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Accurate prediction of HbA1c by continuous glucose monitoring using a kinetic model with patient-specific parameters for red blood cell lifespan and glucose uptake

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Abstract

Background: A recent kinetic model proposed a new individualized glycaemic marker, calculated HbA1c (cHbA1c), based on kinetic parameters and glucose levels that are specific to each person. The aims of the current work were to validate the accuracy of this glucose metric for clinical use and evaluate data requirements for the estimation of personal kinetic factors.
Methods: We retrieved HbA1c and glucose data from a group of 51 Japanese T1D patients under sensor-augmented pump (SAP) therapy. Two patient-specific kinetic parameters were identified by data sections, defined as continuous glucose data between two laboratory HbA1c measurements. The cHbA1c was prospectively validated employing subsequent HbA1c data that were not originally used to determine personal kinetic parameters.
Results: Compared to estimated HbA1c (eHbA1c) and glucose management indicator (GMI), cHbA1c showed clinically relevant accuracy improvement, with 20% or more within ±0.5% (±5.5 mmol/mol) of laboratory HbA1c. The mean absolute deviation of the cHbA1c calculation was 0.11% (1.2 mmol/mol), substantially less than for eHbA1c and GMI at 0.54% (5.9 mmol/mol) and 0.47% (5.1 mmol/mol), respectively.
Conclusion: Our study shows superior performance of cHbA1c compared with eHbA1c and GMI at reflecting laboratory HbA1c, making it a credible glucose metric for routine clinical use.

Keywords

Glycated hemoglobin, continuous glucose monitoring, kinetic modeling, red blood cell turnover, red blood cell glucose uptake, red blood cell lifespan

Key messages

- We validated a novel kinetic model for estimating HbA1c values in an Asian cohort.
- The calculated HbA1c has the potential to replace laboratory HbA1c.
- The kinetic model provides a method to estimate individual red blood cell lifespan.

Introduction

The role of glycated hemoglobin (HbA1c) to track and estimate the risk of diabetes-related complications has been established by landmark clinical trials,[1,2] and has been universally adopted to guide clinical care. However, there are limitations to HbA1c as it is affected by conditions that alter red blood cell (RBC) survival, such as anemia, use of drugs that stimulate erythropoiesis, and kidney disease.[3]

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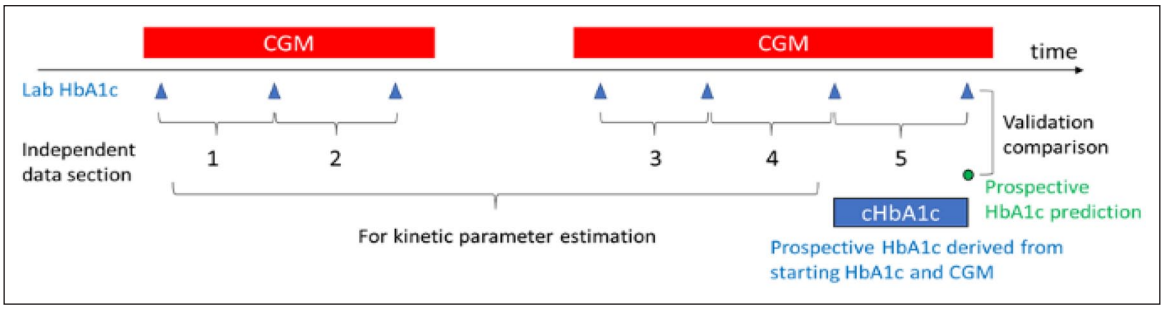

Figure 1. Illustration of data sections, kinetic parameter estimation, and prospective evaluation.

RBC production and removal are in balance during homeostasis, with the production in the bone marrow[4] and removal in the spleen.[5,6] These complex mechanisms result in varying RBC survival, and thus their exposure to circulating glucose levels that in turn determine intracellular hemoglobin glycation and hence HbA1c levels. Experimental evidence has shown there is a variation of mean RBC lifespan between hematologically normal individuals,[7] but accurate assessment of RBC lifespan is both difficult and time-consuming, beyond the capability of routine diabetes management.[8] Further, besides individual variation, there are growing indications for different RBC lifespan across ethnic groups,[9,10] making a further understanding of HbA1c glycation processes key for adequate diabetes management.

