Ethnic differences in glycation & HbA1c-glycemia relationship: Impacts on research, diagnostic cutoffs and treatment

Melvin Leow
Deputy Director, Clinical Nutrition Research Centre
Endocrinologist, Tan Tock Seng Hospital

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Does HbA1c for any given glycemic burden differ by ethnicity?

YES

More recent literature from the past decade onwards suggests inter-ethnic/racial differences in the relationship between HbA1c and glucose exist!

Stereoisomers of D-glucose

99% of glucose are α-D and β-D stereoisomers (cyclic)
1% of glucose in linear aldehyde form
When plasma glucose increases, the conc of aldehyde form increases which increases the reaction with Hb terminal valines

Hemoglobin forms in the circulation

- HbA - α2β2 (95-98%)
- HbA2 - α2δ2 (1.5-3.5%)
- HbF - α2γ2 (<2%)
Glycation vs Glycosylation

- Glycation - addition of glucose to proteins via a non-enzymatic reaction
  - Genetic polymorphisms of enzymes which often account for ethnic differences are not responsible for ethnic variations for the rate and susceptibility of glycation of HbA

- Glycosylation - an enzymatic process to link carbohydrates

RBC age-dependent glycation

- Turnover of HbA1c - dependent on RBC lifespan
- Correlates with the glucose exposure of the blood over a period of the last 90-120 days
- Dynamics - formation, decomposition & destruction of RBC
  - HbA1c weighted more towards plasma glucose in past 4 weeks, with ~ 25% of HbA1c contributed by glycemia 60-120 days prior to the measurement
  
  - *Diabetes Care* 1993; 16: 1313-1314
**HbA1c & FPG thresholds in health & disease**

- **HbA1c Cutoffs**
  - HbA1c - 4.6% to 5.6% (non-DM)
  - HbA1c >= 5.7% to 6.4% (pre-DM)
  - HbA1c >= 6.5% (DM)

- **FPG Cutoffs**
  - FPG < = 5.5 mmol/L (non-DM)
  - FPG 5.6-6.9 mmol/L (pre-DM)
  - FPG >= 7.0 mmol/L (DM)

**HbA1c – Accuracy is critical!**

- Accurate HbA1c measurements are crucial to decision making in both diagnosis and treatment.
- Standards (NGSP/DCCT, IFCC) exist to eliminate technical errors in HbA1c testing, yet various patient factors can confound the result by decreasing or increasing it independent of glycemic status.

**HbA1c vs FPG in Chinese Individuals (N = 8391)**

![Graph showing the correlation between HbA1c and FPG in Chinese individuals.]

**Diagnostic HbA1c Cutoff for DM Diagnosis**

- For most Chinese in China in this study, the diagnostic cutoff HbA1c for DM = 6.5% (similar to ADA for the Caucasians).

  - FPG = (HbA1c – 3.1501)/0.4691 (R2 = 0.5711)
  - Substituting HbA1c = 6.5% into this yields a FPG = 7.1 mmol/L
  - Corresponds to the 1999 ADA FPG cutoff > 7.0 mmol/L to define diabetes.
HbA1c-FPG relationship (Data from Singapore Prospective Study Program 2004-2007) (N = 3895 healthy subjects)

Diabet Med 2012; 29: 911-7

Ethnic variation in the correlation between HbA1c-FPG (N = 479 type 2 DM subjects)


But could such differences vanish if HbA1c is compared against MBG which takes into account of FPG, PPG, RPG & all inter-meal glycemia?

