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ORIGINAL PAPER

Glycated Hemoglobin (HbA1c): Clinical Applications of a Mathematical Concept

Melvin Khee Shing Leow

Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Corresponding author: Melvin K-S. Leow, MD, PhD, FACP, FRCP (Edin).Leow.Department of Endocrinology. Division of Medicine. Tan Tock Seng Hospital. 11 Jalan Tan Tock Seng, Singapore 308433. Tel: (65) 2566011. Fax: (65) 63577588. E-mail: melvin_leow@nuhs.edu.sg

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ABSTRACT

Background and purpose: Glycated hemoglobin (HbA1c) reflects the cumulative glucose exposure of erythrocytes over a preceding time frame proportional to erythrocyte survival. HbA1c is thus an areal function of the glucose-time curve, an educationally useful concept to aid teaching and clinical judgment. **Methods:** An ordinary differential equation is formulated as a parsimonious model of HbA1c. The integrated form yields HbA1c as an area-under-the-curve (AUC) of a glucose-time profile. The rate constant of the HbA1c model is then derived using the validated regression equation in the ADAG study that links mean blood glucose and HbA1c with a very high degree of goodness-of-fit. **Results:** This model has didactic utility to enable patients, biomedical students and clinicians to appreciate how HbA1c may be conceptually inferred from discrete blood glucose values using continuous glucose monitoring system (CGMS) or self-monitored blood glucose (SMBG) glucometer readings as shown in the examples. It can be appreciated how hypoglycemia can occur with rapid HbA1c decline despite poor glycemic control. **Conclusions:** Being independent of laboratory assay pitfalls, computed 'virtual' HbA1c serves as an invaluable internal consistency cross-check against laboratory-measured HbA1c discordant with SMBG readings suggestive of inaccurate/fraudulent glucometer records or hematologic disorders including thalassemia and hemoglobinopathy. This model could be implemented within portable glucometers, CGMS devices and even smartphone apps for deriving tentative 'virtual' HbA1c from serial glucose readings as an adjunct to measured HbA1c. Such predicted 'virtual' HbA1c readily accessible via glucometers may serve as feedback to modify behavior and empower diabetic patients to achieve better glycemic control.

Key words: glycated hemoglobin (HbA1c), mathematical model, area under the curve, diabetes mellitus, self-monitoring of blood glucose (SMBG), glycemic control.

1. BACKGROUND

The glycated hemoglobin (HbA1c) has been established as a time-honored gold standard yardstick of long-term glycemic control. Highly precise state-of-the-art biochemical HbA1c assays in the era of the National Glycohemoglobin Standardization Program (NGSP) certification as a standard of care allow clinicians to judge glycemic control, make treatment decisions and compare outcomes. While this present day practice is highly successful in managing diabetes patients, much additional clinically relevant value stands to be gained from 'virtual' HbA1c computed from discrete blood glucose data, an endeavor seemingly trivialized and eclipsed by modern technology. Yet, a brief revisit of the biochemistry of HbA1c formation will show that a simple computational approach based on serial blood glucose data can allow its reasonable preliminary estimation. The primary motivation for such a mathematical model arises from both its didactic merits as well as its potential clinical utility deserving of further exploration.

Non-enzymatic covalent binding of glucose to hemoglobin begins with an Amadori molecular rearrangement reaction through Schiff base aldimine intermediates resulting in the formation of various glycated hemoglobins (1), of which HbA1c is a ketoamine species specifically derived from the nearly irreversible glycosylation of the N-terminal valine residue of a beta globin chain (2), though some HbA1c molecules are glycated at the N-terminal valine residues of two beta chains (3,

4). The turnover of HbA1c is dependent on the erythrocyte (RBC) lifespan and therefore correlates with the glucose exposure of the blood over a period of the last 90-120 days (5). Due to attainment of a dynamic equilibrium of the formation, decomposition and destruction of RBC together with their HbA1c molecules as the aged RBC cohort leaves the circulation, the HbA1c is more greatly weighted towards plasma glucose concentrations of the past 4 weeks, with only about 25% of HbA1c contributed by glycemia 60-120 days prior to the measurement (6, 7). HbA1c typically ranges between 4.6-6.4% of the total hemoglobin in non-diabetic people or patients with diabetes having excellent glycemic control. This implies conceptually that HbA1c must be a function of the area-under-the-curve (AUC) of the blood glucose-time profile as can be proven mathematically.

