]. Nuclei within the hypothalamus are involved in circadian timing, as well as control of the autonomic nervous system and energy homeostasis [18]. A reduction in early-morning brain dopaminergic signaling and hypothalamic sympathetic tone are thought to be contributory factors in the development of PPHG. The administration of the rapid-acting drug, bromocriptine, has been shown to correct this deficiency and improve glycemic control [19].

The shape of the glucose response curve may be as important as the absolute height. In metabolically healthy individuals, the glucose curve tends to be biphasic, defined as a curve that shows a peak around 30–60 min after a meal, which then decreases but is followed by another elevation 90–120 min after the meal. A biphasic curve is metabolically preferable over a monophasic curve. Recent research demonstrated that the incidence of metabolic dysfunction is higher in individuals with monophasic glucose curves, with these individuals having lower insulin sensitivity, lower beta-cell function, and a higher prevalence of Metabolic Syndrome and prediabetes [20]. A separate study concurs with an

increased health risk following a monophasic response. This study assessed the shape of the glucose curve following an oral glucose tolerance test and observed two distinct groups in glucose response and tolerance. The first group demonstrated a biphasic response to glucose intake and displayed normal glucose tolerance. The second group demonstrated a monophasic response suggestive of impaired glucose tolerance. The individuals who displayed a biphasic curve had a higher likelihood of normal glucose tolerance, and they were also more likely to be younger, with a lower Body Mass Index (BMI), a lower fasting plasma glucose, and a lower hemoglobin A1c (HbA1c) concentration [21]. The phenomenon of monophasic versus biphasic glucose response curves following oral glucose tolerance test has been further demonstrated in individuals with type II DM [22], with the monophasic glucose curve being most common in this patient group. This suggests that the development of a monophasic glucose curve may be an early sign of β -cell function even in asymptomatic individuals.

2.1. Gut microbiome

Links between composition of the gut microbiome and an individual's metabolism have recently been established. Biomarkers of obesity, blood markers of cardiovascular disease, and impaired glucose tolerance are strongly associated with the composition of the microbiome [23]. Intestinal species associated with healthy dietary habits overlapped with those associated with favorable cardiometabolic and postprandial markers. Some microbes such as *Prevotella copri* and *Blas-tocystis* spp., have been shown to be indicators of favorable postprandial glucose metabolism [23].

Diet plays a significant role in shaping the microbiome, and diets high in fiber and prebiotics are associated with the development of a healthy microbiome which has been linked to improved glucose metabolism [24,25]. Zhang et al. [2021] demonstrated butyrate, a short-chain fatty acid (SCFA) and a main product of gut microbial fermentation, is an important mediator of gut microbiota regulation and effects thermogenesis, lipid and glucose metabolism, appetite, and inflammation within an individual [26].

Interestingly, artificial sweeteners commonly used as an alternative to sugar were introduced to help reduce insulin resistance and obesity, but data from animal and human studies suggest that they may impact the microbiome adversely, leading to decreased satiety, altered glucose homeostasis and are ultimately associated with increased caloric consumption and weight gain [27].

The addition of a greater quantity and variety of vegetables to the diet increases fiber intake. The fiber in non-starchy vegetables provides bulk volume to a meal, increasing satiety but it also plays a role as a prebiotic. The fiber ferments in the gut and increases the amount of helpful gut bacteria, which produce beneficial molecules such as butyrate. This appears to play an important role in improving metabolic health with further glucose homeostasis, weight loss and appetite management [28]. SCFAs, such as butyrate, formed in the gut lumen by the microbiome, play an important role in the complex interplay between diet and glucose metabolism. The discovery of SCFA receptors, across a range of cell and tissue types has led to an increased interest in the role of SCFA as signaling molecules between the gut microbiota and the host's health [28].

3. Reactive hypoglycemia

The link between blood glucose and appetite was first described by Mayer in 1953 [29]. It is hypothesized that inadequate glucose delivery to the brain activates neural pathways which drive feeding along with other wide-ranging neuroendocrine and autonomic responses. Wyatt et al. [2021] demonstrated the size of the post-prandial dip in blood glucose predicts the degree of hunger and the subsequent number of calories consumed [30].

Lower glycemic index foods typically induce a less pronounced and

more sustained post-prandial peak glucose response, hence counteracting the reactive hypoglycemia often seen with high-glycemic index foods in the late post-prandial phase [31].

