# Continuous Glucose Monitoring and 1-hour Plasma Glucose Identifies Glycemic Variability and Dysglycemia in High-Risk Individuals with HbA1c <5.7%

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**Short Report**

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# Abstract

**Purpose:** Although commonly used, HbA1c is insensitive for diagnosing prediabetes and diabetes. Glycemic variability (GV) or a 1-hour plasma glucose level (1-h PG) ≥ 155 mg/dL (8.6 mmol/L) during a 75-gram oral glucose tolerance test (OGTT) better identifies individuals with dysglycemia. The objectives were to (1) compare continuous glucose monitoring (CGM) with the OGTT for detecting dysglycemia in high-risk subjects with HbA1c < 5.7% (39 mmol/mol), and (2) correlate the 1-h PG with CGM-derived GV indices.

**Research Design and Methods:** Subjects (n=15) with a HbA1c < 5.7% (39 mmol/mol) and at least one other risk factor for type 2 diabetes such as overweight, obesity, hypertension, or hyperlipidemia were recruited. A 2-h OGTT was performed within 3-7 days of CGM insertion, which was worn up to 14 days.

**Results:** The average age was 50 ± 14 years, with the majority of participants being men (80%) and Caucasian (67%). The mean HbA1c was 5.3±0.2% (34 mmol/mol). The 1-h PG was highly correlated with 1-h CGM glucose levels ($\rho$=0.881, p<0.001) as well GV indices: mean amplitude of glucose excursions ($\rho$ =0.67, p<0.01), standard deviation ($\rho$=0.79, p<0.01), and lability index ($\rho$ =0.64, p=0.001).

**Conclusion:** 1-h interstitial CGM glucose and 1-h PG can detect dysglycemia in high-risk subjects with HbA1c < 5.7% (39 mmol/mol). CGM may be an alternative screening tool for glucose disorders.


# Introduction

The global incidence and prevalence of diabetes continue to rise [1]. Hence, identifying individuals at high-risk for prediabetes and type 2 diabetes is paramount. As glucose levels increase insidiously in the progression from normal glucose tolerance to prediabetes and diabetes, early identification of high-risk individuals could result in the prescription of lifestyle interventions to decrease progression to type 2 diabetes. HbA1c is widely used to screen for prediabetes (5.7% – 6.4% [39–46 mmol/mol]) and type 2 diabetes (≥ 6.5% [48 mmol/mol]) [2]. However, HbA1c has poor sensitivity in identifying early β-cell dysfunction [3]. Individuals with prediabetes, already on the accelerated slope of the glucose trajectory, are diagnosed too late in the progression to T2D when significant β-cell dysfunction has already occurred. Increased 1-h plasma glucose (1-h PG) ≥ 155 mg/dL (8.6 mmol/L) during a 75-gram OGTT is more predictive than HbA1c or 2-h PG for future development of diabetes, complications and mortality [4–6]. However, measurement of the 1-h PG during the OGTT requires fasting. In addition, plasma glucose (PG) levels can become unstable if specimens are not properly handled [7]. A potential alternative approach for detecting early β-cell dysfunction is implementation of continuous glucose monitoring (CGM) during an OGTT. CGM can identify increased glycemic variability (GV), an index of glucose fluctuation, in patients with T2D [8]. However, it is unclear if CGM can detect GV in high risk subjects without diabetes or with HbA1c < 5.7% (39 mmol/mol).

In this study, we compared PG and CGM interstitial glucose levels during an OGTT and analyzed whether 1-h PG and GV indices correlated [9]. Finally, we analyzed CGM GV indices during a 2-week period when

subjects were engaged in real-life activities.

## Methods

# 2.1. Subjects

This was a single-center, prospective study that enrolled 18 subjects. The IRB of NYU Grossman School of Medicine approved this study and written informed consent was obtained from each participant. Inclusion criteria included adults ≥ 18 and < 75 years of age, baseline HbA1c < 5.7% (39 mmol/L), no previous history of prediabetes or type 2 diabetes and one or more of the following conditions: overweight or obese (BMI > 25 kg/$m^2$), non-alcoholic fatty liver disease, history of gestational diabetes mellitus, polycystic ovary syndrome, family history of first degree relative with type 2 diabetes, metabolic syndrome, hypertension, hypertriglyceridemia.

# 2.2. Study Protocol

# 2.1.2. Baseline Data, Blood Collection, CGM Placement, and OGTT

There were two visits during this study at the NYU Clinical and Translational Science Institute (CTSI). At the initial visit, baseline data were recorded including medical history, and body mass index (BMI). HbA1c and PG were measured using the Abbott Architect c8000 clinical chemistry analyzer (Abbott Park, IL, USA).

CGM was inserted using usual clinical methods; a liquid adhesive barrier was applied to the skin, and an Abbott Freestyle Libre Pro CGM (Abbott Park, IL, USA) was then placed on the back of the upper arm. Subjects were instructed to wear the CGM for a 14-day period and continue their usual activities.

