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Evaluation of continuous glucose monitoring-derived person-specific HbA1c in the presence and absence of complications in type 1 diabetes

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Abstract

Aim: To evaluate the accuracy of a novel kinetic model at predicting HbA1c in a real-world setting and to understand and explore the role of diabetes complications in altering the glucose–HbA1c relationship and the mechanisms involved.

Materials and Methods: Deidentified HbA1c and continuous glucose monitoring values were collected from 93 individuals with type 1 diabetes. Person-specific kinetic variables were used, including red blood cell (RBC) glucose uptake and lifespan, to characterize the relationship between glucose levels and HbA1c. The resulting calculated HbA1c (cHbA1c) was compared with glucose management indicator (GMI) for prospective agreement with laboratory HbA1c.

Results: The cohort (42 men and 51 women) had a median age (IQR) of 61 (43, 72) years and a diabetes duration of 21 (10, 33) years. A total of 24 459 days of continuous glucose monitoring (CGM) data were available and 357 laboratory HbA1c were used to assess the average glucose–HbA1c relationship. cHbA1c had a superior correlation with laboratory HbA1c compared with GMI with a mean absolute deviation of 1.7 and 6.7 mmol/mol, $r^2 = 0.85$ and 0.44, respectively. The fraction within 10% of absolute relative deviation from laboratory HbA1c was 93% for cHbA1c and 63% for GMI. Macrovascular disease had no effect on the model's accuracy, whereas microvascular complications resulted in a trend towards higher HbA1c, secondary to increased RBC glucose uptake.

Conclusions: cHbA1c, which takes into account RBC glucose uptake and lifespan, accurately reflects laboratory HbA1c in a real-world setting and can aid in the management of individuals with diabetes.

KEYWORDS

continuous glucose monitoring, diabetes complications, HbA1c, kinetic model, red blood cell glucose uptake, red blood cell lifespan

1 | INTRODUCTION

HbA1c is an established biomarker that reflects glycaemic exposure and predisposition to tissue damage in key organs associated with diabetes complications.[1–5] The primary objective in treatment for persons with diabetes is to prevent or delay long-term microvascular and macrovascular disease thus improving the quality of life and reducing mortality in this population.[6] Self-monitoring of blood glucose and continuous glucose monitoring (CGM) are routinely used to address glycaemic control.[1,7–9] However, discordance between capillary/interstitial glucose levels and HbA1c is not uncommon in clinical practice,[10–14] which can predispose to hypoglycaemic and hyperglycaemic complications, consequently creating management difficulties. Therefore, characterizing the relationship between HbA1c and glucose is imperative for personalized risk management and has key implications for clinical decision-making.

A recent kinetic model[15] proposes an individual-specific relationship between glucose and HbA1c by accounting for both personalized red blood cell (RBC) turnover (k_{age}) and haemoglobin glycation rate (k_{gly}), modulated by RBC glucose uptake, thus creating a personalized glycaemic marker, termed calculated HbA1c (cHbA1c). A key expression of these factors is the apparent glycation ratio (AGR), defined as k_{gly}/k_{age}, which is equivalent to the product of uptake and lifespan. The AGR sets the relationship between steady-state glucose and HbA1c. While the average lifespan of RBCs is believed to be approximately 105 days,[16] experimental studies have recorded a 20% variation in mean RBC lifespan between healthy individuals with no pathological haemoglobin abnormalities.[17] Thus, the differences in RBC turnover across individuals can affect HbA1c and interpretation of glucose exposure of organs prone to diabetes complications.

Recent studies have shown that cHbA1c is more accurate than GMI[13] in predicting laboratory HbA1c values in both type 1 diabetes (T1D) and type 2 diabetes in different age groups.[15,18,19] In a study of 120 adults with T1D and type 2 diabetes on multiple daily insulin injections, cHbA1c showed higher accuracy in predicting laboratory HbA1c than other methods.[15] In a second study on 352 youth with T1D, 82% of all cHbA1c predictions were within ±0.5% of laboratory HbA1c results compared with 25% and 54% of subjects for GMI and estimated HbA1c (eHbA1c), respectively.[12,13,18] In a study evaluating 51 Japanese adults with T1D, cHbA1c had 92.3% of predictions within 0.5% (National Glycohemoglobin Standardization Program (NGSP)) or 5.5 mmol/mol from laboratory HbA1c, compared with 65.4% and 73.1% for eHbA1c and GMI, respectively.[19]

