Differences in A1C by Race and Ethnicity Among Patients With Impaired Glucose Tolerance in the Diabetes Prevention Program

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OBJECTIVE — We sought to examine racial and ethnic differences in A1C in individuals with impaired glucose tolerance (IGT).

RESEARCH DESIGN AND METHODS — We studied 3,819 individuals aged ≥25 years with IGT who were found to be eligible to participant in the Diabetes Prevention Program. A1C was compared among five racial and ethnic groups before and after adjustment for factors that differed among groups or might affect glycemia including age, sex, education, marital status, blood pressure, adiposity (BMI and waist circumference), hematocrit, fasting and post–glucose load glucose levels, glucose area under the curve (AUC), β-cell function, and insulin resistance.

RESULTS — Mean ± SD A1C was 5.91 ± 0.50%. Among whites, A1C was 5.80 ± 0.44%, among Hispanics 5.89 ± 0.46%, among Asian 5.96 ± 0.45%, among American Indians 5.96 ± 0.46%, and among blacks 6.19 ± 0.59%. Age, sex, systolic blood pressure, diastolic blood pressure, BMI, fasting glucose, glucose AUC, corrected insulin response, and insulin resistance were each independent predictors of A1C. Adjusting for these and other factors, mean A1C levels were 5.78% for whites, 5.93% for Hispanics, 6.00% for Asians, 6.12% for American Indians, and 6.18% for blacks ($P < 0.001$).

CONCLUSIONS — A1C levels are higher among U.S. racial and ethnic minority groups with IGT after adjustment for factors likely to affect glycemia. Among patients with IGT, A1C may not be valid for assessing and comparing glycemic control across racial and ethnic groups or as an indicator of health care disparities.

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Abbreviations: AUC, area under the curve; CIR, corrected insulin response; DPP, Diabetes Prevention Program; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Carbohydrates are covalently attached to the NH_2-terminal valine of the β-chain of hemoglobin by a slow nonenzymatic process. The most common modification, glucose attachment, can be measured as A1C. Since the early 1980s, A1C has been used as a clinical measure of average glycemia over the preceding weeks and months (1,2). With publication of the results of the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study, A1C has also come to be used as a measure of risk for the development of diabetes complications.

In a recent systematic review, Kirk et al. (3) summarized 21 studies that compared A1C levels across racial and ethnic groups. Seven of the nine studies that tested differences between blacks and non-Hispanic whites and four of the five that tested differences between Hispanics and non-Hispanic whites demonstrated higher A1C levels among blacks or Hispanics. The authors concluded that blacks and Hispanics with diabetes have poorer glycemic control than non-Hispanic whites (3). Five additional studies compared A1C levels among racial and ethnic groups within organized systems of health care and carefully adjusted for processes of care (4–8). Although adjustment for covariates attenuated racial differences in A1C, the differences between racial groups remained statistically significant. Two reports have also assessed the association between A1C and race and ethnicity in nondiabetic populations. Eberhardt et al. (9) analyzed data from a community-based sample of 3,175 adults in the South Carolina Cardiovascular Disease Prevention Project. After adjusting for age and BMI, A1C remained 0.3 and 0.4% higher in black men and women with no reported diabetes compared with that in white men and women with no reported diabetes ($P < 0.05$). More recently, Saaddine et al. (10) described A1C by race for 7,968 young and apparently healthy participants in the Third National Health and Nutrition Examination Survey. Subjects were aged 5–24 years and had not been treated for diabetes. Mean

A1C was 4.93 ± 0.04% in non-Hispanic whites, 5.05 ± 0.02% in Mexican Americans, and 5.17 ± 0.02% in non-Hispanic blacks. After adjusting for age, sex, overweight, and education, A1C for non-Hispanic blacks and Mexican Americans remained 0.2 and 0.1% higher, respectively, than for non-Hispanic whites.

These studies raise the question whether racial or ethnic differences in hemoglobin glycation or red cell survival rather than average glycemia might account for differences in A1C. We assessed baseline data from the Diabetes Prevention Program (DPP) to compare A1C levels by race/ethnicity among 3,819 participants with impaired glucose tolerance before and after adjustment for factors that differed among groups or were likely to affect glycemia including age, sex, education, marital status, blood pressure, adiposity (BMI and waist circumference), hematocrit, fasting and post–glucose load glucose levels, glucose area under the curve (AUC), β-cell function, and insulin resistance.

