Speaker Financial Disclosure Information

Nothing to disclose

Should Hemoglobin A1c be Used to Diagnose Diabetes?

William H. Herman, MD, MPH

Stefan S. Fajans/GlaxoSmithKline Professor of Diabetes

Professor of Internal Medicine and Epidemiology

University of Michigan

Director, Michigan Center for Diabetes Translational Research

NO

Disadvantages of Glucose Criteria for the Diagnosis of Diabetes

- Inconvenient
- Susceptible to modification by short-term lifestyle changes
- Large intra-individual biologic variation

Advantages of HbA1c for the Diagnosis of Diabetes

- Convenient
- Less susceptible to short-term lifestyle modification
- Small intra-individual biologic variation
- International assay standardization

Disadvantage of HbA1c for the Diagnosis of Diabetes

HbA1c is an indirect measure of average glycemia and may be high or low relative to the true level of glycemia (systematic error)

Assumptions Underlying the Use of HbA1c as a Measure of Glycemia

- Erythrocyte lifespan is constant
- Erythrocytes are freely permeable to glucose
- HbA1c is formed slowly and nonenzymatically
- Rate of HbA1c formation is directly proportional to ambient glucose concentration and provides a measure of average glycemia over the previous 120 days

Red cell life span heterogeneity in hematologically normal people is sufficient to alter HbA1c

RM Cohen. Blood 112:4284-4291, 2008

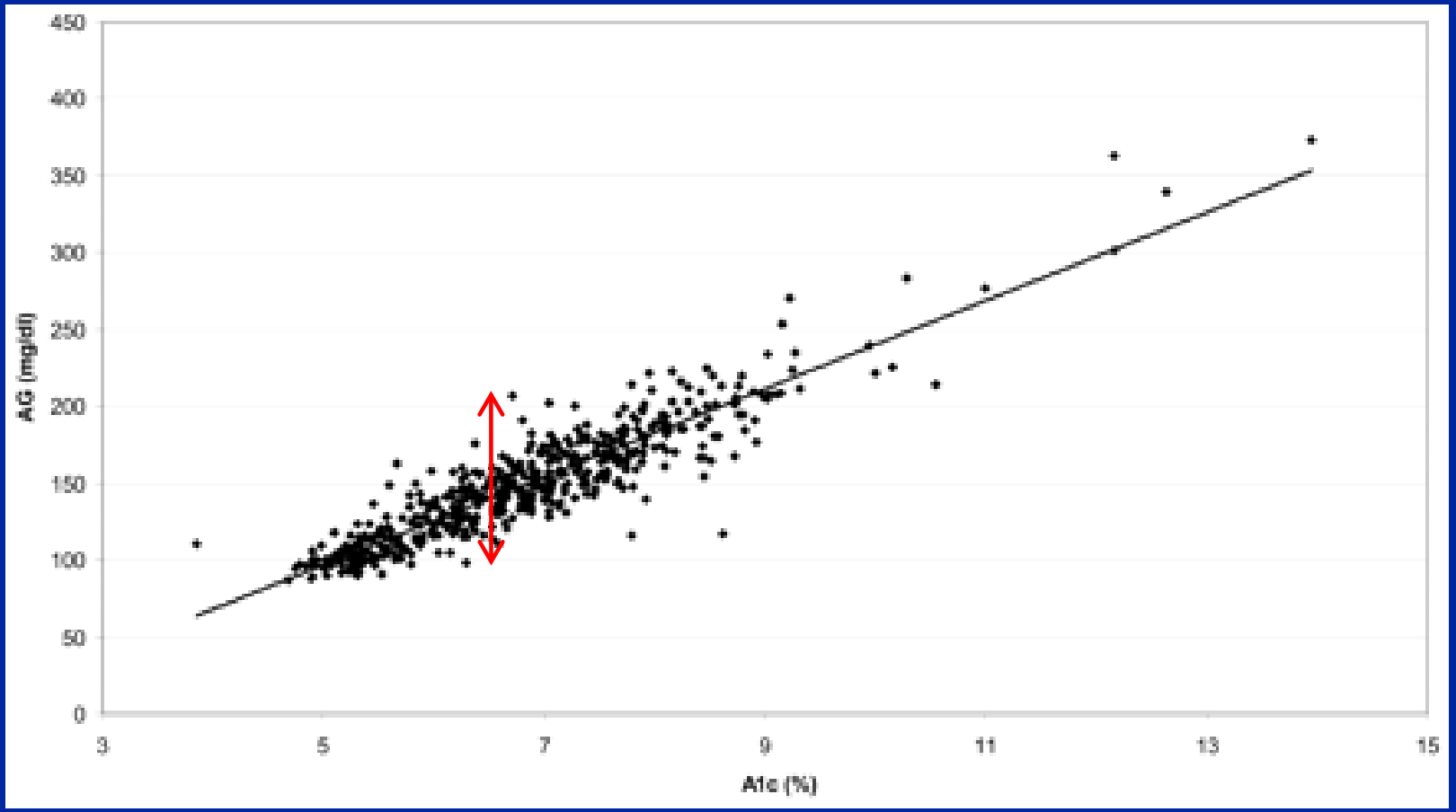
Differences between intracellular measures of glycemia (HbA1c) and extracellular measures of glycemia (mean blood glucose, fructosamine, glycated albumin) are common