Reactive hypoglycemia refers to blood glucose levels below 70 mg/dL (3.9 mmol/L), occurring in the post-prandial period [32]. This state typically occurs within 4 h of eating and is included within this review as it tends to follow periods of PPHG; a large rise in post-prandial glucose leads to an excess of insulin being released, resulting in a transient period of mild hypoglycemia with the individual sometimes experiencing symptoms such as hunger, anxiety, dizziness and sweating. Reactive hypoglycemia is unlikely to be a healthy phenomenon and is more probably an early marker of impaired beta cell function and reduced insulin sensitivity [33].

A study using functional magnetic resonance imaging (fMRI) demonstrated that mild hypoglycemia preferentially activates the limbic-striatal regions of the brain in response to food cues, producing a greater desire for high-calorie foods. In contrast, the investigators found euglycemia preferentially activates the medial prefrontal cortex, resulting in less interest in food stimuli [33]. Consequently, flattening the post-prandial glucose rise by reducing the carbohydrate load, and proportionally increasing intake of protein and fats appears to reduce the incidence of reactive hypoglycemia.

4. Role of continuous glucose monitoring in a healthy population

Continuous Glucose Monitoring (CGM) refers to a medical device which measures glucose levels in dermal interstitial fluid. These levels correspond closely with blood glucose concentrations. Typically employing the use of a sensor or biosensor applied to the back of the upper arm or abdomen, CGM devices provide glucose concentration measurements in an almost continuous fashion for several consecutive days. Due to their wearable, minimally invasive nature, CGM sensors have revolutionized the management of DM. Given their success in DM, many health practitioners have begun to utilize CGMS to better understand the glucose response and the wider metabolic health of individuals without DM.

CGM allows measurement of glucose fluctuations over time. This glucose variability increases during the post-prandial period as nutrients are absorbed from the gut. The carbohydrate load of the food consumed, and its glycemic index contribute to the glycemic variability. These are further modified by an individual's hormonal status, stress levels, metabolic health, intercurrent illness and exercise. Glycemic variation is usually described as a coefficient of variation, with a value below 20 % being considered normal in healthy individuals [34].

In a study of healthy, non-diabetes, non-pregnant individuals, Shah et al. [2019] studied 153 participants using CGM [35]. They found the mean average glucose was 98 to 99 mg/dL (5.4 to 5.5 mmol/L) for all age groups except those over 60 years, in whom the mean average glucose was 104 mg/dL (5.8 mmol/L). The median time spent in the range between 70 and 140 mg/dL (3.9 to 7.8 mmol/L) was 96 % (interquartile range, 93 to 98 %). The median time spent with glucose levels >140 mg/dL was 2.1 % (approximately 30 min/day), and the median time spent with glucose levels <70 mg/dL (3.9 mmol/L) was 1.1 % (approximately 15 min/day).

Freckmann et al. [2007] studied the 24-hour interstitial glucose concentrations under everyday life conditions in 21 healthy individuals and found the highest postprandial glucose concentrations were observed following breakfast: 132.3 ± 16.7 mg/dL (7.4 ± 0.9 mmol/L). Peak concentrations after lunch and dinner were 118.2 ± 13.4 (6.6 ± 0.7 mmol/L) and 123.0 ± 16.9 mg/dL (6.8 ± 0.9 mmol/L) respectively [36].

A study of 1002 healthy adults by Berry et al. [2021] demonstrated large inter-individual variability in post-prandial responses of blood glucose, triglyceride and insulin between subjects following standardized meals. Person-specific factors, such as gut microbiota and genetic

variation, appear to play a role in an individual's post-prandial response to food [37].

Hall et al. [2018] examined the post-prandial glucose patterns of 57 subjects without a diagnosis of DM [14]. The authors identified three distinct glucotypes of increasing variability (low, moderate, and severe) following an identical nutrient challenge, suggesting there is likely to be considerable interpersonal variation in post-prandial glucose metabolism. Similarly, Krishnan et al. [2012] demonstrated three patterns of glucose variability in pre-menopausal women without DM [38]. This suggests phenotyping the glycemic profile of healthy individuals may be a useful method for detecting subclinical metabolic dysfunction.

