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Original Research Article

Association of the glucose patterns after a single nonstandardized meal with the habitual diet composition and features of the daily glucose profile in individuals without diabetes

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A B S T R A C T

Background: The postprandial glucose response (PPGR), contributing to the glycemic variability (GV), is positively associated with cardiovascular disease risk in people without diabetes, and can thus represent a target for cardiometabolic prevention strategies.

Objectives: The study aimed to distinguish patterns of PPGR after a single nonstandardized meal and to evaluate their relationship with the habitual diet and the daily glucose profile (DGP) in individuals at high-cardiometabolic risk.

Methods: Baseline 4-d continuous glucose monitoring was performed in 159 adults recruited in the MEDGI-Carb trial. After a nonstandardized breakfast, parameters of the PPGR were estimated by a mechanistic model: baseline glucose; amplitude—the magnitude of postmeal glucose concentrations; frequency—the velocity of postmeal glucose oscillations; damping—the rate of postmeal glucose decay. PPGR patterns were identified by cluster analysis. Differences between clusters and the relationship between PPGR parameters and individual features were explored by one-way analysis of variance and correlation analysis, respectively.

Results: Two patterns of PPGR emerged. Pattern A had a higher baseline, amplitude, frequency, and damping than B. Individuals in cluster A compared with B had higher energy (2002 ± 526 compared with 1766 ± 455 kcal, $P = 0.025$), protein (82 ± 22 compared with 72 ± 21 g, $P = 0.028$), and fat (87 ± 30 compared with 75 ± 22 g, $P = 0.041$), but not carbohydrate habitual intake. Pattern A compared to B associated with a higher average daily glucose (6.12 ± 0.50 compared with 5.88 ± 0.62 mmol/L, $P = 0.019$) and lower GV (11.67 ± 3.52 compared with 13.43 ± 3.78%, $P = 0.010$). Mean daily glucose correlated directly with baseline ($r_s = 0.419$, $P < 0.001$) and amplitude ($r_s = 0.189$, $P = 0.022$) of the PPGR, whereas DGP variability correlated directly with amplitude ($r_s = 0.218$, $P = 0.008$), and inversely with frequency ($r_s = –0.179$, $P = 0.031$) and damping ($r_s = –0.309$, $P < 0.001$).

Conclusions: Two PPGR patterns after a single nonstandardized breakfast were identified in high-cardiometabolic risk individuals. The habitual diet was associated with the patterns and their dynamic parameters, which, in turn, could predict the individuals' DGP. Our findings could support the implementation of dietary strategies targeting the PPGR to ameliorate the cardiometabolic risk profile.

Trial registration number: This study was registered at clinicaltrials.gov as NCT03410719.

Keywords: diet, continuous glucose monitoring, postprandial glucose response, mechanistic model, glucose dynamic, free-living, precision nutrition, clustering, cardiometabolic risk, CGM metrics, glycemic variability

Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation; CVD, cardiovascular diseases; DGP, daily glucose profile; GV, glycemic variability; HBGI, High Blood Glucose Index; LBGI, Low Blood Glucose Index; MAGE, mean amplitude of glucose excursions; OGTT, oral glucose tolerance test; PPG, postprandial glucose; PPGR, postprandial glucose response; SD, Standard Deviation; T2D, type 2 diabetes.

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Introduction

The prevalence of cardiometabolic diseases has dramatically risen globally in the last decades. Diabetes alone has increased by >90% between 1990 and 2021 and is expected to further increase by around 60% in 2050, resulting in 1.31 billion people living with diabetes [1]. Prediabetes and diabetes are major risk factors for cardiovascular disease (CVD), the leading cause of death worldwide [2]. Within this scenario, the need for highly effective preventive strategies targeting modifiable cardiometabolic risk factors is urgent. Dietary change is one of the most powerful solutions to improve cardiometabolic health. Nevertheless, long-term changes of the diet have proven difficult [3]. Dietary interventions are often not adhered to and the response to such interventions is not consistent in individuals with different phenotypes [4–6]. This calls for more personalized strategies to improve motivation and effectiveness.

Postprandial glucose (PPG) has been proposed as a target for personalized dietary interventions to reduce the risk of cardiometabolic diseases, because it has been consistently associated with CVD incidence in epidemiological studies, particularly among individuals at elevated risk [7–11]. Recurring high postmeal glucose excursions have the potential to induce progressive beta-cell dysfunction and reduced insulin sensitivity, eventually leading to prediabetes and type 2 diabetes (T2D) [12]. Targeting PPG can therefore represent an effective strategy to improve the glycemic variability (GV) and, therefore, contribute to the cardiometabolic risk reduction [13]. The use of machine learning algorithms has already been proven successful in driving blood glucose control strategies tailored to specific characteristics of the study participants [14–16].

In a previous study on individuals at high risk for diabetes, we were able to differentiate PPG responses to a standardized mixed meal which were associated with different cardiometabolic risk profiles and gut microbiota composition [17]. The methodology employed was based on the implementation of a simple mechanistic model of PPG regulation including only 4 dynamic parameters: baseline (that is, the interstitial glucose measured immediately before the start of the meal), amplitude (that is, the magnitude of the glucose concentrations after the meal), frequency (that is, the velocity of glucose oscillations after the meal), and the damping (that is, the rate of glucose decay after the meal), and the identification of clusters that differed in these parameters. However, it is not known whether it is possible to detect different clusters of PPG response in a free-living setting, where people consume their self-chosen, unrestricted habitual diet, and if there are metabolic features and dietary habits associated with the so-identified PPG response patterns.

