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ORIGINAL ARTICLE

Screening for Impaired Glucose Homeostasis: A Novel Metric of Glycemic Control

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Abstract

Objective: To investigate the use of a mathematical model of glucose homeostasis, fit to continuous glucose monitor data, as a metric of dysfunctional glycemic control.

Patients and Methods: Three hundred eighty four participants recruited from 2 studies between October 2020 and June 2022 were equipped with a continuous glucose monitor, and interstitial glucose data were automatically collected for 2 weeks. The participants were assessed by a physician and diagnosed as being diabetic, prediabetic, or healthy according to the American Diabetes Association guidelines. A mathematical model of glucose homeostasis was fitted to the glucose data, and model parameter values were obtained. The participants were classified into the following 2 groups on the basis of their glucose homeostasis parameters: effective and impaired. Finally, glycemic variability metrics were compared with glucose homeostasis classification.

Results: The homeostasis classification resulted in a specificity, sensitivity of individuals with prediabetes, and sensitivity of individuals with type 2 diabetes (T2D) of 0.78, 0.86, and 1.00, respectively, for women and 0.71, 0.86, and 1.00, respectively, for men. This sensitivity was similar to that of glycated hemoglobin A1c measurement (a sensitivity of 0.89 for women and 0.90 for men for prediabetes and a sensitivity of 1.00 for T2D) and superior to that of the oral glucose tolerance test (a sensitivity of 0.18 for women and 0.24 for men for prediabetes and a sensitivity of 0.75 for women and 0.86 for men for T2D). Overall, the individuals classified as impaired had increased glucose variability metrics than the individuals classified as effective ($P<.05$).

Conclusion: The classification of glucose homeostasis on the basis of mathematical modeling of continuous measurements has promising applications as a new metric of dysfunctional glycemic control.

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Diabetes is a monumental health issue. Nearly half a billion people worldwide have diabetes, and 90%-95% of diabetes cases are individuals with type 2 diabetes (T2D), a condition linked to obesity and lack of exercise.[1] If left untreated, T2D can result in serious health conditions such as heart disease, vision loss, kidney disease, and premature death.[1–3] The screening and monitoring of T2D involve reviewing risk factors such as age, body mass index (calculated as the weight in kilograms divided by the height in meters squared), and family history, and diagnosis relies primarily on glycated hemoglobin A1c (HbA1c) and oral glucose tolerance test (OGTT).[4–6]

At the early prediabetes stage, individuals have a reduced likelihood of progressing to full T2D after lifestyle interventions.[7] Unfortunately, most individuals with prediabetes are unaware of their condition, and an estimated 75 million Americans with prediabetes are currently undiagnosed.[2]

In recent years, continuous glucose monitors (CGMs) have become available to individuals with and without T2D.[8] After applying the sensor to the arm, the device automatically measures the interstitial glucose concentration as frequently as every 5 minutes, eliminating the requirement for multiple daily finger pricks. Besides improved user experience, CGMs provide information-rich time-series data that can be analyzed for not only glucose levels but also the dynamic properties of glycemic variability (GV).[9–12]

An opportunity exists with CGMs to create a T2D prescreening method to assess the risk

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of dysglycemia without requiring a blood draw or visit to a laboratory. Furthermore, CGMs provide an opportunity to assess glucose dynamics in an individual's everyday life, which may provide an additional metric of health that cannot be determined under controlled conditions. Prior attempts at creating analysis methods for CGM data involve construction of an index of GV using CGM features such as mean absolute glucose concentration, glucose standard deviation, and glucose time in range (TIR) of the CGM. Many studies have been conducted to relate current GV metrics to diagnostics, outcomes of diabetes, and other metrics of diabetes control; however, no consensus has been reached on implementation.[10–19] Furthermore, the number of GV metrics can make it difficult to determine the most appropriate or accurate value for a given situation.[9,14,15]

Recently, a mathematical model of glucose homeostasis was developed for CGM data. The model accurately reproduces both positive (hyperglycemic) and negative (hypoglycemic) excursions when combined with a computational procedure that can easily be run on a mobile device. Moreover, pilot studies have suggested that tuned model parameters have the potential to be used as biomarkers for diabetic status.[20,21]

Here, we described a novel analysis method that distinguishes individuals with impaired glucose homeostasis (IGH) from individuals with effective glucose homeostasis (EGH). This method, termed as functional assessment of glucose homeostasis (FLAG), is used to compare the distribution of homeostasis model parameters from CGM data with representative parameter distributions from populations without diabetes, with prediabetes, and with T2D. An individual is classified as having IGH if the observed distribution is closest to representative populations with prediabetes or T2D. The primary end point is to develop a classification system to identify individuals with dysfunctional glucose homeostasis and distinguish individuals with T2D and prediabetes from individuals without a diabetes diagnosis. The sensitivity and specificity of this classification were compared with those of the current American Diabetes Association (ADA) standards for OGTT and HbA1c measurement. Finally, the results of FLAG classification were compared with current GV metrics for a better understanding of group characteristics.