RESEARCH DESIGN AND METHODS

— The DPP was a 27-center randomized controlled clinical trial designed to evaluate the safety and efficacy of interventions to delay or prevent the development of diabetes in people at increased risk for type 2 diabetes. The baseline characteristics of the cohort have been described elsewhere (11). In brief, eligibility required age ≥25 years, BMI ≥24 kg/m^2 (≥22 kg/m^2 for Asians), and plasma glucose 2 h after a 75-g oral glucose load of 140–199 mg/dl (7.8–11.1 mmol/l) plus a fasting plasma glucose (FPG) 95–125 mg/dl (5.3–6.9 mmol/l) (or any fasting glucose ≤125 mg/dl [6.9 mmol/l] for American Indians).

The data reported here were obtained before randomization and are based on the 3,819 participants screened and found to be eligible to participate in the DPP. Standardized interviewer-administered questionnaires were used to obtain data on race/ethnicity, education, and marital status. Seated blood pressures were measured twice with a mercury sphygmomanometer. Standing height and weight were determined in duplicate with stadiometers and calibrated balance beam scales by certified clinic staff. Waist circumference was measured at the midpoint between the iliac crest and the costal margin in the midaxillary line. The oral glucose tolerance test (OGTT) was preceded by instructions to consume a usual diet with adequate carbohydrates and was initiated between 0700 and 1100 h after an overnight fast. Blood was sampled from a vein before (0 min) and after 75 g oral glucose (Trutol 75; Custom Laboratories, Baltimore, MD). Blood was drawn during the fasting state for hematocrit, plasma glucose, and insulin; at 30 min for plasma glucose and insulin; and at 120 min for plasma glucose. The 120-min glucose AUC (in millimoles per liter per 120 min) was computed using the trapezoidal rule. Dividing the AUC by 120 min yields the corresponding AUC mean glucose in millimoles per liter. β-Cell function was measured as corrected insulin response (CIR), where CIR = [100 × 30-min insulin (microunits per milliliter)]/[30-min glucose (milligrams per deciliter)] × [30-min glucose (milligrams per deciliter) − 70 mg/dl)]. Insulin resistance was measured as homeostasis model assessment of insulin resistance (HOMA-IR), where HOMA-IR = fasting insulin [microunits per milliliter] × [fasting glucose (milligrams per deciliter)/18.01]/22.5.

Blood samples were collected and processed following the DPP Standardized Manual of Operations. Serum and plasma samples were stored at −20°C for a few days and shipped on dry ice in batches. Whole-blood samples for A1C analysis were shipped by overnight express within 24 h of sample collection. Fasting specimens for A1C were obtained in eligible participants immediately before randomization. The average time interval between OGTT specimens and A1C was 60 ± 20 days. The time interval ranged from 52 days for Hispanics to 60 days for Asians and blacks to 62 days for whites and 69 days for Native Americans. Hematocrit was performed locally. All other analytical measurements were performed at the Central Biochemistry Laboratory at the University of Washington, Seattle, Washington. Plasma glucose was measured on a chemistry autoanalyzer by the glucokinase method. Insulin measurements were performed by a radioimmunoassay method using an anti–guinea pig antibody that measures total immunoreactive insulin. A1C was measured by a dedicated ion-exchange high-performance liquid chromatography instrument (Variant; BioRad, Hercules, CA). The intra-assay coefficient of variation (CV) was 1.36%, and the interassay CV was 1.70%.

A normal-errors multiple linear regression model was used to assess differences between groups and the effects of covariates on levels of A1C (12). Collinearity diagnostics indicated that no statistical problems existed with the use of all the covariates simultaneously in a single multiple-regression model. The normal-errors assumption was verified using the Shapiro-Wilks test of the residuals (13). However, White's test of homoscedasticity was significant (14). Thus, models were refit using White's asymptotic (consistent) robust information sandwich estimate of the covariance matrix of the estimates and these robust estimates used to construct a robust large sample test of the significance of each effect in the models. The results were unchanged; thus, the model-based tests of significance are presented. The strength of the effect of a covariate is expressed using the semipartial R^2, which is the proportion decrease in the total sum of squares [(N-1) × variance] when that covariate is removed from the regression model containing all other covariates. For multiple comparisons among ethnic groups versus whites, the Holm step-down Bonferroni method was used to adjust *P* values for multiple tests (15). All analyses were performed using SAS (SAS Institute, Cary, NC).

