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BRIEF REPORT

Continuous glucose monitoring and 1-h plasma glucose identifies glycemic variability and dysglycemia in high-risk individuals with HbA1c < 5.7%: a pilot study

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Introduction

The global incidence and prevalence of diabetes continue to rise [1]. Hence, identifying individuals at high risk for prediabetes and type 2 diabetes (T2D) is paramount. As glucose levels increase insidiously in the progression from normal glucose tolerance to prediabetes and T2D, early identification of high-risk individuals could result in the prescription of lifestyle interventions to decrease progression to T2D. HbA1c is widely used to screen for prediabetes (5.7–6.4% [39–46 mmol/mol]) and T2D (≥6.5% [48 mmol/mol]) [2]. However, HbA1c has poor sensitivity in identifying early pancreatic 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-hour plasma glucose (1-h PG) ≥ 155 mg/dL (8.6 mmol/L) during a 75-g oral glucose tolerance test (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 pancreatic 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 pilot 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

Subjects

This was a single-center, prospective pilot study that enrolled 18 subjects. The Institutional Review Board 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 T2D, and one or more of the following conditions: overweight or obese (body mass index (BMI) > 25 kg/m^2), nonalcoholic fatty liver disease, history of gestational diabetes mellitus, polycystic ovary syndrome, family history of first degree relative with T2D, metabolic syndrome, hypertension, and hypertriglyceridemia.

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Table 1 Baseline characteristics and continuous glucose monitor glycemic variability indices comparing 1-h low and 1-h high groups

	1-h Low [<155 mg/dL (8.6 mmol/L)] $n = 7$	1-h High [≥155 mg/dL (8.6 mmol/L)] $n = 8$
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 *n* (%)	6 (85.7)	6 (75)
Hyperlipidemia *n* (%)	4 (57.1)	5 (63)
Family History of Diabetes *n* (%)	1 (14.3)	4 (50)
Non-alcoholic Fatty Liver Disease *n* (%)	2 (28.6)	1 (13)
HbA1c (%)	5.4 ± 0.16	5.2 ± 0.2
mmol/mol	[36]	[33]
BMI (kg/m^2)	31.14 ± 5.7	34.88 ± 4.3
Waist-to-Hip ratio	0.96 ± 0.06	1.0 ± 0.058
MAGE (mmol/L)	2.09 ± 0.54	2.93 ± 0.66*
SD (mmol/L)	0.82 ± 0.17	1.15 ± 0.24**
LI (mmol/L)	1.02 ± 0.66	1.87 ± 0.73*

1-hour (h) Low = 1-h plasma glucose < 155 mg/dL (8.6 mmol/L), and 1-h high = plasma glucose ≥ 155 mg/dL (8.6 mmol/L)) during an oral glucose tolerance test; body mass index (BMI), Glycemic variability indices are: mean amplitude of glycemic excursions (MAGE), standard deviation (SD), lability index (LI)

*$p < 0.05$, **$p < 0.001$, comparison of 1-h-High vs. 1-h Low groups

Study protocol

Baseline data, blood collection, CGM placement, and OGTT

There were two visits during this study to the NYU Clinical and Translational Science Institute. At the initial visit, baseline data were recorded including medical history and 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 3–7 days of CGM placement, subjects returned for their second visit and underwent a 2-h OGTT. After an overnight fast for 8–12 h, PG was measured fasting, 1 and 2 h after ingesting a standard 75-g glucose solution. Subjects returned their CGM 14 days after placement or earlier if the sensor became dislodged.

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.

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) was performed to compare PG and CGM glucose levels during a 2-h OGTT. 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).

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. 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

