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Predictive models of post-prandial glucose response in persons with prediabetes and early onset type 2 diabetes: A pilot study

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Abstract

Objective: Post-prandial glucose response (PPGR) is a risk factor for cardiovascular disease. Meal carbohydrate content is an important predictor of PPGR, but dietary interventions to mitigate PPGR are not always successful. A personalized approach, considering behaviour and habitual pattern of glucose excursions assessed by continuous glucose monitor (CGM), may be more effective.

Research Design and Methods: Data were collected under free-living conditions, over 2 weeks, in older adults (age 60 ± 7, BMI 33.0 ± 6.6 kg/m^2), with prediabetes ($n = 35$) or early onset type 2 diabetes ($n = 3$), together with sleep and physical activity by actigraphy. We assessed the predictive value of habitual CGM glucose excursions and fasting glucose on PPGR after a research meal (hereafter MEAL-PPGR) and during an oral glucose tolerance test (hereafter OGTT-PPGR).

Results: Mean amplitude of glucose excursions (MAGE) and fasting glucose were highly predictive of all measures of OGTT-PPGR (AUC, peak, delta, mean glucose and glucose at 120 min; R^2 between 0.616 and 0.786). Measures of insulin sensitivity and β-cell function (Matsuda index, HOMA-B and HOMA-IR) strengthened the prediction of fasting glucose and MAGE (R^2 range 0.651 to 0.832). Similarly, MAGE and premeal glucose were also strong predictors of MEAL-PPGR (R^2 range 0.546 to 0.722). Meal carbohydrates strengthened the prediction of 3 h AUC (R^2 increase from 0.723 to 0.761). Neither anthropometrics, age nor habitual sleep and physical activity added to the prediction models significantly.

Conclusion: These data support a CGM-guided personalized nutrition and medicine approach to control PPGR in older individuals with prediabetes and diet and/or metformin-treated type 2 diabetes.

KEYWORDS
carbohydrates, glucose, post-prandial glucose response, prediabetes

1 | INTRODUCTION

1.1 | Background/rationale

Exposure to elevated post-prandial glucose is a risk factor for type 2 diabetes, and for cardiovascular disease (CVD) in people with[1] and without[2] diabetes. It is a stronger predictor of CVD events than fasting glucose[3] and increased mortality.[4] Although the post-prandial glucose response (PPGR) is largely driven by meal carbohydrates (CHO), studies on best dietary approach to limit PPGR have shown mixed results.[5] Glycaemic response assessed by continuous glucose monitoring system (CGM) can display substantial interindividual variability to identical meals.[6] This is in part explained by meal context (size, frequency, timing, sequence, interval with previous meal and day-to-day variability),[7,8] meal CHO[9] and variability of behaviour including sleep[10] and physical activity.[11] The ever-growing use of personal self-tracking devices such as CGM, ActiGraph and food logging smartphone applications (app) allows for better characterization of individual phenotypes that contribute to PPGR. However, the various inputs from these devices generate a large amount of data that still need integration into actionable tools to assist in defining personalized dietary approaches to improve PPGR.

1.2 | Objectives

The goal of this pilot study was to investigate the predictive values of sleep, physical activity and diet, as well as free-living glucose parameters on PPGR in older adults with overweight or obesity and prediabetes or early onset type 2 diabetes. We hypothesized that the contribution of habitual average glucose excursions and fasting glucose to PPGR would be modulated by sleep and physical activity, as well as indices of insulin secretion and insulin sensitivity.

2 | METHODS

2.1 | Study design

Thirty-eight adult participants enrolled in the NY-TREAT trial[12] after signing informed consent, and wore a CGM for 2 weeks at baseline under three different conditions: (1) ambulatory free living (days 1–12); (2) a 24-h calorie-, composition- and time-controlled mixed meals (day 13); (3) a 2-h 75 gr oral glucose tolerance test (OGTT, day 14). During these 2 weeks, participants completed up to six 24-h dietary recalls with the Automated Self-Administered Dietary Assessment Tool (ASA24®), and time-stamped photos of all eating occasions (EO) in real time with the validated myCircadianClock app (mCC)[13]; in addition, they underwent phenotyping of sleep and physical activity by actigraphy. All study visits took place in a single academic hospital in New York City. Recruitment took place between June 2021 and June 2024. For this study, only baseline data collected over 2 weeks prior to randomization was used for analyses.

