Average glucose and HbA1c display a nonlinear and variable relationship: implications for clinical practice

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Disclosures

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Background and Aims

- Estimation of average glucose (AG) from HbA1c is practiced clinically using an empirical linear relationship

D. M. Nathan, J. Kuenen, R. Borg, H. Zheng, D. Schoenfeld, R. J. Heine, Translating the A1C assay into estimated average glucose values, *Diabetes Care* **31**, 1473–1478 (2008).

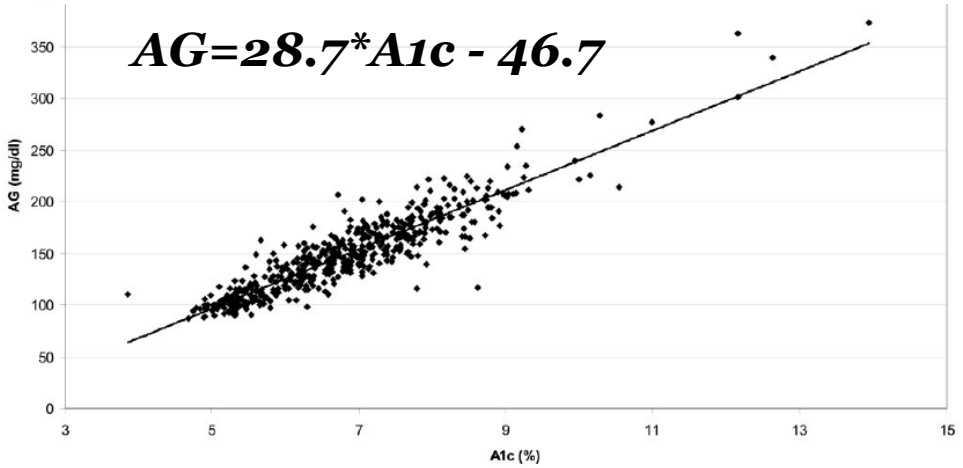

Figure 1—*Linear regression of A1C at the end of month 3 and calculated AG during the preceding 3 months. Calculated* $AG_{mg/dl} = 28.7 \times A1C - 46.7$ ($AG_{mmol} = 1.59 \times A1C - 2.59$) ($R^2 = 0.84$, $P < 0.0001$).

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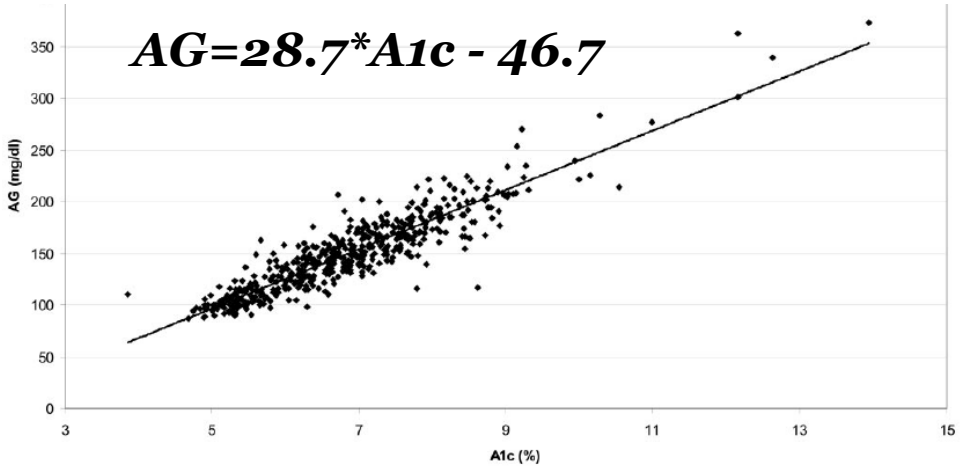

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***Steady-state** relationship*

$$AG^{-1} = PGR * (A1c^{-1} - 0.01) * 10^{-3} - K_M^{-1}$$

mg/dL *ml/g* *NGSP %* *473 mg/dL*

Personal glycation ratio

$PGR = k_{gly} * RBC\ lifespan$

Apparent hemoglobin glycation rate

Xu Y, Dunn TC, Ajjan RA. A Kinetic Model for Glucose Levels and Hemoglobin A1c Provides a Novel Tool for Individualized Diabetes Management. J Diabetes Sci Technol. 2021;15(2):294-302.