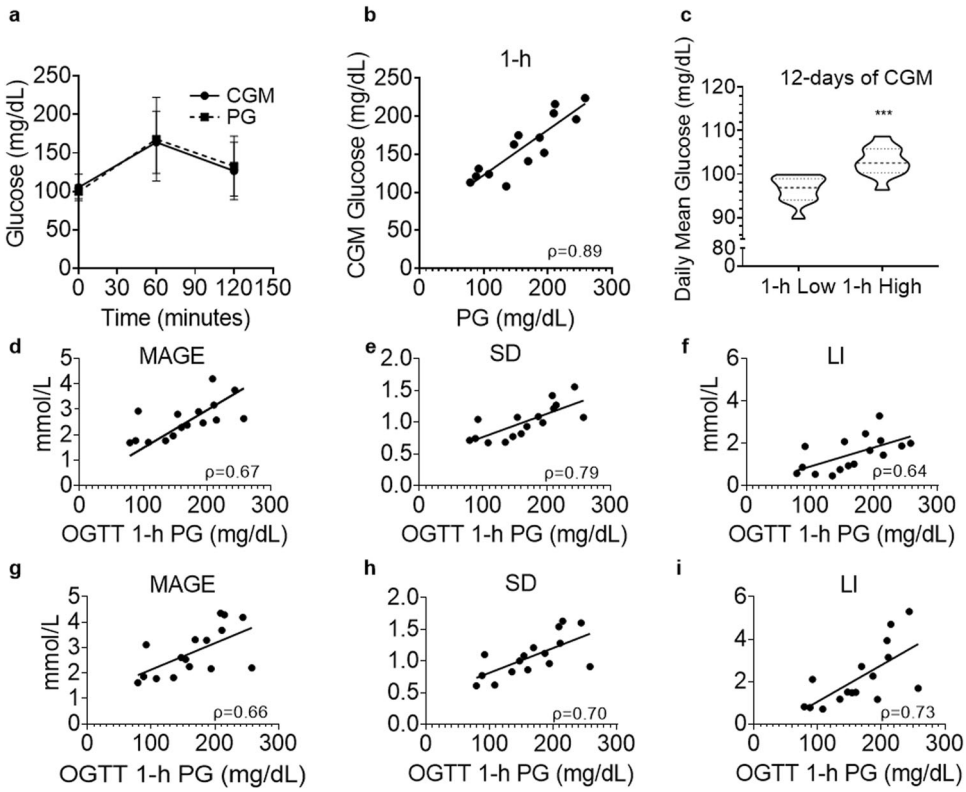

Fig. 1 Plasma and Continuous Glucose Monitor (CGM) Glucose Levels Correlate during an Oral Glucose Tolerance Test (OGTT). **a** Fasting, 60, and 120-minute plasma and CGM glucose levels during an OGTT. **b** Correlation of the 1-hour (h) plasma glucose (PG) and CGM glucose levels during an OGTT ($p < 0.001$). **c** Comparison of daily mean glucose values after 12 days of CGM use from the 1-h low [PG < 155 mg/dL (8.6 mmol/L)] and 1-h high (PG ≥ 155 mg/dL (8.6 mmol/L)) groups. Correlation of OGTT 1-h PG with glycemic variability (GV) indices: **d** mean amplitude of glycemic excursions (MAGE) ($p < 0.01$), **e** standard deviation (SD) ($p < 0.01$), and **f** lability index (LI) ($p = 0.01$) after CGMs are worn for 2 weeks. Correlation of OGTT 1-h PG levels with **g** mean amplitude of glycemic excursions (MAGE) ($p = 0.004$), **h** standard deviation (SD) ($p < 0.01$), and **i** lability index (LI) ($p < 0.01$) after CGMs are worn for 3 days

[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 greater 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 greater ($p < 0.001$) in the 1-h high group than in 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 pilot 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 is highly correlated with GV indices. Thus, either the 1-h PG or CGM interstitial glucose during an OGTT provides information regarding GV. Consistent with previous findings, subjects with a 1-h high PG level had greater 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 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 pancreatic 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. Furthermore, as this was a pilot study with a small sample size, differences in sex, age, race, and ethnicity could not be determined. Most of our participants are Caucasian men, hence our findings cannot be generalized to a broader population. Our preliminary findings need to be further explored in a larger diverse cohort. Although screening with 1-h PG or CGM would lead to more testing and increased diagnosis of early dysglycemia, it would allow for earlier lifestyle interventions that would prevent the progression to diabetes and its complications, which are more impactful and costly. Implementing CGM use in practice can pose some barriers such as increased clinical time for data download and review, and increased need for education on CGM data interpretation for clinicians [16]. In addition, since CGM for dysglycemia screening is not currently an approved indication and therefore not covered by insurance, this would constitute an out-of-pocket expense for patients [17]. As general practitioners are increasingly gaining experience with CGMs to manage diabetes, regulatory approval would allow for dysglycemia screening with CGMs and permit clinicians and patients to review glycemic trends, variability, nutrition, and thereby encourage lifestyle changes. If future studies confirm that CGM use can be limited to 3 days instead of 14 days, this would facilitate screening and limit inconvenience for patients. Finally, periodic reassessment with CGMs can evaluate progress and need to implement further measures such as intensified lifestyle intervention, pharmacotherapy, and/or need for referral to weight management specialists. If our findings are confirmed with a larger study, the ultimate goal is to expand the indication for CGM use to include dysglycemia screening in patients at high-risk even with normal HbA1c levels.

Nonetheless, our pilot 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 T2D. 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.

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Author contributions M.B., K.K., S.M., C.P., and 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.