A study investigating the potential benefit of CGM in an adult population by Dehghani Zahedani et al. [2021] tracked the glucose levels of 448 individuals without DM and 192 individuals with DM [39]. Participants logged food intake and physical activity and compared these with continuous glucose and heart rate data. A smartphone-based app provided feedback to participants, overlaying daily glucose patterns with their activity and information regarding their food intake, including macronutrient breakdown, glycemic load, and glycemic index. CGM identified glucose excursions into the diabetic range among 15 % of healthy people and 36 % of those with prediabetes. 51.4 % of participants improved their Time-in-Range (TIR), defined as 54–140 mg/dL for healthy and prediabetes and 54–180 mg/dL for type II DM; TIR improved by an average of 6.4 % ($p < 0.001$) over 10 days of CGM use. Among non-diabetes individuals with poor TIR (<83 %) at baseline ($n = 24$), 91.7 % showed TIR improvement with a mean TIR increase of 23.2 %. These results suggest that CGM, as a part of multimodal data collection with synthesis and feedback via a smartphone app, can significantly reduce hyperglycemia in non-insulin-treated individuals, including those with early stages of glucose dysregulation.

These findings suggest that while one-size-fits-all dietary guidelines for healthy eating may not adequately meet the metabolic needs of an individual, CGM-guided personalized nutrition, which tailors food consumption to an individual's unique metabolic requirements and glycemic response, may offer health benefits.

5. Long-term consequence of post-prandial hyperglycemia

Recurrent large glucose excursions, such as those that occur in PPHG, lead to insulin resistance and hyperinsulinemia. In turn, these lead to changes in glucose and lipid metabolism [40]. Post-prandial glucose excursions have been shown to induce endothelial dysfunction, inflammatory reactions and oxidative stress, unlike high fasting-glucose levels alone, and have been linked to the development of atherosclerosis and the occurrence of cardiovascular events [3].

Sasso et al. [2004] showed a linear relationship between post-load plasma glucose levels in patients with normal glucose tolerance and the number of stenosed coronary arteries at angiography [41]. This supports the concept that post-prandial glucose levels are an independent risk factor for cardiovascular disease, exerting a greater effect than fasting or baseline glucose levels [42]. Mortality data from nearly 20 years of follow-up has shown that individuals in the highest quintile of two-hour post-prandial glucose response had a risk of mortality of 2.7 times that of individuals in the lowest quintile [43]. Similarly, Oesterle et al. [2022] demonstrated an association between PPHG and the risk of developing heart failure [44] and Brutsaert et al. [2016] identified a link between PPHG and an increased Atherosclerotic Cardiovascular Disease risk score (ASCVD) [45,46].

Cereillo et al. [2008] utilized euinsulinemic, hyperglycemic clamp in diabetic and normal subjects and found glucose levels between 180 mg/dL and 270 mg/dL (10.0 and 15.0 mmol/L) resulted in a concentration-dependent induction of endothelial dysfunction and oxidative stress even in non-diabetes subjects [47]. In addition, the authors demonstrated oscillating blood glucose has more deleterious effects than constant high glucose on endothelial function and oxidative stress.

Oxidative stress due to PPHG is proportional to the magnitude of

glucose excursion after a meal [48]. This transient increase in free radicals acutely triggers inflammation, endothelial dysfunction, hypercoagulability, sympathetic hyperactivity, and a cascade of other atherogenic changes. Studies have demonstrated blunting of the post-prandial glucose and lipid response immediately improves inflammation and endothelial function. Randomized controlled trials indicate that reducing post-prandial dysmetabolism appears to significantly slow atherosclerotic progression and may improve cardiovascular prognosis [48].

Pellegrini et al. [2022] studied the effect of PPHG on atrial fibrillation in an elderly population (age 77.7 $\pm$ 4.4). Abnormal glucose metabolism following an oral glucose tolerance test at baseline was associated with a 10 % higher risk of developing atrial fibrillation per standard deviation increment over a median follow-up period of 11.4 years. Fasting glucose levels and non-esterified fatty acid measures at baseline showed no association with the subsequent development of atrial fibrillation. Similarly, post-prandial glucose levels are associated with increased cardiovascular disease and mortality [49].