The increasing use of continuous glucose monitoring (CGM) systems in research among people without diabetes has shown a great potential in evaluating parameters of the daily glucose profile (DGP) associated with clinical and metabolic features of the individuals that may relate to future disease risk. Recently, Keshet et al. have shown in >7000 individuals without diabetes that some key CGM metrics significantly correlate with clinical measures, including BMI and total fat mass, blood lipids, and liver enzymes [18]. Remarkably, each clinical marker of a metabolic function was correlated with specific CGM parameters. For example, measures of body composition were associated with the average daily glucose, whereas indirect measures related to liver phenotypes were associated with glucose variability. The possibility to uncover different patterns of PPG response in free-living conditions, when the meal composition and the general lifestyle context are not standardized and individuals consume their self-chosen habitual diet, would represent an important step forward in precision nutrition, because it would allow us to test different dietary strategies and to identify the most appropriate ones to improve the specific PPG pattern showed by each group of individuals.

The overall aim of the present study was therefore to investigate whether different patterns of glucose response after a single nonstandardized breakfast meal could be identified using glucose data collected by CGM at home. Moreover, the study aimed to identify which individual features and glucose dynamic parameters contribute to such differential glucose response patterns, and to explore features of the habitual diet associated with the different postbreakfast glucose response patterns. Finally, we also aimed to investigate whether the dynamic parameters of a single glucose response to a nonstandardized breakfast could be used to predict the magnitude and the variability of the whole DGP, as measured by CGM.

Methods

Participants

Middle-aged and older adults (30–69 y) from Sweden, Italy, and the United States at risk of developing T2D recruited for the Mediterranean Glycemic Index-Carbohydrates (MEDGI-Carb) trial were studied at baseline in free-living conditions. The MEDGI-Carb was an international, multicenter, randomized, controlled, parallel-group, 15-wk trial including a 3-wk baseline period, followed by 12 wk of controlled dietary intervention. The trial was registered in the public trial registry clinicaltrials.gov as NCT03410719 before initiating participant recruitment. The study protocol was approved by the intuitional review boards at Purdue University and Federico II University and by the Swedish Ethical Review Authority. The study was conducted at 3 centers: *1*) Federico II University, Naples, Italy, *2*) Chalmers University of Technology, Gothenburg, Sweden, and *3*) Purdue University, West Lafayette, IN, United States. It was initiated in January 2018 and continued through December 2019. All participants (goal of completers: 60 per center) signed the informed consent form reviewed and approved by the above-mentioned institutional boards. Detailed descriptions of the trial can be found in previous publications [19,20].

The flowchart of participants included in the present study is shown in Supplemental Figure 1. All but 1 participant self-reported to be Caucasian not of Hispanic origin (n = 158, 99%), whereas only 1 declared to be of Hispanic origin; no one was Alaska Native, African American, Native Hawaiian or Other Pacific Islander. According to the inclusion criteria of the MEDGI-Carb trial, they all had a waist circumference >102 cm (males) or >88 cm (females) and 1 additional trait of the metabolic syndrome, according to the National Cholesterol Education Program's Adult Treatment Panel III [21]. The additional traits could include blood pressure >130/85 mmHg or taking medication to control high blood pressure; fasting plasma glucose 5.6–7.0 mmol/L; fasting triglycerides 1.7–4.5 mmol/L; HDL < 1.0 mmol/L (males) or <1.3 mmol/L (females).

Study design

To address our objectives, we analyzed the baseline data available from the participants to the MEDGI-Carb trial [20]. This dietary trial aimed to investigate the effects on postprandial glycemia and GV after adopting a Mediterranean-style healthy dietary pattern with low or high glycemic index. As above mentioned, it was an international multicenter randomized, controlled, parallel-group, 15-wk dietary trial, including a 3-wk baseline period followed by a 12-wk controlled

dietary intervention in adults at elevated risk of developing T2D. The major findings are published [17,20,22]. For the present study, only data collected during the baseline period have been used, when the study participants were following their habitual diet and the meal composition and the general lifestyle context were not standardized.

Continuous glucose monitoring

Each participant wore a CGM device (Medtronic iPro2 Professional) for 4 d, to obtain 24-h interstitial glucose concentrations with 5-min intervals. Raw data were entered into the *EasyGV* platform (University of Oxford) for calculation of key CGM-derived GV measurements for 3 d (measurements on the first day were excluded to avoid using data from the calibration period) in individuals without diabetes [18], namely: mean absolute glucose, SD, mean amplitude of glucose excursions (MAGE); High Blood Glucose Index (HBGI), and Low Blood Glucose Index (LBGI). MAGE measures the average changes of blood glucose (both upwards or downwards) that exceed 1 SD for a 24-h period; HBGI and LBGI are risk indices for predicting hypoglycemia (LBGI) or hyperglycemia (HGBI) based on the frequency and extent of low (< 6.25 mmol/L) and high (>5.25 mmol/L) blood glucose readings [23].

Oral glucose tolerance test and insulin sensitivity/secretion indices

An oral glucose tolerance test (OGTT) was performed to evaluate each participant's PPG metabolism in a standardized way. Fasting venous blood samples were collected from an antecubital vein after 15 min of rest and again 10 min later. Soon after, participants were instructed to consume a test beverage containing 75 g glucose dissolved in water within 5 min. No additional fluids were permitted during the test. Blood samples were collected at time point (TP) 60 and TP 120. Glycemia and insulin measurements after OGTT were used to calculate total AUC for glucose and insulin by the trapezoidal rule. Additionally, based on the OGTT data, the Matsuda index [24] and the beta-cell function index [25] were calculated to estimate insulin sensitivity and secretion, respectively.

Dietary assessment

All participants consumed their habitual unrestricted diet during the 3-wk before the baseline measurements. During this period, they performed simultaneously CGM for 4 d and filled in a dietary record, reporting all foods and drinks consumed, including dressing, portions by household measures (cup, spoons, etc.) or weight, and providing as much details as possible (that is, cooking methods and brands names). The food records were discussed with registered dietitians to check for potential missing information. Energy intake and nutrient composition were calculated based on the available data from the national site-specific food composition tables.

