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Reproducibility of continuous glucose monitoring-derived postprandial glucose features and their association with glycemic control in type 2 diabetes

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BACKGROUND/OBJECTIVES: Targeting postprandial glucose response (PPGR) is more effective than lowering fasting plasma glucose in improving glycemic control and reducing cardiovascular risk in individuals with type 2 diabetes (T2D). Continuous glucose monitoring (CGM) has the potential to uncover time-related features of PPGR. This study evaluates the within-subject reproducibility of dynamic PPGR parameters obtained by CGM and explores their potential as independent predictors of glycemic control in T2D.

SUBJECTS/METHODS: A total of 102 individuals with T2D underwent a 7-day CGM and consumed a standardized breakfast twice to assess the 4-h glucose response, described by the following parameters: glucose peak—the highest glucose value; time to peak—time of peak occurrence; delta glucose max—the difference between the peak and fasting glucose; nadir—the lowest post-peak glucose value; incremental area under the glucose curve; mean postprandial glucose—the average interstitial glucose concentration. Intraclass correlation coefficients (ICCs) for both single and average measurements with their 95% confidence intervals (CIs), were calculated for PPGR parameters to estimate their within-subject reproducibility. Multivariable linear regression models assessed the independent predictive contribution of PPGR parameters, fasting glucose, and 2-h postprandial glucose on 7-day CGM metrics and HbA1c.

RESULTS: Moderate to good reproducibility for single measurements was observed for mean glucose (ICC: 0.78, 95%CI 0.69–0.84), glucose peak (ICC: 0.69, 95% CI 0.57–0.78), and nadir (0.74, 95% CI 0.64–0.82). Mean postprandial glucose was the strongest predictor of 7-day time in range ($\beta = -0.772$, $p < 0.001$), 7-day mean glucose ($\beta = 0.800$, $p < 0.001$) and HbA1c ($\beta = 0.434$, $p < 0.001$), whereas the glucose peak was the main predictor of short-term glycemic variability, as reflected by the 7-day coefficient of variation ($\beta = 0.258$, $p = 0.006$) and mean amplitude of glucose excursions ($\beta = 0.613$, $p < 0.001$).

CONCLUSION: In individuals with T2D, CGM-derived parameters of PPGR are reproducible and could represent a practical tool to uncover meaningful information about glucose control, which 2-h postprandial glucose fails to predict.

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INTRODUCTION

The rising global prevalence of prediabetes and diabetes poses major public health challenges due to their significant impact on morbidity, mortality, and healthcare expenditures [1, 2]. Evidence suggests that targeting postprandial glucose excursions is more effective than lowering fasting plasma glucose for improving the overall glycemic control in people with type 2 diabetes (T2D), and for reducing the risk of diabetes-related complications [3, 4]. Indeed, postprandial hyperglycaemia has been recognized as an independent risk factor for atherosclerosis and a stronger predictor of cardiovascular events and all-cause mortality than fasting plasma glucose [5, 6]. Postprandial glucose excursions contribute ~15–20% to HbA1c levels and account for nearly 70% of hyperglycemic exposure in individuals with low HbA1c levels (i.e., <7.3%) [7]. Notably, they are also responsible for about 50% of overall glycemic variability [4, 7].

Despite its relevance, data on the postprandial phase in patients with T2D remain scarce, as fasting glucose measurements and HbA1c are the primary markers of blood glucose control used for diabetes management. When available, postprandial glucose is typically measured 2 h after the start of a meal, a time point theoretically aligned with the peak glucose levels [8]. However, a single measurement does not capture the complex dynamics of the postprandial glucose response. Continuous glucose monitoring (CGM) enables a detailed visualization of the entire postprandial glucose profile, uncovering peaks and dips that may be missed by conventional 2 h postprandial glucose measurement. In the era of precision medicine, this is particularly

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relevant, as distinct features of the PPGR and overall daily glucose profile may reflect the underlying pathophysiological heterogeneity among individuals with T2D [9]. Recent studies have indeed underscored the potential clinical utility of CGM-derived markers of glucose control in identifying subgroups of individuals with T2D who differ in disease status and risk of diabetic complications [10–12]. Another study has demonstrated that short-term CGM home tests combined with standardized mixed-meal challenges can detect subtle postprandial and nocturnal glycemic abnormalities associated with early immunological risk for diabetes, particularly when CGM-derived features are integrated using machine-learning approaches [13].

In this context, the dynamic features of the PPGR represent a particularly relevant and promising target for investigation, as they reflect key pathophysiological pathways involved in glucose regulation—namely, insulin resistance, beta-cell function, and the incretin system. If the dynamic features of a single PPGR obtained by CGM prove to be reproducible over time and meaningfully associated with both short- and long-term markers of glucose control, they could serve as valuable indicators to guide personalized dietary and/or pharmacological strategies for optimizing glycemic control in individuals with T2D.