Presently, many existing HbA1c equations linking it to plasma glucose such as various linear regression equations (8, 9) or curvilinear equation (10) are empirical formulas that do not provide mechanistic insight into the HbA1c-glucose relationship. A mathematical model based on first principles by solving the associated linear ordinary differential equation however reduces the computational algorithm of HbA1c to a calculation of the AUC of a glucose-time profile which can hypothetically be inferred from discrete finger-sticks capillary glucoses performed in the course of self-monitoring of blood glucose (SMBG) or a glucose-time tracing plotted out by a continuous blood glucose monitoring system (CGMS) using numerical methods (11).

2. METHODS

The work described below is the theoretical derivation of a fundamental model of glycated hemoglobin. The data used to evaluate the model are based on normative values of any standard laboratory-quoted reference ranges of blood glucose and the associated HbA1c encountered in human populations that can be found in the published literature. Only an anonymous case example based on data from a previously published paper (16) was used as an illustration of how the model can be applied in clinical scenarios. As such, this work is exempted from the requirement for ethical approval from the local institutional review boards.

2.1. Construction of the mathematical model

The following two assumptions are made in the modeling process. Firstly, we assume that the majority of ambient glucose predominantly reacts with hemoglobin in the circulation to form HbA1c in an approximate 1:1 stoichiometric ratio. This is reasonable if the reaction kinetics and binding affinity does not alter with glycosylation status of each beta chain terminal valine residue. Thus,

$$Hb + glu \rightarrow HbA1c \qquad [1]$$

"Hb" represents hemoglobin and "glu" represents glucose. Next, we assume the rate of HbA1c synthesis is directly proportional to the ambient blood glucose concentration. Notwithstanding the skewed temporal density distribution of HbA1c, it is still reasonably valid as an approximation to model HbA1c as an evenly weighted function of time purely dependent on prevailing glucose concentration and set up a first-order differential equation as follows:

$$\frac{d[HbA1c]}{dt} = k[glu \qquad [2]$$

"k" is a rate constant and square parentheses represent plasma concentrations. This equation can then be integrated to give the mathematical expression of HbA1c that is expressed as an 'areal' function under the glucose-time curve (AUC) between two time points, t_1 and t_2 (Figure 1). When the AUC is then multiplied by the rate constant (k), it becomes converted into actual HbA1c in percentage units. Thus:

$$HbA1c = k\int_{t1}^{t2}[glu]dt = k\,(AUC) \qquad [3]$$

2.2. Estimation of rate constant 'k'

The value of the rate constant, 'k', can be theoretically estimated by dividing HbA1c by an idealized rectangular AUC formed by a constant blood sugar over 120 days using one of the better-established regression equations (Table 1). Such equations are based on the observation that any level of HbA1c reflects the intensity of exposure of hemoglobin to a level of mean blood glucose (MBG) over a period of time. Validated formula exist, such as MBG (mmol/L) = {[HbA1c x 35.6] – 77.3}/18, based on the linear regression equation from over 26,000 data points in the epic DCCT study (9), and MBG (mmol/L) = {[HbA1c x 36] – 100}/18, from the classical UKPDS trial (12). Nathan's formula, MBG (mmol/L) = {[HbA1c x 33.3] – 86}/18, is yet another example of a regression equation linking HbA1c to MBG (13). Probably the most famous study among these which links MBG with HbA1c with a very high degree of goodness-of-fit is the ADAG study (14). As these linear regression equations are for all intents and purposes nearly identical, any of these may be used to generate a corresponding MBG for each level of HbA1c (Table 1). For the sake of illustration, the formula from the ADAG study that is widely recognized as the best study of the relationship between HbA1c and MBG to date is chosen here. Hence, by transposing the two variables,

MBG (mmol/L)	AUC = MBG (mmol/L) x 120 days	HbA1c (%)	k (% per mmol/L-day)
4	480	4.1	0.0086
5	600	4.8	0.0080
6	720	5.4	0.0075
7	840	6.0	0.0072
8	960	6.7	0.0069
9	1080	7.3	0.0067
10	1200	7.9	0.0066
11	1320	8.5	0.0064
12	1440	9.2	0.0064
13	1560	9.8	0.0063
14	1680	10.4	0.0062
15	1800	11.1	0.0061

Table 1. Rate constant (k) as estimated from the use of an idealized situation of a fixed, constant blood glucose concentration maintained throughout a span of 4 months (120 days), thereby implying that the mean blood glucose is identically equal to the blood glucose level at any point in time. Simulated HbA1c across the entire range encountered in clinical practice is then calculated according to the formula from the ADAG study for a corresponding range of values of MBG (4-15 mmol/L), following which the value of 'k' is computed by dividing the predicted HbA1c to the AUC (ie. AUC = MBG x 120; k = HbA1c / AUC). This gives an average 'k' of ~ 0.007 % per mmol/L-day over the range of MBG and HbA1c commonly encountered in clinical practice.

