Racial and Ethnic Differences in an Estimated Measure of Insulin Resistance Among Individuals With Type 1 Diabetes

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OBJECTIVE — Insulin resistance is greater in racial/ethnic minorities than in non-Hispanic whites (NHWs) for those with and without type 2 diabetes. Because previous research on insulin resistance in type 1 diabetes was limited to NHWs, racial/ethnic variation in an estimated measure of insulin resistance in type 1 diabetes was determined.

RESEARCH DESIGN AND METHODS — The sample included 79 individuals with type 1 diabetes diagnosed at age <18 years (32.9% NHWs, 46.8% non-Hispanic black [NHB], 7.6% other/mixed, and 12.7% Hispanic) and their families. Estimated glucose disposal rate (eGDR) (milligrams per kilogram per minute; a lower eGDR indicates greater insulin resistance) was calculated using A1C, waist circumference, and hypertension status.

RESULTS — Mean current age was 13.5 years (range 3.2–32.5) and diabetes duration was 5.7 years (0.1–19.9). eGDR was inversely associated with age. Compared with that in NHWs, age-adjusted eGDR was significantly lower among nonwhites (NHB, other/mixed, and Hispanic: $\Delta = -1.83$, $P = 0.0006$). Age-adjusted eGDR was negatively associated with body fat, triglycerides, urinary albumin/creatinine, acanthosis nigricans, parental obesity, and parental insulin resistance and positively related to HDL and sex hormone–binding globulin. In multivariable analysis, lower eGDR was significantly associated with older age, nonwhite race/ethnicity, acanthosis, and lower HDL.

CONCLUSIONS — Minorities with type 1 diabetes are significantly more insulin resistant, as measured by eGDR, than NHWs. Exploring potential mechanisms, including disparities in care and/or physiological variation, may contribute to preventing racial/ethnic differences in insulin resistance–associated outcomes.

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I nsulin resistance is common in type 2 diabetes (1) and seems to play a role in the natural history (2) and risk of complications (3) in type 1 diabetes as well. Measurement of insulin resistance in type 1 diabetes is difficult because methods used in nondiabetic and type 2 individuals, e.g., insulin or homeostasis model assessment (4), cannot be used in hypoinsulinemia. The euglycemic-hyperinsulinemic clamp has been used; however, it is labor-intensive and invasive and therefore is not suitable for population-based studies. In response, a derived measure of insulin resistance, the esti-

mated glucose disposal rate (eGDR), has been developed using clinical measures and is strongly correlated with clamp-measured insulin resistance (5).

Consistent with clamp studies in type 1 diabetes (2), lower eGDR is associated with older age (6), longer duration of diabetes (6), greater adiposity (6), family history of type 2 diabetes (5), poor glycemic control (5), and elevated lipids (6). Low eGDR predicts incident retinopathy (3), nephropathy (3,6), neuropathy (7), and cardiovascular disease in type 1 diabetes (3,6). These findings are primarily based on non-Hispanic white (NHW) adults.

Previous research shows racial/ethnic differences in insulin resistance for healthy individuals and those with type 2 diabetes. For example, minority adults with and without type 2 diabetes were more insulin resistant than their NHW counterparts (1,8). Similarly, in nondiabetic youth, minorities were more insulin resistant than NHWs (9,10). Despite these findings, to our knowledge, there are no data on insulin resistance in minorities with type 1 diabetes.

Therefore, we sought to determine *1*) whether racial/ethnic differences in insulin resistance, as measured by eGDR, exist in type 1 diabetes and *2*) whether the association of eGDR with factors traditionally related to insulin resistance differed by race/ethnicity. It was hypothesized that insulin resistance is greater in minorities than in whites and that associations with insulin resistance are consistent across race/ethnicity.

RESEARCH DESIGN AND METHODS

— Racially/ethnically diverse individuals with diabetes diagnosed at age <18 years and not due to another condition were recruited through clinics, health fairs, and mailings. All biological first-and second-degree relatives were invited to participate. One hundred probands with childhood-onset diabetes have participated with their families to date; this analysis was restricted to those with type 1 diabetes ($n = 79$). Examinations were conducted in the morning in the University of Chicago General Clinical Research Center or in participants' homes. The University of Chicago Institutional Review Board approved the study. Participants aged ≥18 years and parents of children aged <18 years provided written consent; children 10–17 years old assented.