METHODS

Participants and Study Design

One hundred forty two adult participants without a previous diagnosis of T2D or prediabetes were recruited in India. The participants were recruited into 3 cohorts on the basis of the Canadian Diabetes Risk Questionnaire (CANRISK) risk assessment score for T2D[22]: low-to-moderate risk (CANRISK=0-32 points), high risk (CANRISK=33-42 points), and very high risk (CANRISK≥43 points). Additionally, 440 adult participants were recruited in a follow-up study in India. The participants were recruited into 4 cohorts: low-to-moderate risk (CANRISK=0-32 points), high and very high risk but not diagnosed with T2D (CANRISK≥33 points), previous diagnosis of T2D without treatment by medication, and previous diagnosis of T2D with treatment with metformin. All the participants were fitted with an Abbott Freestyle Libre Pro CGM for monitoring of their interstitial glucose concentration automatically every 15 minutes for 14 days. In both the studies, the participants were blinded to their glucose levels. No lifestyle modification or intervention was implemented. The participants were classified by a physician as nondiabetic, prediabetic, and having T2D at the end of the study according to the ADA guidelines.[23] Participants were excluded if their CGM recorded for less than 10 days, demographic information was not collected, or they were on any medication (including metformin). A total of 123 participants from the initial study and 261 participants from the follow-up study were included in the analysis.

All the participants provided informed consent, and the studies received full ethics clearance from Moraya Institutional Ethics Committee (initial study), Saanvi Ethical Research LLP, Jasleen Hospitals Ethics Committee, Mavens Institutional Ethics Committee (follow-up study), and Ontario Tech University's research ethics board (both studies).[24,25] All methods were conducted in accordance with relevant guidelines and regulations.

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Data Analysis

The average glucose concentration, glucose standard deviation, proportion of data under 3.9 mmol/L (time below range [TBR]), proportion of data between 3.9 and 10 mmol/L (TIR), and proportion of data above 10 mmol/L (time above range [TAR]) were calculated from the CGM data. The participants' CGM data yielded 80-100 data segments that exhibited increases in glucose levels (peaks) over 60-300 minutes. These peaks were extracted automatically using methods described by Ng et al.[21] The area under the curve (AUC), maximum glucose values, maximum glucose deviation, and peak length were calculated for each peak. The AUC was calculated using the following 2 methods: 1) AUC, calculated by integrating the curve using the trapezoid rule, using the difference between the curve and initial glucose value, with all values less than the initial value set to zero; and 2) integrating the curve using the trapezoid rule using the difference between the curve and minimum glucose value (AUCm). The maximum glucose deviation values were calculated as the difference between initial glucose values and maximum glucose values. Peak length is the duration of selected peaks, in minutes.

Functional Assessment of Glucose Homeostasis

The model that FLAG relies on was formulated by Veen et al[20] and is described in equations 1 and 2.

$$\frac{de}{dt} = -A_3 + F(t) - u(e + e_b) \quad [1]$$

$$u = Pe + I \int_{-\infty}^{t} \lambda \exp(-\lambda(t-\tau))e(\tau)d\tau \quad [2]$$

e is the glucose deviation from the glucose baseline, e_b, $F(t)$ is the input function, λ dictates the time delay, A_3 is the base metabolic glucose consumption, and u represents the combined effect of glucose control through hormonal feedback. In earlier models of closed-loop glucose control, combinations of (P)roportional, (I)ntegral, and (D)erivative control have been proposed. The inclusion of derivative control reflects an increase in insulin production when blood glucose concentrations increase, which is speculated to correspond to first-phase insulin release that takes place within 10 minutes of a rise in blood glucose level.[26] This first-phase response, however, has been disputed, especially if the rise in blood glucose levels is due to ingested food rather than an intravenous bolus.[27] Moreover, estimating the derivative of a function from noisy measurements is notoriously unstable and could lead to nonphysiologic fluctuations when conforming to selected peaks. For these reasons and the capability of the proportional-integral model to accurately reproduce both hyperglycemic and hypoglycemic episodes, we chose to exclude derivative control.

All values of the parameters P and I from the homeostasis model from the initial study (n=123) were compiled to form representative parameter distributions for nondiabetic individuals. This was repeated for individuals with prediabetes and T2D so that each diagnosis had a representative parameter distribution for each P and I.

The parameter distribution for each individual was compared with the representative parameter distributions for each diagnosis. The area between an individual's P and I distributions were compared with the representative distributions for individuals without diabetes, individuals with prediabetes, and individuals with T2D for a total of 6 calculated areas. The areas corresponding to the 2 parameter values were combined for each class using a weighted sum (equation 3).

$$k_1 \begin{bmatrix} P \text{ Area to NonDiabetic} \\ P \text{ Area to Prediabetic} \\ P \text{ Area to T2D} \end{bmatrix} + k_2 \begin{bmatrix} I \text{ Area to NonDiabetic} \\ I \text{ Area to Prediabetic} \\ I \text{ Area to T2D} \end{bmatrix} = \begin{bmatrix} \text{Total Area to NonDiabetic} \\ \text{Total Area to Prediabetic} \\ \text{Total Area to T2D} \end{bmatrix} \quad [3]$$

The glucose homeostasis profile of an individual was assumed to be closest to the diabetic class (nondiabetic, prediabetic, and T2D), with the closest parameter distribution to their own. If the minimum area corresponded to the prediabetic or T2D classification, the individual was classified as having IGH. If the minimum area corresponded to that of nondiabetics, the individual was classified as having EGH. k_1 and k_2 were selected to minimize the number of incorrect predictions of the initial calibration dataset such that $k_1+k_2=1$. The optimized k_1 and k_2 were 0.69 and 0.31, respectively, for women and 0.17 and 0.83, respectively, for men.