HbA1c (by ADAG study formula) = (MBG + 2.59) /1.59 [4]

The value of the rate constant is thereby estimated to be approximately equal to 0.007 % per mmol/L-day (Table 1). Notably, MBG as computed from patients' SMBG records may vary slightly from the MBG estimated from HbA1c derived from a population regression equation (otherwise termed estimated average glucose (eAG) or A1c-derived average glucose (ADAG)). This meant that the value of 'k' elucidated from actual patients' MBG may differ slightly from the theoretical value of 0.007 (15). But deriving a highly precise 'k' is beyond the scope of this discussion which only aims to impress upon readers the feasibility and pragmatic applications of calculated HbA1c based on an AUC methodology emerging from a simple mathematical model.

3. RESULTS

3.1. Differences in glycemia status despite similar HbA1c values

A special note is made of the situation in which the HbA1c can be identical despite major differences in the blood glucose variability. Using graphical representations of AUC, it can be clearly seen that identical HbA1c values between different patients can occur despite extensive differences in their glucose-time profiles (Figure 2). This AUC model makes it much easier for students to visualize how different glucose-time curves can lead to numerically equal HbA1c. However, those with profound degrees of glucose variability are more likely to be at risk of complications including serious hypoglycemic hazards as opposed to others with more stable glucose levels.

3.2. Application of the mathematical model of HbA1c to hypoglycemia risk analysis

An analysis using this AUC approach can show how the potential risks of hypoglycemia can be appreciated by simulation of anti-diabetic therapy leading to a sharp decline in HbA1c. For instance, a drop in HbA1c from 18% to 10% as opposed to a gentle decline from 12% to 10% within 4 months carries significantly different clinical consequences even though both cases share a common final HbA1c of 10% which correlates to MBG in the hyperglycemic range between 15-18 mmol/L. Most physiology and medical students may find it counterintuitive how chronic hyperglycemia associated with a MBG > 10 mmol/L can have periods of profound hypoglycemia (i.e. BG < 4 mmol/L) interspersed within. The use of this mathematical model permits an analysis using simple geometry to illustrate exactly how this phenomenon can occur in a manner that is easy to comprehend as described (Figure 3).

For didactic purposes, the examples are deliberately simplified by ignoring uneven weighted distribution of 'glucose contribution' to HbA1c. The shape of the blood-glucose profile is simplified into a series of contiguous trapeziums to facilitate computations of AUCs via simple geometry. The likelihood of hypoglycemia may then be analyzed easily using this technique as we vary the magnitude of ΔHbA1c from a predetermined initial level (Figure 3). This allows both the novice and the experienced clinician to quickly understand the perils of aggressive glycemic control over a short time frame even though the subsequent HbA1c could still remain high above the desired therapeutic goal.