Data collection and variables
Demographics/anthropometrics. Current age, pubertal stage, race/ethnicity, and head of household's education and employment were collected by questionnaire. Pubertal stage was self-assessed with pubic hair Tanner diagrams, with missing values ($n = 9$) imputed using

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age-, sex-, and race/ethnicity-specific estimates (11). Proband race/ethnicity was defined as that reported for ≥3 grandparents; if <3 grandparents shared the same race/ethnicity, the proband was of mixed origin. When race/ethnicity was available on <3 grandparents, parental data were used. If parental data were missing, proband's self-reported race/ethnicity was used. Height was measured using a stadiometer; percent body fat (≥10 years old) and weight were measured with a bioelectrical impedance analyzer scale (TBF-300A; Tanita, Arlington Heights, IL). BMI was transformed into Z scores using the Centers for Disease Control and Prevention Growth Chart (≤20 years old) (12) and National Health and Nutrition Examination Survey III (>20 years old) (13) age-and sex-matched reference data. Proband overweight/obese was defined as a BMI Z score ≥1.04 (≤20 years old) or BMI ≥25 kg/m^2 (>20 years old) (12,13). Parental obesity was defined as BMI ≥30 kg/m^2. Waist circumference was measured twice and averaged.

Diabetes. Age at diagnosis was abstracted from medical records; if unavailable, it was self-reported as were frequency of insulin injections and parental diabetes. Participants reporting ≥3 injections per day or use of a pump were defined as receiving an intensive insulin regimen. Type 1 diabetes was defined as having 1) no C-peptide ($n = 69$) or 2) detectable C-peptide with <2 years duration and either positive islet autoantibodies (GAD, insulinoma-associated protein 2; $n = 10$) or receiving intensive insulin therapy ($n = 1$). Fasting plasma C-peptide was measured in all probands. Those with a fasting blood glucose <150 mg/dl, measured by a glucometer (One-Touch SureStep; LifeScan, Milpitas, CA), also had a stimulated plasma C-peptide measurement 90 min after ingestion of a 6 ml/kg standard nutrient solution (Boost; Novartis Nutrition, Minneapolis, MN). C-peptide in probands whose fasting glucose was ≥150 mg/dl was considered stimulated. C-peptide was determined with a solid-phase, competitive chemiluminescent enzyme immunoassay (Immulite 2000; Diagnostic Products, Bad Nauheim, Germany) in the University of Chicago Diabetes Research and Training Center Laboratory. The lower limit of detection was 0.17 nmol/l, and the intra-assay coefficient of variation (CV) was 8%. Absent C-peptide was defined as a fasting, and stimulated if measured, level below the detection limit. Antibodies to radiolabeled recombinant human GAD65 (whole) and human insulinoma-associated protein 2 (349 amino acid cytoplasmic portion) were quantified by a fluid-phase immunoprecipitation assay.

Clinical measures. Current medications and typical sleep duration were collected by questionnaire. Dyslipidemia was defined by 1) use of lipid-lowering medications and/or 2) for participants aged ≥20 years, total cholesterol ≥200 mg/dl, triglycerides ≥150 mg/dl, LDL ≥100 mg/dl, or HDL ≤59 mg/dl; and for participants aged <20 years, total cholesterol ≥170 mg/dl, triglycerides ≥150 mg/dl, LDL ≥110 mg/dl, or HDL ≤34 mg/dl. Blood pressure was measured three times; the mean of the second and third values was used. Hypertension was defined by 1) use of antihypertensive medications and/or 2) systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg for participants aged ≥18 years old or systolic and/or diastolic blood pressure exceeding the age-, sex-, and height-specific 95th percentile (14) for those aged <18 years. Nephropathy was defined by 1) use of ACE inhibitors for kidney dysfunction and/or 2) an albumin-to-creatinine ratio ≥30 mg/g. The Michigan Neuropathy Screening Instrument examination was administered by a physician; participants completed the Instrument's questionnaire. Neuropathy was defined by 1) a questionnaire score ≥5 and/or 2) an examination score >2 (15). Acanthosis nigricans was assessed by a physician.

Biospecimen measures. Fasting serum insulin was measured with a solid-phase, two-site chemiluminescent immunometric assay (Immulite 1000; Siemens Medical Solutions Diagnostics, Los Angeles, CA) by the Diabetes Research and Training Center Laboratory. The intra-assay CVs were ≤8.0%. The DCA 2000+ analyzer (Bayer Healthcare, Elkhart, IN) was used to measure A1C in whole blood and urinary albumin and creatinine. A1C was measured using a latex immunoagglutination inhibition method, and the intra- and interassay CVs were ≤4.3%. The detection range for A1C was 2.5 to 14.0%. Albumin and creatinine were measured through a Benedict-Behre chemical reaction, and the intra- and interassay CVs were ≤6.6%.