2.2 | Participants

Inclusion and exclusion criteria have been described previously.[12] In brief, participants were between the ages of 50 and 75 years, with overweight or obesity (body mass index [BMI] 25–44.9 kg/m^2), with prediabetes or type 2 diabetes treated with diet and/or metformin and HbA1C <7.5%, with a habitual long daily eating window (≥14 h) and sleep duration of at least 6 h. The diagnostic of diabetes or prediabetes was initially self-reported and confirmed by (1) chart review and documentation of HbA1C history when available; (2) an HbA1C ≥ 6.5% at screening and/or; (3) ADA criteria for glucose levels during the 75 gr OGTT, that is, a fasting glucose ≥126 mg and a 2-h plasma glucose level ≥200 mg/dL during the OGTT. Exclusion criteria included history of sleep disorders, shift work, bariatric surgery and current engagement in weight loss with or without medication.

2.3 | Continuous glucose monitoring (CGM)

Interstitial glucose was recorded continuously for 2 weeks every 15 min with a CGM (Abbott Freestyle Libre Pro, Abbott Park, IL, USA)[14] placed on the non-dominant upper arm during the first visit (Supplemental Figure 1). Participants were blinded to the data. At the end of the 2 weeks, CGM data were downloaded from LibreView software[14] and reviewed. Glucose readings obtained on the day of CGM insertion until 4:00 h the following day were removed from analyses, to allow for equilibrium. Data generated with CGM were computed with EasyGV v8.6 software,[15] and included: (1) mean glucose, (2) mean amplitude of glycaemic excursion (MAGE) ignoring excursions of 1 Standard Deviation (SD) or less, (3) SD of glucose as a marker of glucose variability (GV).

2.4 | Physical activity and sleep

Participants wore the ActiGraph-GT3X on their non-dominant wrist continuously during each 2-week assessment period, except when showering or bathing, to obtain non-invasive measures of sleep and physical activity[16] and completed a sleep log to record wake-up time and in-bed times as a backup measure. Sleep data were validated with a sleep log and include: in-bed time, sleep onset time, wake time, out-of-bed time, total sleep time, sleep onset latency, sleep efficiency, total minutes in bed, wake time after sleep onset, total awakenings after sleep onset, average time per awakening, movement index, fragmentation index and sleep fragmentation index. The manufacturer provided software (ActiGraph LLC, Pensacola, FL) was used to estimate daily/hourly kilocalories, metabolic equivalent of task (METs), amount and per cent of the time in sedentary, light, moderate, vigorous and very vigorous activity.

2.5 | Dietary recalls

Participants were instructed to complete up to six 24-h dietary recalls using the validated web-based, ASA24®[17] on non-consecutive

weekdays and at least one weekend day, with instructions to maintain their typical dietary intake. Participants received email reminders from the study staff to ensure data collection. Responses from dietary recalls were coded and downloaded directly from the ASA24® backend, it included parameters of dietary intake, including caloric intake, grams of carbohydrates (CHO), protein, total fat, sugar, fibre and alcohol. Participants also logged in real time their dietary intake using the mC app.

2.6 | Research meals

During the first 12 days of the 2-week assessment, participants followed a free-living routine and did not receive any dietary instruction. They returned to the Clinical Research Center (CRC) on day 13 and were given a personalized eucaloric diet with calorie needs calculated with the Mifflin-St. Jeor equation[18] and the activity factor reported in the International Physical Activity Questionnaires (IPAQ).[19] The 24-h macronutrient composition was identical for all participants: 56%–59% carbohydrates, 14%–17% protein and 26%–28% fat. The timing of the meals was controlled and identical for all participants. Breakfast (9:00 h, 30% kcal) and lunch (12:30 h, 30%kcal) were consumed in the CRC, and dinner (18:00 h, 30% kcal) and evening snack (22:00 h, 10% kcal) at home. Participants logged the beginning and the end of all research meals by time-stamped-photo with the mCC app, and returned containers, which were inspected for completion of meals. Participants were instructed to eat all research meals without adding any supplements. The breakfast on day 13 was used as a mixed meal test to study PPGR.

2.7 | Oral glucose tolerance test (OGTT)

Participants underwent a 2-h 75 grams OGTT on day 14, following a 24-h controlled eucaloric diet and after 10-h overnight fast. On the morning of day 14, an intravenous catheter was inserted in an antecubital vein by a research nurse. Blood samples at −15 and 0 min were obtained immediately before 75 grams glucose drink at 8:00 AM, and again at 15, 30, 60, 90 and 120 min after the drink, before being centrifuged, aliquoted and stored at −80C.