Postbreakfast glucose response

Raw CGM glucose data collected every 5-min were utilized for the evaluation of the 4-h glucose response to the breakfast meal consumed after overnight fasting on the first day of the glucose monitoring after the calibration period; if on that day the breakfast meal was skipped, the evaluation was postponed to the following day. The breakfast meal could contain any type and amount of foods/beverages, because participants were studied while following their habitual diet.

Considering that information on the exact time at which breakfast was consumed was not available, for each participant the start of the breakfast meal—that is, TP 0—was identified as the time at which the lowest glucose value before a glucose peak was recorded in the time-frame 06:00 to 11:00.

Mechanistic model of glucose regulation and glucose dynamic parameters

To describe the PPG response dynamics from the breakfast in a comprehensive form, a parsimonious kinetic model was used [26,27]. Details on the model derivation are described in the **Supplemental Methods**. In brief, the model was derived using a system of ordinary differential equations which has a compact solution under certain assumptions (Equation *1*)

$$G(t) = G_b + A\,sin(\omega t)\,e^{-\alpha t} \quad (1)$$

The parameters governing the glucose dynamics after the breakfast meal were as follows: *1*) the interstitial glucose baseline concentration (G_b), measured immediately before the start of the meal, *2*) the sinusoidal amplitude (A), representing the amplitude of the glucose concentrations after the meal, *3*) the sinusoidal frequency (ω), describing the velocity of glucose oscillations after the meal, and *4*) the damping coefficient (α) representing the rate of glucose decay after the meal.

Statistical analyses

The parameters of the kinetic model were estimated using the nonlinear mixed effects framework [28] incorporated in the Monlix software (Monolix 2021R2, Lixoft SAS, a Simulations Plus company). Here, regularization was naturally imposed as parameters can be shared within the population whereas others are intended to explain individual variability. Within this framework, we assumed that the individual parameters were drawn from a mixture of Gaussian distributions, effectively allowing for the clustering of individuals in terms of postprandial dynamic parameters. The clusters were identified as latent covariates using the Stochastic Approximation of mean Expectation Maximization (SAEM) algorithm in Monolix [28]. The prior assumption is an equal sample size per cluster while the algorithm finds the proportion that accommodates the best fit regardless of imbalance.

Associations between identified clusters of the postbreakfast glucose response under free-living conditions and features of the study participants were investigated using one-way analysis of variance, where hypothesis tests were considered significant for P values < 0.05. Correlations between each of the 4 parameters of the PPG dynamics measured and the clinical and metabolic features of the participants, as well as the nutrient composition of their habitual diet, were evaluated by the Spearman correlation analysis. Furthermore, the same analysis was used to evaluate the relationship between each of the parameters of the PPG dynamics and CGM metrics of GV.

Results

In total, CGM raw data of 159 participants were used for the extraction of the postbreakfast glucose response in free-living conditions. Data regarding the habitual diet and the estimated daily CGM metrics were available for 127 and 147 individuals, respectively. The characteristics of the total study population and of the subgroups with different data availability are described in Supplemental Table 1.

Postbreakfast glucose response patterns

The model fitted well to the postbreakfast response identified by CGM sampling of interstitial glucose at 5-min intervals ($R^2 = 0.89$)