Accordingly, the first aim of this study was to evaluate the within-subject reproducibility of glucose response parameters derived from CGM time-series following a standardized meal in individuals with T2D and mild metabolic impairment. Additionally, the study investigated whether parameters of the PPGR pattern offer meaningful prediction into overall glycemic homeostasis over extended periods, as assessed by 7-day CGM-derived metrics and HbA1c.

MATERIALS AND METHODS

Study participants

A total of 102 participants (69 men and 33 postmenopausal women) with T2D, attending the Diabetes Care Unit at Federico II University Hospital and able to provide written informed consent, were recruited in the study named: "Exploring individual determinants of postprandial glycemic response in type 2 diabetes to optimize therapeutic strategies with a personalized approach (DIABEST)". The diagnosis of T2D was based on HbA1c or plasma glucose criteria, according to the American Diabetes Association [14]. Eligibility criteria included: age 30–70 years; HbA1c values ≤ 7.5% (58.5 mmol/mol); T2D on treatment with diet alone or diet plus metformin; Body Mass Index (BMI) between 20 and 39.9 kg/m^2. Exclusion criteria consisted of any acute or chronic condition that could interfere with the interpretation of the results (e.g., Celiac disease, liver failure, etc.), unwillingness to consume study-related foods, or inability to complete the activities outlined in the study protocol. All potential participants were screened for eligibility and allowed to ask questions or express any concerns.

Study design

The DIABEST is an ongoing cross-sectional study conducted and reported in accordance with the STROBE guidelines and registered on ClinicalTrials.gov (registration number: NCT06057246). It has been designed to investigate the determinants of the PPGR in individuals with T2D.

For the purposes of the present study, each enrolled participant attended a first visit at the clinic on day 0, followed by a 7-day observational period at home while keeping their lifestyle habits stable. The first clinic visit included placement of the CGM sensor and the delivery of test-meal ingredients along with relevant instructions for home consumption (see below). They were also instructed to complete a 7-day food diary, recording all foods and beverages consumed (except for water), including portion sizes and the timing of each eating occasion, including the test-meals. Each participant received instructions to consume the test-meal once at home and was invited to come back to the clinic on day 8, to repeat the test-meal undergoing venous blood sampling before and up to 4 h after the meal, to evaluate postprandial plasma metabolites, while still wearing the CGM. Participants who declined to attend the clinic for the second test-meal, were provided with duplicate meal ingredients and instructed to repeat the test at home, with the assessment of the PPGR by CGM only.

Test-meal composition and standardized instructions for participants

After completing the baseline visit (day 0), participants received a meal pack containing the test-meal to be consumed at home following standardized instructions—once or twice, depending on their willingness to return to the clinic to repeat the test-meal with 4-h postprandial blood sampling.

The test-meal consisted of white bread (80 g), spreadable cheese (50 g), air-cured beef (50 g) and one apple (150 g). The nutrient composition of the standard meal was as follows: total energy (TE) content 532 kcal, carbohydrates 68,4 g (49.3% TE), total fat 17.1 g (29.5% TE), protein 27.8 g (21.4% TE), and fibre 6 g. The test-meal was consumed between 7:00 and 9:00 AM on day 1 (at home) and on day 8 (either at clinic or at home). Participants were instructed to fast for at least 8 h prior to consuming the standardized meal and for 4 h afterward, while avoiding any moderate to intense physical activity. They were advised to avoid smoking and caffeinated beverages the morning of testing days, as well as to consume the meal within a maximum of 15–20 min and not to warm the bread before eating. In both home and clinic settings, participants were specifically asked about or monitored for adherence to these instructions, and the information was formally recorded. Specifically, a standardized questionnaire was administered to verify adherence to the test-meal instructions, including fasting duration, physical activity restrictions, meal timing, and the complete and proper consumption of all food items. They were also asked about any major deviations from their usual sleep routine or stress levels prior to test-meal consumption. If any relevant deviation from the test-meal instructions was reported, the participant was asked to repeat it at home on another occasion.

Continuous glucose monitoring

Each participant was provided with a CGM device (Dexcom One/One$^+$) at their first clinic visit (day 0). Interstitial glucose concentrations collected at 5 min intervals from day 1 to day 7 were used for the analyses (measurements on day 0 were excluded to avoid using data from the calibration period). Over the 7-day period, the following CGM-derived metrics of the glucose profile were obtained from Dexcom Clarity report (Dexcom, Inc.): percent time in 70–180 mg/dL range (time in range, TIR), time above 180 mg/dL range (TAR 180), mean sensor glucose, standard deviation (SD) and coefficient of variation (CV). Glyculator statistical package [15] was used for the calculation of mean amplitude of glucose excursions (MAGE), measuring the average changes of blood glucose (both upwards and downwards) that exceed 1 SD for a 24 h period.