The appropriate range for glucose levels in individuals without DM is a topic of debate. According to the American Diabetes Association, a glucose level <140 mg/dL (7.8 mmol/L) 2 h after an oral glucose tolerance test is considered healthy for a non-DM population [50]. Bermingham et al. [2021] used a “normal” range of 70–140 mg/dL (3.9–7.8 mmol/L) to examine time in range for healthy individuals [51]. No significant differences in either HbA1c and ASCVD or HbA1c between the top and bottom quintiles of the population were identified. However, when a target range of 70–100 mg/dL (3.9–5.6 mmol/L) was applied as the range for the TIR measure, ASCVD risk and HbA1c was significantly higher in the top versus bottom quintile ($p = 0.0005$ and 0.0002 respectively) suggesting this lower range may be a more appropriate measure for optimal health. Additionally, although HbA1c represents a time-average measure of glycemia, it reveals little information about the extent or frequency of post-prandial glucose excursions. Consequently, HbA1c is a poor means of assessing PPHG [52]. The continuous nature of the glucose levels reported by CGM provides a better measure of predicting the likelihood of individuals developing microvascular and macrovascular complications.

1,5-anhydroglucitol (1,5-AG) is a monosaccharide biomarker for measuring acute hyperglycemia and glucose excursion over a one to three day to two-week period. This test could provide an alternative to HbA1c in studying PPHG. In acute hyperglycemia, renal reabsorption of 1,5-AG is inhibited by glucose so it is excreted in the urine, while its serum level decreases rapidly [53]. In this regard, low levels of serum 1,5-AG can be used as a marker of short-term glycemic derangements, such as PPHG, and could potentially be used as an alternative to CGM for measuring glucose excursions in individuals without DM. However, this would not provide real-time, actionable information relating to glucose as one would see with CGM.

6. Factors affecting post-prandial glucose response

At an individual level, several factors appear to affect an individual's post-prandial glycemic response. These are summarized in Table 1.

7. Methods for reducing post-prandial hyperglycemia

González-Rodríguez et al. [2019] used CGM to examine a population of 148 individuals without DM and reported a higher intake of carbohydrates corresponded to a significantly higher post-prandial glycemic response [67]. Investigators noted as fat intake increased, a flattening of the post-prandial glycemic curve was observed, and a significantly lower glycemic response was observed in individuals whose fiber intake during mealtimes was higher. Mendes-Soares et al. [2019] demonstrated providing individuals with tools to manage their glycemic responses may allow them to reduce the incidence of PPHG and maintain their blood glucose levels within limits associated with good health [71].

Table 1

Factors affecting post-prandial glucose response.

Individual characteristics
Age [54]
Body Mass Index (BMI) [55]
Pre vs. Peri vs. Post-Menopause Status in Women [56]
Genetic Factors impacting beta cell performance [57] and insulin sensitivity [58]
Gut Microbiome [59,60]
Lifestyle
Activity/Exercise [61]
Timing of meals/Time Fasting [62]
Sleep timing/duration/quality [63]
Morning dopamine action/Sympathetic tone [64]
Lifestyle factors impacting insulin sensitivity
Smoking [65]
Stress/Cortisol [66]
Dietary composition
Glycemic Load [8,9]
Glycemic Index [8,9]
Amount and quality of other nutrients: proteins and fats [67]
Dietary factors impacting insulin sensitivity
Chemical/pharmacological
Medications: β -blockers, thiazide diuretics, corticosteroids, and statins [68,69]
Caffeine [70]

Similarly, Chekima et al. [2022] showed the continuous glycemic information provided by CGM could serve as an effective educational tool which motivates eating behavior changes among overweight and obese young adults [72].

Meal timing influences an individual's glycemic response. Tsereteli et al. [2022] demonstrated poor sleep and a later-than-usual sleep time are associated with more pronounced PPHG in response to the following morning's breakfast [63]. Similarly, levels of the stress hormone cortisol correlated with increased PPHG as well as with other markers of poor health such as higher HbA1c and higher blood pressure [73].

Physical activity following a meal has been shown to be an effective way of decreasing post-prandial glucose excursions [74–80]. In addition, the direct feedback and visualization of success provided by CGM appears to be a strong motivating factor for individuals to undertake regular physical activity [81,82]. Frampton et al. [2022] demonstrated acute aerobic exercise performed in the post-prandial period decreased glucose and insulin concentrations in healthy adults [83]. Effective physical activity for reducing PPHG includes low-intensity regimes such as walking but can also be as modest as “soleus push-ups” while seated [84].

