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Use of a model for A1c formation to estimate average glucose operative between short-interval measurements of %A1c

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ABSTRACT

Background: Estimated average glucose (AG) is generally reported along with hemoglobin A1c measurements according to a standard calculation. Given a normal red blood cell lifetime of 120 days, serial A1c measurements at intervals < 120 days are not completely independent. For short interval measurements, a change in AG (ΔAG) necessarily underestimates the change in average glucose operative during the interval (ΔG). We use a model for kinetics of HbA1c to evaluate the theoretical relationship between ΔAG and ΔG for HbA1c measurements made at intervals between 0 and 120 days.

Methods: From any given starting point for A1c, step changes in G were simulated using model calculations to determine the extent to which A1c could change as a function of the interval of exposure. Values for ΔAG were compared to the operative ΔG as a function of the interval between A1c measurements.

Results: Results of model simulations are a single graph for relationship of ΔAG to ΔG as a function of the interval between A1c measurements. ΔAG for (15, 30, 45, 60, 76, and 90) day intervals underestimated operative ΔG by (73, 51, 34, 21, 11, and 5)%, respectively.

Conclusions: Model calculations predict the relationship between changes in estimated average glucose to changes in operative glucose for serial A1c measurements made at intervals < 120 days. Given that serial measurements of A1c made at short intervals are not uncommon in practice, physicians may find this information to be useful.

1. Introduction

As a marker for prevailing glucose, measurement of hemoglobin A1c (as %A1c) up to 4 times per year (every 90 days) is recommended by the American Diabetes Association standards of care for patients not meeting treatment goals [1]. Reporting of estimated average glucose (AG) accompanying measurement of %A1c is recommended practice [1], using the AG vs. %A1c correlation of Nathan et al. [2].

In normal subjects, a period of approximately 120 days is needed for the circulating red blood cell (RBC) population to have been completely replaced [3]. For this reason, serial measurements of A1c made at intervals that are < 120 days are not fully independent. In practice, serial A1c measurements are often made at intervals that are < 90 days [4–7]. For instance, at Jefferson University Hospital, > 20% of serial measurement A1c pairs in 2016 had between-measurement intervals of < 60 days. Short interval measurements can allow physicians to discern whether glycemic control is improving or deteriorating. It is difficult, however, to interpret the extent to which a change in glucose has been operative in short intervals. Because short interval measurements are not fully independent, the difference in reported AG between measurements must be an underestimate of the change in glucose operative during the interval. We present use of a mathematical model for kinetics of A1c formation to characterize maximum changes in %A1c per change in glucose as a function of intervals between measurements that are < 120 days, in order to evaluate the theoretical information content of such short interval measurements with respect to the operative change in glucose.

2. Methods

2.1. Mathematical model for A1c formation and whole blood A1c fraction

A model for the relationship between AG and whole blood %A1c was recently presented in the context of a theoretical investigation of the effects of variation of RBC lifetime on %A1c [8]. The relationship was comprised of two parts: first, a model for the kinetics of formation

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of A1c within an RBC as a function of its age, and second, a calculation of the relationship of A1c as a function of RBC age to whole blood %A1c when accounting for a non-even distribution of cell ages within a given maximum RBC lifetime (nominally, 120 days). Modeling of kinetics of A1c formation involved a simple kinetic mass balance involving transitions between native hemoglobin (A), reversibly glycated hemoglobin (B), and stable hemoglobin A1c (C): $A \leftrightarrow B$; $B \rightarrow C$. With simplifying assumptions, the rate of formation of C can be modeled as first order with respect to glucose (G) and the concentration of non-C:

$$dC/dt = k\,G\,(1 - C) \quad (1)$$

Eq. (1) has a simple analytical solution for C (A1c fraction of total hemoglobin) as a function of cell age, C(t). For C(0) = 0:

$$C(t) = 1 - \exp(-k\,G\,t) \quad (2)$$

Calculation of whole blood average %A1c is by partitioning of C(t) into the average C within discrete age fractions (e.g., C(i), for i = 1,2,3, …120 days) and summing across age fractions weighted according to the % of cells of that age, f(i):

$$A1c\,(\%) = \Sigma\,(C(i) \times f(i)(\%)),\ i = 1 \text{ to } 120 \quad (3)$$

Values for f(i) were obtained from a purely empirical equation characterizing experimental data for cell survival as a function of age (probability vs. age) for a normal maximum RBC lifetime of 120 days, given by

$$p(t) = 1.87\ \exp(-t/\tau) - 0.87;\ t \leq 120 \text{ days} \quad (4)$$

From Eq. (4), f(i) (%) across the *i*th interval ranging from t_1 to t_2 is given by.

$$f(i) = (p(t_1) - p(t_2)) * 100;\ t_2 \leq 120 \text{ days} \quad (5)$$

Use of $k = 1.33 \times 10^{-4}\,day^{-1}\,(mmol/L)^{-1}$ and $\tau = 157$ days in model calculations produces a reasonably close approximation to the established relationship of %A1c to average glucose for A1c in the range of 6–14% ($r^2 > 0.99$) [8].