Postprandial glucose response parameters

Raw CGM glucose data collected every 5 min were utilized for the evaluation of the 4 h glucose response to the two test-meals. Glucose values from time 0 (i.e., the reported start time of the meal in the food record) to 240 min post-meal, represented the PPGR. The following parameters were used to describe the extracted 4-h PPGR:

(1) Glucose peak: the highest glucose value;
(2) Time to peak: the time at which the glucose peak occurs;
(3) Delta glucose max: the difference between the glucose peak and the fasting glucose;
(4) Nadir: the lowest glucose value recorded after the peak;
(5) iAUC: the incremental area under the glucose calculated by the trapezoidal rule [16];
(6) Mean postprandial glucose: the average interstitial glucose concentrations.

Statistical analysis

Intraclass correlation coefficients (ICCs) and their 95% confidence intervals (CIs) were calculated to assess the intra-individual variability of PPGR parameters measured during two test-meals consumed by participants on separate occasions. The analysis was conducted using a two-way linear mixed-effects model assessing absolute agreement between the repeated measurements. This approach quantifies the proportion of total variance attributable to between-subject variability relative to the total variance (including within-subject variability), providing an estimate of the reliability

and consistency of the PPGR over repeated testing. ICC values below 0.5 indicated poor reliability, whereas values between 0.5 and 0.75 were regarded as moderate, and values between 0.75 and 0.9 were regarded as good. ICCs above 0.9 were regarded as excellent [17]. Agreement between repeated PPGR measurements was represented using Bland–Altman plots, in which the difference between the two measurements was plotted against their mean to evaluate absolute bias. In addition, relative bias was calculated to account for differences in scale between PPGR parameters. Relative bias was expressed as the mean difference between the second test-meal (TM2) and the first one (TM1), divided by the mean of the paired measurements and reported as a percentage.

The assumption of normality for each variable was assessed using the Shapiro–Wilk test. Correlations between parameters describing the glucose response to the first test-meal—consumed at home by each participant—and 7-day CGM-derived metrics of the glucose profile, as well as HbA1c, were evaluated using Spearman correlation analysis, adjusting for potential confounders: age, diabetes duration, BMI, and metformin use. This approach was chosen to provide a more robust assessment of monotonic associations for variables that did not meet the normality assumptions required for Pearson correlations. Multivariable linear regression models were used to assess the distinct predictive contribution of the PPGR parameters (independent variables) on the 7-day CGM parameters of the glucose profile and on HbA1c (dependent variables).

RESULTS

All participants ($n = 102$) consumed the TM1 at home under standardized conditions. The second test-meal (TM2) was consumed at the clinic by 54 participants, while the remaining 48 consumed it at home. The characteristics of the study population are described in Supplemental Table 1. Most participants were men ($n = 69$), with a mean age of 61 years. On average, participants had a BMI of 30.1 ± 4.7 Kg/m^2 and showed mildly impaired glucose metabolism according to HbA1c levels (6.4% ± 0.5, 46 ± 6 mmol/mol). The mean duration of diabetes was 5.2 ± 5.2 years. Metformin was used by 60.8% of participants, while the remaining were managed with diet alone. The majority (64.7%) were on antihypertensive and cholesterol-lowering medications. There were no statistically significant differences in the characteristics of participants who consumed the TM2 at the clinic compared to those who repeated the test-meal at home.

Reproducibility of postprandial glucose response parameters

Glucose curves representing responses to the test-meal on the two administrations, as recorded by CGM, are shown in Fig. 1. Out of 204 test-meals, six (about 3%) had missing CGM data as recordings ended before the full 240-minute postprandial period. For three additional meals with fewer than three missing values at the end, linear interpolation was used to complete the PPGR extraction.

ICCs for single and average measurements of the parameters characterizing the postprandial glucose responses are reported in Table 1. Good to moderate reproducibility was observed for several features of the PPGR; specifically, reproducibility was good for mean glucose (ICC: 0.78, 95% CI 0.69–0.84), while it was moderate for glucose peak (ICC: 0.69, 95% CI 0.57–0.78) and nadir (0.74, 95% CI 0.64–0.82). In contrast, delta glucose max and time to peak showed lower reproducibility. Notably, averaging two repeated measurements improved reliability from moderate to good for both glucose peak (ICC: 0.82, 95% CI 0.73–0.88) and nadir (ICC: 0.85, 95% CI 0.78–0.90). Similarly, the reproducibility of time to peak and delta glucose max reached moderate levels when ICCs for average measurements were considered (Table 1). The agreement between repeated measurements of PPGR parameters is illustrated in Fig. 2, where the differences between TM2 and TM1 assessments are plotted on the y-axis against their mean on the x-axis. Glucose peak, nadir and mean postprandial glucose showed the smallest differences, whereas $iAUC_{0\text{-}4h}$ and delta glucose max exhibited the largest intra-individual variability. For all parameters, systematic bias was close to zero. When expressed as relative bias, mean differences were small across all PPGR parameters (generally < 5%), with the largest relative bias observed for $iAUC_{0\text{-}4h}$ (-7.2%).