2.8 | Variables

Delta (Δ) glucose was the difference between peak glucose and fasting glucose. Total area under the curve (tAUC) was calculated with the trapezoid method for glucose and insulin; Homeostatic Model Assessment of beta cell function (HOMA-B) = 20 × fasting insulin (mU/mL)/fasting glucose (mg/dL) −63; insulin sensitivity by the Matsuda index, calculated as: 10000/([fasting insulin (mU/mL) × fasting glucose (mmol/L)] × [mean OGTT insulin (mU/mL) × mean OGTT glucose (mmol/ L)]), and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), calculated as [fasting insulin (mU/ mL) × fasting glucose (mmol/L)]/22.5 (69–71); the insulinogenic index (IGI) as [Δinsulin (30–0 min) (μU/mL)/Δglucose (30–0 min) (mg/dL)] or as Total AUC insulin/ total AUC glucose; Disposition index or the product of IGI and HOMA-IR.

The PPGR during the OGTT, or OGTT-PPGR was assessed as mean blood glucose 2-h post oral glucose load, Δ glucose rise from fasting to peak glucose, 2 h-total AUC glucose and glucose at 120 min.

The PPGR during the first controlled meal (breakfast) on day 13 (MEAL-PPGR) was assessed as the 3-h mean CGM glucose after the start of the meal, Δ glucose rise from pre-meal glucose to peak glucose in the following 3-h and 3 h-total AUC glucose.

2.9 | Statistical analyses

Linear regressions were used to build simple, clinical and research predictive models of OGTT-PPGR. We first tested a simple model using MAGE measured by CGM over the 2-week assessment, and fasting blood glucose on day 14, the day of the OGTT, as predictors, and various measures of OGTT-PPGR described above as dependent variables or outcomes. We then tested a clinical model adding to fasting glucose and MAGE, the waist circumference, the BMI and the preceding ecological assessment of habitual behaviour measured over 2 weeks by actigraphy (sleep, physical activity) or self-reported (diet composition), as predictors, with PPGR as outcome. Finally, we tested a research model, adding calculations of insulin resistance, the HOMA-IR and the Matsuda index to other predictors, with PPGR as outcome. The construction of predictive models for MEAL-PPGR was similar as described above for OGTT-PPGR but using, in addition to MAGE, the premeal CGM glucose reading instead of the fasting glucose, as predictors, in addition to the other predictors described above, and with MEAL-PPGR variables described above as outcomes. All models were assessed using SAS PROC GLM (version 9.4), with p-value <0.05 considered statistically significant and with the R^2 an indicator of the performance of each model.

3 | RESULTS

3.1 | Participants

A total of 38 participants, 13 men, mean age 60.4 ± 7.0 years, mean BMI 33.0 ± 6.6 kg/m2, 36 with prediabetes and two with diabetes, one of 15 months known diabetes duration the other one diagnosed during the OGTT, seven on metformin, 28% Hispanic or Latino, 44% Black, 12% Asian, 28% White, 16% other or more than on race, completed the baseline assessment (Please see flow diagram in supplemental). Average diet composition, and composition of day-13 breakfast research meal and evening snack are shown in Table 1. Average total sleep time was 452.1 ± 107.6 min and sleep fragmentation index 13.8 ± 10.1. Participants spent 52.7 ± 8.3% of their time in sedentary activity, with an average metabolic equivalent (METS) of 1.47 ± 0.21. CGM and OGTT glucose variables are presented in Table 2.

TABLE 1 Habitual diet composition by repeated ASA24 diet recalls ($n = 3$ to 6), day 13 breakfast meal nutrient composition, and day 13 evening snack nutrient composition.