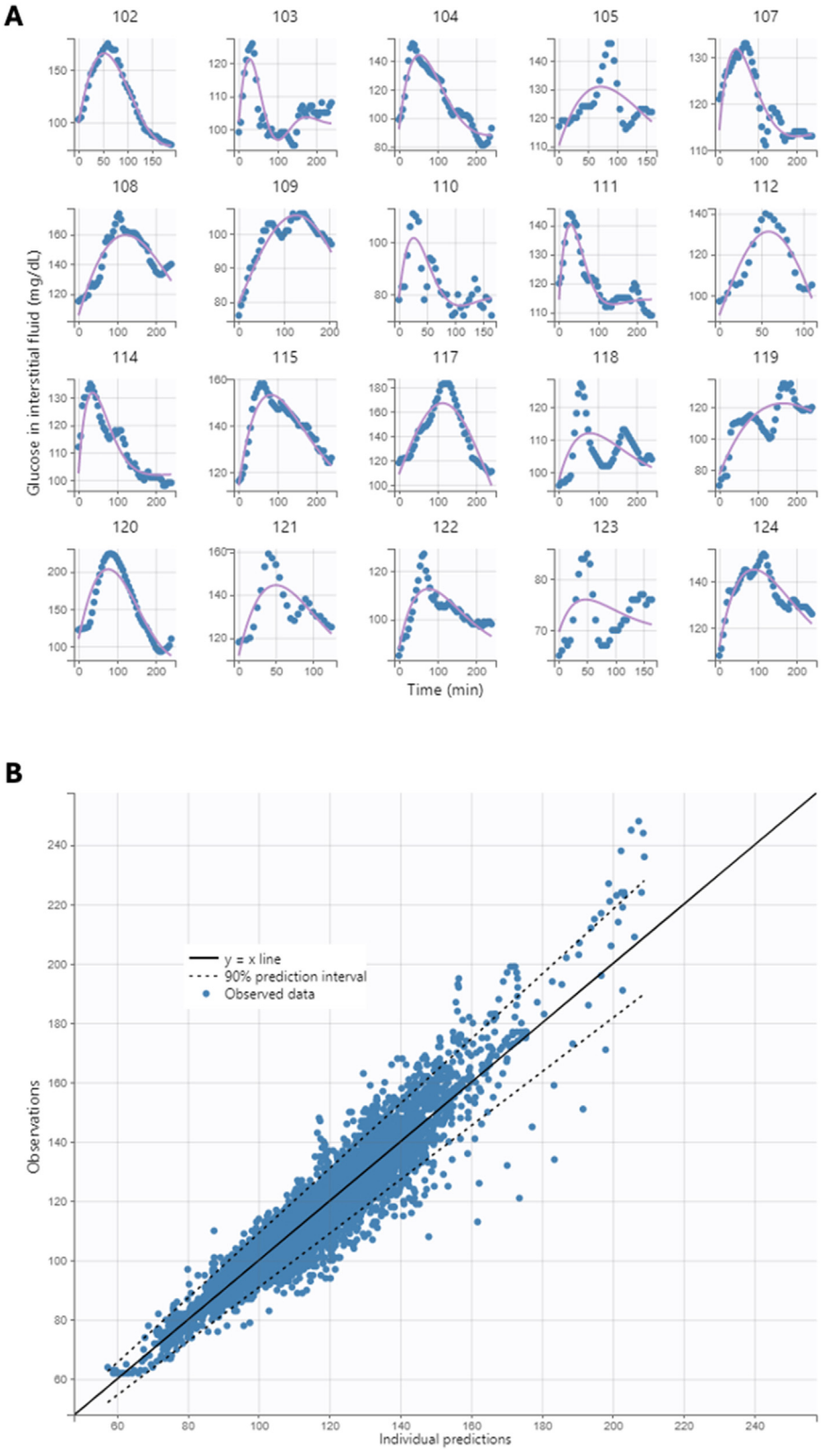

FIGURE 1. (A) Glucose response and model predictions (Equation *1*) of the glucose response by continuous glucose monitoring (CGM) sampling after nonstandardized breakfast meals. (B) Individual model fits glucose responses by CGM sampling.

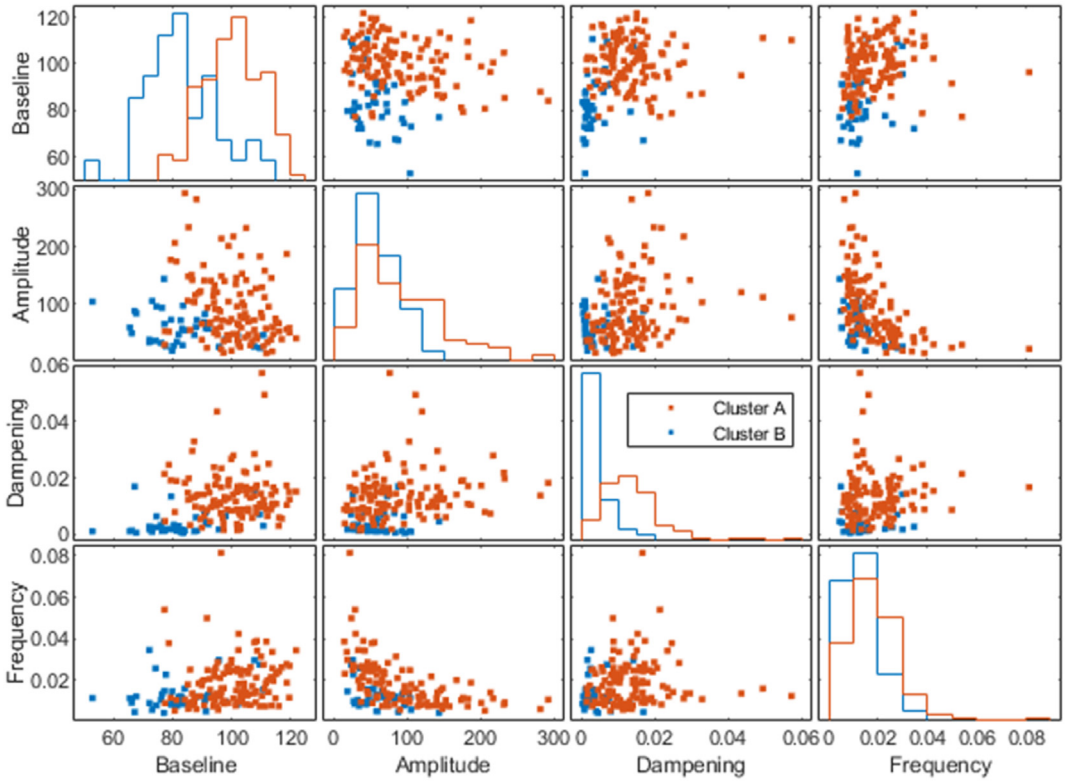

FIGURE 2. Joint parameter distribution obtained by fitting the model in Equation *1* to the glucose response by continuous glucose monitoring sampling after the nonstandardized breakfast meal. The parameter estimation was done using the nonlinear mixed effects framework.

(Figure 1A). Some systematic variance was not captured for larger values as can be seen in Figure 1B. Specifically, individuals with ID numbers 105, 118, and 123 did not yield good fits, because the glucose model (Equation *1*) fails to account for a largely delayed initial phase of the glucose rise. Such model inadequacy resulted in a discrepancy between the predicted and actual glucose dynamic for these subjects. To account for the inadequate fits of these individuals in the cluster identification, they were excluded in a parallel analysis, which however led to similar results (Jaccard similarity index of 0.92). All the model parameters were estimated within statistical confidence relative SE <37%, where <50% is considered a certain estimate [29].

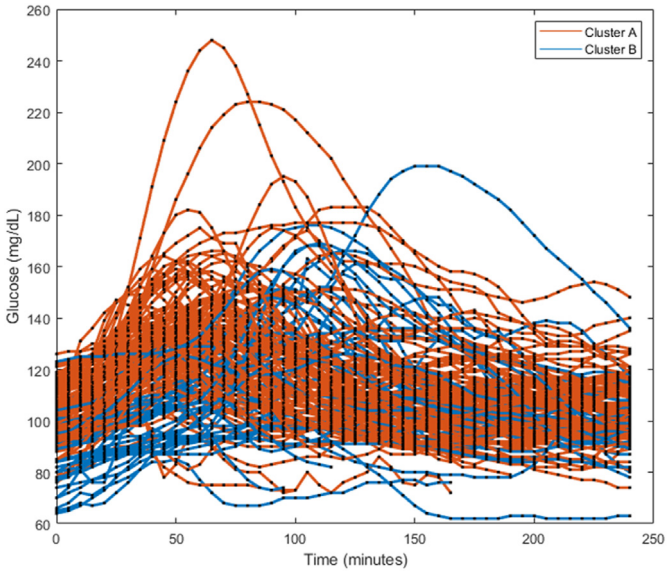

FIGURE 3. Glucose response by continuous glucose monitoring sampling after nonstandardized breakfast meals color-coded by the clusters, estimated as latent covariates in the nonlinear mixed effects framework.