The within-subject reproducibility of PPGR parameters was also assessed separately in the subgroup of participants who performed the TM2 at the clinic ($n = 54$) and in those who repeated the test-meal at home $n = 48$). The results are shown in Supplemental Table 2 and Supplemental Table 3, respectively. Overall, the findings were consistent with those observed in the total sample, with a moderate to good reproducibility for glucose peak, nadir, and mean glucose of the PPGR. Similar results were observed in subgroup analyses by diabetes treatment (Supplemental Table 4 and Supplemental Table 5) and sex (Supplemental Table 6 and Supplemental Table 7).

Relationship between postprandial glucose response parameters and markers of short- and long-term glucose control

Most glucose response parameters following the TM1 showed statistically significant associations with markers of short-term glucose control, as assessed by CGM-derived metrics over the 7-day monitoring period, as well as with HbA1c (Table 2).

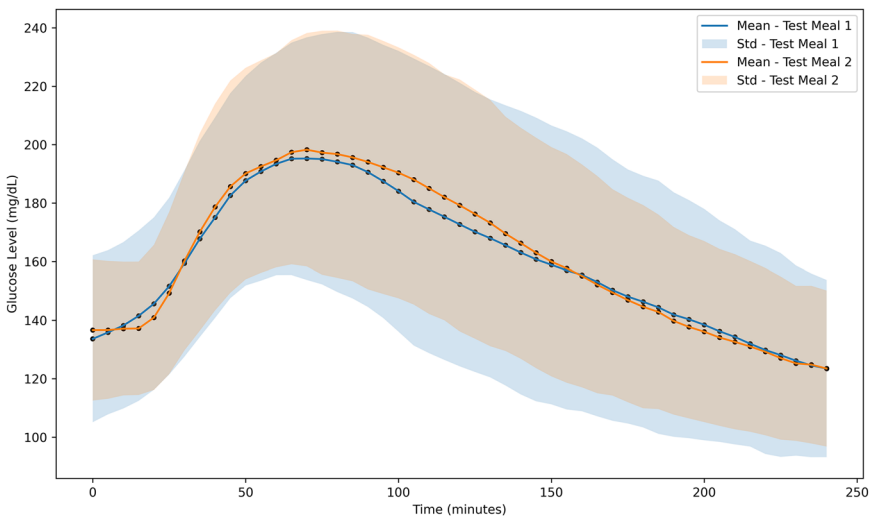

Fig. 1 Average glucose responses following the two test-meals ($n = 102$). The central dotted line represents the mean postprandial glucose response, while variability bands represent the standard deviation (Std).

Table 1. Reproducibility of the glucose response parameters following duplicate consumption of the test-meal (TM1 and TM2), as assessed by intra-class correlation coefficients (ICCs) ($n = 102$).

PPGR parameter	Mean ± SD	ICC for single measurements (95% CI)	ICC for average measurements (95% CI)
Glucose peak (mg/dL)	TM1: 210.83 ± 42.05	0.69 (0.57–0.78)	0.82 (0.73–0.88)
	TM2: 210.95 ± 38.89		
Time to peak (min)	TM1: 78.87 ± 33.86	0.40 (0.22–0.55)	0.57 (0.36–0.71)
	TM2: 79.66 ± 29.71		
Delta glucose max (mg/dL)	TM1: 77.19 ± 28.17	0.41 (0.24–0.56)	0.59 (0.39–0.72)
	TM2: 74.31 ± 26.92		
Nadir (mg/dL)	TM1: 119.36 ± 31.15	0.74 (0.64–0.82)	0.85 (0.78–0.90)
	TM2: 120.02 ± 27.39		
$iAUC_{0\text{-}4h}$ (mg·min/dL)	TM1: 5417.87 ± 4200.31	0.55 (0.40–0.68)	0.71 (0.57–0.81)
	TM2: 5318.73 ± 3798.87		
Mean postprandial glucose (mg/dL)	TM1: 160.93 ± 35.35	0.78 (0.69–0.84)	0.88 (0.82–0.92)
	TM2: 162.18 ± 30.41		

iAUC incremental Area Under the Curve, *SD* Standard Deviation, *CI* Confidence Interval.

Specifically, all PPGR parameters were significantly and inversely correlated with the 7-day TIR and directly correlated with the mean glucose of the 7 days. Parameters of the glucose response following TM1 were also directly correlated with metrics of short-term glycemic variability, particularly the SD of the 7-day glucose profile (all $p < 0.05$) and the 7-day MAGE (all $p < 0.05$ except for the correlation with time to peak). Finally, the most reproducible PPGR parameters—namely glucose peak, nadir, and the mean glucose—showed significant positive correlations with HbA1c (Table 2). These findings were confirmed in subgroup analyses by diabetes treatment (Supplemental Table 8 and Supplemental Table 9) and sex (Supplemental Table 10 and Supplemental Table 11), although direct correlations between nadir and 7-day MAGE and HbA1c did not reach statistical significance in smaller subgroups (i.e., participants treated with diet alone and females), whereas the correlation with 7-day TIR remained unchanged.

