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# On the Weighted-Average Relationship Between Plasma Glucose and HbA$_{1c}$

Tahara and colleagues (1–3) have reported results of experimental investigations concluding a relationship between plasma glucose level and HbA$_{1c}$ (A1C), defined as

$$H(t) = K \int_0^t W(t - \zeta)G(\zeta)d\zeta$$

(Eq. 1)

Their expression for $W(s)$ is

$$W(s) = \begin{cases} 2(T - s)/T^2, & 0 \le s \le T \\ 0, & s > T \end{cases}$$

(Eq. 2)

The experimental mean fasting plasma glucose (MFPG) results reported in ref. 1 were analytically modeled and then used to determine the corresponding mean A1C curve (Eq. 1). Excellent correlation was obtained between experimental mean A1C and analytical A1C curves. The specific curve for MFPG is

$$G(t) = G_s + G_d \exp(-\gamma t)$$

(Eq. 3)

where $\gamma$ is constant in time but nonetheless adjustable to designate different decay rates. The MFPG curve reported in ref. 1 is found from Eq. 3 for $G_s = 6.6$, $G_d = 6.2$, and $\gamma = 1$. The related expression for A1C derived from Eq.1 is

$$\frac{H(t)}{2K} = G_s\left[ \left(\frac{t}{T}\right) - 0.5\left(\frac{t}{T}\right)^2 \right]$$
$$+ \left(\frac{G_d}{\gamma T}\right)\left(1 - \frac{t}{T}\right)\left[ 1 - \exp\left(-\gamma t\right) \right]$$
$$+ \frac{G_d}{\gamma^2 T^2}\left[ 1 - \left(1 + \gamma t\right)\exp\left(-\gamma t\right) \right]$$

(Eq. 4)

Values of $H(t)$ versus $t$ obtained using Eq. 4, with $K = 0.75$, $T = 17$ weeks, and $\gamma = 1$ were subtracted from the mean of patient-admission A1C values to approximate the mean A1C curve reported in ref. 1.

Adjusting $\gamma$ to designate different decay rates, as would be the case for patients using only diet and exercise to control their plasma glucose levels, it is evident from Eq. 3 that as $\gamma$ decreases from (say) $\gamma = 1$ to $\gamma = 0.1$, e.g., $\gamma = 0.8, 0.4, 0.2, 0.1$, a family of $G(t)$ curves will be generated whose corresponding decay is slower. Given that 50% of the GHb level at any time is determined by the plasma glucose level during the preceding 1-month period, 25% by the plasma glucose level during the 1-month period before that, and the remaining 25% by the plasma glucose level during the 2-month period before the first 2 months (1–3), it follows that if the plasma glucose curve decays, the corresponding A1C curve will

also decay. Results reported in ref. 1 confirm this, as do results from a study by Rohlfing et al. (4), where an algebraic relationship between FPG and A1C is reported.

However, the $\gamma$ curves of A1C determined from Eq. 4 display a faster decay as $\gamma$ decreases. This inverted decay suggests the weighted-average relationship between plasma glucose and A1C reported in ref. 1 is questionable. As functions of $\gamma$, both plasma glucose and A1C curves should decay faster as $\gamma$ increases and slower as $\gamma$ decreases, not one slower and the other faster (or vice versa).

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# On the Weighted-Average Relationship Between Plasma Glucose and HbA$_{1c}$

Response to Treviño

Dr. Treviño (1) has derived a mathematical formula for HbA$_{1c}$ (A1C) change in response to exponential plasma glucose decay. His analysis has shown a faster decay of A1C associated

with a slower decay of plasma glucose and posed a question to the weighted-average relationship between plasma glucose and A1C, which we proposed in our previous study (2). Since his derived formula is very complicated and the detailed analytical method is not given, I cannot exactly reply to his question. However, I propose here a new physiological model, which deals with the kinetics of GHb production in red cells, and explain the relationship between plasma glucose and A1C.