Calibration of the linear combination parameters and representative parameter distributions was performed using the CGM data from the participants in the initial dataset (n=123). Method validation was performed on the follow-up dataset (n=261) using the same representative distributions and parameter values as in the calibration.

Previous research has indicated that glycemic control can vary between men and women because of differences in hormone concentrations; so, men and women were separated during FLAG implementation and parameter optimization.[28,29]

Statistical Analyses

The accuracy of the method was calculated using the sensitivity and specificity of FLAG in the 3 diabetic classes. A positive result was an EGH classification if the individual was nondiabetic and an IGH classification if the individual had a prediabetes or T2D diagnosis. Correlations were determined using Pearson correlation, and GV metrics were compared among the diabetic statuses using the Kruskal-Wallis nonparametric test with Dunn test post hoc. The significance of the result of FLAG classification GV metrics was determined using 1-sided Mann-Whitney U test, and normality was assessed using the Kolmogorov-Smirnoff test. A P value less than .05 was considered statistically significant.

RESULTS

The participants' demographic information is presented in Table 1, and the results of the comparison of OGTT and HbA1c measurement with ADA diagnosis are presented in Table 2. Participants from the initial study were included in the OGTT comparison, and participants from the initial and follow-up studies were included in the HbA1c comparison. Furthermore, OGTT alone was unable to identify 15 women and 24 men with

TABLE 1. Participants' Demographic Information[a,b]

Characteristic	Calibration study (n=121)			Validation study (n=261)		
	T2D	Prediabetes	Nondiabetic	T2D	Prediabetes	Nondiabetic
Number	18	46	57	71	52	138
Sex (male/female)	14/4	29/17	28/29	48/23	27/25	84/54
Age, y	45.400±9.104	40.462±9.127	38.429±10.251	50.098±9.664	44.36±10.842	32.344±11.079
BMI, kg/m^2	31.292±4.472	28.629±4.356	27.719±5.125	27.022±4.839	27.155±4.334	25.580±4.905
Height, cm	1.612±0.079	1.590±0.093	1.628±0.084	1.647±0.097	1.657±0.077	1.636±0.095
Weight, kg	81.375±13.874	72.469±12.609	74.485±13.690	73.037±12.553	74.806±13.740	70.719±11.830
HbA1c, %	7.772±1.753	5.897±0.332	5.279±1.190	8.313±2.037	5.980±0.235	5.099±0.387
2h-OGTT, mmol/L	12.020±5.224	6.856±1.589	5.339±3.422	N/A	N/A	N/A
FBG, mmol/L	8.000±3.276	5.426±0.607	5.046±1.769	N/A	N/A	N/A
Systolic blood pressure, mmHg	123.00±6.782	124.290±12.984	120.091±8.072	127.658±9.574	125.761±11.488	122.533±9.630
Diastolic blood pressure, mmHg	80.833±6.450	82.158±10.623	80.036±5.095	84.051±6.620	82.848±6.828	81.350±7.001

[a]2h-OGTT, 2-hour oral glucose tolerance test; BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; T2D, type 2 diabetes.
[b]Values are displayed as mean ± SD.

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TABLE 2. Confusion Matrices of Diabetic Status Prediction on the Basis of Oral Glucose Tolerance Test and Glycated Hemoglobin[a]

	Prediction					
Physician diagnosis	ND	PD	T2D	Recall	Recall (grouped)[c]	Specificity/sensitivity[d]
OGTT prediction[b]						
Female						
ND	29	0	0	1.00	1.00	Specificity
PD	14	3	0	0.18	0.18	PD sensitivity
T2D	1	1	2	0.50	0.75	T2D sensitivity
Male						
ND	28	0	0	1.00	1.00	Specificity
PD	22	7	0	0.24	0.24	PD sensitivity
T2D	2	1	11	0.79	0.86	T2D sensitivity
HbA1c prediction[e]						
Female						
ND	83	0	0	1.00	1.00	Specificity
PD	4	37	1	0.88	0.90	PD sensitivity
T2D	0	0	27	1.00	1.00	T2D sensitivity
Male						
ND	112	0	0	1.00	1.00	Specificity
PD	6	50	0	0.89	0.89	PD sensitivity
T2D	0	2	60	0.97	1.00	T2D sensitivity