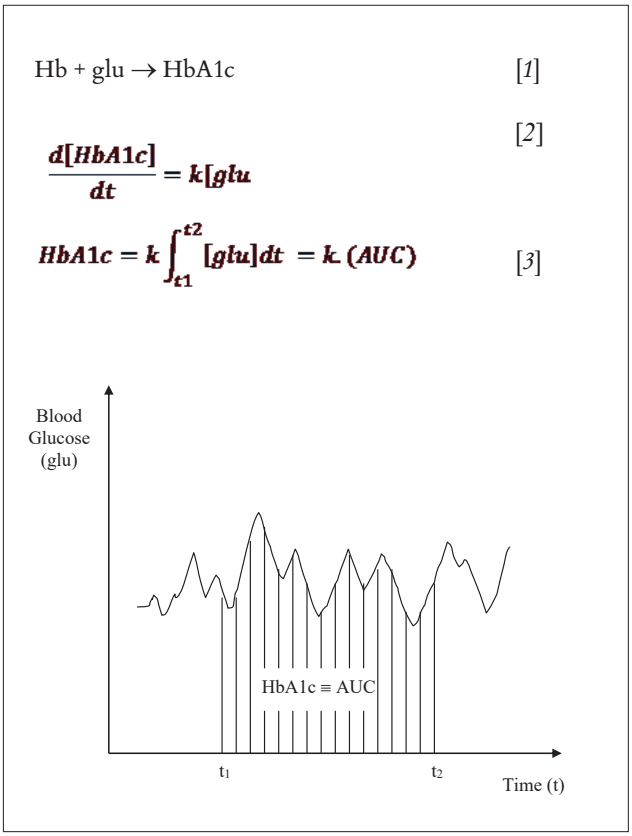


Figure 1. Modeling HbA1c formation. The synthesis of HbA1c is represented by the abbreviated reaction between hemoglobin (Hb) and glucose (glu) as shown. Using calculus notation to define the rate of formation of HbA1c, equation (1) states that this is proportional to the blood glucose concentration at any given time, with k as the constant of proportionality. Upon integration, this yields equation (2), which is the mathematical expression of the area under the curve (AUC) between time points, t1 and t2, of the glucose-time curve as shown in the graph.

In the example shown in Fig. 3, a drop of HbA1c from 18.5% to 14.7% over an interval of 2 months can result in a temporary MBG of 4 mmol/L as the final HbA1c is approached. The probability of hypoglycemia is high as daily glucose variability up to a standard deviation of +/- 2 mmol/L can result in a blood glucose range of 2-6 mmol/L. Hence, this analysis predicts that hypoglycemia (ie. plasma glucose < 4 mmol/L) can occur when HbA1c falls precipitously at a rate exceeding 3-4% per month.

To reinforce this concept, an example from a previously published case report of a 20-year old type 1 diabetic female with poorly controlled diabetes is highlighted (16). Her initial HbA1c was 13.4%. She deliberately self-escalated her own insulin doses in an attempt to bring her diabetes to better control upon confirmation of pregnancy. She then developed a first trimester miscarriage and needed hospitalization. Her HbA1c on admission was 8.2%, which was consistent with prevailing poor glycemic control. Despite her elevated MBG of 10-12 mmol/L as determined from her SMBG records, this was interspersed with frequent profound hypoglycemic episodes evidenced by finger-stick capillary glucoses as low as 2-4 mmol/L, values which she had never attained for many years prior to her pregnancy. Hence, hypoglycemia can coexist with poor glycemic control given that her HbA1c declined sharply by 5.2% (ie. ΔHbA1c = 13.4%–8.2%) within a space of barely 2 months. This paradox can be understood in

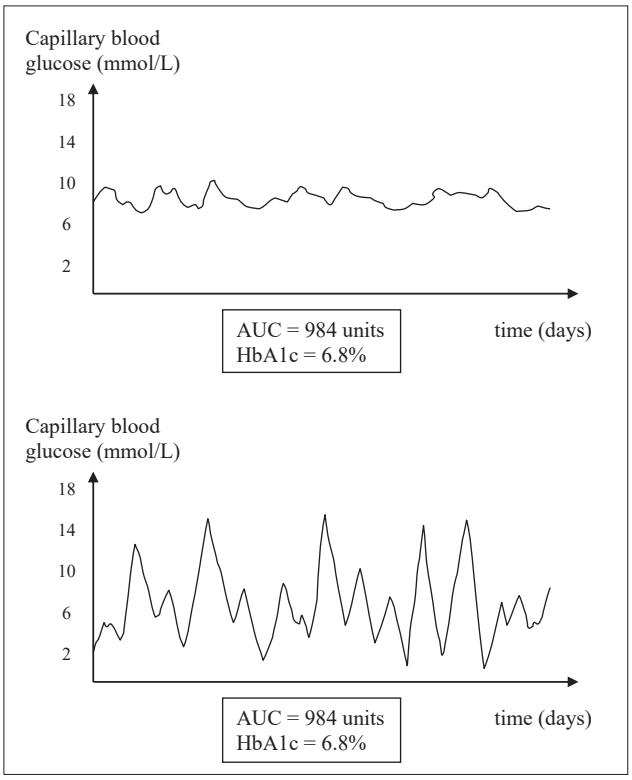


Figure 2. Different glycemic profiles despite equal HbA1c levels. The above 2 examples illustrate the scenario of markedly different glycemic profile between 2 patients with similar HbA1c. Even though their HbA1c are equal, the upper graph shows a patient with stable capillary glucoses between 6-10 mmol/L, whereas the lower graph shows a patient with erratic capillary glucoses ranging from hypoglycemic values below 2 mmol/L to frankly hyperglycemic values above 14 mmol/L.

the context of this mathematical model.