RESULTS

— Table 1 presents the characteristics of DPP participants at randomization by self-reported race and ethnic group. Of the 3,819 participants, 55% were white, 20% were black, 16% were Hispanic, 5% were American Indian, and 4% were Asian. Mean age was 51 years. Two-thirds were women. Approximately two-thirds were married, and one-quarter had college or higher educations. Mean blood pressure was 124/78 mmHg. Among women, mean BMI was 35 kg/m^2 and mean waist circumference 104 cm. Among men, mean BMI was 32 kg/m^2 and mean waist circumference 108 cm. Mean hematocrit was 41.1%. Mean fasting glucose was 106 mg/dl (5.9 mmol/l) and fasting insulin 184.5 pmol/l. Mean CIR was 0.6 and mean HOMA-IR 7. Mean A1C was 5.91%.

Compared with whites, blacks, Hispanics, American Indians, and Asians tended to be younger. Compared with whites, blacks, Hispanics, and American Indians were more likely to be women and Asians more likely to be men. Compared with whites, Asians and Hispanics were more likely to be married and Asians more likely to be college graduates. Compared with whites, blacks and Asians had higher and American Indians lower blood pressure levels. Compared with whites, blacks had slightly higher BMIs and His-

Table 1—*Participant characteristics by racial and ethnic group*

Clinical characteristic	All	White	Black	Hispanic	American Indian	Asian	*P*
n	3,819	2,117	752	609	174	167	
Age (years)	50.7 ± 10.6	51.9 ± 10.6	50.5 ± 10.1*	48.4 ± 10.1†	44.5 ± 9.8†	49.8 ± 10.1*	<0.001
Sex (female)	2,576 (67.5)	1,387 (65.5)	559 (74.3)†	408 (67.0)	153 (87.9)†	69 (41.3)†	<0.001
Marital status (married/living together)	2,493 (65.3)	1,471 (69.5)	353 (46.9)†	421 (69.1)	113 (64.9)	135 (80.8)‡	<0.001
Education (years)							
13–16	1,821 (47.7)	1,048 (49.5)	335 (44.6)†	260 (42.7)†	92 (52.9)‡	86 (51.5)	<0.001
≥17	1,018 (26.7)	667 (31.5)	204 (27.1)†	71 (11.7)†	18 (10.3)†	58 (34.7)	<0.001
Blood pressure (mmHg)							
Systolic	123.9 ± 14.6	123.8 ± 14.1	127.0 ± 15.3†	122.2 ± 14.3*	116.0 ± 12.4†	124.8 ± 16.3	<0.001
Diastolic	78.4 ± 9.3	78.0 ± 9.1	79.8 ± 10.0†	77.9 ± 8.7	75.3 ± 8.6†	82.2 ± 9.7†	<0.001
BMI (kg/m^2)	33.9 ± 6.7	34.1 ± 6.8	35.2 ± 7.0†	33.1 ± 5.7‡	33.6 ± 6.1	29.5 ± 5.3†	<0.001
Men	32.0 ± 5.6	32.4 ± 5.9	32.6 ± 5.8	31.4 ± 4.8	31.2 ± 4.0	28.5 ± 3.8†	<0.001
Women	34.9 ± 6.9	34.9 ± 7.1	36.2 ± 7.1†	33.9 ± 5.9*	33.9 ± 6.3	30.9 ± 6.5†	<0.001
Waist circumference (cm)							
Men	107.7 ± 13.5	110.2 ± 13.4	106.9 ± 13.9†	104.5 ± 12.3‡	107.0 ± 11.0	97.1 ± 9.6†	<0.001
Women	103.6 ± 14.9	104.1 ± 14.8	106.1 ± 16.3*	99.6 ± 12.6†	105.2 ± 13.2	93.5 ± 14.0†	<0.001
Hematocrit (%)	41.1 ± 3.5	41.4 ± 3.3	39.6 ± 3.4†	41.2 ± 3.7	41.5 ± 3.5	42.9 ± 3.7†	<0.001
Plasma glucose (mmol/l)							
Fasting	5.9 ± 0.5	5.9 ± 0.5	6.0 ± 0.5	5.9 ± 0.5	5.6 ± 0.5	6.0 ± 0.4	<0.001
30 min	9.4 ± 1.4	9.5 ± 1.4	9.0 ± 1.2	9.6 ± 1.4	9.3 ± 1.3	9.8 ± 1.5	<0.001
120 min	9.1 ± 1.0	9.2 ± 0.9	9.1 ± 1.0	9.1 ± 1.0	9.1 ± 1.0	9.3 ± 0.9	0.211
Glucose AUC	8.9 ± 0.8	8.9 ± 0.8	8.7 ± 0.8	9.0 ± 0.9	8.8 ± 0.8	9.1 ± 0.9	<0.001
Fasting insulin (pmol/l)	184.5 ± 104.1	177.8 ± 100.4	189.7 ± 98.1	198.0 ± 113.9	207.2 ± 125.0	173.4 ± 107.8	<0.001
CIR	0.6 ± 0.4	0.6 ± 0.4	0.7 ± 0.5†	0.7 ± 0.5†	0.9 ± 0.5†	0.6 ± 0.4	<0.001
Insulin resistance (HOMA-IR)	7.0 ± 4.2	6.8 ± 4.0	7.3 ± 3.9*	7.5 ± 4.6†	7.4 ± 4.7	6.7 ± 4.3	<0.001
A1C (%)	5.91 ± 0.50	5.80 ± 0.44	6.19 ± 0.59†	5.89 ± 0.46†	5.96 ± 0.46†	5.96 ± 0.45†	<0.001