[a]HbA1c, glycated hemoglobin A1c; ND, nondiabetic; OGTT, oral glucose tolerance test, PD, prediabetic, T2D, type 2 diabetic.
[b]Diagnosis was performed by a physician according to American Diabetes Association criteria. Individuals predicted to be nondiabetic solely according to their OGTT had an OGTT glucose concentration of less than 140 mg/dL. Individuals predicted to be prediabetic according to their OGTT had an OGTT glucose concentration of 140-200 mg/dL. Individuals predicted to have T2D had an OGTT glucose concentration of more than 200 mg/dL after 2 hours.[23]
[c]Grouped recall assumes a correct prediction when the diagnostic predicts either PD or T2D when the individual is PD or has T2D.
[d]Specificity and sensitivity correspond to the recall values within the same row.
[e]Diagnosis was performed by a physician according to American Diabetes Association criteria. Individuals predicted to be nondiabetic solely according to their HbA1c had an HbA1c level of less than 5.7%. Individuals predicted to be prediabetic according to their HbA1c had an HbA1c level 5.7%-6.4%. Individuals predicted to have T2D had an HbA1c level of more than 6.5%.[23]

prediabetes or T2D. The OGTT values for these individuals were below 140 mg/dL; so, if this method were used independently, it would inaccurately classify them as being nondiabetic. The HbA1c results were slightly better, in which only 4 women and 6 men with prediabetes or T2D would not have been identified with HbA1c alone (the HbA1c values were less than 5.7%).

The summary statistics, GV metrics, and homeostasis model parameters of the CGM data can be found in Table 3. Overall, nondiabetic individuals had lower GV metrics than individuals with prediabetes, and individuals with prediabetes had lower GV metrics than individuals with T2D. The correlations between GV metrics and the homeostasis model parameters are displayed in Supplemental Table 1 (available online at http://www.mcpiqojournal.org).

The sensitivity and specificity results of FLAG are displayed in Table 4. When the sensitivity and specificity results of HbA1c measurement and OGTT were compared, both FLAG and HbA1c measurement had a sensitivity of 1.00 for individuals with T2D, in contrast to OGTT, which had a sensitivity of 0.75 (women) and 0.86 (men) for individuals with T2D (Table 2). The FLAG prediabetic sensitivity was 0.86 for both men and women, and HbA1c measurement had a sensitivity of 0.89 and 0.90 for women and men, respectively. Moreover, OGTT had a lower sensitivity toward individuals with prediabetes, with sensitivities of 0.18 and 0.24 for women and men, respectively. Finally, both OGTT and HbA1c measurement had a specificity of 1.00, whereas the FLAG specificity was 0.78 (women) and 0.71 (men).

TABLE 3. Glycemic Variability Metrics Across Diabetic Status

Glycemic variability metric	ND (mean ± SD)	PD (mean ± SD)	T2D (mean ± SD)	KW *P* value	Dunn post hoc *P* value		
					ND vs PD	PD vs T2D	ND vs T2D
Females	n=83	n=42	n=27				
AUC (mmol minutes/L)	572.64±571.04	639.44±529.20	1143.08±1167.52	<.001	<.001	<.001	<.001
AUCm (mmol minutes/L)	644.36±618.24	725.72±575.84	1294.96±1184.68	<.001	<.001	<.001	<.001
Max glucose (mmol/L)	6.07±0.98	6.50±1.04	7.93±2.31	<.001	<.001	<.001	<.001
Max deviation (mmol/L)	1.89±0.77	2.12±0.93	2.82±1.59	<.001	<.001	<.001	<.001
Peak length (minutes)	154.11±72.24	157.56±69.36	194.38±93.19	<.001	.048	<.001	<.001
Mean glucose (mmol/L)	4.66±0.74	4.98±0.62	6.08±1.68	<.001	<.001	<.001	<.001
Glucose SD (mmol/L)	0.91±0.41	1.03±0.27	1.52±0.51	<.001	<.001	<.001	<.001
TIR proportion	0.61±0.25	0.75±0.21	0.80±0.35	.02	.02	.72	0.11
TAR proportion	0.001±0.007	0.002±0.005	0.08±0.19	.36	-	-	-
TBR proportion	0.38±0.26	0.24±0.21	0.12±0.11	.02	.02	.17	0.008
P model parameter (L/[mmol minutes])	0.01±0.05	0.001±0.047	-0.02±0.04	<.001	<.001	<.001	<.001
I model parameter (L/[mmol minutes])	0.081±0.035	0.082±0.032	0.086±0.033	.39	.25	.12	0.02
Males	n=112	n=56	n=62				
AUC (mmol minutes/L)	636.08±598.96	873.84±870.28	1661.56±1940.48	<.001	<.001	<.001	<.001
AUCm (mmol minutes/L)	718.72±634.04	997.12±911.40	1940.28±2071.72	<.001	<.001	<.001	<.001
Max glucose (mmol/L)	6.19±0.94	6.92±1.39	10.54±4.45	<.001	<.001	<.001	<.001
Max deviation (mmol/L)	2.12±0.94	2.50±1.28	3.25±2.14	<.001	<.001	<.001	<.001
Peak length (minutes)	158.21±76.34	174.73±85.12	214.11±107.14	<.001	<.001	<.001	<.001
Mean glucose (mmol/L)	4.60±0.59	5.21±0.74	8.49±3.70	<.001	<.001	<.001	<.001
Glucose SD (mmol/L)	1.00±0.26	1.25±0.29	2.04±0.73	<.001	<.001	<.001	<.001
TIR proportion	0.65±0.22	0.75±0.22	0.62±0.35	.003	.008	.23	0.78
TAR proportion	0.001±0.009	0.005±0.012	0.31±0.38	<.001	<.001	<.001	<.001
TBR proportion	0.35±0.22	0.25±0.22	0.07±0.15	.002	.006	<.001	<.001
P model parameter (L/[mmol minutes])	0.005±0.047	-0.01±0.05	-0.02±0.04	<.001	<.001	<.001	<.001
I model parameter (L/[mmol minutes])	0.084±0.032	0.089±0.033	0.075±0.035	<.001	<.001	<.001	<.001
All participants	n=195	n=98	n=89				
AUC (mmol minutes/L)	613.24±588.32	758.20±724.80	1557.80±1823.84	<.001	<.001	<.001	<.001
AUCm (mmol minutes/L)	692.00±627.20	864.16±766.80	1811.12±1944.00	<.001	<.001	<.001	<.001
Max glucose (mmol/L)	6.14±0.95	6.73±1.23	10.01±4.24	<.001	<.001	<.001	<.001
Max deviation (mmol/L)	2.04±0.89	2.32±1.14	3.16±2.05	<.001	<.001	<.001	<.001
Peak length (minutes)	156.79±74.89	166.43±78.15	210.16±104.76	<.001	<.001	<.001	<.001
Mean glucose (mmol/L)	4.62±0.64	5.11±0.67	8.01±3.52	<.001	<.001	<.001	<.001
Glucose SD (mmol/L)	0.97±0.32	1.15±0.29	1.94±0.72	<.001	<.001	<.001	<.001
TIR proportion	0.64±0.23	0.76±0.21	0.66±0.33	<.001	<.001	.14	0.35
TAR proportion	0.001±0.009	0.003±0.009	0.26±0.36	<.001	<.001	<.001	<.001
TBR proportion	0.36±0.24	0.23±0.21	0.08±0.15	<.001	<.001	<.001	<.001
P model parameter (L/[mmol minutes])	0.007±0.048	-0.006±0.047	-0.02±0.04	<.001	<.001	<.001	<.001
I model parameter (L/[mmol minutes])	0.083±0.034	0.086±0.033	0.077±0.035	<.001	<.001	<.001	<.001