The strength of this simple model of HbA1c lies in its applicability in such analyses. Indeed, a computer program based on this model can potentially be developed to analyze hypoglycemia risk for any level of HbA1c to be achieved within a given time frame for any patient prior to treatment implementation. This can then guide clinicians on the most appropriate rate of achieving patient-specific glycemic targets in diabetes management.

3.3. Computed or predicted HbA1c

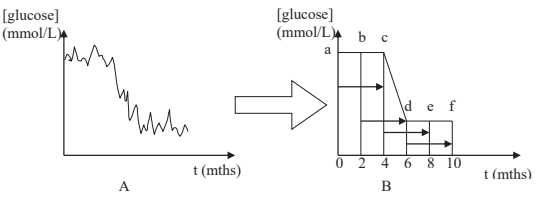
Working backwards, it can be appreciated that HbA1c may thus be computed via AUC calculations as an estimate of the actual HbA1c determined by the laboratory. This can be seen as a possible step in developing relevant computer software that programs point-of-care-testing (POCT) glucometers in future to make tentative 'predicted' HbA1c computations when a minimum threshold number of SMBG measurements are taken so as to allow AUC to be calculated with sufficient accuracy for comparison to actual HbA1c measured by conventional laboratory techniques. The software itself can include educational modules and graphical illustrations that can readily allow both physiology students, doctors and patients to rapidly appreciate the concept of HbA1c and how it is closely linked to preceding blood glucose levels.

4. DISCUSSION

The primary purpose of this AUC model is three-fold. First, it serves as a complementary measure of HbA1c independent of laboratory or point-of-care test (POCT)-based HbA1c in clinical practice. This aids glycemia assessment and trouble-shooting in the face of discrepancies between SMBG records and standard HbA1c values. Secondly, it serves as a pedagogic tool to analyze glycemia scenarios and provide the rationale as to why patients should be routinely evaluated for hypoglycemia whenever sharp declines of HbA1c are encountered irrespective of HbA1c. Thirdly, it opens the possibility for HbA1c to be calculated based on the SMBG data and judiciously used as predictive 'virtual' HbA1c that provides patients an earlier feedback of their diabetes control even before their scheduled doctors' follow-up visits. 'Virtual' HbA1c may in turn motivate patients to alter their lifestyle behaviors such that their measured HbA1c may subsequently be closer to their targets. This is likely achievable as modern glucometers are increasingly interfaced with computers for more precise and effective overall comprehensive diabetes management (17).

Continuous glucose monitoring system (CGMS) can also accurately provide the AUC of the glucose profile and has been shown to correlate with HbA1c very well (18,19). Insulin pumps are presently being wirelessly linked to CGMS as a self-regulating artificial pancreas (20,21). With this version of the insulin pump-cum-CGMS, it can be envisaged that a relatively complete history of blood glucoses will be available for very precise AUC calculations, which in turn can be converted to HbA1c values using this mathematical model.

A useful aspect of the model's predicted 'virtual' HbA1c is that such results, though not robust enough to substitute for actual HbA1c measurements, can be useful as a self-checking



Let $[HbA1c]_1$, $[HbA1c]_2$, $[HbA1c]_3$ and $[HbA1c]_4$ represent the HbA1c measured at 4, 6, 8 and 10 months respectively. Assuming the initial plasma glucose concentration at time 0 is 22 mmol/L (ie. point 'a'). Note that the average glucose concentration plunges down from 22 mmol/L at point 'c' to 4 mmol/L at point 'd', as HbA1c declines by 3.8% within 2 months (between 4th to 6th months).

Calculations:

$[HbA1c]_1 \equiv$ area bounded by '04ca' = 22 x 4 = 88 mths-mmol/L = 2640 days-mmol/L

Taking the value of the proportionality constant, k ~ 0.007, then the approximate $[HbA1c]_1 = 0.007 \times 2640 = 18.5\%$, when measured at the 4th month.

$[HbA1c]_2 \equiv$ sum of areas bounded by '2bc4' + '4cd6' = (22x2) + 0.5(4+22)2 = 70 mths-mmol/L = 2100 days-mmol/L. $[HbA1c]_2 = 0.007 \times 2100 = 14.7\%$ at the 6th month.

Similarly, $[HbA1c]_3 \equiv$ area of '4cd6' + '6de8' = 34 mths-mmol/L = 1020 days-mmol/L. Therefore $[HbA1c]_3 = 0.007 \times 1020 = 7.1\%$, when measured at the 8th month.