Counter-intuitively, cessation of smoking is often associated with worsening insulin resistance and worsening PPHG, with an increased risk of type II DM [85]. This occurs during the initial months following smoking abstinence and appears to be, partially at least, secondary to dietary changes and weight gain experienced by many individuals who stop smoking. These effects seem to resolve within two years of smoking cessation. Therefore, it is important to educate individuals who stop smoking about the necessity of regulating food consumption and controlling weight during smoking cessation.

Espeland et al. [1998] demonstrated an improvement in glucose kinetics and insulin sensitivity for post-menopausal women commenced on estrogen-replacement therapy compared with those taking placebo [86].

8. Additional benefits of flattening post-prandial hyperglycemic episodes

The use of CGM in individuals without DM is a fledgling area of research, however, interest in this area is growing. Irrespective of whether CGM or another scientific method was used to evaluate glycemic response, fewer glucose excursions have been linked to several health benefits in addition to reducing long-term cardiovascular risk.

8.1. Aid to weight loss

In a study of overweight young adults ($n = 40$), Chekima et al. [2022] demonstrated that individuals with access to CGM data, improved their body weight, Body Mass Index (BMI), fat mass, fasting plasma glucose, HbA1c, total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol more than individuals not using CGM after eight weeks, suggesting that participants were able to use CGM as a real-time feedback device or motivational tool for improving their behavior [87]. The GLYNDIET study, a six month randomized, parallel, controlled clinical trial conducted in 122 overweight and obese adults, showed a low-glycemic index and energy-restricted diet containing moderate amounts of carbohydrates was more effective than a high-glycemic index and low-fat diet at reducing body weight and controlling glucose and insulin [88]. During the first twelve weeks of the study, no significant differences in body weight were observed between groups, but at weeks 16, 20, and 24, decreases in BMI were higher in the low-glycemic index-diet group. Similarly, Yancy et al. [2004] studied 120 generally healthy, overweight individuals, comparing the effect of a low-carbohydrate diet and a low-fat diet. Over a 24-week period, the mean body weight reduction of 12.0 kg was seen in the low-carbohydrate diet group compared with 6.5 kg in the low-fat diet group [89].

A 2013 meta-analysis identified 13 randomized controlled studies which examined the effectiveness of the low-carbohydrate diet in promoting weight loss when compared with a low-fat diet. Individuals assigned to a low-carbohydrate diet achieve significantly greater weight loss than those assigned to a low-fat diet with one year or longer follow-up ($n = 1415$) [90].

8.2. Reduction in hunger

In a study evaluating the role of glycemic load on hunger, Chang et al. [2017] determined that a diet with a lower glycemic load is associated with less hunger than one with a higher glycemic load [91]. Wyatt et al. [2021] demonstrated the size of the post-prandial dip in CGM-measured glucose which follows the PPHG rise predicts the degree of hunger and the number of subsequent calories consumed [30].

8.3. Improvements in mental health

A study of 82 individuals by Breymeyer et al. [2016] explored the effect of glycemic load upon mood and demonstrated the consumption of a high-glycemic load diet resulted in a 38 % higher score for depressive symptoms compared with a low-glycemic load diet as well as a 55 % higher score for total mood disturbance, and a 26 % higher score for fatigue and inertia. Symptoms were most noticeable in overweight and obese individuals [92].

With the understanding that macronutrient composition is known to modify endocrine signals, Strang et al. [2017] demonstrated that alterations in macronutrients modulate human social behavior. Specifically, in a study of 24 young adult male subjects, breakfasts with a high carbohydrate to protein ratio (~80 % carbohydrate: 20 % protein) increased adverse behaviors compared with that in response to a lower carbohydrate/protein meal (~50 % carbohydrate: 25 % protein) [93].

In a multi-decade observational study of 3307 participants, Bancks et al. [2018] showed that despite being below the threshold for DM,

greater glycemic variation during young adulthood is associated with worse mental processing speed, memory, and language fluency in middle age, independent of fasting glucose levels [94].

Nilsson et al. [2009] demonstrated in 40 adults aged 49–70 that subjects with higher glucose tolerance performed better in the cognitive tests after a low-glycemic index breakfast compared with a high-glycemic index breakfast [95].