In accordance with that, markers of short- and long-term of glucose control were found to be correlated, as reported in Table 3. Specifically, 7-day TIR was inversely associated with HbA1c ($r_s = -0.559$, $p < 0.001$), while the mean weekly glucose levels were directly correlated with HbA1c ($r_s = 0.520$, $p < 0.001$). In addition, metrics of glycemic variability, namely SD and MAGE, showed significant positive correlations with HbA1c.

Relation between features of the 7-day glucose profile and postprandial glucose response parameters

To test whether PPGR parameters derived by CGM time-series could reflect key features of the daily glucose profile, as compared to standard measurements available in patients with T2D (i.e., fasting glucose and 2-h postprandial glucose), linear regression models were implemented.

Parameters of the glucose response to TM1 (i.e., glucose peak, time to peak, nadir, and mean glucose), along with fasting glucose and 2-h postprandial glucose, were included as input variables in multivariable linear regression models to predict 7-day CGM-derived metrics of average glucose and glucose variability—namely mean glucose, CV, and MAGE—as well as HbA1c. As reported in Table 4, the adjusted proportion of variance in 7-day TIR explained by mean glucose of the PPGR was 59.2% in Model 1, with nadir accounting for an additional 2.3% in Model 2. Other PPGR parameters were not included in the models. For 7-day mean glucose, Model 1 revealed that the mean glucose of the PPGR explained 63.7% of the variance. Fasting glucose contributed an additional 3% in Model 2, and the nadir accounted a further 2.1% in Model 3. In the analysis of the 7-day CV, glucose peak explained 5.8% of the variance in Model 1. The inclusion of fasting glucose in Model 2 improved the explanatory power by an additional 12.5%, but it remained overall limited, with an adjusted R^2 of 0.183. For 7-day MAGE, glucose peak was the sole predictor included in the Model, explaining 37% of the variance. Lastly, HbA1c was regressed on the mean glucose concentrations after TM1, which accounted for 18.1% of the variance, while all other parameters were excluded from the Model.

DISCUSSION

This study demonstrated that key parameters characterizing the glucose response over the 4-h period following a standardized meal, are generally reliable when measured by CGM at home. Moderate to good reproducibility was observed for glucose peak, glucose nadir, and mean glucose, showing that a single determination well reflects an individual's parameters. Notably, a non-invasive and feasible method, such as the CGM, was used to assess PPGR parameters and their reproducibility in people with T2D for the first time. So far, large-scale studies have reported a low intra-individual variability of PPGR evaluated as the 2-h iAUC via CGM, in individuals without diabetes [18, 19]. In patients with T2D, no data using the same methodology are currently available. Instead, reproducibility of glucose responses to mixed meals has been assessed by measuring blood glucose at 30 min or hourly intervals after a standardized meal [20, 21] to calculate the AUC, which demonstrated good reproducibility. However, these evaluations were performed in inpatient settings and did not consider other features of the PPGR.

Before applying measurements of CGM-derived PPGR parameters at a large scale in individuals with T2D to fully realize their potential for guiding personalization of T2D management, a fundamental premise is that their assessment must be reproducible within the same individual when the meal composition remains unchanged. To the best of our knowledge, this is the first study reporting that most parameters of the glucose response obtained by CGM after a single meal consumed at home exhibit good reproducibility in individuals with T2D. When individuals repeated the meal in different settings (i.e., at home or at the clinic), the results remained consistent, with only a slight improvement in reproducibility when the meal was replicated at the clinic. Our study identified the glucose peak, the average glucose level over four h after the meal, and the glucose nadir as the most reproducible features of the PPGR. These parameters capture aspects of the postprandial glucose dynamics that are not