Khera. Diabetes **57:2445-2452,** *2008*

- **At the lower end of the HbA1c range, HbA1c levels vary considerably among individuals, but within individuals, change little over time**
- **Among nondiabetic individuals, only ~1/3 of the variance in HbA1c can be explained on the basis of measures of glycemia**
- **Factors other than glycemia must operate to produce consistent changes in HbA1c**

JS Yudkin. Diabetelogia 33:208, 1990

The A1c-Derived Average Glucose Study
HbA1c (study end) vs Average Glucose
(~2,700 readings per subject over 3 months)



DM Nathan. Diabetes Care 31:1473, 2008

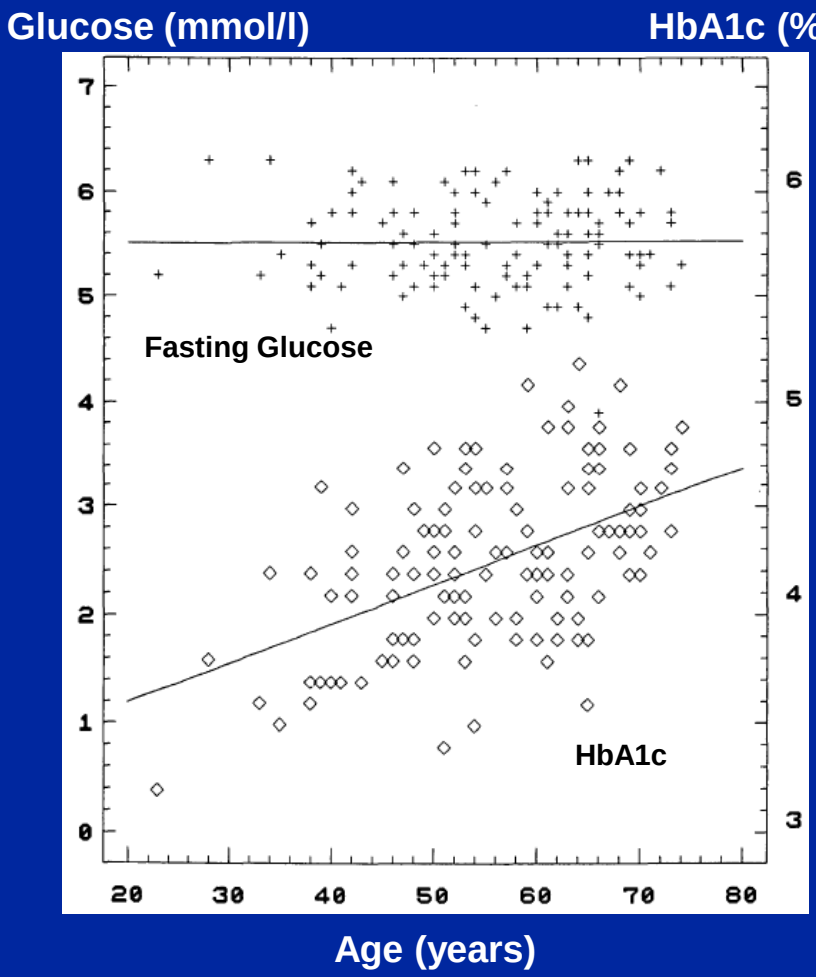
Factors that May Alter HbA1c Independently of Glycemia