	Mean ± SD	Min	Max	Median
Habitual diet composition				
Kcal	1908 ± 825	648	7048	1767
CHO (gr)	203 ± 112	49.1	931.1	187.0
CHO %	42.6 ± 11.6	13.1	73.4	41.9
PROT (gr)	77.7 ± 34.9	24.1	214.2	71.0
PROT %	17.0 ± 5.90	5.68	35.1	16.2
FAT (gr)	87.0 ± 46.4	14.9	333.5	78.6
FAT %	40.4 ± 9.82	16.1	76.6	41.0
Fibre (gr)	20.7 ± 13.1	2.06	83.2	16.7
Sugar (gr)	81.2 ± 51.0	6.74	350.6	72.9
Day 13 breakfast meal composition				
Kcal	646 ± 139	388	1008	605
CHO (gr)	113 ± 33.0	61.46	191	113
CHO (%)	69.1 ± 9.01	46.9	76.6	75.4
PROT (gr)	21.8 ± 6.3	13.8	36.1	19.1
PROT (%)	13.6 ± 3.03	9.92	20.7	12.2
FAT (gr)	14.2 ± 4.32	8.78	25.4	12.4
FAT (%)	20.6 ± 8.03	14.2	37.8	15.8
Fibre (gr)	10.8 ± 2.7	5.496	17.26	10.06
Sugar (gr)	55.1 ± 16.3	29.6	86.7	51.0
Meal duration (mins)	26.1 ± 10.7	9	63	24
Day 13 evening snack composition				
Kcal	213 ± 45	162.6	358.8	194.7
CHO (gr)	21.7 ± 14.6	5.9	55.9	21.6
CHO (%)	41.6 ± 25.0	14.1	92.0	45.1
PROT (gr)	6.0 ± 2.3	3.5	12.6	4.9
PROT (%)	11.3 ± 3.02	6.53	21.5	10.1
FAT (gr)	12.9 ± 7.6	1.26	31.5	11.7
FAT (%)	54.0 ± 24.8	5.28	79.1	54.3
Sugar (gr	7.6 ± 6.2	0.876	21.862	7.9125
Fibre (gr)	5.1 ± 1.7	0.611	6.793	5.896

Kcal: kilocalories; CHO: carbohydrates; PRO: protein; FAT: fat.

3.2 | Prediction of OGTT-PPGR

3.2.1 | Simple and clinical predictive models

Both blood fasting glucose and MAGE (simple model) were strongly associated with mean glucose, peak glucose, Δ glucose, AUC glucose and 120 min glucose (R^2 between 0.616 and 0.786) (Table 3).

Neither anthropometrics (BMI, waist circumference), age, 2-week average sleep duration or sleep fragmentation, 2-week average step count, nor the habitual average self-reported CHO intake were associated with any of the OGTT-glucose outcomes nor enhanced the simple model prediction when added individually (data not shown). The preceding evening 22:00 h snack CHO content was associated with AUC glucose ($p = 0.04$) with a trend for mean glucose ($p = 0.07$), Δ glucose ($p = 0.05$) and peak glucose ($p = 0.05$), and strengthened the prediction of the simple model when added to fasting glucose and MAGE (R^2 values 0.620 to 0.811, $p < 0.05$) (Table 3).

3.2.2 | Research models

When added separately to the simple model, the Matsuda index and HOMA-B were each associated with all OGTT-glucose outcomes with only a trend for 120 min glucose ($p = 0.07$ and 0.06 respectively). HOMA-IR was significantly associated with all outcome variables. The Matsuda index, HOMA-B and HOMA-IR each strengthened the prediction (Table 3). IGI was not associated with OGTT-PPGR outcomes.

TABLE 2 Glucose variables during the oral glucose tolerance test and derived from the CGM.

	Mean ± SD	Min	Max	Median
OGTT				
Fasting glucose (mmol/L)	5.93 ± 0.75	4.92	8.59	5.83
120 min glucose (mmol/L)	8.60 ± 3.43	4.63	20.09	7.30
Peak glucose (mmol/L)	10.68 ± 3.06	6.30	20.09	10.42
Δ peak−fasting glucose (mmol/L)	4.76 ± 2.56	1.09	12.08	4.43
2-h AUC (mmol/L/2 h)	1077 ± 283	529	1875	1050
Mean 2-h glucose (mmol/L)	8.95 ± 2.35	4.62	15.79	8.66
IGI	8.91 ± 49.9	−0.150	320.7	0.90
HOMA-IR	4.32 ± 3.54	0.71	17.90	3.32
HOMA-B	7.87 ± 7.19	2.35	38.04	6.08
Matsuda index	3.21 ± 2.38	0.63	12.66	2.65
CGM				
Fasting glucose (mmol/L)	5.21 ± 0.99	3.22	8.44	5.02
180 min glucose (mmol/L)	5.37 ± 1.74	2.94	10.99	5.02
Peak glucose (mmol/L)	8.24 ± 2.44	3.44	14.71	8.21
3-h AUC (mmol/L/3 h)	1308 ± 427	346	2523	1251
Mean 3-h glucose (mmol/L)	6.33 ± 1.85	3.29	12.01	5.96
GV (%)	21.13 ± 6.95	5.22	40.03	21.00
MAGE (mg/dL)	51.1 ± 22.4	0.0	105.6	49.0

Note: OGTT: 2 h AUC: total area under the curve for glucose over the 2 h of the OGTT; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; HOMA-B = Homeostatic Model Assessment of beta cell function; IGI = insulinogenic index; CGM: CGM-glucose values during research breakfast meal on day 13 (fasting, 180 min glucose, peak glucose, 3-h mean glucose, 3-h AUC glucose), and CGM-derived variables from the 2-week assessment period: GV = glucose variability; MAGE = mean amplitude of glycaemic excursion.