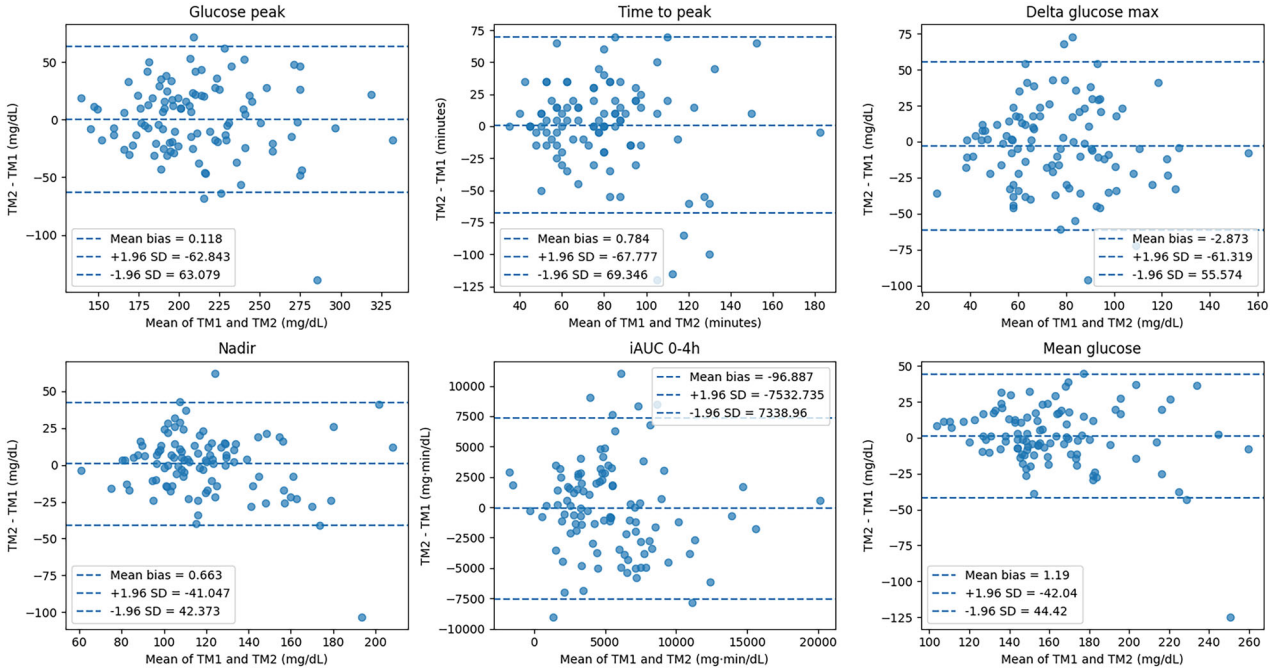

Fig. 2 Bland–Altman plots showing agreement between repeated standardized test-meals (TM1 and TM2) for CGM-derived postprandial glucose response parameters. For each participant, the difference between parameters from test-meal 2 (TM2) and test-meal 1 (TM1) is plotted against the mean of the two measurements. The central dashed line represents the mean bias between measurements, while the upper and lower dashed lines indicate the 95% limits of agreement (mean difference ± 1.96 standard deviation, SD). The plots illustrate the degree of agreement and intra-individual variability of postprandial glucose response parameters between repeated standardized test-meals.

Table 2. Correlations between parameters of the 4-h glucose response to the test-meal consumed the first time at home (TM1), and 7-day CGM-derived glucose metrics as well as HbA1c ($n = 102$).

	TAR 180 7 days	TIR 7 days	TBR 70 7 days	Mean glucose 7 days	SD of the mean glucose 7 days	MAGE 7 days	HbA1c
Glucose peak TM1	$r_s = 0.730$ $p < 0.001$	$r_s = -0.726$ $p < 0.001$	$r_s = -0.233$ $p = 0.022$	$r_s = 0.700$ $p < 0.001$	$r_s = 0.562$ $p < 0.001$	$r_s = 0.627$ $p < 0.001$	$r_s = 0.339$ $p < 0.001$
Time to peak TM1	$r_s = 0.297$ $p = 0.003$	$r_s = -0.281$ $p = 0.006$	$r_s = -0.180$ $p = 0.079$	$r_s = 0.298$ $p = 0.003$	$r_s = 0.215$ $p = 0.036$	$r_s = 0.135$ $p = 0.201$	$r_s = 0.163$ $p = 0.112$
Delta glucose max TM1	$r_s = 0.393$ $p < 0.001$	$r_s = -0.416$ $p < 0.001$	$r_s = 0.013$ $p = 0.902$	$r_s = 0.266$ $p = 0.009$	$r_s = 0.485$ $p < 0.001$	$r_s = 0.525$ $p < 0.001$	$r_s = 0.184$ $p = 0.072$
Nadir TM1	$r_s = 0.610$ $p < 0.001$	$r_s = -0.579$ $p < 0.001$	$r_s = -0.423$ $p < 0.001$	$r_s = 0.744$ $p < 0.001$	$r_s = 0.283$ $p = 0.005$	$r_s = 0.230$ $p = 0.028$	$r_s = 0.294$ $p = 0.004$
$iAUC_{0\text{-}4h}$ TM1	$r_s = 0.329$ $p = 0.001$	$r_s = -0.338$ $p < 0.001$	$r_s = 0.023$ $p = 0.827$	$r_s = 0.208$ $p = 0.042$	$r_s = 0.400$ $p < 0.001$	$r_s = 0.320$ $p = 0.002$	$r_s = 0.182$ $p = 0.076$
Mean glucose TM1	$r_s = 0.762$ $p < 0.001$	$r_s = -0.741$ $p < 0.001$	$r_s = -0.311$ $p = 0.002$	$r_s = 0.795$ $p < 0.001$	$r_s = 0.489$ $p < 0.001$	$r_s = 0.470$ $p < 0.001$	$r_s = 0.373$ $p < 0.001$