While prior studies show promising accuracy of cHbA1c at predicting laboratory HbA1c, most glucose data were obtained from randomized controlled trials and it is essential to continue to evaluate the glucose–HbA1c relationship in different populations and in routine clinical practice. Also, it is currently unknown whether the model's accuracy is affected by clinical factors, especially diabetes complications, through modulation of the RBC factors of glucose uptake and RBC lifespan. Therefore, the objectives of this study were: (i) to retrospectively evaluate the accuracy of the kinetic model under real-world settings using a T1D cohort; (ii) to investigate the role of age, gender and body mass index (BMI), as well as microvascular and macrovascular disease in modulating the accuracy of the model; and (iii) to assess the associations between kinetic variables (k_{gly}, k_{age}, AGR) and age, gender, BMI, Hb level and microvascular and macrovascular outcomes.

2 | METHODS

2.1 | Data acquisition

The kinetic model requires patient-specific variables from concurrent CGM and HbA1c values. A CGM–HbA1c data section is defined to have frequent glucose readings (at least every 15 minutes) between two laboratory HbA1c values at least 1 week apart (Figure 1).[15] The time intervals between HbA1c measurements vary because of the patient's needs for clinical care. The average (median, interquartile [IQR], minimum, maximum) interval between HbA1c measurements was 68 (76, 18-89, 3, 230) days. Our kinetic model requires one or more data sections to estimate the personal kinetic variables k_{gly} and k_{age}. We used at least two data sections to estimate the personal kinetic variables k_{gly} and k_{age} for higher confidence. For that reason, each individual needs to have at least three data sections, two or more for kinetic variable estimation, and the last one for validation. In our dataset, each subject had 70 days or more CGM coverage. To ensure acceptable accuracy, each data section is required to have at least 80% CGM coverage and less than 60 hours for any continuous CGM data gap. In our analysis, each patient had three or more data sections, at least two for kinetic variable estimation and one held out for validation.

HbA1c and CGM data from 93 individuals (age 16-93 years) with T1D attending the outpatient diabetes clinic of the Mouscron Hospital in Belgium were evaluated. We included all patients with sufficient data, as described above. Anthropometric and biological data were collected through medical records, while glucose measurements were accessed using the FreeStyle Libre flash continuous glucose monitor (Abbott, Witney, UK) without hypoglycaemic/hyperglycaemic alert. CGM data collection was routinely performed during consultations via the Libreview platform in the clinic. HbA1c values were measured by a Tosoh HLC-723G8 Automated Glycohemoglobin Analyzer. All data were deidentified; each participant provided written informed consent for their data to be used as per European privacy guidelines. According to Belgian law, the study was observational and retrospective and did not require formal ethics committee approval, particularly as patients provided consent for their glucose levels to be analysed and the fact that data were deidentified.

In this analysis, the RBC variables are considered constant during the entire analysis period. However, clinical conditions may introduce more variability to the RBC variables over time and, therefore, may be expected to have larger deviations for the validation evaluation. To investigate this effect, individuals were partitioned into Group A if they had no conditions that are known to alter RBC lifespan, while Group B consisted of those who had physiological or pathological conditions that may alter RBC turnover (pregnancy and renal failure).