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Compliance with ethical standards

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

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

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.

References

1. IDF Diabetes Atlas, 9th edn. Brussels [Internet]. 2019. https://www.diabetesatlas.org
2. American Diabetes Association Professional Practice Committee. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. Diabetes Care **45**(Suppl 1), S17–S38 (2022). https://doi.org/10.2337/dc22-S002
3. E. Bonora, J. Tuomilehto, The pros and cons of diagnosing diabetes with A1C. Diabetes Care **34**(Suppl 2), S184–S190 (2011). https://doi.org/10.2337/dc11-s216
4. L. Cao, P. Wang, H. Luan et al. Elevated 1-h postload plasma glucose levels identify coronary heart disease patients with greater severity of coronary artery lesions and higher risk of 1-year readmission. Diab. Vasc. Dis. Res. **17**(1), 1479164119896978 (2020). https://doi.org/10.1177/1479164119896978

5. M. Pareek, D.L. Bhatt, M.L. Nielsen et al. Enhanced predictive capability of a 1-hour oral glucose tolerance test: a prospective population-based cohort study. Diabetes Care **41**(1), 171–177 (2018). https://doi.org/10.2337/dc17-1351
6. M. Bergman, A. Chetrit, J. Roth et al. One-hour post-load plasma glucose level during the OGTT predicts dysglycemia: observations from the 24 year follow-up of the Israel Study of Glucose Intolerance, Obesity and Hypertension. Diabetes Res. Clin. Pract. **120**, 221–228 (2016). https://doi.org/10.1016/j.diabres.2016.08.013
7. Y. Thewjitcharoen, A. Jones Elizabeth, S. Butadej et al. Performance of HbA1c versus oral glucose tolerance test (OGTT) as a screening tool to diagnose dysglycemic status in high-risk Thai patients. BMC Endocr. Disord. **19**(1), 23 (2019). https://doi.org/10.1186/s12902-019-0339-6
8. G.E. Umpierrez, B. PK, Glycemic variability: how to measure and its clinical implication for type 2 diabetes. Am. J. Med. Sci. **356** (6), 518–527 (2018). https://doi.org/10.1016/j.amjms.2018.09.010
9. J.B. Su, T. Chen, F. Xu et al. Glycemic variability in normal glucose regulation subjects with elevated 1-h postload plasma glucose levels. Endocrine **46**(2), 241–248 (2014). https://doi.org/10.1007/s12020-013-0047-3
10. N.R. Hill, N.S. Oliver, P. Choudhary et al. Normal reference range for mean tissue glucose and glycemic variability derived from continuous glucose monitoring for subjects without diabetes in different ethnic groups. Diabetes Technol. Ther. **13**(9), 921–928 (2011). https://doi.org/10.1089/dia.2010.0247
11. M.A. Abdul-Ghani, T. Abdul-Ghani, N. Ali et al. One-hour plasma glucose concentration and the metabolic syndrome identify subjects at high risk for future type 2 diabetes. Diabetes Care **31**(8), 1650 (2008). https://doi.org/10.2337/dc08-0225
12. M. Bergman, M. Abdul-Ghani, J.S. Neves et al. Pitfalls of HbA1c in the diagnosis of diabetes. J. Clin. Endocrinol. Metab. **105**(8), 2803–2811 (2020). https://doi.org/10.1210/clinem/dgaa372
13. G. Peddinti, M. Bergman, T. Tuomi et al. 1-hour post-OGTT glucose improves the early prediction of type 2 diabetes by clinical and metabolic markers. J. Clin. Endocrinol. Metab. **104**(4), 1131–1140 (2018). https://doi.org/10.1210/jc.2018-01828
14. R. Jagannathan, M.A. Sevick, D. Fink et al. The 1-hour post-load glucose level is more effective than HbA1c for screening dysglycemia. Acta Diabetol. **53**(4), 543–550 (2016). https://doi.org/10.1007/s00592-015-0829-6
15. M. Hanefeld, S. Sulk, M. Helbig et al. Differences in glycemic variability between normoglycemic and prediabetic subjects. J. Diabetes Sci. Technol. **8**(2), 286–290 (2014). https://doi.org/10.1177/1932296814522739
16. E.M. Miller, Using continuous glucose monitoring in clinical practice. Clin. Diabetes **38**(5), 429–438 (2020). https://doi.org/10.2337/cd20-0043
17. T.W. Martens, Continuous glucose monitoring in primary care—are we there? Curr. Opin. Endocrinol. Diabetes Obes. **29**(1), 10–16 (2022). https://doi.org/10.1097/med.0000000000000689