Distribution of HbA1c in Singapore population

Regression Equations HbA1c-MBG

- MBG (mmol/L) = \{[HbA1c x 35.6] – 77.3\}/18
  - DCCT
- MBG (mmol/L) = \{[HbA1c x 36] – 100\}/18
  - UKPDS
- HbA1c = (MBG + 2.59) /1.59
  - ADAG study
**Racial Difference between HbA1c-MBG in T1DM**

Blacks still had higher HbA1c after adjustment for red blood cell indices, age, and sex

*J Pediatr 2016; 176: 197-6*

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**Racial Differences in the Relationship of Glucose Concentrations and Hemoglobin A1c Levels**

For any given mean glucose concentration level among patients with type 1 DM

- mean HbA1c was 0.4% points \( \geq \) in black than those of white individuals.

Importantly, no significant racial differences were present in relationship of fructosamine levels with the mean glucose concentration.

Inter-racial glycation rate appears to differ mainly at the hemoglobin molecule

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**Fructosamine & Glycated Albumin in White vs Black Persons**

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**HbA1c – Magnitude of Differences**

- For any given mean glucose concentration level among patients with type 1 DM
  - mean HbA1c was 0.4% points \( \geq \) in black than those of white individuals.

- Importantly, no significant racial differences were present in relationship of fructosamine levels with the mean glucose concentration.
  - Inter-racial glycation rate appears to differ mainly at the hemoglobin molecule.
**Limitations & Implications**

- **Limitation:** number with HbA1c <6.5% few
  - Difficult to extrapolate results to normal & pre-DM

  - revealed a similar racial difference in HbA1c even for people without DM - mean HbA1c was 0.26 percentage points higher in black compared to white people

- This implies the present use of the HbA1c cutoff of 6.5% as a diagnostic criterion for diabetes as presently endorsed by the ADA >> lead to substantively higher prevalence estimates of DM from over-diagnosis especially when applied to the black population.

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**Racial Differences in the Relationship of Glucose Concentrations and Hemoglobin A1c Levels**

- All current evidence on the clinical benefits of glycemic control is based on HbA1c
  - Therefore, HbA1c goals should remain the same in Blacks as in Whites. However, be aware that the risk of hypoglycemia is higher in Blacks for achieving the same HbA1c levels

- This gave rise a question how racial difference affects on glycation of hemoglobin because the process goes non-enzymatically
  - Inherited hemoglobin variants or hemoglobinopathies & thalassemias mostly excluded in this study

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**Mechanisms for ‘Glycation Gap’ Differences**

- Kinetics of glycation of albumin in the circulation are similar

- Assuming no biological/structural variation in the hemoglobin macromolecule between racial groups

- Any detectable racial difference in glycation gap (defined as the difference between the measured HbA1c and that which is predicted from glycated serum albumin/fructosamine) under the same conditions could be mechanistically explained by these factors:

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**Mechanistic Explanations**

- Heterogeneity in glucose concentration gradient across the red cell membranes

- Rates of glucose transport via GLUT1 into the erythrocytes

- Racial variances in enzymatic activity of the fructosamine 3-kinase gene which influences protein deglycation and HbA1c levels
**Diagnosis of DM using HbA1c locally?**

- At present, diagnosis of DM is mainly via:
  - Fasting plasma glucose
  - 75g OGTT
  - HbA1c

- Use of HbA1c instead of FPG leads to a higher prevalence of pre-DM and DM
  - *Int J Diabetol Vasc Dis Res 2015; Suppl 2. pii001*

- Use of HbA1c >6.5% performs reasonably well among 3 Asians ethnic groups in Singapore despite some interethnic variations
  - Population based cross-sectional studies n=13170
  - *J Clin Endocrinol Metab 2015; 100:689-96*

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**Implications for Treatment**

- Population-specific cut-off points have NOT been established
  - Since optimum cut-offs vary by ethnic group

- Treatment wise – HbA1c is still applied without ethnic consideration in terms of treatment targets

- As HbA1c diverges with higher MBG, ethnic differences likely more important among poorly controlled DM

- Important to consider risk of hypoglycemia in Malays and Indians when aiming at HbA1c < 6.5-7.0% as FPG & MBG are lower than Chinese for any given HbA1c level

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*Thank you for your kind attention!*