It is important to note that A1c of Eq. (3) does not correspond to %A1c as reported in Canada and the U.S. ("NGSP" %A1c), which has a constant bias with respect to true %A1c ("IFCC" %A1c) as described in the model [8]. For simplicity, results reported here convert model %A1c calculations ("IFCC" %A1c) to "NGSP" %A1c as reported by convention in the U.S. and Canada.

2.2. Simulation of C(t) after step changes in glucose

Our objective in use of the model was to evaluate the maximum amount that %A1c can change over a given interval as a function of the magnitude of a step change in glucose. We start with %A1c in steady-state (as derived from a C(t) profile under conditions of constant glucose). From the associated profile for C(t), changes in C(t) were calculated by a step-wise simulation of the model for the number of days that a step change in glucose (ΔG) was assumed to be operative. Simulation calculations were conducted in increments of 1 day ($\Delta t = 1$), with an exit from the cell population each day of the fraction of cells of age 120 days, and entry into the cell population each day of a new cell fraction of age zero days:

$$C(t + \Delta t) = 1 + (C(t) - 1)\exp(-k\,G\,\Delta t) \quad (6)$$

This is a step-wise version, for use in simulation, of the solution for Eq. (1) for arbitrary initial conditions of C starting at any given time interval (that is, for $C(0) \neq 0$):

$$C(t) = 1 + (C(0) - 1)\exp(-k\,G\,t) \quad (7)$$

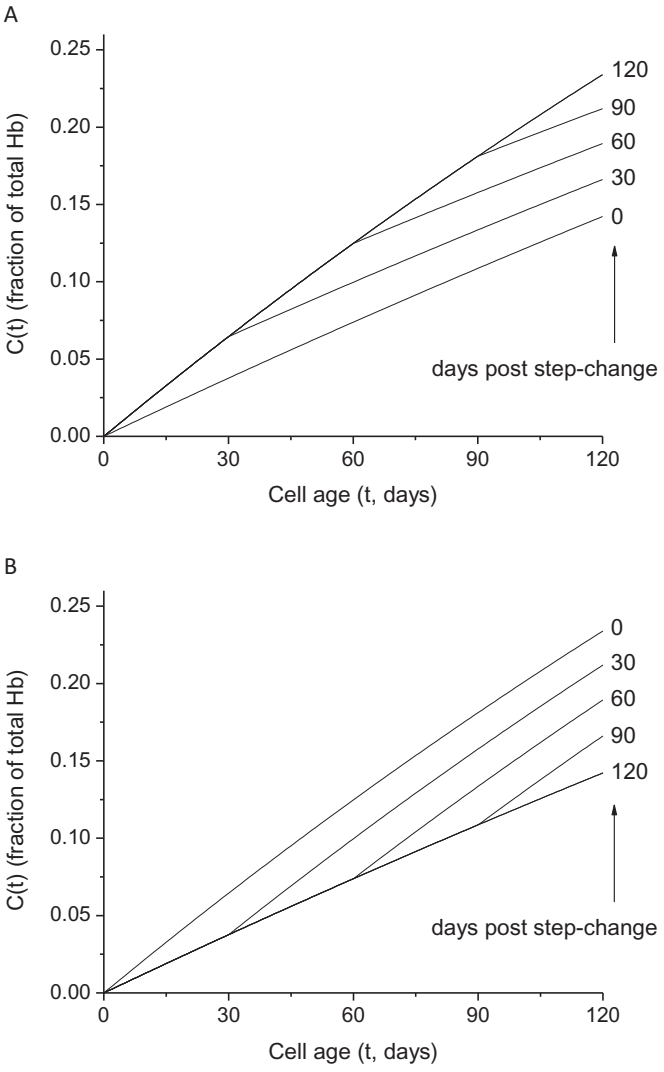

Fig. 1. Examples of C(t) profiles after step changes in G of differing durations. A. Initial condition of G = 8 mmol/L, with step change to G = 12 mmol/L. B. Initial condition of G = 12 mmol/L, with step change to G = 8 mmol/L. Parameter = duration of step change (0, 30, 60, 90, or 120 days). %A1c range = 7.1% (G = 8 mmol/L) to 9.4% (G = 12 mmol/L).

3. Results

3.1. Examples of C(t) profiles for step changes in G across intervals < 120 days

Examples of C(t) profiles for simulations of step changes in G from a prior steady-state condition of constant G are shown in Fig. 1, assuming normal maximum RBC lifetime of 120 days. Fig. 1A illustrates C(t) vs. cell age when the initial condition is for G = 8 mmol/L (using Eq. (2)), followed by a step change in G to 12 mmol/L (simulated using Eq. (6)). Fig. 1B illustrates C(t) vs. cell age when the initial condition is for G = 12 mmol/L, followed by a step change in G to 8 mmol/L. Note that C(t) can only increase with time for any cell; there is simply a discontinuity in slope of C(t) vs. cell age (an increase or decrease) at the point of introduction of the step change in G.

3.2. Examples of change in %A1c vs. for step changes in G across intervals < 120 days

Whole blood %A1c can be calculated for C(t) profiles such as in Fig. 1 using Eq. (3). In Fig. 2, results of such calculations for changes in