Adjustment variables: age, BMI, diabetes duration, metformin use.
TAR Time Above Range 180 mg/dL, *TIR* Time In Range 70–180 mg/dL, *TBR* Time Below Range 70 mg/dL, *SD* Standard Deviation, *MAGE* Mean Amplitude of Glucose Excursions.

reflected by the widely used 2-h postprandial glucose measurement. Furthermore, this study showed that the average time to glucose peak is around 80 min, indicating that a capillary blood sample taken 120 after the meal occurs nearly halfway between the glucose peak and the return to baseline. Notably, the poor reproducibility and high intra-individual variability of the time of the peak suggest that a single -2-h postprandial glucose value does not represent a reliable marker of the PPGR. This also highlights that specific unmeasured variables—mainly related to the meal context, such as physical activity levels and sleep quantity/quality—may warrant further investigation, as they could account for differences in glucose absorption and management, even when the same individual consumes the same meal. However, the reliability of time to peak and of the maximal postprandial glucose excursion (delta glucose max) increased when averaging two repeated measurements, indicating that these parameters can be more precisely defined when repeated assessment is feasible, such as in research settings. The same applies to $iAUC_{0\text{-}4h}$, whose larger variability may partly reflect the propagation of measurement variability across multiple time points used in the area calculation, as well as sensitivity to small differences in the shape of the PPGR curve between repeated test-meals. From a clinical perspective, the most reproducible PPGR parameters (i.e., 4-h mean glucose, glucose peak and nadir) may be generally sufficient to guide personalized dietary strategies, particularly regarding carbohydrate quantity and quality intake.

Table 3. Correlations between 7-day CGM-derived glucose metrics and HbA1c ($n = 102$).

	HbA1c
TAR 180 7 days	$r_s = 0.549$ $p < 0.001$
TIR 7 days	$r_s = -0.559$ $p < 0.001$
Mean glucose 7 days	$r_s = 0.520$ $p < 0.001$
SD of the mean glucose 7 days	$r_s = 0.474$ $p < 0.001$
MAGE 7 days	$r_s = 0.409$ $p < 0.001$

TAR 180 Time Above Range 180 mg/dL, *TIR* Time in Range 70–180 mg/dL, *SD* Standard Deviation, *MAGE* Mean Amplitude of Glucose Excursions.

Table 4. Multivariable linear regression models of 7-day CGM-derived glucose metrics and HbA1c based on parameters of the glucose response to the first test-meal consumed at home (TM1).

	Parameter of the glucose response to TM1		
7-day TIR		Model 1 Adjusted $R^2 = 0.592$	
		B	*p*
	Mean glucose	−0.772	<0.001
		Model 2 Adjusted $R^2 = 0.615$	
		B	*p*
	Mean glucose	−0.461	<0.001
	Nadir	−0.352	0.007
7-day mean glucose		Model 1 Adjusted $R^2 = 0.637$	
		B	*p*
	Mean glucose	0.800	<0.001
		Model 2 Adjusted $R^2 = 0.667$	
		B	*p*
	Mean glucose	0.533	<0.001
	Fasting glucose	0.324	0.001
		Model 3 Adjusted $R^2 = 0.688$	
		B	*p*
	Mean glucose	0.275	0.037
	Fasting glucose	0.279	0.004
	Nadir	0.333	0.005
7-day CV		Model 1 Adjusted $R^2 = 0.058$	
		B	*p*
	Glucose peak	0.258	0.006
		Model 2 Adjusted $R^2 = 0.183$	
		B	*p*
	Glucose peak	0.665	<0.001
	Fasting glucose	−0.546	<0.001
7-day MAGE		Model 1 Adjusted $R^2 = 0.370$	
		B	*p*
	Glucose peak	0.613	<0.001
HbA1c		Model 1 Adjusted $R^2 = 0.181$	
		B	*p*
	Mean glucose	0.434	<0.001

TIR Time in Range 70–180 mg/dL, *CV* Coefficient of Variation, *MAGE* Mean Amplitude of Glucose Excursions.

For example, individuals with a lower nadir may benefit from increasing fiber intake, those with higher peaks from consuming low-GI foods, and those with elevated mean postprandial glucose from reducing carbohydrate quantity.

In this paper, we have verified that CGM-derived parameters characterizing the glucose response are consistent with relevant features of the ambulatory glucose profile and with HbA1c, confirming the significant contribution of distinct features of the PPGR to both short- and long-term glycemic control. Furthermore, we showed that parameters of glycemic control evaluated by CGM over a one-week observational period correlate with HbA1c, providing a promising perspective for capturing meaningful information about an individual's daily glucose profile in a simple and affordable manner. This approach would be particularly advantageous for individuals with early-onset T2D and mild metabolic impairment, where targeting the optimization of the PPGR and reducing glycemic variability is critically important [7]. Moreover, in patients treated with diet alone or diet plus metformin, the limited pharmacological interference allows evaluation of the pathophysiological mechanisms underlying the PPGR, thereby providing a basis for targeting the predominant impairment in T2D through precision strategies aimed at maximizing clinical benefits.