Two clusters characterized by a different glucose response pattern (A and B) after nonstandardized breakfast meals were successfully identified (Figure 2).

Participants in cluster A generally had higher baseline glucose concentrations and a greater amplitude of the postbreakfast glucose response than those in cluster B, together with a higher frequency—indicating that the glucose peak appeared earlier. Participants belonging to cluster A also had a faster rate of glucose disposal, as indicated by the higher damping parameter. These features were also evident when investigating the shape of postbreakfast glucose patterns based on the raw CGM data of the individuals grouped in clusters A (orange) and B (blue), as shown in Figure 3.

The clusters consisted of ~75% individuals grouped in cluster A and 25% in cluster B. The clustering showed a weak association with the participants' country of origin (Chi-square $P = 0.046$), but redoing model fitting and clustering analysis per country yielded similar results (Cohen's kappa, Italy = 0.65, Sweden = 0.64, United States = 0.5).

Clinical, metabolic and habitual diet features and their relation to the 2 identified postbreakfast glucose response clusters

All the parameters—that is, baseline, amplitude, frequency, and damping—identifying the postbreakfast glucose response dynamics were significantly higher in cluster A compared with cluster B (all $P < 0.005$) (Table 1).

No significant differences were found between individuals in clusters A and B for the anthropometric parameters (BMI and waist

TABLE 1
Glucose dynamic parameters and clinical and metabolic characteristics of the individuals allocated in clusters A and B of the postbreakfast glucose response.

	Postbreakfast glucose response cluster A (n = 120)	Postbreakfast glucose response cluster B (n = 39)	P value
Glucose dynamic parameters			
Baseline	100.41 ± 10.20	82.91 ± 12.46	<0.001
Amplitude	93.57 ± 58.27	58.84 ± 28.15	<0.001
Frequency	0.019 ± 0.011	0.013 ± 0.007	0.003
Damping	0.014 ± 0.009	0.004 ± 0.004	<0.001
Clinical and metabolic features			
BMI (kg/m^2)	30.78 ± 3.26	30.37 ± 2.96	0.484
Waist Circumference (cm)	106.42 ± 8.55	105.22 ± 8.84	0.449
Fasting glucose (mg/dL)	103.90 ± 10.34	104.70 ± 10.65	0.703
Fasting insulin (μU/mL)	14.18 ± 7.80	17.63 ± 10.86	0.032
HbA1c (%)	5.47 ± 0.35	5.47 ± 0.37	0.760
Matsuda index	4.10 ± 2.64	3.85 ± 3.05	0.635
β-cell function index (%)	58.57 ± 26.55	52.69 ± 23.49	0.218

Abbreviations: ANOVA, analysis of variance; HbA1c, glycated hemoglobin.
Data are expressed as mean ± SD. P values refer to one-way ANOVA analysis and the results are considered statistically significant for $P < 0.05$.

TABLE 2
The habitual diet composition of the individuals allocated in clusters A and B of the postbreakfast glucose response.

Composition of the habitual diet	Postbreakfast glucose response cluster A (n = 95)	Postbreakfast glucose response cluster B (n = 32)	P value
Energy (kcal/d)	2002 ± 526	1766 ± 455	0.025
Protein (g/d)	82 ± 22	72 ± 21	0.028
Fat (g/d)	87 ± 30	75 ± 22	0.041
Carbohydrates (g/d)	228 ± 66	205 ± 60	0.078
Sugars (g/d)	72 ± 37	70 ± 31	0.758
Fiber (g/d)	21 ± 7.1	19 ± 5.4	0.217
Glycemic Index	59 ± 10	59 ± 8.4	0.933
Alcohol (g/d)	8.6 ± 11.3	9.6 ± 14.3	0.709

Abbreviation: ANOVA, analysis of variance.
Data are expressed as mean ± SD. P values refer to one-way ANOVA analysis and the results are considered statistically significant for $P < 0.05$.

circumference) and the global long-term markers of glucose metabolism [that is, glycated hemoglobin (HbA1c)]. Conversely, plasma concentrations of fasting insulin were higher in cluster B compared with cluster A ($P = 0.032$); however, indices of both body insulin sensitivity (Matsuda) and beta-cell function, did not differ between the 2 clusters (Table 1). Glucose tolerance as well as the insulin levels after the oral glucose load were not different between the 2 clusters (data not shown).

As for differences in the habitual diet composition of participants grouped in the 2 clusters, individuals in cluster A in comparison with those in cluster B were characterized by a higher daily intake of total energy (2002 ± 526 compared with 1766 ± 455 kcal, $P = 0.025$), protein (82 ± 22 compared with 72 ± 21 g, $P = 0.028$), and fat (87 ± 30 compared with 75 ± 22 g, $P = 0.041$). Total carbohydrate content of the habitual diet was also higher among people in cluster A, but the difference did not reach statistical significance (Table 2).

Relationships between the dynamic parameters of the postbreakfast glucose response, individuals' characteristics and their habitual diet

Because the participant segregation into the 2 clusters was based on the combination of 4 glucose dynamic parameters capturing different aspects of the glucose response to the meal, we further explored the relationship between each of these parameters and the individuals' characteristics, as well as the features of their habitual diet (Table 3).

Baseline glucose parameter showed a positive correlation with fasting blood glucose ($r_s = 0.178$, $P = 0.025$) and HbA1c ($r_s = 0.210$, $P = 0.009$), both representing reliable markers of glucose homeostasis in the short and the long term. Among other individual features, baseline glucose was the only parameter directly related to the waist circumference ($r_s = 0.207$, $P = 0.009$). Finally, baseline glucose was directly correlated with energy, protein, and fat content of the habitual diet but not with that of carbohydrates, sugars, and fiber.