8.4. Improved sleep quality

A systematic review published in 2022 explored the relationship of glycemic index on sleep quality. Ten studies were identified - six with clinical trial and four with cross-sectional design. Among the six clinical trials, three indicated a significant effect of high glycemic index on sleep (two in young male athletes ($N = 8$ and $N = 9$) and one in adults ($N = 8$), while three others failed to detect any significant effect (young males ($N = 12$)). Among the cross-sectional studies, high glycemic index meals were associated with improved sleep duration or quality in two studies (1848 adults), however, contrastingly, high glycemic index diet was associated with sleep disturbances in other groups (108 students and 53,069 postmenopausal women). This suggests high glycemic index foods may influence sleep latency, duration and quality in some individuals, however, glucose is only one of many factors which influence sleep [96].

A CGM study of 104 adults without DM demonstrated sleep duration was negatively correlated with blood glucose levels ($p = 0.032$) [97]. A diet high in sugar, starch and refined grains is associated with higher rates of insomnia. In contrast, a diet higher in fruit and vegetables, dietary fiber and whole grains was associated with significantly improved sleep [98]. Tsereteli et al. [2021] showed that poor sleep and later bedtime routines are associated with more pronounced PPHG responses to breakfast the following morning as measured by CGM ($n = 953$). In addition, deviation from an individual's typical bedtime routine and sleep pattern was also associated with poorer post-prandial glycemic control [69].

9. Interventions to reduce post-prandial hyperglycemia

9.1. Diet

Freckmann et al. [2007] analyzed the continuous glucose profiles of individuals without DM and demonstrated that differences in meal composition are reflected in postprandial interstitial glucose concentrations, suggesting PPHG can be blunted by dietary adjustment [36].

A diet consisting of a greater proportion of calories from protein and fat with a reduction in carbohydrates has been shown to facilitate steady glucose levels. While capable of supporting gluconeogenesis, protein alone has been found to impart minimal impact on glucose levels. Protein has a slower rate of digestion when compared to carbohydrate, consequently, a diet rich in protein can support steadier glucose absorption and can reduce PPHG [99].

Consumption of healthy fats supports lipolysis, can reduce hunger while providing satiation, and supports the absorption of fat-soluble vitamins. Healthy fats do not include trans fats or oxidized fats. All other edible fats can be part of a healthy diet, including saturated fatty acids, monounsaturated fatty acids and polyunsaturated fatty acids [100].

Globally, the intake of vegetables falls far below recommended intake even though the addition of nutrient-rich vegetables at the beginning of a meal physically slows intake, reduces overall caloric consumption, occupies stomach share that would otherwise be taken by more calorically dense foods as well as carbohydrate-containing foods. Combining vegetables with fat improves taste, increases vitamin absorption, and reduces hunger [101]. Zeevi et al. [2015] suggest personalized diets may influence an individual's microbiota and modify the post-prandial glucose response and its metabolic consequences

[102].

Meal frequency has been shown to impact PPHG in individuals without DM. In a randomized, crossover comparison study of 18 individuals, Hibi et al. [2019] evaluated effects of meal frequency on blood glucose levels and glucose metabolism. Subjects were provided isocaloric high carbohydrate (55 %) diets, divided across nine eating occasions or three eating occasions each day. The group provided with an isocaloric diet three times a day had higher daytime maximum blood glucose levels, a wider glucose range, greater duration of glucose levels ≥ 180 mg/dL, and higher night-time maximum glucose levels than those provided with an isocaloric diet nine times a day [103]. Those receiving meals nine times a day demonstrated significantly improved glucose metabolism than those receiving meals three times a day. The authors hypothesize this may be due to increased glucagon-like peptide secretion and could improve insulin secretion in those receiving more frequent meals. However, other authors suggest shortening the daily eating window, from a typical 14-hours a day frequently observed in obese and overweight individuals to 8 to 10 h per day to allow for a longer overnight fast during which glucose and insulin are more likely to be low and stable [104,105].

9.2. Physical activity

Fat oxidation is the body's primary fuel at rest and during low-intensity exercise with a shift towards an increased reliance on glucose oxidation at moderate to high exercise intensities [106]. Exercise also increases muscle glucose uptake via glucose transporter type 4 (GLUT4) translocation [61]. Thus, the incorporation of exercise can offset a significant rise in glucose levels and benefits the user by supporting the maintenance and accretion of muscle.

Lunde et al. [2012] showed that peak blood glucose values in the post-prandial period and the incremental area under the two-hour blood glucose curve decreased following the introduction of a slow walk following a meal [107]. In addition, these changes in glucose metabolism were associated with a reduction in blood pressure. Similarly, other authors have demonstrated the blunting effect the introduction of exercise has on PPHG [108].