Background and Aims

- Estimation of average glucose (AG) from HbA1c is practiced clinically using an empirical linear relationship
- A recent kinetic model indicates this relationship to be nonlinear due to red blood cell factors
- The aim of this study was to compare the empirical linear and theorical nonlinear models using real-world data
  - verify ~20% PGR variabilities from our previous estimation

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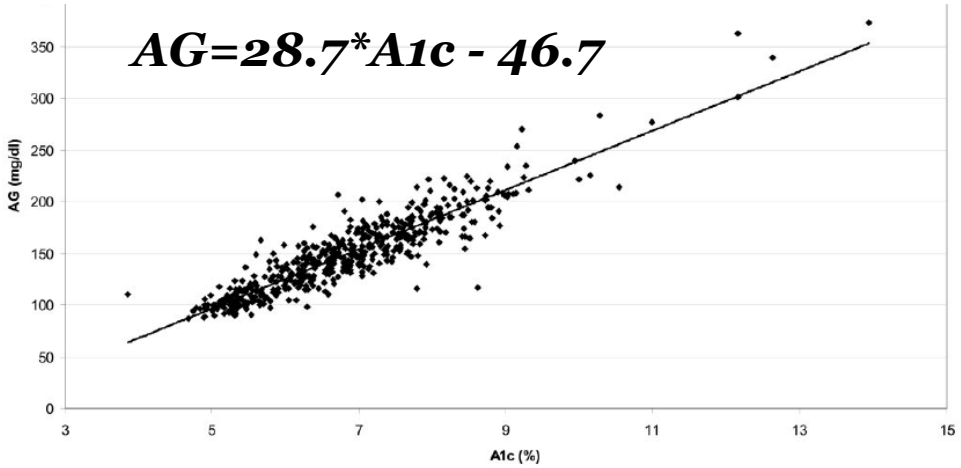

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reference PGR: 65.1 ml/g
From literature k_{gly} and
105 days RBC lifespan

$$PGR = k_{gly} * RBC\ lifespan$$

Apparent hemoglobin glycation rate

$$\boldsymbol{AG^{-1} = 0.0651 * A1c^{-1} - 0.00277}$$

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Real-world data

- **Linked data project - deidentified**
  - LibreView data management platform
  - Quest lab HbA1c
- **Pairing of glucose and A1c**
  - HbA1c and AG pairs determined from CGM in a 56 days period before HbA1c measurement
- **Restrictions and exclusions**
  - >50% of CGM coverage in each periods
  - Steady-state requirement: Maximum 14-day AG difference less than 20 mg/dL

Method – models to consider

Linear regression model from ADAG study (2008):

$$AG = 28.7 * A1c - 46.7$$

Nonlinear kinetic model steady-state AG-A1c relationship:

$$AG^{-1} = 0.0651 * A1c^{-1} - 0.00277$$

Compare both models with average AG and A1c pairs from 100 bins by the sum of AG and A1c ranks