Beyond RBC survival, the second key variable factor in determining HbA1c is the facilitated cross-membrane transport of glucose into RBCs by GLUT1 transporters.[11] The majority of glucose is consumed by the Embden–Meyerhof–Parnas pathway to support the energy requirements of the RBC.[4] The fraction of glucose that binds irreversibly to hemoglobin, resulting in "glycated hemoglobin," is detected via the HbA1c assay.[12]

Recent work has proposed a novel relationship between the time-course of glucose concentration and HbA1c that takes RBC survival and glucose uptake into account.[13] This kinetic model incorporates patient-specific parameters of red blood cell production, elimination (i.e. RBC lifespan), and the apparent hemoglobin glycation rate governed by glucose transport across RBC membrane, with all controlling intracellular glycation of the hemoglobin molecule. The model has been developed and validated using data from European clinical trial cohorts and one specific continuous glucose monitor (CGM) technology (FreeStyle Libre®, Abbott Diabetes Care). Due to the potential to affect clinical decisions, the model needs additional verification across various patient groups and using different CGM technologies. In this study, we validated the model for the first time with data from an Asian cohort and Medtronic MiniMed™ 640G CGM device. Due to the high consistency of the data, we have also been able to evaluate the data requirements for reliable estimation of HbA1c and the kinetic constants.

Methods

Data acquisition

The kinetic model takes one or more data sections to estimate patient-specific kinetic parameters. Each data section consists of a frequent glucose trace (at least every 15 min) between two laboratory HbA1c values at least two weeks apart. To ensure acceptable accuracy of estimates, we required that at least 80% of CGM data points should be present, and any continuous gap should be less than 24-h within a data section. The final data section of each subject was excluded from the parameter estimation. The parameters were then fixed and used to prospectively calculate an HbA1c value (termed "cHbA1c") for comparison to the final laboratory HbA1c. We required that each individual had a total of three or more data-sections and therefore at least two for parameter estimation. Figure 1 is an example of data sections and prospective evaluation for an individual.

In this cohort, all subjects had type 1 diabetes treated with the sensor-augmented pump (SAP) from Kobe University Hospital in Japan. All glucose readings were collected by a capillary blood-calibrated CGM sensor (Enlite™, Metronic). HbA1c values were measured by a central laboratory (Kobe University Hospital, HPLC with Arkray HA8181). This analysis received Kobe University's ethical approval (B190322). Within available data collected by Kobe University, 51 subjects met the pre-specified quality and sufficiency criteria for analysis (Table 1).

Statistical and computation methods

For each individual, two kinetic parameters were calculated using the kinetic model with all data sections except the last. These parameters are RBC turnover rate k_{age} (or RBC lifespan $= 1/k_{age}$) and the apparent hemoglobin glycation rate k_{gly} (dominated by cross-membrane glucose uptake). As shown in Figure 1, the prospective use of the model with the kinetic parameters on the final data section produced cHbA1c throughout the data section and comparison was at the day aligned with laboratory HbA1c. Both kinetic parameter estimation and prospective cHbA1c calculations were performed according to

Table 1. Subject and data descriptions.

Subject count		51
Gender M/F		14/37
Age (years): median [IQR] [range]		42 [37–55] [6–73]
CGM usage per subject (days): median [IQR] [range]		440 [176–489] [112–541]
Data section count per subject: median [IQR] [range]		13 [6–15] [3–17]
Ending HbA1c (%)	Median [IQR]	6.9 [6.6–7.5]
	Mean (STD)	7.1 (0.96)
Ending 14-day average glucose (mg/dL)	Median [IQR]	143 [127–160]
	Mean (STD)	145 (27)

previous publication,[13] which is listed in the supplemental materials for convenience.

For comparison to final laboratory HbA1c, the corresponding estimated HbA1c (eHbA1c)[14] and glucose management indicator GMI[15] values were determined by 14-day average CGM glucose (AG). The performances of these methods were compared by the agreements between estimated and laboratory HbA1c values. Specifically, the absolute deviation and R^2 values from Pearson's correlation of linear regression were compared.