No statistically significant relationship emerged between amplitude with either the composition of the habitual diet or the metabolic characteristics of the study participants, though a direct correlation of borderline statistical significance was found with the Matsuda index.

Frequency was correlated with the habitual energy intake ($r_s = 0.182$, $P = 0.040$), and with carbohydrate ($r_s = 0.183$, $P = 0.040$) and sugar ($r_s = 0.182$, $P = 0.040$) content of the habitual diet.

Damping was the parameter with the highest number of correlations with the metabolic features of the study participants: it was inversely correlated with fasting glucose ($r_s = –0.223$, $P = 0.005$) and insulin concentrations ($r_s = –0.267$, $P < 0.001$), and directly correlated with the Matsuda index and the beta-cell function index ($r_s = 0.304$, $P <$ 001 and $r_s = 0.253$, $P = 0.001$, respectively). Moreover, it was directly correlated with the energy ($r_s = 0.212$, $P = 0.017$) and the protein ($r_s =$ 0.186, $P = 0.037$) content of the habitual diet.

CGM-derived metrics of GV for the 2 postbreakfast glucose response clusters

The 2 clusters of postbreakfast glucose response differed also with regard to key CGM-derived measures of GV. As shown in Table 4, cluster A had a higher average interstitial glucose concentration during a 3-d period of CGM than cluster B (6.12 ± 0.50 compared with 5.88 ± 0.62 mmol/L, $P = 0.019$), whereas the coefficient of variation (CV) as

TABLE 3
Correlations between the individuals' clinical and metabolic features, as well as the nutrient composition of their habitual diet, and each dynamic parameter of the postbreakfast glucose response.

	Baseline	Amplitude	Frequency	Damping
Fasting glucose	$r_s = 0.178 P = 0.025$	$r_s = –0.028$	$r_s = –0.017$	$r_s = –0.223$
		$P = 0.725$	$P = 0.829$	$P = 0.005$
Fasting insulin	$r_s = 0.002$	$r_s = –0.131$	$r_s = –0.002$	$r_s = –0.267$
	$P = 0.985$	$P = 0.101$	$P = 0.975$	$P < 0.001$
BMI	$r_s = –0.009$	$r_s = 0.008$	$r_s = –0.002$	$r_s = –0.076$
	$P = 0.907$	$P = 0.924$	$P = 0.980$	$P = 0.339$
Waist circumference	$r_s = 0.207$	$r_s = –0.059$	$r_s = –0.002$	$r_s = –0.136$
	$P = 0.009$	$P = 0.459$	$P = 0.975$	$P = 0.087$
HbA1c	$r_s = 0.210$	$r_s = 0.008$	$r_s = 0.037$	$r_s = –0.149$
	$P = 0.009$	$P = 0.921$	$P = 0.651$	$P = 0.065$
Matsuda index	$r_s = –0.004$	$r_s = 0.141$	$r_s = –0.027$	$r_s = 0.304$
	$P = 0.965$	$P = 0.076$	$P = 0.738$	$P < 0.001$
Beta-cell function index	$r_s = –0.016$	$r_s = 0.024$	$r_s = 0.114$	$r_s = 0.253$
	$P = 0.840$	$P = 0.761$	$P = 0.152$	$P = 0.001$
Energy content of the habitual diet	$r_s = 0.174$	$r_s = 0.053$	$r_s = 0.182$	$r_s = 0.212$
	$P = 0.051$	$P = 0.555$	$P = 0.040$	$P = 0.017$
Carbohydrate content of the habitual diet	$r_s = 0.075$	$r_s = 0.032$	$r_s = 0.183$	$r_s = 0.172$
	$P = 0.400$	$P = 0.721$	$P = 0.040$	$P = 0.053$
Sugar content of the habitual diet	$r_s = 0.109$	$r_s = –0.006$	$r_s = 0.182$	$r_s = 0.114$
	$P = 0.221$	$P = 0.951$	$P = 0.040$	$P = 0.202$
Fiber content of the habitual diet	$r_s = 0.064$	$r_s = –0.031$	$r_s = 0.131$	$r_s = 0.152$
	$P = 0.476$	$P = 0.727$	$P = 0.141$	$P = 0.088$
Protein content of the habitual diet	$r_s = 0.218$	$r_s = 0.062$	$r_s = 0.083$	$r_s = 0.186$
	$P = 0.014$	$P = 0.489$	$P = 0.353$	$P = 0.037$
Fat content of the habitual diet	$r_s = 0.202$	$r_s = 0.064$	$r_s = 0.129$	$r_s = 0.156$
	$P = 0.023$	$P = 0.47$	$P = 0.148$	$P = 0.081$

Abbreviations: ANOVA, analysis of variance; HbA1c, glycated hemoglobin.
r_s: Spearman's coefficient. Results of the Spearman correlation analysis are considered statistically significant for $P < 0.05$.

TABLE 4
Key CGM-derived metrics of glycemic variability of the individuals allocated in clusters A and B of the postbreakfast glucose response.

CGM metric	Postbreakfast glucose response cluster A ($n = 109$)	Postbreakfast glucose response cluster B ($n = 38$)	P value
Mean glucose (mmol/L)	6.12 ± 0.50	5.88 ± 0.62	0.019
SD	0.72 ± 0.23	0.80 ± 0.26	0.081
CV (%)	11.67 ± 3.52	13.43 ± 3.78	0.010
LBGI	0.71 ± 0.64	1.30 ± 0.93	<0.001
HBGI	0.62 ± 0.49	0.69 ± 0.70	0.499
MAGE	1.84 ± 0.64	1.95 ± 0.72	0.392

Abbreviations: ANOVA, analysis of variance; CGM, continuous glucose monitoring; CV, coefficient of variation; LBGI/HBGI, Low Blood Glucose Index and High Blood Glucose Index; MAGE, mean amplitude of glycemic excursions.
Data are expressed as mean ± SD. P values refer to one-way ANOVA analysis and the results are considered statistically significant for $P < 0.05$.

well as the risk of low glucose levels (LBGI) was lower (11.67 ± 3.52 compared with 13.43 ± 3.78, $P = 0.010$ and 0.71 ± 0.64 compared with 1.30 ± 0.93, $P < 0.001$, respectively). Therefore, on the overall, the DGP of people allocated in cluster A was set at higher glucose values than cluster B, thus accounting for a higher average daily glucose, but with a lower risk of hypoglycemia and a lower GV.