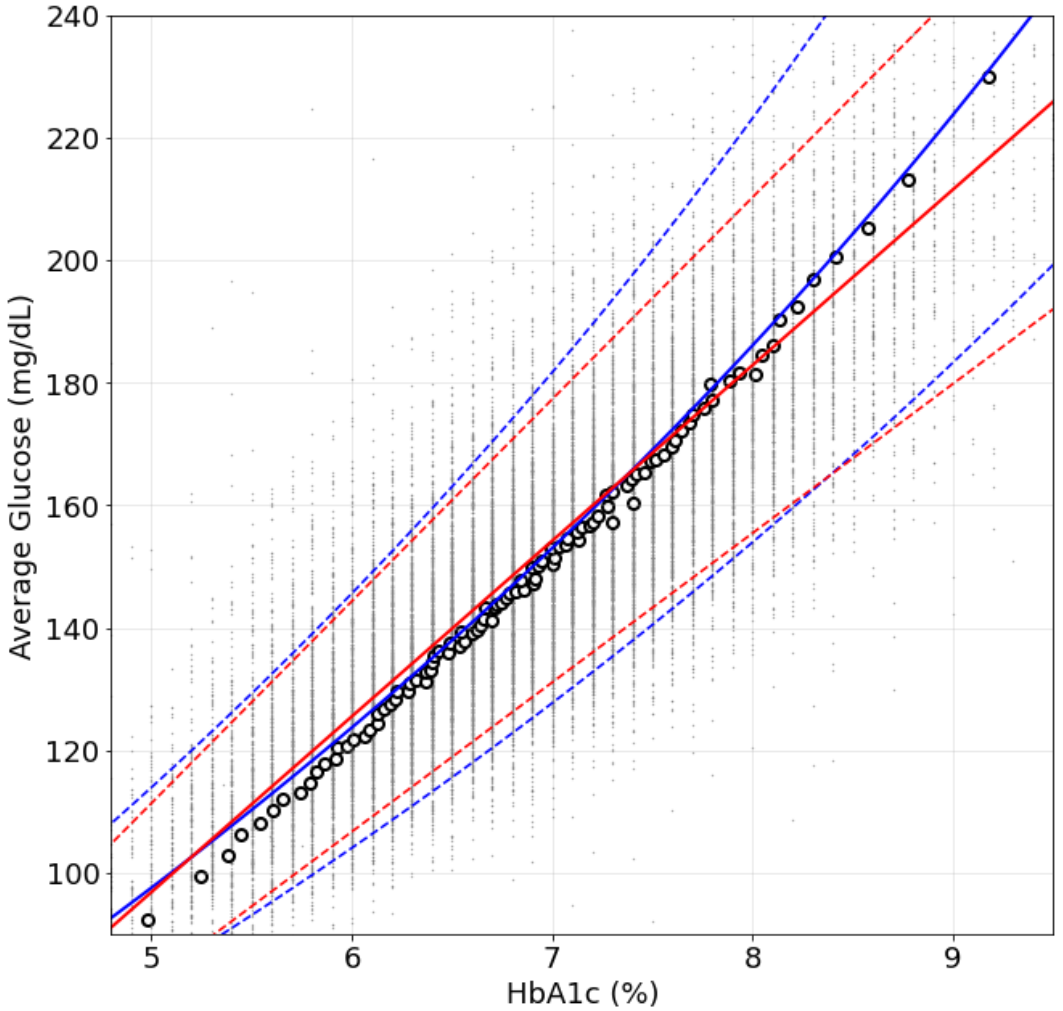
Result

- **25,346 AG and HbA1c pairs from 18,186 individuals were analyzed**
- **Non-linear model has a better agreement with data** – larger difference at higher HbA1c
- **Large 95% prediction interval suggests**
  - Individual variation in RBC physiology
  - PGR range of 57-75 ml/g, a range about 26% of reference value 65.1 ml/g

HbA1c	AG (mg/dL)			
	Linear ADAG	Non-linear steady-state	difference between models	AG from Data
8.5%	197	204	7	203
9%	212	224	12	223

	R^2	Mean absolute deviation (mg/dL)
Linear ADAG	0.977	3.0
Nonlinear steady-state	0.995	1.1*

$^*p < 0.001$



Summary

- The nonlinear model had superior agreement with the data, comparing to ADAG model which has good agreement with data.
- Clinical implications:
  - The linear model increasing underestimates AG at higher A1c
  - The spread of data match the expected about 20% spread of PGR, based on the variation in observed variations in RBC glucose uptake rate
  - The large 95th prediction interval indicates large individual variation of AG for any given HbA1c – supporting moving on to CGM metrics for management

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