Within 3 to 7 days of CGM placement, subjects returned for their second visit and underwent a 2- hour OGTT. After an overnight fast for 8–12 hours, PG was measured fasting, 1 and 2 hours after ingesting a standard 75-gram glucose solution. Subjects returned their CGM 14 days after placement or earlier if the sensor became dislodged.

# 2.2. Glycemic Definitions

GV indices calculated using EasyGV© software (University of Oxford, England, UK, www.easygv.co.uk) included: standard deviation (SD), mean amplitude of glycemic excursions (MAGE), and Lability Index (LI) [10]. To assess if similar GV values could be obtained in a shorter time frame, GV indices were analyzed after 3 days of wearing CGM as well as 14 days.

# 2.3. Statistical Analysis

Methods and groups were compared using the Mann-Whitney test. The pairwise correlation between PG and CGM glucose, and 1-h PG and GV indices were computed using Spearman's rank correlation

coefficient. Chi-square tests were used to compare proportions between groups. Data are reported as mean ± SD unless otherwise stated. Area under the curve (AUC) and receiver operating characteristic analysis were performed to identify the GV index thresholds for the 1-h high group.

Statistical analyses were conducted using SPSS version 23.0 (IBM SPSS Statistics, Armonk, New York, USA), with the alpha level set at $p < 0.05$.

# Results

We enrolled 18 subjects: 3 were excluded from analysis since 1 subject did not complete the OGTT and 2 had missing CGM values. Thus, data from 15 subjects were analyzed. The baseline characteristics of the 15 subjects are shown in Table 1. On average, subjects were 50 ± 14 years of age, and majority were men (80%). The average HbA1c was 5.3 ± 0.2% (34 mmol/mol) and BMI was 32.7 ± 5.0 kg/m$^2$. Although their HbA1c was < 5.7% (39 mmol/mol), 53% of subjects had 1-h high PG levels. Subjects were divided into two groups based on 1-h PG levels during the OGTT: 1-h low or 1-h PG ≤ 155 mg/dL (8.6 mmol/L) (n = 7) and 1-h high or 1-h PG ≥ 155 mg/dL (8.6 mmol/L) (n = 8) (Table 1).

Table 1
Baseline Characteristics and CGM GV indices Comparing 1-h Low and 1-h High Groups

| | 1-h Low<br>n = 7 | 1-h High<br>n = 8 |
|---|---|---|
| **Age (Years)** | 48.9 ± 17.9 | 50.8 ± 13 |
| **Men n (%)** | 4 (57) | 8 (100) |
| **Ethnicity** | | |
| **Caucasian n (%)** | 3 (42.9) | 7 (88) |
| **Asian n (%)** | 2 (28.6) | 1 (13) |
| **African-American n (%)** | 2 (28.6) | 0 |
| **Hypertension** | 6 (85.7) | 6 (75) |
| **Hyperlipidemia** | 4 (57.1) | 5 (63) |
| **Family History of Diabetes** | 1 (14.3) | 4 (50) |
| **Non-alcoholic Fatty Liver Disease** | 2 (28.6) | 1 (13) |
| **HbA1c (%)**<br>**mmol/mol** | 5.4 ± 0.16<br>[36] | 5.2 ± 0.2<br>[33] |
| **BMI** | 31.14 ± 5.7 | 34.88 ± 4.3 |
| **Waist-to-Hip Ratio** | 0.96 ± 0.06 | 1.0 ± 0.058 |
| **Mean Amplitude of Glycemic Excursions (MAGE, mmol/L)** | 2.09 ± 0.54 | 2.93 ± 0.66* |
| **Standard Deviation (SD, mmol/L)** | 0.82 ± 0.17 | 1.15 ± 0.24** |
| **Lability Index (LI, mmol/L)** | 1.02 ± 0.66 | 1.87 ± 0.73* |
| Data are mean ± SD | | |
| *p < 0.05, **p < 0.001, comparison of 1-h-High vs. 1-h Low groups | | |

Next, we compared PG and CGM interstitial glucose levels. The total AUC during the OGTT for PG [17029 mg/dL*120 min (95% CI: 11936 to 22122 mg/dL*120 min)] and for CGM interstitial glucose [16772 mg/dL*120 min (95% CI: 12643 to 20901 mg/dL*120 min)] were similar ($p > 0.05$) (Fig. 1A). There were no statistical differences in PG and CGM interstitial glucose levels during the OGTT (Fig. 1A). The CGM and PG glucose levels were positively correlated at 1-h ($\rho = 0.89$, $p < 0.001$) (Fig. 1B).

The CGM was worn for an average of 12 days [range 3–15] and CGM mean glucose levels were compared between the 1-h high and low groups. Although, HbA1c was the same in both groups, the CGM mean glucose over 12 days was lower ($p < 0.001$) in the 1-h low group [97 ± 3.0 mg/dL (5.4 ± 0.2 mmol/l)]

than the 1-h high group [103 ± 3.4 mg/dL (5.7 ± 0.2 mmol/L)] (Fig. 1C). When CGM mean glucose was analyzed over 3 days, the differences remained, with 1-h low mean glucose of 96 ± 1.7 mg/dL (5.3 ± 0.1 mmol/l) and 1-h high mean glucose of 101 ± 1.1 mg/dL (5.6 ± 0.1 mmol/L). Thus, 1-h high group had higher daily mean glucose levels than the 1-h low group whether worn for 3 or 12 days.