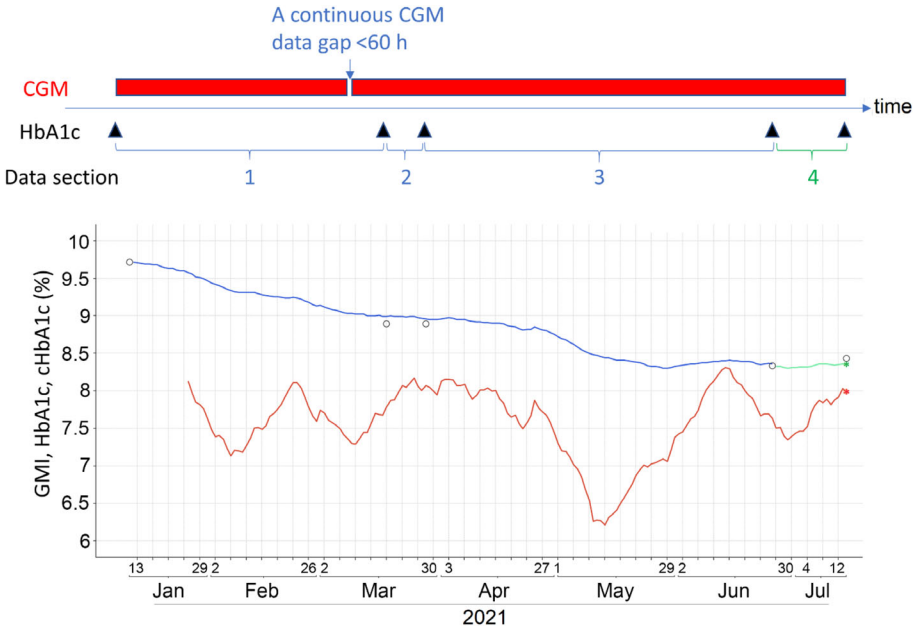

FIGURE 1 Diagram and example of data sections for analysis. Top: illustration of data sections. Bottom: data from one subject as an example. Red line: 14-day glucose management indicator (GMI); black circle: laboratory HbA1c; blue line: best-fitted calculated HbA1c (cHbA1c) for training; green line: projected cHbA1c in the testing data sections. This study compares the accuracy of the final HbA1c projections in the testing data section (* with circle). CGM, continuous glucose monitoring

2.2 | Statistical and computation methods

Two kinetic variables were calculated using the training data sections for each subject. These variables are RBC turnover rate k_{age} (or RBC lifespan $ls_{RBC} = 1/k_{age}$) and the apparent haemoglobin glycation rate constant k_{gly}, presumed to be primarily affected by cross-membrane glucose uptake. The calculation method was previously published[15] and is briefly summarized here. Calculated HbA1c ($cHbA1c_z$) value in a data section can be estimated using the following equation:

$$\mathbf{cHbA1c_z} = \mathbf{A1c_0}\prod_{j=1}^{z} \mathbf{D_j} + \sum_{i=1}^{z-1}\left[\mathbf{EA_i}(\mathbf{1}-\mathbf{D_i})\prod_{j=i+1}^{z}\mathbf{D_j}\right] + \mathbf{EA_z}(\mathbf{1}-\mathbf{D_z})$$

In this calculation, CGM data represent a sequence of average glucose ($[G_i]$) in multiple time intervals (t_i), where $A1c_0$ is the starting laboratory HbA1c in a data section. In each time interval i, $D_i = e^{-(k_{gly}*g_i+k_{age})t_i}$, $EA_i = g_i/\left(\frac{k_{age}}{k_{gly}}+g_i\right)$, where $g_i = (K_M*[G_i])/(K_M+[G_i])$ and $K_M = 473$ mg/dl.[15] With training data sections, we optimized individual k_{gly} and k_{age} values so that ending cHbA1c values best agree with corresponding laboratory HbA1c measurements at the same time point. In validation data sections, an ending cHbA1c is calculated with optimized individual k_{gly} and k_{age} variables from the prior training periods and compared with the final laboratory HbA1c.

In addition, we evaluated AGR as k_{gly}/k_{age}. Any glucose tracing gaps of less than 45 minutes had missing values imputed with the nearest immediate observation before or after the gap. In any case of long gaps up to 60 hours, missing values were interpolated with the average of the observations at the same time from the previous and following days.

GMI values were determined by 14-day average CGM glucose (AG) for comparison. The performance of GMI and cHbA1c were compared by their agreement with the final, held-out laboratory HbA1c values by mean bias, absolute deviation (AD), absolute relative deviation (ARD) and percentage absolute deviation within 5.5 mmol/mol or 0.5% NGSP.

To study the associations between the RBC variables (k_{gly}, k_{age} and AGR) and clinical observations and outcomes, we compared distributions in subgroups by BMI (above and below 25 kg/m^2), age (above and below 60 years), gender, low haemoglobin (below 12 g/dl for females and below 13.5 g/dl for males), hypoglycaemia awareness (Clarke score four and above), and the presence of microvascular or macrovascular complications. The presence of a microvascular complication was defined as having any of the following: persistent (at least 1 year) microalbuminuria, clinical neuropathy (monofilament test positive and/or electromyogram positive) or established diabetic retinopathy (defined by an ophthalmologist). In these dichotomous subgroupings, thresholds were chosen by clinically relevant criteria, and the resulting subgroup sizes were not even; however, the smaller subgroup contained at least 30% of subjects.