3.3 | MEAL-PPGR

3.3.1 | Simple and clinical predictive models

Both premeal CGM glucose and MAGE (simple model) were strongly associated and predictors (R^2 range 0.546 and 0.722) of meal-derived glucose values (mean, peak, 3-h AUC glucose and 180 min glucose (Table 4)). When added to the simple model, BMI, waist circumference, age, average self-reported CHO intake, average sleep or physical activity (clinical models) showed no significant associations with any MEAL-PPGR outcome (data not shown).

The overall CHO content of the meal, but not the sugar content alone, was associated with AUC glucose only. When added separately or together to the simple model, they tended to strengthen the prediction. The meal duration did not associate with any outcomes.

3.3.2 | Research models

The Matsuda index was only associated with mean 3-h post-meal glucose ($p = 0.03$), and HOMA-IR showed a trend for association with 3-h post-meal glucose ($p = 0.08$). Neither HOMA-B nor IGI was associated with any meal-related glucose outcomes. (Table 4).

3.4 | Diabetes status

While the distribution of participants with prediabetes and type 2 diabetes was unbalanced, analyses were also re-run excluding the two participants without type 2 diabetes. The trend of the results were overall not very different from results obtained with the entire cohort, even if some subtle differences emerged (Please see Supplemental).

4 | DISCUSSION

In this pilot study, we aimed to develop prediction models to investigate the factors that influence PPGR response to a 75 gr of oral glucose and to a kilocalories- and CHO-controlled breakfast meal in individuals with prediabetes or early onset type 2 diabetes. We capitalized on CGM data, habitual sleep, physical activity and diet collected over 2 weeks. We tested three types of models: a simple model that could be used in all patients wearing a CGM (simple model), a clinical model that could easily be used in clinical practice as it requires non-invasive monitoring of behaviour and simple anthropometrics and a third 'research' model requiring an OGTT with glucose and insulin assays.

We show that both fasting glucose and 2-week average glucose excursions (MAGE) are strong predictors of PPGR after oral

TABLE 3 Simple, clinical and research predictive models of OGTT-PPGR.

Predictors	Outcomes				
	2-h mean	Δ glucose Peak-0	tAUC	120 min	PEAK
Simple model					
Fasting glucose	<0.0001	0.016	<0.0001	0.005	<0.0001
MAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
R^2	0.784	0.696	0.786	0.616	0.787
Clinical models					
Fasting glucose	<0.0001	0.017	<0.0001	0.005	<0.0001
MAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
BMI	0.422	0.346	0.303	0.455	0.346
R^2	0.789	0.704	0.793	0.622	0.793
Fasting glucose	<0.0001	0.017	<0.0001	0.008	<0.0001
MAGE	0.0001	<0.0001	0.0001	0.002	<0.0001
WC	0.127	0.068	0.107	0.217	0.068
R^2	0.794	0.699	0.799	0.601	0.802
Fasting glucose	<0.0001	0.019	<0.0001	0.006	<0.0001
MAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
AGE	0.471	0.447	0.539	0.292	0.447
R^2	0.788	0.701	0.789	0.628	0.791
Fasting glucose	<0.0001	0.019	<0.0001	0.006	<0.0001
MAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
TST	0.546	0.651	0.571	0.717	0.651
R^2	0.787	0.698	0.788	0.617	0.788
Fasting glucose	<0.0001	0.014	<0.0001	0.005	<0.0001
MAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
SFI	0.492	0.553	0.464	0.669	0.553
R^2	0.787	0.699	0.790	0.618	0.789
Fasting glucose	<0.0001	0.013	<0.0001	0.005	<0.0001
MAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
STEPS	0.477	0.371	0.491	0.689	0.371
R^2	0.788	0.703	0.789	0.618	0.792
Fasting glucose	<0.0001	0.008	<0.0001	0.005	<0.0001
MAGE	<0.0001	<0.0001	<0.0001	0.0002	<0.0001
SNACK CHO	0.066	0.053	0.042	0.531	0.053
R^2	0.805	0.728	0.811	0.620	0.810
Research models					
Fasting glucose	<0.0001	<0.0001	<0.0001	0.044	0.0002
MAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
MI	0.007	0.005	0.007	0.073	0.005
R^2	0.826	0.760	0.829	0.650	0.832
Fasting glucose	<0.0001	0.0043	<0.0001	0.0018	<0.0001
MAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
HOMA-B	0.013	0.017	0.016	0.055	0.017
R^2	0.821	0.743	0.820	0.656	0.820
Fasting glucose	<0.0001	0.116	<0.0001	0.049	0.0001
MAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
HOMA-IR	0.016	0.036	0.020	0.027	0.035