AUC, area under the curve; AUCm, area under the curve calculated from minimum glucose; KW, Kruskal-Wallis; Max, maximum; ND, nondiabetic; PD, prediabetic; T2D, type 2 diabetes; TAR, time above range; TBR, time below range; TIR, time in range.

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TABLE 4. Confusion Matrices of Functional Assessment of Glucose Homeostasis Classification Results[a]

Physician diagnosis[b]		Prediction		Recall	Specificity/sensitivity[c]
		EGH	IGH		
Calibration study					
Female	ND	23	6	0.79	Specificity
	PD	2	15	0.88	PD sensitivity
	T2D	0	4	1	T2D sensitivity
Male	ND	20	8	0.71	Specificity
	PD	3	26	0.9	PD sensitivity
	T2D	0	14	1	T2D sensitivity
Validation study					
Female	ND	42	12	0.78	Specificity
	PD	4	21	0.84	PD sensitivity
	T2D	0	23	1	T2D sensitivity
Male	ND	60	24	0.71	Specificity
	PD	5	22	0.81	PD sensitivity
	T2D	0	48	1	T2D sensitivity
Combined calibration and validation results					
Female	ND	65	18	0.78	Specificity
	PD	6	36	0.86	PD sensitivity
	T2D	0	27	1	T2D sensitivity
Male	ND	80	32	0.71	Specificity
	PD	8	48	0.86	PD sensitivity
	T2D	0	62	1	T2D sensitivity

[a]EGH, effective glucose homeostasis; IGH, impaired glucose homeostasis; ND, nondiabetic; PD, prediabetic; T2D, type 2 diabetes.
[b]Diagnosis was performed by a physician according to American Diabetes Association criteria.[24]
[c]Specificity and sensitivity correspond to the recall values within the same row.

Individuals classified as having IGH had a larger AUC, AUCm, maximum glucose concentration, maximum glucose deviation, peak length, average glucose concentration, and glucose standard deviation than individuals classified as having EGH ($P<.05$), as shown in Table 5. In nondiabetic women and in men and women with prediabetes, the TIR increased and TBR decreased in IGH-classified individuals compared with those classified as having EGH, a trend that can also be seen in Table 2, as the diabetic status progressed from nondiabetic to prediabetes. The Kolmogorov-Smirnoff test for normality was performed for all metrics for FLAG classifications and diabetic status, and all distributions were nonnormal ($P<.001$ for all groups).

Confusion matrices comparing FLAG classification with the current diagnostic metrics of HbA1c and OGTT are displayed in Supplemental Table 2 (available online at http://www.mcpiqojournal.org), and a summary of the diagnostic metrics of individuals with prediabetes who were classified as having EGH is presented in Supplemental Table 3 (available online at http://www.mcpiqojournal.org).

