Independent Effect of Ethnicity on Glycemia in South Asians and White Europeans

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OBJECTIVE—HbA_{1c} levels are higher in most ethnic groups compared with white Europeans (WEs) independent of glycemic control. This comparison has not been performed between South Asians (SAs) and WEs. We analyzed the independent effect of ethnicity on HbA_{1c} and fasting and 2-h plasma glucose (FPG and 2hrPG, respectively) between these groups.

RESEARCH DESIGN AND METHODS—Analysis of the ADDITION-Leicester study, in which 4,688 WEs and 1,352 SAs underwent oral glucose tolerance testing, HbA_{1c}, and other risk factor measurements.

RESULTS—Significant associations with HbA_{1c} included ethnicity, FPG, 2hrPG, and homeostasis model assessment of β-cell function ($P < 0.001$); age and sex ($P < 0.01$); and fasting insulin and potassium ($P < 0.05$). After adjusting for these and other risk factors, SAs demonstrated higher HbA_{1c} (6.22 and 6.02%, mean difference 0.20%, 0.10–0.30, $P < 0.001$), FPG (5.15 and 5.30 mmol/L, mean difference 0.15 mmol/L, 0.09–0.21, $P < 0.001$), and 2hrPG (5.82 and 6.57 mmol/L, mean difference 0.75 mmol/L, 0.59–0.92, $P < 0.001$) compared with WEs, respectively.

CONCLUSIONS—HbA_{1c}, FPG, and 2hrPG levels were higher in SAs independent of factors affecting glycemic control.

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Glycated hemoglobin (HbA_{1c}) is now recommended as a diagnostic tool for detecting type 2 diabetes, alongside fasting and 2-h plasma glucose (FPG and 2hrPG, respectively), and remains the standard test for monitoring disease progression (1). Previous studies demonstrate HbA_{1c} values are higher in some black and minority ethnic groups compared with white Caucasians independent of glycemic control or factors that differ between ethnic groups (2–5). These studies suggest HbA_{1c} levels are higher in African Americans by 0.2–0.4%, in Hispanics by 0.1–0.3%, and in Southeast Asians by 0.2–0.3% (2–5). Because this analysis has not been performed in South Asians (people of Indian, Pakistani, and Bangladeshi origin), our aim was to evaluate the independent effect of ethnicity on glycemia among South Asians and white Europeans and to quantify the magnitude of any differences.

RESEARCH DESIGN AND METHODS

The analysis was performed using cross-sectional data from the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION)-Leicester population-based diabetes screening study. An in-depth description of study methods has been published previously (6). In brief, primary care participants aged 40 to 75 years underwent an oral glucose tolerance test (OGTT), classified using World Health Organization 1999 criteria (7), and other measurements, including HbA_{1c}, from 2005 to 2009. HbA_{1c} samples were measured on a Bio-Rad VARIANT II high-performance liquid chromatography instrument (Hemel Hempstead, U.K.), which is standardized to current recommendations for diagnosis of diabetes and has a coefficient of variation <2% (1). This analyzer detected hemoglobinopathies (S and C) and such results were excluded.

Statistical analysis was performed using SPSS version 18.0 (Chicago, IL). Multiple regression analysis was used to determine all significant associations of HbA_{1c}. Insulin resistance and β-cell function were calculated using homeostasis model assessment equations (8). Ethnicity was classified using U.K. national census categories (9). ANCOVA modeling was used to calculate the mean difference of HbA_{1c} between South Asians and white Europeans using stepwise models. Model 1 compared unadjusted HbA_{1c} values. Model 2 adjusted HbA_{1c} levels for age, sex, BMI, waist circumference, systolic and diastolic blood pressure, LDL and HDL cholesterol, triglycerides, creatinine, albumin-to-creatinine ratio, FPG, and 2hrPG. Model 3 included fasting insulin as well. Model 4 was similar to model 2 but excluded FPG and 2hrPG. Adjustments for multiple comparisons were made using Bonferroni corrections. $P < 0.05$ was considered significant.

RESULTS

There were 6,040 people (4,688 white Europeans and 1,352 South Asians) included in the analysis. The significant associations of HbA_{1c} were ethnicity, FPG, 2hrPG, and homeostasis model assessment of β-cell function ($P < 0.001$); age and sex ($P < 0.01$); and insulin and potassium ($P < 0.05$), producing an adjusted R^2 of 0.639.