TABLE 3 (Continued)

Predictors	Outcomes				
	2-h mean	Δ glucose Peak-0	tAUC	120 min	PEAK
R^2	0.819	0.733	0.818	0.668	0.813
Fasting glucose	<0.0001	0.019	<0.0001	0.0058	<0.0001
MAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
IGI	0.135	0.554	0.086	0.863	0.554
R^2	0.798	0.699	0.804	0.616	0.789

Note: Predictors: BMI = body mass index; fasting glucose; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; HOMA-B = Homeostatic Model Assessment of β-cell function; IGI = insulinogenic index; MAGE = mean amplitude of glycaemic excursion; MI = Matsuda index; snack CHO = preceding evening snack carbohydrate; SFI = sleep fragmentation; TST = total sleep time; WC = waist circumference. Outcomes: 2 h-mean = average of glucose values during the 2 h after oral glucose; Δ glucose = peak glucose minus fasting glucose; tAUC = 2 h total glucose area under the curve; 120 min: glucose at 120 min; PEAK: highest glucose value during OGTT.

glucose and after breakfast. Both breakfast meal CHO content and the CHO content of the preceding evening snack were also predictors of MEAL-PPGR and OGTT PPGR, respectively. However, contrary to our hypothesis, neither anthropometrics and age nor habitual sleep and physical activity in the preceding 2 weeks contributed significantly to PPGR. Indices of insulin secretion and sensitivity, either measured under fasting condition (HOMA-IR and HOMA-B) or during the OGTT (Matsuda index) were strongly associated with the OGTT-PPGR but were not or only weakly associated with the MEAL-PPGR.

The contribution of post-prandial glucose exposure to HbA1c is greater in individuals with near normoglycaemia, while fasting glucose is the main determinant of HbA1c in individuals with poorly controlled diabetes.[20] The combination of pre-prandial glucose exposure, glycaemic variability and PPGR explained 35% of the variance of HbA1c in individuals without diabetes but PPGR exposure is the strongest predictor.[21] This highlights the importance of understanding the determinants of PPGR in a cohort with prediabetes or early onset type 2 diabetes. We found that the stronger predictors of PPGR were pre-prandial, or fasting glucose, and glucose variability, or MAGE. Others have also shown that MAGE correlates with the one hour glucose during an OGTT in 12 individuals without diabetes[22]; FG was shown to be strongly associated with PPGR in individuals with type 2 diabetes.

As predicted, the CHO content of the breakfast meal was highly predictive of the 3-h PPGR. Many studies have established that the macronutrient composition of a meal, specifically the CHO content, has a direct effect on the PPGR.[8,23] However, the contribution of habitual diet to PPGR has been less studied and appears relatively small. In large studies food groups or nutrients explained only 9% of the variation in PPGR in middle-aged and older adults.[24] In a controlled randomized study, fibre intake was inversely related to change in post-prandial 2-h glucose levels in individuals with impaired glucose tolerance.[25] In our study, we did not find an effect of habitual free-living CHO intake, self-reported by dietary recalls over the 2-week assessment period, on PPGR, likely due to the small size of our cohort. Other meal-related factors impact PPGR: meal sequence and timing,[26] meal duration[27] and sequence of nutrient ingestion.[8] Targeted manipulations of these factors demonstrate their effect on PPGR. For example, a more rapid eating rate is associated with higher glucose excursions in healthy women.[27] In our study, the observed duration of the research breakfast meal, relatively short, was not associated with PPGR.

Insulin resistance is predictive for type 2 diabetes and associates with metabolic abnormalities in fasting conditions. Fewer data are available on how IR affects post-prandial metabolic responses.