Distributions were characterized by mean and standard deviation (SD) for normally distributed data and by median and IQR for non-normally distributed data, with comparisons carried out using *T*-test and *F*-test, respectively. The comparisons between fractions were made with Chi^2 statistic. Python/SciPy was used for all analyses.

3 | RESULTS

3.1 | Subject characteristics

Among 93 subjects, we separately analysed 14 individuals as Group B, which included individuals having renal dialysis (n = 8) and pregnant/early postpartum women (n = 6). No patient received a blood transfusion during the analysis period or was known to have any haematological abnormality. The remaining 79 individuals without known conditions causing unstable RBC kinetic variables comprised Group A. Table 1 lists the patient distribution in this study.

TABLE 1 Subject characteristics

		All	Group A	Group B
Subject count		93	79	14
Gender M/F		42/51	39/40	3/11
Age (y): Median [IQR]		61 [43, 72]	62 [44, 72]	56 [27, 76]
Diabetes duration (y): Median [IQR]		21 [10, 33]	21 [8, 31]	29 [14, 46]
BMI (kg/m^2): Median [IQR]		27 [24, 32]	27 [24, 32]	27 [22, 32]
Haemoglobin (g/dl): Median [IQR]		11.3 [12.1, 14.5]	13.6 [12.8, 14.6]	11.6 [11.1, 11.8]
CGM usage per subject (d): Median [IQR]		263 [189, 381]	263 [193, 376]	260 [186, 441]
Data section count per subject: Median [IQR]		3 [2, 4]	3 [2, 4]	4 [3, 6]
Ending HbA1c (%)	Median [IQR]	7.9 [7.3, 8.6]	8.0 [7.3, 8.6]	7.3 [6.6, 8.5]
	Mean (SD)	8.0 (1.1)	8.0 (1.1)	7.6 (1.3)
Ending 14-d average glucose (mg/dl)	Median [IQR]	172 [148, 199]	176 [151, 199]	143 [123, 191]
	Mean (SD)	177 (41)	181 (40)	159 (44)

Abbreviations: BMI, body mass index; CGM, continuous glucose monitor; F, female; M, male.

TABLE 2 Comparison of kinetic model estimated HbA1c (cHbA1c) and GMI in the test set. The standard deviation (SD) and IQR are included to compare the deviation distribution or variation

Subgroup		cHbA1c			GMI (AG)		
		All (n = 93)	Group A (n = 79)	Group B (n = 14)	All (n = 93)	Group A (n = 79)	Group B (n = 14)
AD (NGSP %)	Mean ± SD	0.27^A ± 0.31	0.22^B ± 0.23	0.56 ± 0.53	0.72^A ± 0.60	0.72^B ± 0.59	0.74 ± 0.67
	Median [IQR]	0.16 [0.05, 0.39]	0.15 [0.04, 0.28]	0.44 [0.13, 0.77]	0.61 [0.31, 1.05]	0.63 [0.31, 1.04]	0.49 [0.28,1.06]
AD (mmol/mol)	Mean ± SD	3.0^A ± 3.4	2.4^B ± 2.5	6.1 ± 5.8	7.9^A ± 6.5	7.9^B ± 6.4	8.1 ± 7.3
	Median [IQR]	1.8 [0.5, 4.3]	1.6 [0.5, 3.1]	4.8 [1.5, 8.4]	6.6 [3.4, 11.5]	6.9 [3.4, 11.4]	5.3 [3.1, 11.5]
MARD ± SD (%)		3.4^A ± 3.9	2.8^B ± 3.0	6.9 ± 6.0	9.1^A ± 7.7	9.1^B ± 7.9	9.1 ± 6.4
Fraction of AD <0.5% or 5.5 mmol/mol		82%^{A}	86%^{B}	57%	44% ^{A}	43%^{B}	50%
Average bias ± SD (NGSP %)		0.0^A ± 0.4	0.0^B ± 0.3	0.0 ± 0.8	−0.4^A ± 0.9	−0.4^B ± 0.9	−0.5 ± 0.9
Average bias ± SD (mmol/mol)		0.0^A ± 4.4	0.0^B ± 3.3	0.0 ± 8.8	−4.4^A ± 9.9	−4.4^B ± 9.9	−5.5 ± 9.9
Fraction within ARD	5%	74%^{A}	81%^{B}	36%	33%^{A}	33% ^{B}	35%
	10%	93%^{A}	96% ^{B}	71%	62%^{A}	62% ^{B}	64%
	15%	98%^{A}	100% ^{B}	86%	87%^{A}	87% ^{B}	86%
Linear regression	R^2 (R)	0.85 (0.93)	0.92 (0.96)	0.67 (0.82)	0.44 (0.66)	0.40 (0.63)	0.58 (0.76)
	Slope	0.99	0.97	1.15	0.75	0.70	0.99
	Intercept	0.06	0.23	−1.16	2.28	2.65	0.58