The mean (SE) crude HbA_{1c} in white Europeans and South Asians was 5.65 (0.01) and 5.81% (0.01), respectively, producing a mean difference of 0.22% (95% CI 0.18–0.25; $P < 0.001$) (Table 1). After adjustment for risk factors, HbA_{1c} remained higher in South Asians, with a mean difference of 0.19% (0.11–0.27; $P < 0.001$). Stratification by OGTT result demonstrated similar findings. When FPG was

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Table 1—*A comparison of crude and adjusted differences for HbA_{1c} in white Europeans and South Asians*

	Total population		Normal OGTT		T2DM + IGR on OGTT	
	HbA_{1c} (%)	Mean difference (95% CI)	HbA_{1c} (%)	Mean difference (95% CI)	HbA_{1c} (%)	Mean difference (95% CI)
Model 1						
WE	5.65 (0.01)	0.22 (0.18–0.25)*	5.56 (0.01)	0.16 (0.13–0.18)*	6.12 (0.04)	0.27 (0.13–0.42)*
SA	5.87 (0.01)		5.72 (0.01)		6.39 (0.06)	
Model 2						
WE	5.65 (0.01)	0.17 (0.14–0.20)*	5.55 (0.01)	0.17 (0.14–0.21)*	6.08 (0.02)	0.17 (0.09–0.25)*
SA	5.82 (0.03)		5.73 (0.01)		6.25 (0.03)	
Model 3§						
WE	5.92 (0.02)	0.19 (0.11–0.27)*	5.60 (0.04)	0.17 (0.08–0.27)†	6.19 (0.03)	0.18 (0.05–0.31)†
SA	6.10 (0.32)		5.77 (0.03)		6.37 (0.05)	
Model 4						
WE	5.63 (0.01)	0.25 (0.21–0.30)*	5.55 (0.01)	0.19 (0.16–0.22)*	6.06 (0.04)	0.28 (0.13–0.44)*
SA	5.88 (0.02)		5.74 (0.02)		6.34 (0.07)	

HbA_{1c} data presented as mean (SE). Model 1 is unadjusted. Model 2 is adjusted for age, sex, deprivation level, systolic and diastolic blood pressure, creatinine, albumin-to-creatinine ratio, BMI, waist circumference, triglycerides, HDL, LDL, potassium, FPG, and 2hrPG. Model 3 is adjusted for model 2 plus fasting insulin. Model 4 is adjusted for model 2 without FPG and 2hrPG. T2DM, type 2 diabetes mellitus; IGR, impaired glucose regulation; WE, white European; SA, South Asian. §Subsample population only. *$P < 0.001$ between WE and SA. †$P < 0.01$ between WE and SA.

the dependent variable, mean crude values were 5.18 (0.01) and 5.27 mmol/L (0.03) in white Europeans and South Asians, respectively, a mean difference of 0.09 mmol/L (0.03–0.14; $P < 0.01$). After adjustment, these values were 5.15 (0.01) and 5.30 mmol/L (0.03), a mean difference of 0.15 mmol/L (0.09–0.21; $P < 0.001$) higher in South Asians. Using 2hrPG as the dependent variable, the mean crude values were 5.89 (0.08) and 6.46 mmol/L (0.07) in white Europeans and South Asians, respectively, producing a mean difference of 0.58 mmol/L (0.43–0.73; $P < 0.001$). After adjustment, these values were 5.82 (0.04) and 6.57 mmol/L (0.07), a mean difference higher in South Asians of 0.75 mmol/L (0.59–0.92; $P < 0.001$).

CONCLUSIONS—In this multiethnic cohort of adults undergoing an OGTT, HbA_{1c} values were 0.2% higher in South Asians than white Europeans, even in analysis stratified by glucose intolerance status. The current study is the first to demonstrate this effect persisted after adjusting for factors that may affect glycemia or that differed between these ethnic groups. The strengths of this study include the large numbers of white Europeans and South Asians who underwent robust measurement of risk factors, allowing detection of any clinically significant differences. The diabetes risk factors included in the multiple regression analysis explained 63.9% of the variation in HbA_{1c}, which is relatively higher than other studies (3). However, there may be other unmeasured factors that influence HbA_{1c}. FPG and 2hrPG levels may not give a robust representation of 24-h glucose profile, a problem recognized in similar studies (3,4). Other examples include dietary intake, genetic influences, and iron deficiency anemia (10,11). Therefore, our finding that sex independently associates with HbA_{1c} should be interpreted with caution. Studies that account for either hematocrit or hemoglobin provide contradictory reports of an independent effect of sex on HbA_{1c} (3,4). Our results showing a higher HbA_{1c} level of 0.2% in South Asians was consistent when separated by males and females (data not shown).