DISCUSSION

The FLAG classification system has the potential to be used as a prescreening method with a specificity, sensitivity of individuals with prediabetes, and sensitivity of individuals with T2D of 0.78, 0.86, and 1.00, respectively, for women and 0.71, 0.86, and 1.00, respectively, for men. This sensitivity was similar to that of HbA1c measurement (a sensitivity of 0.89 for women and 0.90 for men for prediabetes and a sensitivity of 1.00 for T2D) and superior to that of OGTT (a sensitivity of 0.18 for women and 0.24 for men for prediabetes and a sensitivity of 0.75 for women and 0.86 for men for T2D). Additionally, the 2 classes from FLAG classification, EGH and IGH, had different GV metrics. The classification of EGH corresponded to decreased AUC,

TABLE 5. Glycaemic Variability Metrics Across Diabetic Status and Homeostasis Classification[a]

Glycemic variability metric across diabetic status	ND (mean ± SD)		PD (mean ± SD)		T2D (mean ± SD)
	EGH	IGH	EGH	IGH	IGH
Female					
Number of participants	n=65	n=18	n=6	n=36	n=27
AUC (mmol minutes/L)	492.16±376.4[a*,c*,d*]	687.24±752.24[a*,e*,f,g*]	464.96±368.52[e*,h*,i*]	698.12±560.84[c*,f,h*,j*]	1143.08±1167.52[d*,g*,i*,j*]
AUCm (mmol minutes/L)	546.96±395.92[a*,c*,d*]	783.08±818.56[a*,e*,f*,g*]	516.04±375.76[e*,h*,i*]	796.24±612.8[c*,f*,h*,j*]	1294.96±1184.68[d*,g*,i*,j*]
Max glucose (mmol/L)	5.81±0.62[a*,c*,d*]	6.45±1.23[a*,e*,f*,g*]	5.9±0.69[e*,h*,i*]	6.7±1.06[c*,f*,h*,j*]	7.93±2.31[d*,g*,i*,j*]
Max deviation (mmol/L)	1.82±0.66[a,c*,d*]	2.0±0.9[a,e,f*,g*]	1.84±0.71[e,h*,i*]	2.21±0.98[c*,f*,h*,j*]	2.82±1.59[d*,g*,i*,j*]
Peak length (minutes)	146.9±66.82[a*,c*,d*]	164.39±78.14[a*,e*,g*]	139.88±61.33[e*,h*,i*]	163.51±70.83[c*,h*,j*]	194.38±93.19[d*,g*,i*,j*]
Mean glucose (mmol/L)	4.35±0.44[a*,b*,c*,d*]	5.11±0.85[a*,e,g]	4.47±0.39[b*,e,h*,i]	5.15±0.58[c*,h*,j*]	6.08±1.68[d*,g,i,j]
Glucose SD (mmol/L)	0.78±0.14[a*,c*,d*]	1.09±0.57[a*,e]	0.79±0.11[e,h*,i*]	1.1±0.26[c*,h*,j]	1.52±0.51[d*,i*,j]
TIR proportion	0.68±0.21[a*,c*,d]	0.84±0.14[a*,e]	0.69±0.18[e,h,i]	0.86±0.13[c*,h]	0.80±0.35[d,i]
TAR proportion	0.0±0.0[a,c,d*]	0.004±0.008[a,g]	0.0±0.0[i]	0.004±0.013[c,j]	0.08±0.19[d*,g,i,j]
TBR proportion	0.32±0.21[a*,c*,d]	0.16±0.15[a*,e]	0.31±0.18[e,h,i]	0.14±0.13[c*,h]	0.12±0.11[d,i]
Male					
Number of participants	n=80	n=32	n=8	n=48	n=62
AUC (mmol minutes/L)	582.48±495.2[a*,c*,d*]	719.72±720.64[a*,f*,g*]	576.8±389.28[h*,i*]	918.88±912.8[c*,f*,h*,j*]	1661.56±1940.48[c*,f*,h*,j*]
AUCm (mmol minutes/L)	653.96±515.88[a*,c*,d*]	818.4±768.32[a*,f*,g*]	676.04±425.56[h*,i*]	1045.8±954.12[c*,f*,h*,j*]	1940.28±2071.72[d*,g*,i*,j*]
Max glucose (mmol/L)	6.08±0.83[a*,c*,d*]	6.36±1.06[a*,f*,g*]	6.14±0.72[h*,i*]	7.04±1.43[c*,f*,h*,j*]	10.54±4.45[d*,g*,i*,j*]
Max deviation (mmol/L)	2.0 ±0.81[a*,c*,d*]	2.3±1.09[a*,e,f*,g*]	2.0±0.73[e,h*,i*]	2.58±1.33[c*,f*,h*,j*]	3.25±2.14[d*,g*,i*,j*]
Peak length (minutes)	155.58±73.12[a,c*,d*]	162.62±80.88[a,f*,g*]	159.91±68.71[i*]	176.98±87.08[c*,f*,j*]	214.11±107.14[d*,g*,i*,j*]
Mean glucose (mmol/L)	4.56±0.52[a,c*,d*]	4.69±0.65[a,f,g*]	4.61±0.4[h,i*]	5.3±0.73[c*,f,h,j*]	8.49±3.70[d*,g*,i*,j*]
Glucose SD (mmol/L)	0.9±0.16[a*,c*,d*]	1.15±0.31[a*,f,g*]	0.94±0.12[h*,i*]	1.29±0.28[c*,f,h*,j*]	2.04±0.73[d*,g*,i*,j*]
TIR proportion	0.63±0.23[c]	0.68±0.18[e,f*]	0.66±0.29[e]	0.78±0.17[c,f*]	0.62±0.35
TAR proportion	0.0±0.0[a,c*,d*]	0.004±0.016[a,g*]	0.0±0.0[i*]	0.007±0.014[c*,j*]	0.31±0.38[d*,g*,i*,j*]
TBR proportion	0.37±0.32[c,d*]	0.32±0.18[f,g*]	0.34±0.29[i*]	0.21±0.17[c,f,j*]	0.07±0.12[d*,g*,i*,j*]
All participants					
Number of participants	n=145	n=50	n=14	n=84	n=89
AUC (mmol minutes/L)	552.84±461.72[a*,c*,d*]	701.84±724.88[a*,e*,f*,g*]	505.48±380[e*,h*,i*]	811.16±767.28[c*,f*,h*,j*]	1557.8±1823.84[d*,g*,i*,j*]
AUCm (mmol minutes/L)	618.68±482.28[a*,c*,d*]	798.56±778.68[a*,e*,f*,g*]	574±401.96[e*,h*,i*]	924.96±809.8[c*,f*,h*,j*]	1811.12±1944[d*,g*,i*,j*]
Max glucose (mmol/L)	5.98±0.78[a*,c*,d*]	6.38±1.11[a*,e*,f*,g*]	5.98±0.71[e*,h*,i*]	6.89±1.26[c*,f*,h*,j*]	10.01±4.24[d*,g*,i*,j*]
Max deviation (mmol/L)	1.94±0.77[a*,c*,d*]	2.19±1.03[a*,e*,f*,g*]	1.9±0.72[e*,h*,i*]	2.4±1.19[c*,f*,h*,j*]	3.16±2.05[d*,g*,i*,j*]
Peak length (minutes)	152.99±71.42[a*,c*,d*]	162.49±79.37[a*,e*,f*,g*]	147.14±64.82[e*,h*,i*]	170.47±80.06[c*,f*,h*,j*]	210.16±104.76[d*,g*,i*,j*]
Mean glucose (mmol/L)	4.49±0.5[a*,c*,d*]	4.83±0.74[a*,e,f,g*]	4.52±0.4[e,h*,i*]	5.24±0.64[c*,f,h*,j*]	8.01±3.52[d*,g*,i*,j*]
Glucose SD (mmol/L)	0.86±0.16[a*,c*,d*]	1.12±0.42[a*,e*,f,g*]	0.85±0.14[e*,h*,i*]	1.21±0.27[c*,f,h*,j*]	1.94±0.72[d*,g*,i*,j*]
TIR proportion	0.61±0.23[a,c*]	0.73±0.18[a,f]	0.62±0.25[h]	0.84±0.16[c*,f,h,j]	0.66±0.33[j]
TAR proportion	0.0±0.0[a*,c*,d*]	0.004±0.015[a*,g*]	0.0±0.0[h,i*]	0.004±0.011[c*,h,j*]	0.26±0.36[d*,g*,i*,j*]
TBR proportion	0.39±0.23[a,c*,d*]	0.27±0.19[a,f*,g*]	0.38±0.25[h,j*]	0.16±0.16[c*,f*,h,j*]	0.08±0.12[d*,g*,i*,j*]