Correlations between the dynamic parameters of the postbreakfast glucose response and CGM-derived metrics of GV

As shown in Table 5, the baseline glucose was directly correlated with the mean daily glucose and inversely correlated with SD, CV, and LBGI. The amplitude was directly correlated with all the indices of GV, except for LBGI. An inverse correlation was observed for the frequency parameter with SD ($r_s = –0.179$, $P = 0.031$), and, though marginal, with CV ($r_s = –0.146$, $P = 0.078$). The damping was inversely correlated with all the metrics of GV but not with the mean daily glucose.

Discussion

We found it possible to fit a simple mechanistic model of glucose dynamics to the PPG response measured by CGM after a single non-standardized breakfast consumed in free-living conditions in individuals without diabetes, and we were able to identify 2 different patterns of PPG response. In particular, in indivuduals grouped in cluster A compared with those in cluster B, the pattern was characterized by significantly higher values of all parameters—that is, baseline, amplitude, frequency, and damping identifying the glucose dynamics after food ingestion. This means that people in cluster A, besides having higher glucose values in the post-absorptive phase, were also characterized by a higher and earlier glucose response after a

TABLE 5
Correlations of the dynamic parameters of the postbreakfast glucose response with key CGM-derived metrics of glycemic variability.

	Mean	SD	CV	MAGE	LBGI	HBGI
Baseline	$r_s = 0.419$	$r_s = –0.192$	$r_s = –0.326$	$r_s = –0.154$	$r_s = –0.593$	$r_s = –0.023$
	$P < 0.001$	$P = 0.020$	$P < 0.001$	$P = 0.063$	$P < 0.001$	$P = 0.785$
Amplitude	$r_s = 0.189$	$r_s = 0.287$	$r_s = 0.218$	$r_s = 0.299$	$r_s = –0.109$	$r_s = 0.324$
	$P = 0.022$	$P < 0.001$	$P = 0.008$	$P < 0.001$	$P = 0.188$	$P < 0.001$
Frequency	$r_s = –0.060$	$r_s = –0.179$	$r_s = –0.146$	$r_s = –0.143$	$r_s = –0.044$	$r_s = –0.135$
	$P = 0.469$	$P = 0.031$	$P = 0.078$	$P = 0.085$	$P = 0.596$	$P = 0.105$
Damping	$r_s = –0.070$	$r_s = –0.294$	$r_s = –0.309$	$r_s = –0.244$	$r_s = –0.216$	$r_s = –0.215$
	$P = 0.403$	$P < 0.001$	$P < 0.001$	$P = 0.003$	$P = 0.009$	$P = 0.009$

Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation; LBGI/HBGI, Low Blood Glucose Index and High Blood Glucose Index; MAGE, mean amplitude of glycemic excursions.
r_s: Spearman's coefficient. Results of the Spearman correlation analysis are considered statistically significant for $P < 0.05$.

nonstandardized breakfast, followed by a faster decay of the glucose levels.

Interestingly, individuals with 2 different postbreakfast glucose response patterns did not show any significant differences in terms of clinical and metabolic features, except for lower fasting insulin levels in the study participants allocated in cluster A. In contrast, the dietary habits of the individuals grouped in the 2 clusters were different. In fact, individuals in cluster A were characterized by a higher energy intake, largely attributable to dietary protein and fat, but also to dietary carbohydrates, although this difference was only of borderline statistical significance. This suggests that, regardless of the metabolic and clinical characteristics, in individuals without diabetes, a habitual diet enriched in energy and in macronutrients (and not just in carbohydrates) can induce a postmeal glucose response that is sharp, quick, and rapidly reverting to baseline glucose values. This is in line with the significant direct correlation found between the frequency parameter of the PPG dynamic—referring to the velocity of the PPG response—and dietary energy, carbohydrate, and sugar intake. Further, this is supported by the direct correlations between the energy as well as the protein and fat content of the habitual diet with the baseline glucose concentration, and the direct correlations of the energy and protein content with the damping values. Conversely, no significant correlations were observed between habitual diet features and the amplitude of the postbreakfast glucose response.

So far, the available knowledge about the impact of the habitual diet composition on the PPG response in individuals without diabetes is limited [30]. Furthermore, most of the available studies did not use a direct measurement of the PPG values and utilized the 2-h glucose levels after an OGTT as a proxy for the PPG response [14,15]. However, the relationship between the habitual diet and the PPG response has been given attention in recent studies exploring the variability of the PPG response in large samples of individuals without diabetes. In the PREDICT-1 study, the habitual diet measured by a food frequency questionnaire was only weakly associated with the PPG responses measured as iAUC 0–2 h [15]. Conversely, in another recent study by Reik et al. the habitual carbohydrate intake was negatively associated with glucose iAUC 0–4 h among healthy adults, possibly as a result of adaptive mechanisms occurring when the carbohydrate stimulation of the regulatory system is frequent [31].

As for the metabolic features of the participants, the fasting insulin levels—usually considered a marker of insulin resistance—were lower in those grouping in cluster A. This suggests that participants in this group could be characterized by a lower insulin resistance, which, in turn, might have amplified the effects of the postbreakfast insulin response on the glucose dynamic, particularly inducing a quicker return of the glucose values to baseline. This interpretation is supported by the significant direct correlation of the damping parameter—a marker of the rapidity of blood glucose disposal after the meal—with the Matsuda index and the beta-cell function index, markers of insulin sensitivity (the reverse of insulin resistance) and insulin secretion, respectively. However, it is of note that the beta-cell function index was calculated using only the fasting, 1-h and 2-h glucose values during the OGTT, without including the 30-min evaluation, as desirable.