Ethnic variation in HbA_{1c} levels could be attributed predominantly to biological variation in hemoglobin glycation and differential erythrocyte survival. However, African Americans, who also possess higher HbA_{1c} levels than white Caucasians, have more adverse profiles of glycemic markers unaffected by hematological factors, suggesting this does not explain HbA_{1c} differences (2).

Implications for policy makers and clinicians

First, international organizations have recommended using ethnic-specific cut points for South Asians in relation to BMI, waist circumference, and metabolic syndrome, which came as a response to high rates of diabetes within this group (12). However, there is no suggestion of ethnic-specific cut points for diagnosis of diabetes using HbA_{1c} (1). The prevalence of diabetes using HbA_{1c} ≥6.5% is higher in South Asians than white Europeans compared with using an OGTT, with a similar finding for detecting high-risk individuals (13,14). Second, it is reported that a greater proportion of South Asians with established diabetes do not achieve glycemic guideline targets in comparison with white Europeans (15). Because our study demonstrates independently higher HbA_{1c}, FPG, and 2hrPG levels in South Asians, this result may be partially explained by factors related to glycemia. Future research should address the relationship between HbA_{1c} and the onset of diabetes complications, including prevalent retinopathy, between South Asians and white Europeans in well-designed outcome studies to determine if ethnic-specific cut points are required for diabetes diagnosis in South Asians.

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S.A.M. conceived and designed the study, had access to the databases, conducted the statistical analysis under supervision, and wrote the manuscript. M.J.D. and K.K. conceived and designed the study; obtained funding for ADDITION-Leicester and provided administrative, technical, and material support; and contributed to results interpretation and drafting of the manuscript. D.R.W. and B.T.S. contributed to results interpretation and drafting of the manuscript. L.J.G. (statistician) had access to the databases, supervised statistical analysis, and contributed to results interpretation and drafting of the manuscript. S.A.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Executive summary: standards of medical care in diabetes—2010. *Diabetes Care* 2010; 33(Suppl. 1):S4–S10
2. Selvin E, Steffes MW, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL. Racial differences in glycemic markers: a cross-sectional analysis of community-based data. Ann Intern Med 2011;154: 303–309
3. Herman WH, Ma Y, Uwaifo G, et al.; Diabetes Prevention Program Research Group. Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. Diabetes Care 2007; 30:2453–2457
4. Ziemer DC, Kolm P, Weintraub WS, et al. Glucose-independent, black-white differences in hemoglobin A1c levels: a cross-sectional analysis of 2 studies. Ann Intern Med 2010;152:770–777
5. Herman WH, Dungan KM, Wolffenbuttel BH, et al. Racial and ethnic differences in mean plasma glucose, hemoglobin A1c, and 1,5-anhydroglucitol in over 2000 patients with type 2 diabetes. J Clin Endocrinol Metab 2009;94:1689–1694
6. Webb DR, Khunti K, Srinivasan B, et al. Rationale and design of the ADDITION-Leicester study, a systematic screening programme and randomised controlled trial of multi-factorial cardiovascular risk intervention in people with type 2 diabetes mellitus detected by screening. Trials 2010;11:16
7. World Health Organization. *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications: Report of a WHO Consultation*. Geneva, World Health Organization, 1999
8. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28: 412–419
9. U.K. Office for National Statistics. Population estimates by ethnic group: methodology paper [article online], May 2011. Available from http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Population+Estimates+by+Ethnic+Group. Accessed 18 May 2012
10. Kim C, Bullard KM, Herman WH, Beckles GL. Association between iron deficiency and A1C levels among adults without diabetes in the National Health and Nutrition Examination Survey, 1999-2006. Diabetes Care 2010;33:780–785
11. Paré G, Chasman DI, Parker AN, et al. Novel association of HK1 with glycated hemoglobin in a non-diabetic population: a genome-wide evaluation of 14,618 participants in the Women's Genome Health Study. PLoS Genet 2008;4:e1000312
12. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–163
13. Mostafa SA, Khunti K, Srinivasan BT, Webb D, Gray LJ, Davies MJ. The potential impact and optimal cut-points of using glycated haemoglobin, HbA1c, to detect people with impaired glucose regulation in a UK multi-ethnic cohort. Diabetes Res Clin Pract 2010;90:100–108
14. Mostafa SA, Davies MJ, Webb D, et al. The potential impact of using glycated haemoglobin as the preferred diagnostic tool for detecting type 2 diabetes mellitus. Diabet Med 2010;27:762–769
15. Millett C, Netuveli G, Saxena S, Majeed A. Impact of pay for performance on ethnic disparities in intermediate outcomes for diabetes: a longitudinal study. Diabetes Care 2009;32:404–409