In our study, fasting indices of insulin secretion and sensitivity (HOMA-B and HOMA-IR) and the MI were strongly associated with the OGTT-PPGR but were not associated or only weakly with the MEAL-PPGR. This is in agreement with a study showing that together with diet macronutrient composition, fasting insulin resistance was shown to affect post-prandial glycaemic responses in older individuals.[28]

Insulin resistance is associated with abnormal post-prandial metabolism in Finnish individuals with normal glucose tolerance.[29] Detailed metabolomic profiling of post-prandial response to a glucose challenge highlights clear effects of insulin resistance, on many metabolic pathways, including in individuals with prediabetes[30] and non-diabetic individuals.[31]

Contrary to our hypothesis, we found no effect of habitual physical activity, sleep, age and anthropometrics on PPGR. The importance of exercise in decreasing the risk of type 2 diabetes[32] or in ameliorating glycaemic control, assessed by HbA1C, in individuals with type 2 diabetes is well documented.[33] Exercise interventions decrease PPGR. Acute timed post-prandial exercise blunt glucose excursions,[34] regardless of its intensity and training conditions.[35] Short bouts of moderate intensity walking after meals reduced PPGR compared to no exercise.[36] A one-week training with various intensity and duration of exercise decreased PPGR after a 50 gr glucose load in healthy men.[37] However, we found no effect of habitual physical activity (METS and step count), assessed over 12 days, on either meal- or OGTT-PPGR calculated on day 13 and 14 respectively. This is in agreement with others who found no association of 7-day habitual physical activity with 2-h and AUC glucose during an OGTT in adults with IGT or recently diagnosed with diabetes.[38] It is likely that more

TABLE 4 Simple, clinical and research predictive models of MEAL-PPGR.

Predictors	Outcomes			
	3 h mean GLU	3 h tAUC	180 min GLU	PEAK GLU
Simple models				
Pre-meal-GLU	0.03	<0.0001	<0.0001	<0.0001
MAGE	<0.0001	0.0002	0.0108	<0.0001
R^2	0.546	0.722	0.584	0.676
Clinical models				
Pre-meal-GLU	0.03	<0.0001	<0.0001	<0.0001
MAGE	<0.0001	0.0002	0.0097	<0.0001
Steps	0.9055	0.5618	0.1263	0.8418
R^2	0.546	0.725	0.611	0.676
Pre-meal-GLU	0.03	<0.0001	<0.0001	<0.0001
MAGE	0.0001	0.0001	0.0123	<0.0001
TST	0.4276	0.2749	0.8581	0.1201
R^2	0.554	0.731	0.585	0.698
Pre-meal-GLU	0.03	<0.0001	<0.0001	<0.0001
MAGE	0.0001	0.0003	0.0163	<0.0001
SFI	0.7752	0.8759	0.9227	0.3173
R^2	0.547	0.722	0.584	0.685
Pre-meal-GLU	0.02	<0.0001	<0.0001	<0.0001
MAGE	0.0001	0.0002	0.0067	0.0001
AGE	0.3436	0.6992	0.2127	0.4720
R^2	0.557	0.723	0.602	0.680
Pre-meal-GLU	0.05	<0.0001	<0.0001	<0.0001
MAGE	<0.0001	0.0001	0.0097	<0.0001
MEAL-CHO	0.2108	0.0437	0.2000	0.0936
R^2	0.566	0.761	0.622	0.709
Pre-meal-GLU	0.05	<0.0001	<0.0001	<0.0001
MAGE	<0.0001	0.0001	0.0095	<0.0001
MEAL-SUGAR	0.368	0.1769	0.5681	0.2591
R^2	0.556	0.745	0.607	0.696
Pre-meal-GLU	0.04	<0.0001	<0.0001	<0.0001
MAGE	<0.0001	0.0002	0.0136	<0.0001
MEAL-DUR	0.3446	0.4821	0.1442	0.7448
R^2	0.556	0.726	0.609	0.677
Pre-meal-GLU	0.03	<0.0001	<0.0001	<0.0001
MAGE	0.0001	0.0002	0.0205	0.0001
BMI	0.6272	0.9163	0.4118	0.7417
R^2	0.549	0.7220	0.592	0.677
Pre-meal-GLU	0.01	<0.0001	<0.0001	<0.0001
MAGE	0.0034	0.0247	0.3521	0.006
WC	0.3859	0.1237	0.3679	0.1764
R^2	0.544	0.797	0.742	0.709
Research model				
Pre-meal-GLU	0.02	<0.0001	0.0006	0.001
MAGE	<0.0001	0.0002	0.0062	0.0001
MI	0.0304	0.4273	0.6328	0.4274