Distributions were characterized by the mean and standard deviation for normally distributed data and by median and interquartile range for non-normally distributed data. Any glucose trace gaps less than 45 min had missing values imputed with the nearest observation or average of nearest observations if both were available (the observations immediately before or after the gap). For a longer gap, each missing value was imputed with the average of the observations at the same time in previous and next days. Python/SciPy[16] was used for all analyses.

Based on the model,[13] HbA1c is sensitive to k_{gly} and k_{age} during or after a significant day-to-day glucose change. In a period of steady day-to-day glucose, HbA1c is only sensitive to the ratio of k_{gly} and k_{age}. For this reason, it is harder to estimate kinetic parameters than their ratio. As a consequence, a reasonable HbA1c prediction, for steady-state, can be provided when only the ratio of k_{gly} and k_{age} is available. Therefore, fewer data sections are usually required for HbA1c prediction than RBC lifespan (or k_{age}) estimation. Also, since the individual ratio of k_{gly} and k_{age} is usually easy to determine, we can estimate k_{gly} when k_{age} is available and *vise versa*.

Since the model also assumes no k_{gly} and k_{age} change during the study period, we defined a higher confidence group for subjects with more day-to-day glucose change (between-day glucose CV $>$ 17%), and no major life/therapeutic changes that affect RBC metabolism. These changes include childbirth, iron deficiency treatment, hospitalization, and major drug changes. From the higher confidence group, those with more than 10 data sections were evaluated further to examine the effect of increasing the number of data sections to improve the accuracy of kinetic parameters and HbA1c estimations. By sequentially including additional data sections, we calculated mean absolute deviations to the final RBC lifespan and laboratory HbA1c for each individual. This should set an expectation on the number of data sections required for accurate estimation of HbA1c and individual RBC lifespan.

Results

Prospectively calculated HbA1c and validation of the method

Prospective use of the model with patient-specific kinetic constants produced significantly more accurate predictions of the laboratory HbA1c compared to eHbA1c and GMI. Table 2 lists the comparison metrics of HbA1c estimation using the kinetic model, eHbA1c, and GMI. The kinetic model had the smallest median and mean absolute deviation of 0.10% and 0.11% (1.1 and 1.2 mmol/mol), respectively. The mean absolute deviations from eHbA1c and GMI were significantly larger ($p < 0.001$), approximately four to five times as large. As an HbA1c difference of 0.5% (5.5 mmol/mol) is usually considered clinically relevant, the rates of correspondence within this range were evaluated. The cHbA1c has minimal clinically relevant deviation with 92.3% of individuals within 0.5% (5.5 mmol/mol), compared to eHbA1c and GMI at 65.5% and 73.1% of individuals, respectively.

Figure 2 shows the improved agreement between cHbA1c and laboratory HbA1c, compared to eHbA1c and GMI. The cHbA1c had no overall bias, whereas the eHbA1c and GMI had clinically significant biases of −0.4% and −0.3%, respectively. The superior accuracy of cHbA1c was also indicated by a tighter association with laboratory HbA1c, having a coefficient of determination (R^2) of 0.91 compared to 0.65 for both eHbA1c and GMI.

Laboratory HbA1c ranged between 4.9% and 9.9% (30–85 mmol/mol), with a mean value of 7.1% (54 mmol/mol). At this mean value, cHbA1c had a 95% prediction confidence interval range from 6.9% to 7.3% (52–56 mmol/mol), which is a 78% reduction compared to either eHbA1c (6.5%–8.3% or 48–67 mmol/mol) or GMI (6.5%–8.3% or 48–67 mmol/mol).

Table 2. Accuracy comparison among HbA1c estimation methods.