Note: Group B includes patients on dialysis and pregnant or early postpartum women. Group A consists of all other subjects without known conditions causing unstable RBC turnover. Pairwise mean value comparisons (*T*-test) were performed between the two methods in all subjects and in Group A, with cHbA1c significantly more accurate than GMI ($P < .001$ for within-row pairwise comparisons^{A,B}).
Abbreviations: AD, absolute deviation; AG, average glucose; ARD, absolute relative deviation; cHbA1c, calculated HbA1c; GMI, glucose management indicator; MARD, mean absolute relative deviation; NGSP, National Glycohemoglobin Standardization Program; RBC, red blood cell.

3.2 | Prospectively calculated HbA1c and validation of the method

Although data were collected retrospectively, we held out the last data section of each individual to validate the accuracy of the model. Therefore, the evaluation at the final HbA1c was prospective in nature. In Table 2 and Figure 2, we show that cHbA1c more accurately reflected laboratory HbA1c compared with GMI. From the clinical point of view, cHbA1c was within 0.5% (NGSP) of laboratory HbA1c for 82% of individuals, compared with 44% of GMI values ($P = .001$). The model displayed reduced accuracy in Group B individuals but still performed better than GMI.

To investigate the role of age, gender, BMI, hypoglycaemia unawareness, and microvascular and macrovascular disease in modulating the accuracy of the model, we compared the average absolute deviations from cHbA1c and GMI in each binary subgroup. In all subgroups, cHbA1c