Physical Activity Guidelines for Americans set by the U.S. Department of Health and Human Services encouraging individuals to move more during the day and after meals assists individuals in reaching the goal that adults should have a minimum of between 150 min and 300 min of moderate-intensity aerobic exercise and a minimum of between 75 min and 150 min vigorous-intensity aerobic exercise during the week [109].

Ehrhardt et al. [2020] surveyed 40 CGM users with prediabetes or DM. 90 % of these felt that CGM use contributed to a healthier lifestyle. 47 % of CGM users reported being more likely to go for a walk or undertake physical activity if they saw a rise in their glucose levels. 87 % of CGM users felt they modified their food choices based on CGM use [110]. There is no reason to believe that CGM only functions as a behavior modification tool in individuals with DM, and it will be interesting to see if these findings can be duplicated in CGM users without DM. In a randomized controlled trial, Martens et al. [2021] studied the impact of CGM use among individuals with type II DM receiving basal insulin. CGM use was associated with significantly greater decrease in HbA1c levels over eight months than blood glucose meter use, further supporting the notion that CGM use leads to positive behavior change [111].

10. Discussion

The introduction of CGM has revolutionized the management of DM and has shown promise in improving general health and wellness across a variety of healthy populations. It is expected that these devices will evolve to empower a greater population to better understand the unique impacts that diet, exercise, and lifestyle habits have on an individual's

metabolic health.

The identification of three distinct glucotypes by Hall et al. shows that glucose dysregulation is more prevalent and heterogeneous than previously thought, even affecting individuals considered normoglycemic by standard measures [14]. The inter-individual variability of glycemic responses to standardized meals highlights the personal nature of glucose regulation and how it can affect individuals who are asymptomatic. Based on the published evidence, we suggest most adults could potentially benefit from wearing a CGM, at least for a two-to-four-week period, to better understand their glucotype and recognise how different foods affect their own glycemic response.

In addition to reducing the long-term risk of cardiovascular disease such as coronary artery disease and stroke, there is evidence to support controlling post-prandial glucose excursions for weight loss, optimized mental health, suppressed hunger, and improved sleep.

It should be noted that although the individuals recruited into the studies described above may not have had a formal diagnosis of DM, some may have had impaired glucose tolerance, insulin resistance and hyperinsulinemia. Such subclinical conditions are widespread in the general so-called "healthy" population. Similarly, the beneficial effects seen by the investigators could be influenced by other salutary effects such as weight loss, improved insulin sensitivity and improved diet over the course of the study. Nonetheless, CGM appears to be a useful tool for tracking an individual's post-prandial glycemic response by allowing them to observe the impact of their diet upon their glucose levels and adjust their diet accordingly. This personalization of an individual's nutrition is something which is overlooked by current published guidelines and is not practical on a large scale using episodic blood testing. Without the visibility of the glycemic response in real-time, it is unlikely adherence to dietary recommendations will be as high.

With the provision of real-time, continuous glucose data, it is expected that CGMs will help broaden our knowledge of the impact of PPHG in individuals without DM. Offering improved treatments for a variety of metabolic disease states, and ultimately playing a key role in improving the health of the entire population.

10.1. Areas for further research

Hyperglycemia is a pro-inflammatory state [112], and there is growing evidence linking reduced PPHG and glycemic variability with improved health in individuals without DM. In vivo and in vitro studies have demonstrated that glycemic variability is associated with greater reactive oxygen species production and vascular damage and explains why DM is associated with a two to three-fold increase in the risk of cardiovascular disease when compared with a healthy population [113]. However, to date, there have been no randomized clinical trials to quantify this relationship in individuals without DM. Consequently, the frequency and magnitude of glucose excursions sufficient to cause harm in a healthy population needs to be established.

It is unlikely glucose causes vascular dysfunction only above levels >140 mg/dL (>7.8 mmol/L) in individuals without DM or >180 mg/dL (>10.0 mmol/L) in those with DM. The 140 (7.8 mmol/L) and 180 mg/dL (10.0 mmol/L) cut-points for PPHG are designed for glucose management in DM and are unlikely to represent risk thresholds. It is more plausible that overall glucose exposure and the severity of post-prandial glucose excursions are likely to be harmful across a continuum of responses. Studies are required to further evaluate this hypothesis. As a result, the desirable glucose range, TIR and average glucose values need to be quantified for a population without DM.