	Method		cHbA1c	eHbA1c(AG)	GMI(AG)
Comparing estimated HbA1c against lab HbA1c	Absolute deviation (%)	Mean (STD)	0.11 (0.06)	0.54 (0.47)	0.47 (0.46)
		Median [IQR]	0.10 [0.07, 0.13]	0.42 [0.21, 0.81]	0.36 [0.18, 0.62]
	Absolute deviation (mmol/mol)	Mean (STD)	1.2 (0.7)	5.9 (5.1)	5.1 (5.0)
		Median [IQR]	1.1 [0.8, 1.4]	4.6 [2.3, 8.9]	3.9 [2.0, 6.8]
	MARD (%)		3.1	7.5	6.3
	Fraction of AD < 0.5% (AD < 5.5 mmol/mol) (%)		92.3	65.4	73.1
	Average bias (%)		0	−0.4	−0.3
	Average bias (mmol/mol)		0	−4.4	−3.3
	Fraction within ARD (%)	5	79	57	49
		10	94	68	82
		15	100	96	96
	Linear regression	R^2	0.91	0.65	0.65
		Slope	0.94	0.84	1.22
		Intercept	0.49	1.5	−1.17

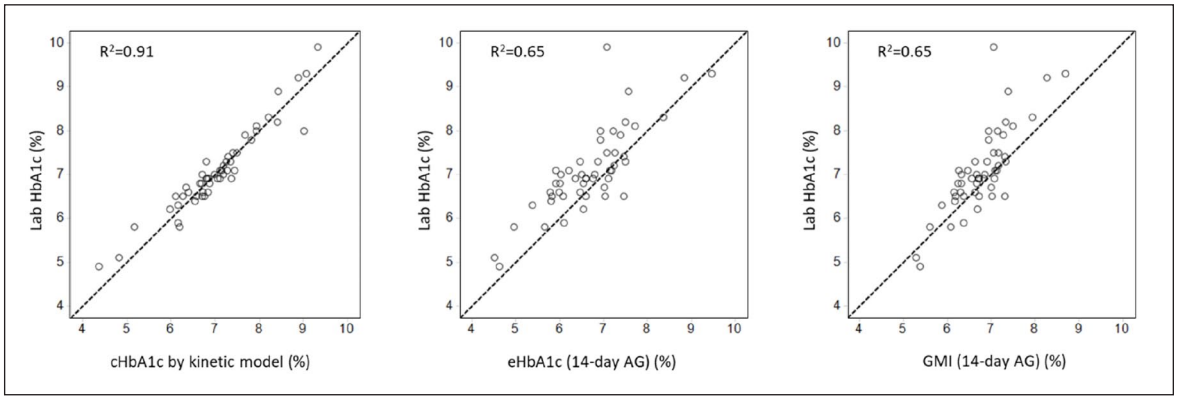

Figure 2. Comparison of correlation between three CGM-derived HbA1c estimates and lab HbA1c.

Estimation of RBC lifespan

Within this cohort, we were able to calculate RBC lifespan in the higher confidence group of 26 subjects. This subgroup has a similar age distribution to the overall study cohort with a median (IQR) of 44 (37–55) years and a range of 10–70 years. The gender distribution was also similar, with 7 males and 19 females. In this subgroup, the median (IQR) RBC lifespan was 74 (66–88) days with a range of 56–120 days. Two subjects had compromised kidney function measured as eGFR less than 44 (mL/min/1.73m^2), and one 14 years old patient. All three individuals showed short RBC lifespans of 55 to 68 days.

Within the 26 higher confidence subjects with relatively larger day-to-day glucose variability and without major life/therapeutic changes during data collection, 12 patients had at least 10 data sections. Figure 3 shows the prospective absolute deviations of cHbA1c compared with last laboratory HbA1c as well as the absolute deviations of RBC lifespan compared with the final RBC lifespan estimated using all data sections. The average absolute deviations of the cHbA1c predictions decreased sharply and then stabilized after the third data section. The absolute deviations of RBC lifespan also decreased longitudinally, reaching stability after the fifth data section.

Discussion

The kinetic model evaluated here explains the relationship between glucose levels and HbA1c with two kinetic rate parameters for RBC turnover and intracellular glucose transfer. The performance of the model was previously evaluated in 120 European adults[13] and using flash glucose monitoring for glucose levels. In this work, we examined the kinetic model in 51 Japanese patients with diabetes managed with SAP therapy and continuous glucose monitoring using a different device. The superior accuracy of the personalized model has been confirmed in this cohort when compared to established non-personalized methods of eHbA1c and GMI.

The model provides estimates for the kinetic parameters associated with RBC lifespan and glucose uptake.