Nonetheless, these patients may show low acceptance of extended CGM use, as they are less medically engaged. In this regard, we showed that limited use of CGM to evaluate a single PPGR can provide insights into both short- and potentially long-term glucose control. Such targeted, short-term utilization could improve patient acceptance and adherence. Also with respect to economic evaluations—indicating that CGM is a cost-effective option compared to standard self-monitoring blood glucose (SMBG) when long-term health outcomes and quality of life improvements are considered [22]—the limited but informative use demonstrated in our study may represent a cost-sustainable approach, especially when compared with the more frequent SMBG that would otherwise be required to support personalized management of T2D.

However, as this study included only individuals with mild metabolic impairment, the ability to evaluate PPGR parameters across different levels of glycemic control and diabetes duration was limited.

A key finding of this study is that some CGM-derived parameters of PPGR were more strongly associated with the main features of the overall individual daily glucose profile than fasting or 2-h postprandial glucose. Specifically, we showed that the 4-h mean glucose from the PPGR was the main predictor of both weekly TIR and average daily glucose levels, suggesting that prolonged and continuous glucose measurements after a single meal better reflect average glucose control in individuals with T2D than single time-point values, such as the glucose peak or the traditional 2h postprandial glucose. This was further supported by the findings on HbA1c, reflecting the average glucose levels over the previous three months, which were again primarily associated with the mean glucose recorded by CGM following the test-meal instead of fasting or 2-h postprandial glucose. In contrast, CGM-derived metrics of glycemic variability were mainly predicted by the peak of the single 4 h PPGR rather than by the 2-h postprandial glucose value. Indeed, although the latter has been associated with cardiovascular outcomes [5, 23, 24], it remains unclear whether individuals with T2D who exhibit the highest 2-h postprandial glucose values also experience the greatest long-term glycemic variability [25]. As a matter of fact, the 2-h

postprandial glucose is only a modest proxy for glycemic variability, whereas the o28verall PPGR pattern offers much more detailed insights into the shape and dynamics of glucose excursions over a prolonged period. Therefore, in epidemiological studies, the comprehensive assessment of PPGR may represent a more accurate marker of glycemic variability, potentially improving the prediction of cardiovascular events in patients with T2D. In this context, prospective studies are needed to evaluate the association of reproducible CGM-derived PPGR parameters with clinical endpoints and to determine which parameters may serve as reliable predictors beyond surrogate glycemic markers. However, even without information on the long-term relationship between CGM-derived PPGR parameters and diabetes-related outcomes, their value in predicting medium-term glucose control supports their use for personalized dietary management. Given that CGM-derived postprandial features have been shown to capture early dysglycemic signatures beyond established diabetes, particularly when combined with genetic risk information, standardized CGM-based meal tests may also hold broader potential for early disease stratification [26]. Future studies may further benefit from integrating postprandial summary features with intrinsically dynamic CGM markers—such as entropy rate or Poincaré plot–based indices—to more fully characterize the progression of glycemic dysregulation across diabetes stages [27].

Taken together, the evidence presented supports the reproducibility of PPGR dynamic parameters obtained by CGM, and reinforces the notion that the whole PPGR pattern offers more comprehensive insights into individual glycemic control than the traditional 2-h postprandial value alone. Within the framework of precision medicine for T2D, identifying by CGM features of the PPGR that predict key aspects of glucose homeostasis could represent a strategy for tailoring nutritional and pharmacological strategies to optimize blood glucose control.

DATA AVAILABILITY

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

CODE AVAILABILITY

The code used to generate the results of this study was written in Python (version 3.10) using standard scientific libraries, including NumPy, pandas, scikit-learn, statsmodels, and pingouin. Statistical analyses were also performed using IBM SPSS Statistics, version 29.0.1.0 (IBM Corp., Armonk, NY, USA). As the analyses are based on established and widely available statistical methods, the code is not publicly archived but can be made available from the corresponding author upon request.

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AUTHOR CONTRIBUTIONS

AG was responsible for writing the protocol, screening potentially eligible participants, extracting and analysing data, interpreting results, and drafting the manuscript. GR, OV, and LB conceived the study idea, designed the research, and contributed to data interpretation. VS and AC provided statistical expertise and verified the analyses. AG, GDB, RT, MV, and GC were responsible for participant recruitment and data collection. RL, GR, OV, and LB provided critical revision on the manuscript. All authors read and approved the final manuscript.

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COMPETING INTERESTS

AG, RT, GDA, MV, GR, OV, AC, VS, RL, GC, and LB declare that there is no duality of interest associated with this manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol and the procedures for obtaining informed consent were reviewed and approved by the Federico II University Institutional Review Board (IRB Protocol #31/2023). Informed consent was obtained from all participants.

ADDITIONAL INFORMATION

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