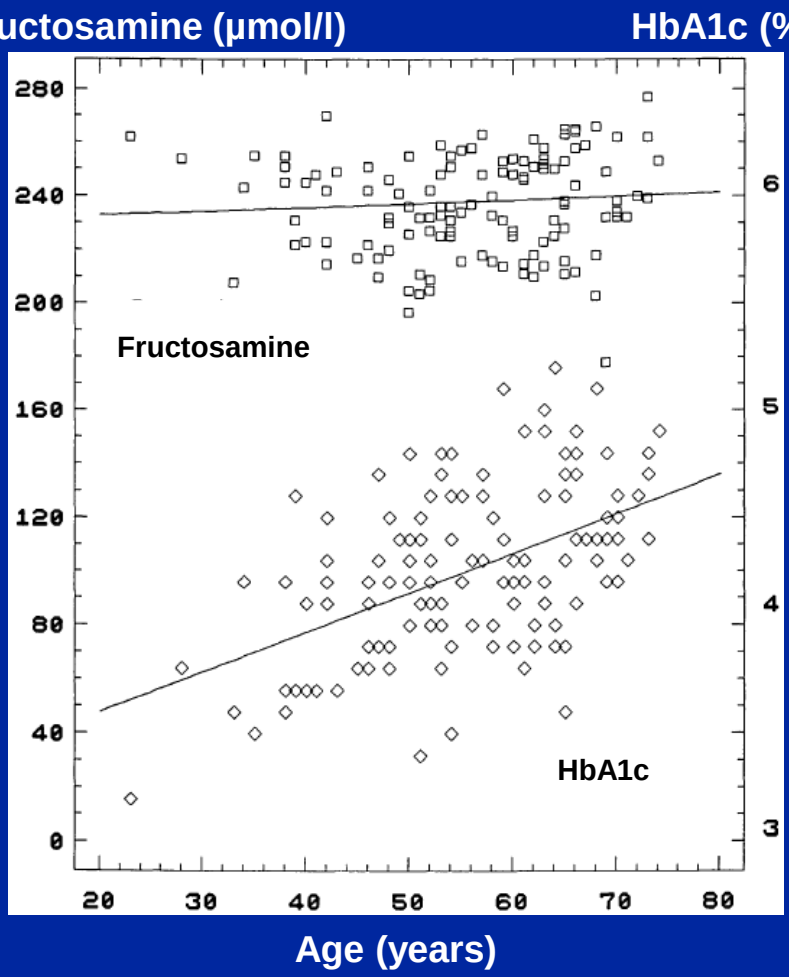
- Hemoglobinopathies
- Thalassemia syndromes
- G6PD deficiency
- Shorter RBC survival
  (hemolytic anemia)
- Longer RBC survival (post splenectomy, aplastic anemia)
- Decreased RBC age
  (recovery from acute blood loss, transfusion, erythropoietin therapy, pregnancy)

Factors that May Alter HbA1c (cont'd)

- Older age
- Uremia
- Hyperbilirubinemia
- Iron deficiency
- Smoking
- Alcohol consumption
- Dietary fat
- Race and ethnicity

Age and HbA1c
(126 nondiabetic subjects)





ES Kilpatrick. Q J Med 89:307, 1996

Smoking and HbA1c

In the general adult population (n=35,425), HbA1c was 0.10% higher in smokers compared to never-smokers*

***adjusted for age, sex, and BMI, and despite no difference in FPG and lower 2-hr PG in smokers compared to never-smokers**