GV indices MAGE, SD, and LI correlated with 1-h PG when the CGM was worn for 12 days (Fig. 1D-F), and 3-days (Fig. 1G-I). Furthermore, MAGE, SD, and LI were significantly higher ($p < 0.001$) in the 1-h high group than the 1-h low group (Table 1). Thus, the 1-h PG correlates with GV indices and can be assessed after only 3 days of wearing the CGM.

# Discussion

In this study, we show that both the 1-h PG during an OGTT and CGM-derived GV indices identify individuals with dysglycemia despite having normal HbA1c. In addition, both PG and CGM during an OGTT can detect early β-cell dysfunction, that is not captured by HbA1c.

We demonstrate that PG and CGM glucose levels correlate during an OGTT and that the 1-h PG highly correlated with GV indices. Thus, either the 1-h PG or CGM interstitial glucose during an OGTT provide information regarding GV. Consistent with previous findings, subjects with a 1-h high PG level had higher GV indices which included MAGE, SD, and LI, compared to those with 1-h low levels [9]. Moreover, 1-h PG ≥ 155 mg/dL (8.6 mmol/L) during an OGTT is a sensitive predictor for future development of diabetes, cardiovascular risk, and mortality [4, 11, 12].

Previous studies have found that 1-h PG outperforms HbA1c, and 2-h PG in detecting dysglycemia [13, 14]. Our findings further demonstrate that the 1-h PG tracks with GV indices, thus CGM-derived GV indices can be used to identify early β-cell dysfunction. A previous study showed that both SD and MAGE were increased in patients with prediabetes identified by OGTT compared to those with normal glucose tolerance [15]. Our study adds the important observation that high-risk individuals with HbA1c < 5.7% (39 mmol/mol) can have increased GV. CGM can further analyze daily and time-related glycemic patterns that may provide valuable feedback and educate patients regarding benefits derived from improved food choices and exercise. CGMs therefore add information beyond the diagnostic information obtained with a 1-h PG alone.

Although all subjects had a HbA1c < 5.7% (39 mmol/mol), 53% of subjects had 1-h PG ≥ 155 mg/dL (8.6 mmol/L). Once the HbA1c is in the prediabetes range (5.7–6.4% [39–46 mmol/mol]), β-cell dysfunction may already have reached an advanced stage, making reversibility less likely. Early identification of dysglycemia is therefore paramount. These findings underscore that a normal HbA1c underestimates the prevalence of individuals with dysglycemia or early β-cell dysfunction. Therefore, detecting GV using either 1-h PG or CGM interstitial glucose values appears to be more sensitive than the HbA1c in screening high-risk individuals [14]. We have demonstrated that CGM is also useful in screening for dysglycemia in subjects with normal HbA1c since it captures considerable glucose determinations up to 2 weeks in a “free-living” environment. A limitation to our study is that it took place during the COVID-19 pandemic

which restricted recruitment. Nonetheless, our study shows that 1-h PG and 1-h CGM interstitial glucose are useful for identifying GV and dysglycemia in individuals with normal HbA1c but at high-risk for type 2 diabetes. Moreover, CGM can identify dysglycemia and may be a potential alternative to PG determinations during an OGTT. Future studies should recruit a larger, more diverse cohort to show the utility of the CGM in predicting early dysglycemia in a broader population.

# Declarations


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### Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could inappropriately influence the work reported in this paper.


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### Authors' Contributions

M.B., K.K., S.M., C.P., M.S., designed the study and assisted with manuscript preparation. E.S., A.D, B.D. recruited subjects and assisted with data collection. B.D provided statistical analysis and prepared the manuscript. R.J. and M.C. assisted with data analysis. R.J., J.O.A., and I.J.G., critically edited the manuscript. All authors reviewed the article and revised it for important intellectual content.

### Ethical Approval

This study was approved by the NYU Grossman School of Medicine Institutional Review Board. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

### Consent to participate

Written informed consent was obtained from all participants in the study.

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# Figures

### Figure 1

Plasma and CGM Glucose Levels Correlate during an Oral Glucose Tolerance Test

A) Fasting, 60 and 120 minute plasma and CGM glucose during an OGTT. B) Correlation of the 1-h PG and CMG glucose levels during and OGTT ($p<0.001$), C) Comparison of the daily mean glucose values after 12 days of CGM use between the 1-h low and 1-h high groups. Correlation of OGTT 1-h PG with GV indices D) MAGE ($p<0.01$), E) SD ( $p<0.01$), and F) LI ($p=0.01$) after CGMs are worn for 2 weeks. Correlation of OGTT 1-h PG levels with GV indices E) MAGE ($p=0.004$), E) SD ($p<0.01$), and F) LI ($p<0.01$) after CGMs were worn for 3 days. ***$p<0.001$