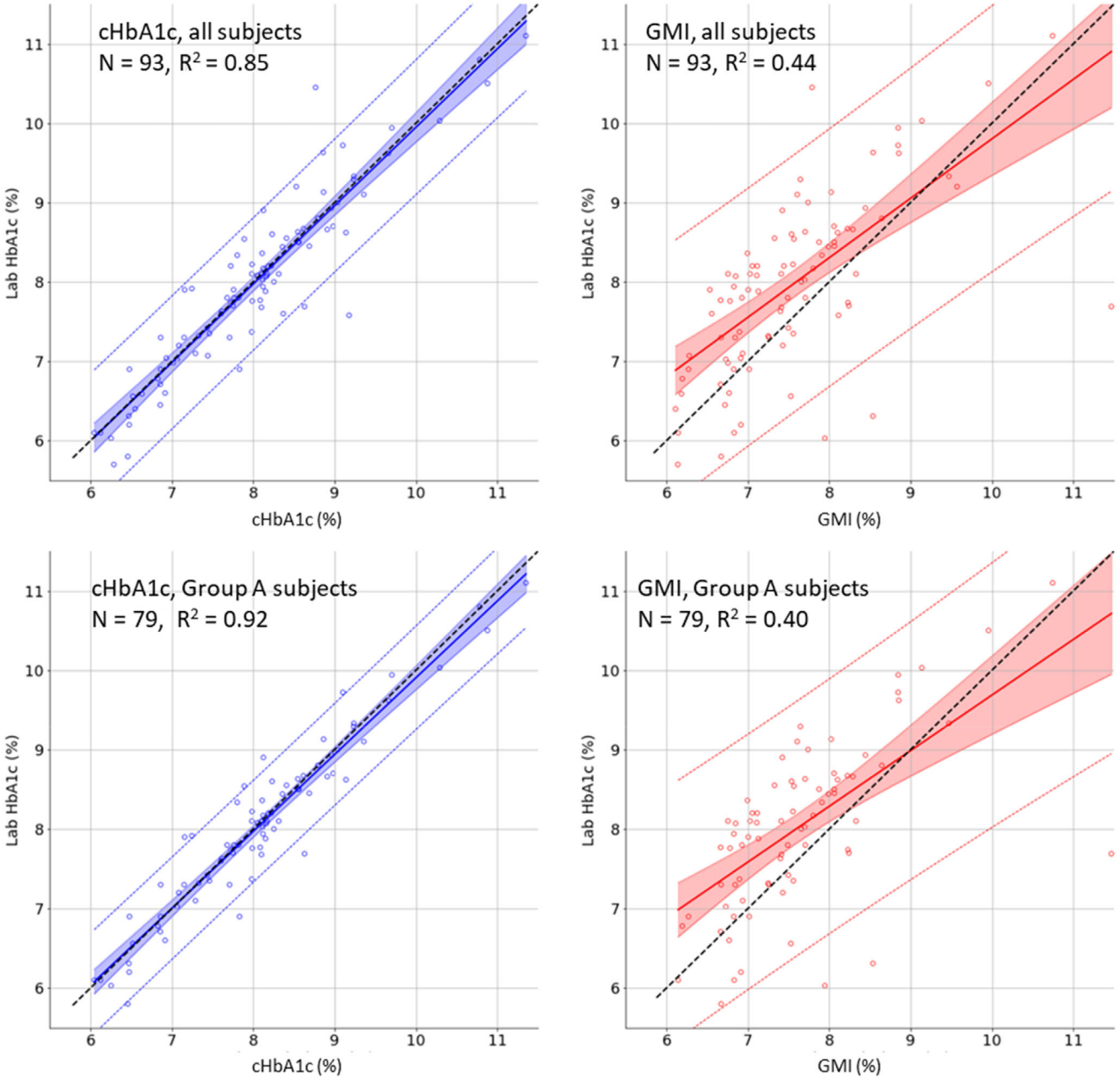

FIGURE 2 Comparison of the kinetic model calculated HbA1c (cHbA1c) and glucose management indicator (GMI) in the test set. The regressions and distributions of cHbA1c are plotted in blue and GMI in red; 95% regression confidence intervals are shown in shades, and the prediction intervals are plotted with coloured dotted lines. Black dashed lines represent unity lines

remained superior in accuracy compared with GMI. For both cHbA1c and GMI, the accuracies, measured by mean absolute deviations, were not affected by age, gender, BMI, hypoglycaemia awareness, or microvascular and macrovascular diseases (between subgroup *P* values > .05).

3.3 | Clinical observations and kinetic variables

To study the associations between kinetic variables (k_{gly}, k_{age}, AGR) and the available clinical observations, between-group means and SDs were compared for Group A.

3.3.1 | Presence of microvascular and macrovascular complications

The presence of macrovascular complications had no effects on the mean and SDs of the RBC variables. However, those with microvascular complications showed a wider k_{gly} distribution ($P < .001$) and a trend towards a higher k_{gly} value ($P = .08$). This translated into a trend towards a higher HbA1c value in the presence of microvascular disease ($P = .09$) without a difference in average glucose measured as GMI ($P = .57$; Table 3).

TABLE 3 The association between microvascular complications and RBC kinetic variables. Differences in mean values were calculated using the *T*-test, while the *F*-test was employed to calculate differences between standard deviations (SDs)

	k_{gly} (ml/g/d)		RBC lifespan (d)		AGR (ml/g)		HbA1c (%)		Average glucose in GMI (%)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
With microvascular complication (N = 46)	0.95	0.46	88.3	25.4	66.6	7.5	8.30	0.98	7.75	0.81
Without microvascular complication (N = 33)	0.79	0.24	93.2	24.7	65.4	6.9	7.88	1.07	7.64	0.87
P value (*T*-test for mean, *F*-test for SD)	*.08*	**<.001**	.39	.88	.46	.63	*.09*	.58	.57	.67

Abbreviations: AGR, apparent glycation ratio; GMI, glucose management indicator; RBC, red blood cell. Bold values denote statistical significance at the $P < .05$ level. Italic valus denote possible significant at the $P < .1$.