AUC, area under the curve; AUCm, area under the curve calculated from minimum glucose; EGH, effective glucose homeostasis; IGH, impaired glucose homeostasis; Max, maximum; ND, nondiabetic; PD, prediabetic, T2D, type 2 diabetes; TAR, time above range; TBR, time below range; TIR, time in range.

[a-j]Indicates statistical significance ($P<.05$) result from Mann Whitney U test within the same row. Subscript with asterisk (ex. [a*]) indicates $P<.001$.

AUCm, maximum glucose concentrations, maximum glucose deviations, length of the glucose peak, mean glucose concentrations, and glucose standard deviation compared with the classification of IGH. This result was consistent across all diabetic statuses.

In previous studies, the TIR increased and TAR decreased for individuals without T2D or prediabetes.[30,31] This result was true for TAR (increasing for individuals with T2D); however, the TIR decreased for individuals without prediabetes or T2D, primarily because of an increase in TBR. Nonnegligent TBR has been reported in individuals without T2D or prediabetes, although to a lesser proportion than seen in this analysis.[32] This discrepancy may have occurred because of Freestyle Libre's underestimation of low glucose levels[33] and may not be reflective of the actual TBR. However, high glucose levels have a very small absolute error to actual glucose values in Freestyle Libre devices.[33] In this case, TAR would be reflective of the individual's actual TAR, and a similar increase in TAR was seen compared with that in previous studies.