Data are means ± SD or *n* (%). Glucose AUC was calculated using the trapezoidal rule from 2-h OGTT values. We compared values for whites vs. those for other racial groups (significant *P* values [*P* for test of difference in means or percentages among the ethnic groups] are shown as *$P < 0.05$, †$P < 0.001$, and ‡$P < 0.01$). Step-down Bonferroni method (ref. 15) was used to adjust for multiple comparisons.

panics and American Indians slightly lower BMIs. Asians had substantially lower BMIs, reflecting that Asians with IGT and BMIs ≥22 kg/m^2 were eligible to participate. A similar pattern was observed with respect to waist circumference, with the exception that black and American Indian women had the highest waist circumferences. Compared with whites, blacks had lower and Asians higher hematocrits. FPG levels were quite similar across groups except for American Indians, who had lower fasting glucose levels, reflecting that American Indians with IGT had no lower eligibility limit for FPG to participate in the DPP, a protocol variation based on their known high rate of conversion to diabetes regardless of FPG level. Compared with whites, Hispanics, Asians, blacks, and American Indians tended to have lower 30-min post–glucose load glucose values. Because all DPP participants were required to have IGT, 2-h plasma glucose levels did not differ among groups. Whites and Hispanics had similar glucose AUCs, blacks and American Indians lower glucose AUCs, and Asians higher glucose AUC means. Whites and Asians had lower CIRs and were less insulin resistant. Compared with whites, all racial and ethnic groups had significantly higher A1C levels.

Table 2 presents a multiple regression model of the joint association of all covariates in Table 1 with A1C. The racial and ethnic differences in A1C persisted after adjusting for variables that might be related to the differences in A1C. The covariate-adjusted mean A1C levels estimated from the model were 5.78% for whites, 6.18% for blacks, 5.93% for Hispanics, 6.12% for American Indians, and 6.00% for Asians. The values for all racial and ethnic groups were significantly higher than for whites (each $P < 0.0001$ adjusted for multiple comparisons). Nonwhite race, older age, female sex, lower systolic blood pressure, higher diastolic blood pressure, greater BMI, higher FPG, greater glucose AUC, lower CIR, and higher HOMA-IR were all independently associated with higher A1C and, together, explained 22% of the variance.

Because the DPP used race- and ethnic group–specific cut points for BMI (BMI ≥24 kg/m^2 except ≥22 kg/m^2 for Asians) and FPG (95–125 mg/dl except ≤125 mg/dl for American Indians), we reran the analyses using common criteria for all groups (i.e., BMI ≥25 kg/m^2 and FPG 95–125 mg/dl [5.3–6.9 mmol/l]). The results were not substantially changed, and all differences between racial and ethnic groups remained statistically significant ($P < 0.0001$ adjusted for multiple comparisons).

Because there was a 60-day time interval between the OGTT and A1C, we reran the full model for the 2,022 participants who had not developed diabetes at 1 year of follow-up and had OGTTs and A1Cs performed on the same day. Compared with whites, the covariate-adjusted A1C values for all other racial and ethnic groups remained significantly higher ($P < 0.0001$ adjusted for multiple comparisons).