TABLE 4 Factors that may be associated with RBC kinetic variables. Differences in mean values were calculated using the *T*-test, while *F*-test was employed to calculate differences between standard deviations (SD)

	k_{gly} (ml/g/d)		RBC lifespan (d)		AGR (ml/g)		HbA1c (%)		Average glucose in GMI (%)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Older >60 y (N = 41)	0.84	0.48	93.4	26.9	67.3	8.8	8.13	0.88	7.64	0.67
Younger ≤60 y (N = 38)	0.77	0.28	93.8	23.9	65.9	4.9	8.15	1.18	7.76	0.98
P value (*T*-test, *F*-test)	.42	**.002**	.95	.48	.40	**<.001**	.92	.07	.53	**.02**
BMI > 25 kg/m^2 (N = 55)	0.88	0.35	90.4	23.9	66.5	7.4	8.2	1.04	7.69	0.91
BMI ≤ 25 kg/m^2 (N = 24)	0.89	0.48	91.1	28.2	65.1	6.7	8.1	1.03	7.72	0.66
P value (*T*-test, *F*-test)	.92	*.054*	.86	.32	.41	.57	.79	.98	.90	*.09*
Normal haemoglobin (12 [F] or 13.5 [M] to 17.5 g/dl) (N = 58)	0.81	0.24	94.5	21.0	66.9	5.7	8.27	1.07	7.77	0.86
Low haemoglobin <12 g/dl for females, <13.5 g/dl for males (N = 21)	1.09	0.61	78.8	31.8	63.8	10.1	7.78	0.85	7.52	0.73
P value (*T*-test, *F*-test)	**.004**	**<.001**	**.013**	**.015**	*.092*	**.001**	*.056*	.26	.24	.4

Abbreviations: AGR, apparent glycation ratio; BMI, body mass index; F, female; GMI, glucose management indicator; M, male; RBC, red blood cell. Bold values denote statistical significance at the $P < .05$ level. Italic valus denote possible significant at the $P < .1$.

3.3.2 | Effects of other clinical markers

For comparisons by age, gender, BMI, hypoglycaemia unawareness and haemoglobin level, only age, BMI and haemoglobin level appeared to modulate the kinetic variables (Table 4). The most significant effect on the kinetic variables was related to changes in haemoglobin; low haemoglobin levels were associated with higher k_{gly}, lower RBC lifespan and a trend towards lower AGR and HbA1c, as well as higher variabilities in all three kinetic variables. Younger age was associated with a significantly tighter spread of k_{gly} ($P = .002$), AGR ($P < .001$), average glucose ($P < .02$) and a trend towards wider HbA1c distribution ($P = .07$). High BMI was associated with a tendency towards a tighter distribution of k_{gly} ($P = .054$) and higher average glucose ($P = .09$).

4 | DISCUSSION

HbA1c is routinely used for monitoring the response to hypoglycaemic therapies in individuals with diabetes.[20] The glycation of haemoglobin represents a long-term biochemical and clinical marker of intracellular glucose that is unaffected by day-to-day glycaemic fluctuations. While blood glucose levels are undoubtedly a primary driver of HbA1c levels, personal differences arising from biological and cellular factors also play a crucial role. A quantitative evaluation of these personal factors explains the discordance between glucose levels and HbA1c, which can cause confusion in glycaemic management of individuals with diabetes. The use of cHbA1c, which includes personal kinetic variables, allows for an accurate prediction of laboratory HbA1c, thus removing any confusion. Having a better understanding of the relationship between average glucose and HbA1c will address concerns over the role of the glycation gap in future diabetes complications[17] and help to optimize glycaemic management in individuals with diabetes.

Existing variables computed from glucose history include eA1c and GMI, which can be significantly different from laboratory HbA1c,[10,11] because of alterations in RBC lifespan and/or glucose uptake, personal kinetic measures that are accounted for by cHbA1c. Given the high accuracy of cHbA1c, it can be argued that repeated laboratory HbA1c, which remains a clinically important measure, will become unnecessary as it can be replaced with cHbA1c, at least intermittently. Under real-life conditions, this study confirms the superior accuracy of the cHbA1c in predicting laboratory HbA1c compared with established models. We also confirm that the model's accuracy is independent of age, gender, BMI, macrovascular and microvascular complications, and hypoglycaemia unawareness, which suggests the

accuracy, consistency and generalizability of the model. However, we show that microvascular disease, but not macrovascular complications, may be associated with RBC glucose uptake and/or lifespan, thus altering the relationship between average glucose and HbA1c.