The individuals with prediabetes who were identified using FLAG as having EGH had lower GV metrics than both nondiabetic and prediabetic EGH-classified individuals. Early T2D is a manageable disease, with lifestyle changes, and, in some instances, can go into remission with proper lifestyle modification.[1,34] Glycated hemoglobin A1c reflects the average glucose response over the past 2-3 months; so, decreased mean glucose concentrations, glucose standard deviations, and overall GV would result in lower HbA1c values.[35] Because HbA1c is the preferred indicator of T2D remission,[34] repeated classification of EGH may be indicative of a higher likelihood of remission to normoglycemia. Future work will monitor individuals with prediabetes in a longitudinal, observational study to observe the relationship between FLAG classification and disease regression. Furthermore, the fourth cohort of the validation study containing individuals with T2D and prescribed metformin was excluded from the current analysis. Future work will evaluate these individuals to explore EGH and IGH classification in controlled T2D.

Nondiabetic individuals were predominantly classified as having EGH. However, 22% of nondiabetic women and 29% of nondiabetic men were classified as having IGH. These individuals had higher GV than nondiabetic individuals and individuals with prediabetes classified as having EGH. High glucose levels and high glucose variability can result in complications, such as retinopathy, nephropathy, and vascular disease, even in nondiabetic individuals.[36] In fact, a study conducted on 411 patients with myocardial infarction determined that individuals who had elevated glucose concentrations on admission had greater myocardial damage and an increased risk of major cardiovascular events, regardless of diabetic status. Furthermore, the risk of severe myocardial injury for nondiabetic patients increased for individuals whose mean glucose levels were above 7.8 mmol/L.[37] Additionally, nondiabetic individuals with increased glucose levels are more likely to experience infection or acute myocardial infarction after orthopedic trauma or surgery than nondiabetic individuals with normoglycemia.[38]

There are a few drawbacks to CGM use. They can be expensive if they are not covered by insurance and used regularly. Skin irritation may occur, and the sensor may fall off before the 2-week period is completed.[39] Some sensors, such as those produced by Medtronic Guardian Connect, require daily calibration (although devices produced by Abbott and Dexcom do not require self-calibration). Individuals may have issues with self-administering the device onto their arm or may need to go to a nurse to administer it for them.[40] Furthermore, there is concern regarding the accuracy of the devices, particularly in hypoglycemic ranges.[33,39–41] However, these concerns may be outweighed by convenience in some situations. For example, individuals in remote communities may prefer a self-administered CGM screening tool before committing to traveling to a physician or undergoing laboratory workup.

Undiagnosed prediabetes and T2D or misdiagnosed as being nondiabetic can have detrimental effects on an individual, such as heart disease, vision loss, kidney disease, and premature death.[1,4] However, overdiagnosis of prediabetes and T2D is a real concern for the medical community, even with an increase in prevalence. A prediabetes diagnosis may lead

to issues with insurance, employment, or self-image and increase the burdens and costs of health care.[42] When employing a prescreening tool such as the one described here, care must be taken to avoid overdiagnosis of healthy individuals while still maintaining specificity for individuals with prediabetes and T2D. A simple solution is to exclusively use CGMs and their corresponding analysis methods as a checkpoint or precursor to accepted blood tests (OGTT and HbA1c measurement) and not for diagnostics. This approach would also decrease the frequency of unnecessary blood tests and give physicians a better understanding of the patient's glucose control in normal, day-to-day situations. Rather than ordering blood work on complaints of hyperglycemia-related symptoms, a physician would prescribe a CGM to be worn for the next 2 weeks. The necessity for blood tests could be re-evaluated after the 2-week CGM period.

CONCLUSION

The increased availability of CGMs allows for at-home monitoring of glycemic control. Employing a previously developed mathematical model allows for rapid interpretation of CGM data and provides an insight into glucose control. The method proposed in this article separated individuals into groups with increased and decreased glucose variability, labeled as IGH and EGH, respectively. This classification had a sensitivity similar to HbA1c measurement and superior to OGTT. Future work will explore FLAG implementation in a multicohort, longitudinal study to assess T2D remission or progression and assess metformin use for T2D control.

POTENTIAL COMPETING INTERESTS

J.M.K. and Y.F. are employed by Klick Inc. Y.F. and L.v.V. are inventors on a patent owned by Klick Inc. for the mathematical model used in this article (patent number: WO/2021/087608).

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at https://www.mcpdigitalhealth.org/. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AUC,** area under the curve calculated using the initial glucose value; **AUCm,** area under the curve, calculated using the minimum glucose value; **CANRISK,** Canadian Diabetes Risk Questionnaire; **CGM,** continuous glucose monitor; **EGH,** effective glucose homeostasis; **FLAG,** functional assessment of glucose homeostasis; **GV,** glycemic variability; **HbA1c,** glycated hemoglobin A1c; **IGH,** impaired glucose homeostasis; **OGTT,** oral glucose tolerance test; **T2D,** type 2 diabetes; **TAR,** time above range; **TBR,** time below range; **TIR,** time in range

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