A major finding of our study is the association between the patterns of the postbreakfast glucose response in free-living conditions and the features of the DGP as estimated by the CGM. In fact, the study participants with pattern A showed a higher average daily glucose, but a lower risk of hypoglycemia and a lower daily glucose variability as compared with people grouping in cluster B. All parameters of the postbreakfast glucose dynamics evaluated by our model contributed to this difference within the DGPs. Indeed, as expected, the average daily glucose concentrations measured by the CGM were significantly correlated with the baseline glucose values and with the amplitude of the postbreakfast glucose responses as assessed by the glucose dynamic model. In other words, the average daily glucose can be predicted by both the fasting glucose values and the magnitude of the glucose response after a nonstandardized breakfast as measured by CGM. Moreover, all parameters of the daily glucose variability measured by the CGM—namely the SD of the daily glucose values, the CV, and the mean amplitude of the glucose excursions—were directly correlated with the amplitude of the postbreakfast glucose response (all statistically significant) and inversely correlated with the baseline (statistically significant for SD and CV), the frequency (statistically significant for SD), and the damping (always statistically significant) as measured by our glucose dynamic model. This indicates that the daily glucose variability increases with the magnitude of the glucose response after a single nonstandardized breakfast, whereas it decreases according to the rapidity of the PPG peak and of its disappearance, as indicated, respectively, by the frequency and the damping parameter of our model of glucose dynamic. In other words, the daily glucose variability is higher when the postmeal glucose response is high, delayed, and prolonged over time. This suggests that the parameters of the glucose response to a single nonstandardized meal evaluated by CGM in free-living conditions could predict the features and the trend of the overall DGP of people without diabetes in the following days. This may have important implications for the extended use of CGM data to predict the individuals' DGPs by evaluating the glucose response to a single meal, thus tailoring dietary strategies to improve the glucose metabolism in the perspective of a reduction of the cardiometabolic risk. In this regard, appropriate intervention studies should follow to test the effects

of specific dietary strategies on the dynamic parameters of the glucose responses so identified; it would be worthwhile, for instance, to see how pattern B of glucose response would look like if the dietary fiber intake was improved.

Strengths of this study are the accurate assessment of the habitual diet of the study population, as well as the evaluation of the glucose response to a nonstandardized breakfast consumed in the context of the habitual lifestyle. Moreover, an important aspect of the methodology here adopted is the continuous measurement of the glucose levels both after the breakfast meal and during the following 3 d.

The study also has some limitations that should be acknowledged. First, the mechanistic model of glucose regulation assumes a linear relationship between glucose and insulin secretion; this feature, although oversimplifying to some extent the contribution of other mechanisms involved, such as the role of incretin hormones and glucagon, makes it more suitable to be used in a setting where insulin measurements cannot be performed, as during CGM executed at home. Second, although the parameters of the reduced model have no one-to-one correspondence to specific body functions, they provide a reliable characterization of the PPG response. Third, the limited number of participants did not allow to perform subgroup analyses like, for instance, that for recruitment site or for sex; this study should therefore be regarded as a pilot one, requiring confirmation through further research. Fourth, given their suitability for enrolment in the MEDGI-Carb trial [20], the participants included in the present study were nondiabetic and characterized by a somewhat similar metabolic profile; this could have reduced the chance of finding associations between patterns of PPG response and metabolic impairments.

In conclusion, this study has clearly demonstrated that 2 different patterns of glucose response after a single nonstandardized breakfast meal could be identified using glucose data collected by CGM, in individuals at high-cardiometabolic risk without diabetes, under free-living conditions—that is, following their habitual lifestyle and dietary habits. These 2 patterns were associated with different energy and nutrient composition of the habitual diet and with different fasting insulin values of the study participants, usually considered as markers of insulin sensitivity. In addition, this study showed that the different dynamic parameters of the postbreakfast glucose response could be used to predict the magnitude and the variability of the daily glucose profile measured by CGM over the following days.

It seems therefore worthwhile to apply the methodology here described to large population groups with an adequate follow-up, to evaluate the long-term association of the individuals' dynamic parameters here identified with the cardiometabolic risk. If confirmed in future studies with an appropriate design (for example, a replicate crossover), these findings could advance the implementation of personalized nutritional strategies targeting specific features of the PPG response (for example, magnitude, velocity of the glucose rise and decay, etc.), with the aim of improving the daily glucose profile, thus contributing to the prevention of diabetes and CVDs.

Author contributions

The authors' responsibilities were as follows – AG, VS, RL, GR: conceived the study idea, designed the research, and analyzed the data; TH, AH, RB, MV, GC, RG: collected the baseline information and biochemical evaluations and had the responsibility for the baseline data; CB, MJ, MW: provided statistical expertise and verified the analyses; AG, GR, RL, VS: drafted the manuscript; AG, VS: had primary responsibility for final content; and all authors: provided critical revision of the manuscript and approved the final manuscript.

Conflict of interest

GR is a member of the Scientific Advisory Board of the Nutrition Foundation of Italy and the Istituto Nutrizionale Carapelli Foundation; he is a member of the Health and Wellbeing Advisory Board of the Barilla G&R. Fratelli Company and Consultant for a Metabolic Health Masterclass sponsored by Nestlè. RB is currently employed by ADM; the research presented in this paper was conducted in a former role and has no connection with ADM. RL received funding grants from Barilla Center for Food and Nutrition Foundation and from Lantmännen Research Foundation. All other authors report no conflicts of interest..

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Data availability

Because of participant confidentiality and privacy concerns, data cannot be shared publicly and further request about data described in the manuscript should be submitted to annalisa.giosue@unina.it and vikska@chalmers.se.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2024.11.028.

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