In our analysis, we separated the subjects into two groups. Most of the subjects (79/93) were without known conditions that could affect RBC turnover and were designated as Group A. The remaining subjects (14/93) presented various conditions that could alter RBC kinetic variables and were placed into Group B. Compared with GMI, cHbA1c performed better when assessed using various methodologies in both groups. Not surprisingly, Group A performed better than Group B with our kinetic model, given the conditions of the latter group introducing additional variation in the RBC factors. Even at a lower accuracy in Group B, the kinetic model is still more accurate than GMI. Despite the limited cohort size, we were able to perform subgroup analyses to identify possible relationships between RBC kinetic variables and clinical observations. Gender, BMI, macrovascular complications and hypoglycaemia unawareness did not appear to be associated with three RBC kinetic variables (k_{gly}, RBC lifespan and AGR) and therefore had no effect on the relationship between glucose levels and HbA1c. By contrast, the presence of microvascular complications and changes in haemoglobin level did have an effect. In particular, individuals with microvascular complications had higher k_{gly} with a larger spread of the data despite similar average glucose and glucose variability, suggesting increased and more variable intracellular glucose exposure in this subpopulation. These findings emphasize the connection between intracellular glucose levels of RBC and microvascular complications and suggest that glucose uptake rates are coordinated between RBC and non-erythrocytic cells of target organs for microangiopathy.[21] Whether the k_{gly} change is the cause or a consequence remains to be elucidated and, either way, this will have important clinical implications. However, given the small sample size, we should be cautious in our interpretations, and future large-scale longitudinal studies are required to confirm the relationship between high k_{gly} and the risk of microvascular complications.

For the older age group (>60 years), a significant increase in the spread was seen for k_{gly} and AGR, which is consistent with a previous observation.[22] This suggests that some older individuals will have higher HbA1c for given average glucose, which may lead to overtreatment and precipitation of hypoglycaemia that can have detrimental effects on this population.[23–25] Clinically, knowing such a difference can have an immediate benefit. While BMI did not affect $k_{gly,}$ there was a suggestion for tighter distribution of this variable in those with higher BMI (SD = 0.36 compared with 0.48 in the normal group, F-test $P = .08$). However, the difference was comparatively small, and the practical implications of this finding are currently unclear.

We also analysed the effects of haemoglobin levels, which showed that those with abnormally low levels had altered k_{gly}, RBC lifespan and AGR distribution, consequently impacting HbA1c readings. While this observation has been known, it further confirms the validity of the kinetic model and the ability of this system to pick up the effects of comparatively small changes in haemoglobin.

The study strengths include a 'real world' patient cohort and analysis of different factors that may impact the HbA1c–glucose relationship, including the presence of diabetes complications. However, there are a number of limitations to be acknowledged. First, this was a single-centre study and it may not be generalizable to general diabetes patients. The reasons for this include a lack of diversity in race and ethnicity, a lack of geographical distribution, and also that only T1D patients were included. Second, the sample size was modest and therefore subgroup analyses can be regarded as hypothesis-generating rather than confirmatory, and this limits generalizability. Third, it was cross-sectional in relation to diabetes complications and therefore longitudinal studies investigating the role of the kinetic variables in predisposition to vascular complications of diabetes may be warranted.

In summary, this study provides real-world data showing the accuracy of the model in predicting HbA1c from CGM, and alterations in the relationship between HbA1c and glucose in subgroups of patients with T1D. In particular, it shows that gender, BMI and the presence of macrovascular disease have no effect on the relationship, whereas age, the presence of microvascular complications and haemoglobin levels affect this relationship. Future longitudinal studies are warranted to understand the impact of HbA1c–glucose mismatch on future diabetes complications. Moreover, further clinical work is required to address RBC kinetic variable differences between different ethnic groups and the role of these markers in better predicting the risk of diabetes complications. This should be complemented by molecular and cellular studies to fully understand their inter-individual differences and how they affect HbA1c. Collectively, these studies will help to optimize glycaemic care in individuals with diabetes and minimize vascular complications in this high-risk population.

AUTHOR CONTRIBUTIONS

PO collected and organized the data. YX developed and performed all computations and analyses. All authors worked collaboratively to review and prepare the final manuscript.

CONFLICT OF INTEREST

YX, TCD, YR and AC are employees of Abbott Diabetes Care. MPH and PO have no conflicts of interest to declare in relation to this study. PO reports no funding and no personal compensation from Abbott Diabetes Care for the duration of the study. RAA received no payment for this work but has received research support and/or honoraria from Abbott Diabetes Care, Novo Nordisk, Eli Lilly, Johnson & Johnson, Boehringer Ingelheim, Bayer, Sanofi and AstraZeneca.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data is available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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