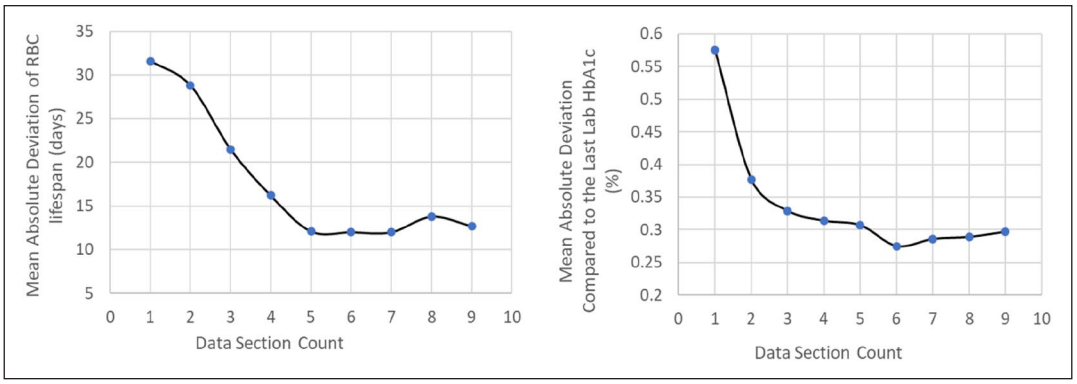

Figure 3. Longitudinal accuracy changes with data section count.

The longitudinal analysis showed that the kinetic parameter estimation usually converges after five data sections. The median RBC lifespan in this cohort was relatively short, around 74 days. In the previous study with the European cohort,[13] we observed a similar median RBC lifespan of 78 days (or RBC turnover rate k_{age} = 1.29%/day). These RBC lifespans are within or slightly lower than the reported range of mean RBC age by Cohen et al.[7] In their experiment, utilizing data from six individuals with diabetes, the mean RBC age range was 38–56 days, giving RBC lifespans of 76–112 days. The observed shorter RBC lifespans might be related to the disease stage of both Japanese and European cohorts. Notably, in this study, the three subjects expected to have shortened RBC lifespans (either adolescent or with kidney disease) had the lowest RBC lifespans of 55–68 days. Having a routine manner of monitoring RBC lifespan and glucose uptake will aid in accurately predicting the future risks of diabetes complications.

While some conditions are known to affect the reliability of laboratory HbA1c as a marker of average glycaemic control (such as anemia and advanced renal disease),[3] our work has the capability of identifying additional individuals in whom laboratory HbA1c can be unreliable. Those with reduced RBC lifespan may be at risk of hyperglycemic damage in tissues affected by diabetes complications, as laboratory HbA1c would underreport hyperglycemic exposure of the organ. Conversely, those with extended RBC lifespan may be at risk of hypoglycemia if treatment is escalated in order to "normalize" HbA1c when tissue exposure to hyperglycaemia is not excessive. Furthermore, RBC lifespan variation may have an impact on the accuracy of HbA1c for the diagnosis of prediabetes and diabetes, which may have major clinical implications.

This study has several strengths. First, it has consistent and high-quality laboratory HbA1c data and this is critical to the accuracy of the model. Second, each individual had high-quality, long term CGM and several concurrent laboratory HbA1c measurements. These longitudinal data were able to confirm the role of additional measurements to improve the accuracy of the personal glycation factors. Third, this is the first analysis in such an ethnic group and also the first analysis using a different CGM technology, further demonstrating the robustness of the method. However, there are limitations to be acknowledged. First, the cohort size is relatively small, which makes further subgroup analyses difficult. Second, only those with type 1 diabetes under SAP therapy were evaluated and therefore generalizability of the results can be questioned.

In conclusion, this study validated the superior performance of an individualized model for glucose-derived HbA1c in Japanese individuals with type 1 diabetes and SAP therapy. The kinetic model offers mechanistic insight into the relationship between glucose levels and glycated hemoglobin with two individualized kinetic parameters for RBC lifespan and glucose uptake. This study extends the model validation to a different CGM technology and further inspires confidence in applying the kinetic model in real-world clinical applications. The work also suggests that two data sections are usually sufficient for accurate HbA1c prediction, while the good estimations of RBC lifespan and glucose uptake likely requires five data sections.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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