Table 2—*Racial and ethnic differences in A1C in a multiple-regression model adjusting for the effects of other covariates on A1C*

Parameter	Estimate	SE	*P*	Type II semipartial R^2
Race (vs. white)				
Black	0.404	0.0205	<0.0001	0.0811
Hispanic	0.149	0.0220	<0.0001	0.00959
American Indian	0.206	0.0374	<0.0001	0.00630
Asian	0.343	0.0376	<0.0001	0.0173
Age at randomization	0.0105	0.000833	<0.0001	0.0328
Sex (female vs. male)	0.0786	0.0224	0.0005	0.00256
Systolic blood pressure	−0.00146	0.000700	0.0371	0.00091
Diastolic blood pressure	0.00357	0.00105	0.0007	0.00239
BMI	0.00527	0.00234	0.0240	0.00106
Fasting glucose	0.259	0.0205	<0.0001	0.0335
Glucose AUC	0.0245	0.0112	0.0286	0.00010
CIR	−0.0641	0.0231	0.0055	0.00160
Insulin resistance (HOMA-IR)	0.00543	0.00242	0.0251	0.00104

Data are also adjusted for education, marital status, waist circumference, and hematocrit; all not significant at 0.05 level.

CONCLUSIONS — In this cohort of adults with IGT enrolled in the DPP, blacks, Hispanics, American Indians, and Asians had higher A1C levels than whites. This effect persisted after adjusting for differences among groups in age, sex, education, marital status, blood pressure, BMI, hematocrit, fasting and post–glucose load glucose levels, glucose AUC, β-cell function, and insulin resistance. Taken together, these factors explained 22% of the variance in A1C.

Previous studies have demonstrated higher A1C levels among blacks and Hispanics, but these results have been attributed to poorer glycemic control among racial and ethnic minority groups (3). However, studies of nondiabetic populations and studies that have compared A1C levels among racial and ethnic groups within organized systems of health care and have carefully adjusted for processes of care have still demonstrated persistent differences in mean A1C (4–8). Our findings that factors that differed among racial and ethnic groups or were likely to affect glycemia did not explain differences in A1C suggest that hemoglobin glycation or red cell survival may differ among racial and ethnic groups.

Previous studies in nondiabetic individuals have shown that A1C levels in the same individual change little over time but that levels vary markedly between individuals (16–18). Additional variation in A1C levels between individuals has been shown to be related to factors independent of glycemia such as female sex (19), sex hormones (20), differences in visceral fat (21), and biologic variation in hemoglobin glycation or red cell survival. Recent studies have suggested that interindividual differences in intra-erythrocyte 2,3-diphosphoglycerate, which catalyzes the production of A1C, may in part account for the variability of A1C observed in nondiabetic subjects (22). Similarly, interindividual variation in intra-erythrocyte fructosamine 3-kinase, which deglycates intracellular fructosamines, might partially explain nonglucose-mediated interindividual variation in A1C (23). Evidence from diabetic twin studies have suggested that A1C levels are genetically determined (24,25). Interindividual variation in A1C may also be explained by differences in erythrocyte survival. Studies in both type 1 (26) and type 2 (27) diabetes have, for example, demonstrated that hyperglycemia is associated with decreased erythrocyte survival. In the DPP population, there were significant differences in hematocrit among racial and ethnic groups. Hemoglobinopathies were not systematically assessed but are generally more common in nonwhites and are associated with decreased erythrocyte survival and decreased glycohemoglobin percentages.

In conclusion, our analyses demonstrate that A1C levels are higher among U.S. racial and ethnic minority groups with IGT after adjustment for differences among groups in age, sex, education, marital status, blood pressure, adiposity, hematocrit, fasting and post–glucose load glucose levels, β-cell function, and insulin resistance. Thus, the racial and ethnic differences in A1C are not explained by differences in these factors. We appreciate that these glucose levels may not be a robust reflection of the 24-h glucose profile and that other unmeasured or suboptimally measured risk factors may explain some of these racial and ethnic differences in A1C. Clearly, further studies are needed to confirm our observation. It is not known whether these racial and ethnic differences in A1C lead to differences in the risk of microvascular, neurologic, or macrovascular complications. Our results raise the possibility that A1C may not be valid for assessing and comparing glycemic control across racial and ethnic groups or as an indicator of health care disparities. They also raise the important question of whether A1C can be used as a diagnostic test for diabetes.

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