S Soulimane. Diabetologia 57:30, 2014

Alcohol Consumption and HbA1c

In diabetic patients ≥18 years of age (n=38,564), alcohol consumption was inversely associated with HbA1c*

Consumption	Δ HbA1c
≥3 drinks/day	reference
2.0 – 2.9 drinks/day	-0.08
1.0 – 1.9 drinks/day	0.04
0.1 – 0.9 drinks/day	0.24
<0.1 - 0 drinks/day	0.43
former drinkers	0.32
lifelong abstainers	0.41

*adjusted for age, sex, ethnicity, education, duration of diabetes, obesity, hypertension, dyslipidemia, and self-care behaviors

AT Ahmed. J Gen Intern Med 23:275, 2007

Dietary Fat and HbA1c

In nondiabetic subjects 40-78 years of age (n=6,223), a one standard deviation or 6% increase in total daily energy intake from fat was associated with a 0.04% increase in HbA1c*.

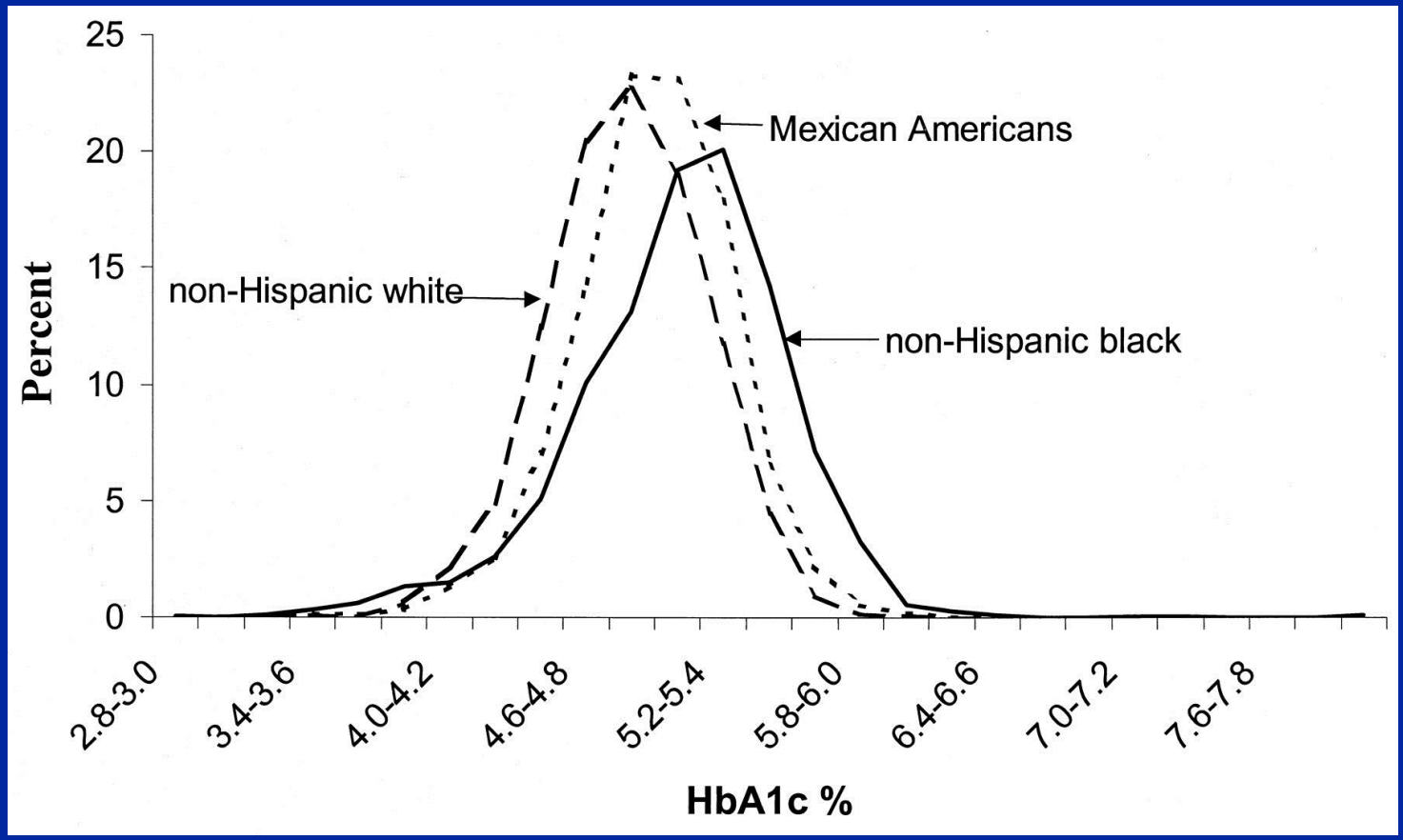
***adjusted for age, sex, FH, BMI, WHR, total energy intake, physical activity, alcohol, and smoking**