GHb is not contained in the newly born red cells, formed every day in proportion to plasma glucose level during red cell life, and finally removed from blood together with the end of red cell life. Hemoglobin in the red cells aged 1 day is therefore glycated during the preceding 1 day, whereas hemoglobin in the red cells aged 2 days is glycated during the preceding 2 days, and so on. Thus, GHb produced on the day just before A1C measurement is contained in the red cells aged 1 to $T$ days ($T$ is the red cell life span), whereas GHb produced on the day 2 days before is contained in the red cells aged 2 to $T$ days. Generally, GHb produced on the day $s$ days before A1C measurement is contained in the red cells aged $s$ to $T$ days. This means that the total amount of GHb produced on the day $s$ days before A1C measurement is proportional to the volume of the red cells aged $s$ to $T$ days. In a steady-state condition where the distribution function of red cell age is constant, the contributory rate of the plasma glucose in the day $s$ days before A1C measurement is proportional to $T-s$, and is given by $W(s) = 2(T-s)/T^2$ ($0 \leq s \leq T$), where the coefficient $2/T^2$ is a normalization factor.

This result is just the same as in our previous report (2). Area under the weight function curve shows contributory rate of plasma glucose for each period. For $T = 120$ days, 50% of A1C is determined by the plasma glucose level during the preceding 35 days, 25% by the plasma glucose level during 25 days before this period, and the remaining 25% by the plasma glucose level during the 2-month period before these periods. The present model clearly shows the relationship between plasma glucose and A1C. Introduction of distribution function of red cell age to this model further enables analysis of A1C behavior when the red cell kinetics is disturbed by various physiological or medical conditions.

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# Hypoglycemia Preceding Fatal Car Collisions

Hypoglycemia significantly impairs driving performance (1,2), and driving collisions involving diabetic individuals are frequently attributed to hypoglycemia (3). Further, driving mishaps are often preceded by frequent mild symptomatic hypoglycemia while driving (4). It is reasonable to expect that before a hypoglycemia-related driving mishap, drivers with type 1 diabetes may experience frequent episodes of hypoglycemia.

We recently conducted a study in which 100 adults and 100 children with type 1 diabetes were given memory meters and strips (OneTouch Ultra; LifeScan, Milpitas, CA) and asked to record all blood glucose readings for 6 consecutive months. Tragically, during this study, two subjects died in vehicular collisions. Subject A was a 47-year-old male with a 30-year history of type 1 diabetes and an HbA$_{1c}$ (A1C) of 7.6%. Witnesses reported that the subject had been swerving out of his lane, with erratic speed, and was unresponsive to the honks of other drivers before crashing into a tree. Subject B was a 15-year-old male with a 7-year history of type 1 diabetes and an A1C of 7.0%. The accident occurred when his ATV flipped while driving through the woods.

The low blood glucose index (LBGI) is a composite score reflecting the frequency and extent of low blood glucose over a month of routine self-monitoring of blood glucose (5–7). The LBGI accounts for 40–60% of the variance of future severe hypoglycemic episodes within the following 3–6 months (5–7), whereas A1C accounts for only 6% of the variance

(8). An LBGI of >5 places an individual at significantly elevated risk of future severe hypoglycemic episodes; this represents a 10-fold increase in the occurrence of future severe hypoglycemic episodes compared with an LBGI of <2.5 (5–7). The LBGI can significantly change within 2–4 weeks with changes in diabetes regimen, while A1C is a more stable measure, taking 2–3 months to incur a significant change.

After the second death, we analyzed memory meter data for subjects' LBGI. For the 3 months before these fatalities, monthly LBGI steadily rose for subject A from 6.2, to 7.0, to 7.5 and for subject B from 3.3, to 5.0, to 6.6. During this period, subject A reported four episodes of severe hypoglycemia, while subject B experienced one episode of severe hypoglycemia the week before the collision.

If these individuals had been informed about their elevating risk of future severe hypoglycemia and given the opportunity to reduce this risk, these deaths may have been avoided. It must be pointed out that the LBGI is certainly not specific to driving collisions. Currently, the LBGI is not available to patients on any memory meter display program, but its computation is straightforward and can be computed on any data spreadsheet. A less sophisticated and less sensitive alternative is to have patients compute the percent of blood glucose readings <3.9 mmol/l. An LBGI ≥5 is equal to roughly >15% of an individual's self-monitoring of blood glucose readings being <3.9 mmol/l. If patients recognize when they are having frequent low blood glucose values and take steps to reverse this, it is possible that some of these tragic events could be avoided. It is exposure to frequent hypoglycemia, not low A1C, that increases the risk of severe hypoglycemic episodes (5–7).

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