Ehrhardt and colleagues' demonstration of CGM being used to influence dietary choices and encourage exercise in a population consisting of individuals with either prediabetes or DM would suggest similar benefit could be seen in healthy individuals [110]. Exploration of the role of CGM as a tool for behavioral change needs to be explored in individuals without DM.

It is clear that the gut microbiome plays a significant role in glucose

metabolism. Further research is required to identify which are the best biomarkers for monitoring the health of the microbiome and to further understand how it influences glucose metabolism.

The monosaccharide biomarker 1,5-anhydroglucitol (1,5-AG) offers an alternative to CGM for measuring acute hyperglycemia and glucose excursion. Studies are required to evaluate whether one of these methods offers any additional benefit over the other.

10.2. The future for CGM use in individuals without diabetes

The importance of metabolic health and preventative medicine has become significant areas of research in the last decade. There is a growing body of evidence showing the benefits of an individual managing their glucose profile through lifestyle adaptations. Until the health benefits of using this technology are widely accepted, it is likely the funding of this technology will be via out-of-pocket expenses paid by the user. It is our contention that CGM offers a convenient, minimally-invasive means of improving an individual's health and wellbeing, and in the future, this technology could be widely available over-the-counter, recommended by physicians, and reimbursed by insurance coverage for uses beyond DM.

Currently, the accepted boundaries for blood glucose excursions are based primarily on thresholds used in the management of DM. Further research is required to demonstrate the appropriate boundaries for individuals without DM, and the relevance of TIR and average blood glucose need to be established. Most people with prediabetes and/or Metabolic Syndrome already have a degree of insulin resistance and hyperinsulinemia [114,115]. Currently, hyperinsulinemia is not classified as a disease unlike other endocrine disorders such as hyperthyroidism or hyperadrenalinism. We believe PPHG in a non-DM population is a visible symptom of early hyperinsulinemia. CGM provides a much more accessible method for ongoing measurement rather than episodic blood draws for insulin levels which are not frequent enough to be actionable or provide feedback following dietary behavior changes.

CGM technology has the ability to report a glucose level as frequently as every minute, similar to what is seen in the CGM management of DM. The frequency of these readings empowers the user to make real-time adjustments to their lifestyle, either through dietary correction or exercise. As the vascular endothelial damage associated with hyperglycemia is likely to be dose dependent, we propose that dietary and lifestyle changes should be used to reduce an individual's overall glucose exposure. The primary benefit of CGM over other methods of episodic blood glucose testing or other forms of assessing glucose homeostasis and endothelial inflammation is the provision of real-time feedback to drive behavior changes as well as convenience to the user, transferring some of the responsibility for an individual's health data and health intervention from the physician to the individual. It is our contention that physicians should be involved in managing an individual's wellness as a means of disease prevention as much as they are involved in disease management. As interested patients share their CGM findings with their healthcare providers, opportunities for follow-up testing outside of current practice guidelines could yield valuable insights for the detection of early subclinical disease progression. These include blood insulin levels, a marker of endocrine dysfunction that can precede diabetes and even pre-diabetes [116], high sensitivity C-reactive protein (hsCRP) as a marker of current inflammation [117], and coronary artery calcium scanning which uses low-dose radiation to quantify atherosclerotic disease [118]. Other markers of endothelial damage and inflammation, while widely used in research are rarely used in clinical practice [119].

10.3. Strengths and weaknesses

The strength of this article is that it is the first review of CGM use in general health and wellness to focus on postprandial hyperglycaemia and to connect the CGM technology opportunity to the broader literature on PPHG in non-diabetes populations. Among its weaknesses, the

paper is not a systematic review nor a meta-analysis. Its references are not exhaustive. For a more complete set of citations, we direct readers to the review of PPHG by Blaak et al. from 2012 with its 464 references [31]. Additionally, few studies to date have examined prospective health outcomes in a randomized controlled trial where participants use access to CGM data and guidance to make behavioral change in their nutrition, exercise, and lifestyle. We expect to see such studies performed in the next several years so that a future review may be able to make more definitive statements about the effects of CGM in a healthy population rather than relying on the many associated studies provided here.

11. Conclusion

To date, most of the research in the area of PPHG has been in the context of DM, and further studies in the setting of metabolic health in the absence of overt disease is required to improve understanding of PPHG and to raise awareness of its impact on general health and wellbeing.

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Data availability

Not applicable.

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