AH Harding. Diabetes Care 24:1911, 2001

Racial and ethnic differences in HbA1c have been demonstrated in nondiabetic children and young adults after adjusting for age, sex, weight, and education.

JB Saaddine. Diabetes Care 25:1326, 2002

HbA1c Distribution by Ethnicity in U.S. Children and Young Adults Ages 5-24 Years (NHANES III, 1988-1994)



JB Saaddine. Diabetes Care 25:1326, 2002

Racial differences in HbA1c have also been demonstrated in adults with IGT[1], recent onset type 2 diabetes[2], established type 2 diabetes[3], and type 1 diabetes[4] independent of glycemia.

[1]WH Herman. Diabetes Care 30:2453, 2007
[2]G Viberti. Diabet Med 23:1289, 2006
[3]WH Herman. J Clin Endocrinol Metab 94:1689, 2009
[4]RM Bergenstal. Ann Int Med 167:95, 2017

Adjusted HbA1c by Race among Subjects with IGT in the DPP*

	White	African American
n	(2,117)	(752)
HbA1c (%)	5.8±0.4	6.2±0.6**
Adjusted† HbA1c (%)	5.8	6.2**

* eligibility based on age ≥25 years, BMI ≥24 kg/m^2, FPG 95-125 mg/dl and 2 hr PG 140-199 mg/dl.

** p <0.0001 vs. White.

† adjusted for age, sex, BMI, blood pressure, fasting glucose, glucose area under the curve, corrected insulin response, and HOMA-IR.

WH Herman. Diabetes Care 30:2453, 2007

DPP Genetic Studies

- 13 genetic variants that cause hemoglobinopathies or influence RBC biology accounted for 0% of the difference in HbA1c by race
- A genetic risk score based on 60 variants associated with HbA1c accounted for 14% of the difference
- Principal components analysis factors that reflect genetic variation due to continental ancestry accounted for 59% of the difference

MF Hivert. JCEM 104:328, 2019

Conclusion

As yet unidentified genetic markers that are specific to individuals of African descent (and were not identified in the latest GWAS in which only 2 of 60 loci were specific to individuals of African descent) may account for racial differences in hemoglobin glycation

Should hemoglobin A1c be used to diagnose diabetes?

Yes, when…

- Clinical laboratory-based HbA1c assay is available
- Glucose testing is not convenient
- There are no patient factors that preclude interpretation of HbA1c

Patient Factors that Preclude Interpretation of HbA1c

- Hemoglobinopathies
- Thalassemias
- G6PD deficiency
- Hemolysis
- Blood loss
- Uremia
- Hyperbilirubinemia
- Iron deficiency
- Smoking
- Alcohol consumption
- High-fat diet
- Non-white race

If only HbA1c is measured, undetected systematic bias may exist and repeated measurements of HbA1c will not reveal the true level of glycemia

Glucose testing should be used when…

- It is convenient
- Insufficient clinical data are available to rigorously exclude all of the factors that might preclude interpretation of HbA1c

If glucose is measured, random error may occur, but repeated measurements will reveal the true level of glycemia

Conclusions

- HbA1c is a systematically biased measure of glycemia
- Many reasons are known
- Some reasons remain unknown
- Glucose is a less precise but unbiased measure of glycemia and remains the preferred diagnostic test

Hemoglobin A1c should NOT be used to diagnose diabetes!