$[HbA1c]_4 \equiv$ area bounded by '6df10' = 16 mths-mmol/L = 480 days-mmol/L. Thus, $[HbA1c]_4 = 0.007 \times 480 = 3.4\ \%$, when measured at the 10th month.

Figure 3 Didactic theoretical example of computed HbA1c for analysis of hypoglycemic risk during intensive glycemic control. Given that the normal erythrocyte lifespan is 120 days (ie. ~ 4 months), the HbA1c measured at any time-point ideally represents the glycosylated hemoglobin dating back to the past 4 months. Thus, if 2 consecutive measurements of HbA1c were made over a period shorter than 4 months in between, the respective AUCs will "overlap" as shown in the example above. For the sake of illustration of the concept, the fluctuations of the glucose-time curve (A) are approximated by trapezoids with constant width of 2 months as shown by B. The above mathematical analysis leads to the conclusion that a rapid decline of HbA1c by about 3-4% in 2 months or less is associated with a high risk of inducing hypoglycemia, even if the final HbA1c value well exceeds 8%.

system for internal consistencies and laboratory errors, particularly when the laboratory-measured HbA1c appear to be discrepantly incongruent with SMBG records. To maximize accuracy of AUC calculations, the AUC algorithm might be programmed within glucometers to trigger HbA1c computations only if a threshold minimum number of finger-stick glucose measurements within a specified timeframe is available (22). This obligatory requirement may motivate diabetic patients to do SMBG more frequently to be able to generate a predicted virtual HbA1c as a "reward", a behavioral change that is desirable especially for type 1 diabetes patients and insulin-treated type 2 diabetes patients. In the future, it may be possible to compute more reliable HbA1c using a more sophisticated mathematical model that takes into account the differential glycosylation of the hemoglobin terminal beta chain valines and unequal weighting of contribution of blood glucose to HbA1c over the past 3-4 months, together with advanced numerical algorithms that calculate AUC with extreme precision. Such a model of HbA1c may find useful applications in the setting of advanced handheld glucometers, CGMS monitors and even smartphone apps programmed to calculate HbA1c from SMBG and CGMS data. This remains true even if HbA1c assays can be miniaturized to fit into POCT glucometers in future because computed virtual HbA1c can always be compared against a reliable assay for consistency evaluation.

Lastly, computed HbA1c can also serve as an independent glycemic assessment in diabetic patients with abnormal hemoglobinopathies or thalassemias that invalidate certain HbA1c assay methodologies (23) and where alternative surrogate measurements of intermediate-term glycemic control, such as serum fructosamine (24) are unavailable.

Limitations

This mathematical model does not take into account of variations in HbA1c due to factors apart from blood glucose. For instance, it has been found in recent years that HbA1c may differ between people of different ethnicity despite the same degree of glycemic exposure due to biological variation though this is still debatable (25-27). This phenomenon may be related to factors yet unknown and unrelated to certain hemoglobinopathies or thalassemias that are more commonly found in certain races which are known to confound the laboratory measurement of HbA1c (23). However, when measured HbA1c is discordant with SMBG results due to abnormal hemoglobins, it is expected that the mathematical model should perform better if sufficient SMBG results are available for computation of HbA1c. Similarly, glucometers utilizing glucose dehydrogenase-pyrroloquinoline quinone (GDH-PQ Q) methodology instead of glucose oxidase can produce falsely elevated readings as icodextrin can cross-react with the detection system in renal failure patients on icodextrin-containing peritoneal dialysis fluids (28,29). Such erroneous SMBG results will obviously invalidate any estimation of HbA1c using the mathematical model.

5. CONCLUSIONS

Mathematical modeling of HbA1c deserves further considerations, given its educational potential and possible applications to complement existing superior HbA1c assays. Sophisticated numerical techniques could eventually allow highly precise and efficient calculations of AUC to make computed HbA1c an invaluable addition to the armamentarium of routine diabetes management in the foreseeable future.

- Shortcut: M.L.K.S. is the sole contributor to the entire manuscript in terms of conception, evaluation of the mathematical model and writing of the manuscript.
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- Authorship Contribution: The author is fully responsible for all scientific and technical aspects of the paper from beginning to finish, inclusive of conceiving the hypothesis, mathematical modeling, model testing, drafting the manuscript and critically reviewing it.
- Conflict of interest: none declared.

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