TABLE 4 (Continued)

Predictors	Outcomes			
	3 h mean GLU	3 h tAUC	180 min GLU	PEAK GLU
R^2	0.596	0.661	0.516	0.614
Pre-meal-GLU	0.02	<0.0001	0.0007	0.0008
MAGE	0.0001	0.0002	0.0065	0.0001
HOMA-B	0.6209	0.4907	0.8058	0.9283
R^2	0.534	0.659	0.514	0.606
Pre-meal-GLU	0.02	<0.0001	0.0007	0.0008
MAGE	0.0002	0.0004	0.0077	0.0002
IGI	0.2635	0.743	0.975	0.5413
R^2	0.549	0.655	0.513	0.611
Pre-meal-GLU	0.07	0.0001	0.0013	0.0019
MAGE	<0.0001	0.0001	0.0072	0.0001
HOMA-IR	0.0778	0.2392	0.9313	0.6777
R^2	0.575	0.669	0.513	0.608

Note: Predictors: BMI = body mass index; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; HOMA-B = Homeostatic Model Assessment of beta cell function; IGI = insulinogenic index; MAGE = mean amplitude of glycaemic excursion; MEAL-CHO = carbohydrate amount of research meal; MEAL-SUGAR = sugar amount of first meal; MEAL-DUR = meal duration; MI = Matsuda index; Pre-meal-GLU = CGM pre-meal glucose; SFI = sleep fragmentation; TST = total sleep time; WC = waist circumference. Outcomes: 3 h-mean = average of CGM glucose values over 3 h after first meal of the day; tAUC = 2 h AUC glucose; 180 min: CGM glucose at 180 min after the meal; PEAK: glucose highest value during the meal.

intense exercise routine and their time in relation to meals is necessary to blunt PPGR.

We found no effect of habitual sleep on PPGR. In the large Predict trial ($n = 953$), poor sleep efficiency and later bedtime routines were associated with more pronounced PPGR to breakfast the following morning.[10] We previously showed that a 6-week intervention that reduced total sleep time by 75 min increased fasting insulin resistance but had no effect on glucose in a cohort of women with normal glucose tolerance.[39]

The absence of effect of age, BMI or waist circumference on PPGR is likely due to a narrow age distribution (50–75 y), and a relatively small sample size. Large epidemiological studies did find that age and BMI and waist circumference[40] were positively associated with 2-h glucose. However, the contribution of age, sex, BMI and ethnicity to overall glucose control was shown to be minimum, compared to PPGR and MAGE, among individuals with type 2 diabetes and HbA1c < 6.5%.[21]

In summary this pilot study shows a strong predictive value of fasting glucose and MAGE, and meal CHO, on PPGR, but no effect of habitual behaviour and diet in older adults with overweight or obesity and prediabetes or diet and/or metformin-treated type 2 diabetes.

Our study has several strengths: assessment of PPGR under two fully controlled conditions, a standardized OGTT and a research MMT, CGM over 2 weeks allowing historical MAGE calculation in parallel with sleep and physical activity and diet recalls. Limitations include the absence of a validation cohort, the lack of controlled ingestion sequence of the meals, lack of assessment of gastric emptying, incretins and glucagon, all important determinant factors of PPGR and the variable composition of the breakfast meal and the evening snack. While 24-h diet kilocalorie composition and meal distribution were identical, the first meal and the evening snacks differed in kilocalorie and CHO for each participant. The unbalanced distribution of participants with prediabetes and type 2 diabetes did not allow to test the effect of diabetes on the models. Future studies will need to test these models in validation cohorts of prediabetes, normoglycemic insulin resistance and diabetes.

In conclusion, CGM provides valuable insights in glucose dynamics and patterns in individuals with overweight and dysglycaemia. Understanding modifiable dietary and behavioural determinants of PPGR will help to develop targeted personalized interventions to improve glucose excursions and reduce CVD risk. Our data support a CGM-guided personalized nutrition and medicine approach to control PPGR in older individuals with prediabetes and diet/metformin-controlled type 2 diabetes.

AUTHOR CONTRIBUTIONS

BL was involved in the conception, design and conduct of the study and interpretation of the results and wrote the first draft of the manuscript. LS SB; D DR; RB, ASG, DD, EM, SP, all contributed to data collection and some data analyses; BC performed data analyses. All authors edited, reviewed and approved the final version of the manuscript. BL is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICT OF INTEREST

The authors declare no conflict of interest pertinent to this work.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request and according to institutional policies.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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