Total cholesterol and HDL were measured in whole blood by the Cholestech LDX System using reflectance photometry (Cholestech, Hayward, CA). LDL was calculated using total cholesterol and HDL. Triglycerides were also measured by the Cholestech LDX System by an enzymatic method. For all cholesterol measures, the intra- and interassay CVs were ≤6.3%. C-reactive protein was measured by the University of Chicago Clinical Laboratory using the CRPLX immunoturbidimetric assay (Roche Diagnostics, Indianapolis, IN). The intra- and interassay CVs were ≤4.6%. An elevated level was defined as >3 mg/dl. The COT One Step Cotinine Test Device (QuikTest USA, Boca Raton, FL) was used to detect urine cotinine using a lateral flow chromatographic immunoassay. Positive cotinine was defined as >200 ng/ml.

Serum leptin was determined by the Diabetes Research and Training Center Laboratory using the Human Leptin Radioimmunoassay kit (Millipore, St. Charles, MO). The intra- and interassay CVs were ≤7%. Serum adiponectin was measured using the Human Adipokine Panel A-3 Plex assay (Millipore) by Dr. Mark Atkinson (University of Florida, Gainesville, FL). The intra-assay CVs were 1.4–7.9% and interassay CVs were <21%. Plasma total and free testosterone and sex hormone–binding globulin (SHBG) were measured in those aged ≥10 years old by the University of Chicago Endocrine Laboratory. Total and free testosterone were determined by a solid-phase ^{125}I radioimmunoassay (Siemens Medical Solutions Diagnostics). SHBG was measured with an assay standardized to the dialysis technique (16). Intra-assay CVs were ≤10%.

Insulin resistance. Insulin resistance in probands was assessed using eGDR, a measure derived from clamp studies in 24 NHW adults with long-standing type 1 diabetes using hypertension status, waist-to-hip ratio, and glycemic control (5). Because hip circumference was not available, the comparable equation with waist circumference was provided: eGDR (mg · kg^{-1} · min^{-1}) = 21.158 − [3.407 × hypertension status (yes = 1; no = 0)] − [0.090 × waist circumference (cm)] − [0.551 × A1C (%)]. eGDR was highly correlated with clamp-measured insulin resistance ($r = 0.79$), and eGDR calculated using waist-to-hip ratio or waist circumference was highly correlated ($r = 0.87$) (T.J. Orchard, University of Pittsburgh, personal communication, 2007). Lower values indicate greater insulin resistance. The range of clamp-measured glucose disposal rates in the eGDR validation study was 3.8 to 13.4, with a

range of ~9 to 11 in those with normal insulin resistance (5).

With the use of fasting insulin and glucose, insulin resistance was determined in the parents (excluding four with type 1 diabetes and two pregnant mothers) by homeostasis model assessment, version 2.0 (17). Parental insulin resistance was defined as a value ≥2.5 (4).

Statistical analyses

Analyses were performed in SAS (version 9.1; SAS Institute, Cary, NC); statistical tests were considered significant at $P < 0.05$. Racial/ethnic groups were compared using t tests for continuous and χ^2 tests for categorical variables. The nonwhite groups (NHB, other/mixed, and Hispanic) were combined owing to small sample sizes and similar mean eGDR. Associations with eGDR were determined using unadjusted and multivariable linear regression. Dummy variables were created for categorical variables. Triglycerides, albumin-to-creatinine ratio, and leptin were log-transformed. Associations of eGDR with hypertension, waist circumference, and A1C were not studied because they were used to calculate eGDR; the association with BMI Z score was not analyzed because it was highly correlated with waist circumference ($r = 0.92$, $P < 0.0001$). The multivariable model estimating eGDR was built by first entering all variables with $P < 0.15$ from the age-adjusted regressions and then using a stepwise approach to remove the nonsignificant covariates. Interactions with race/ethnicity and age were tested, but none were significant. Age-adjusted logistic regression tested the difference in hypertension prevalence by race/ethnicity.

RESULTS — For the 79 probands (Table 1), mean current age was 13.5 years (range 3.2–32.5); 32.9% were NHW, 46.8% were NHB, 7.6% were other/mixed, and 12.7% were Hispanic. Mean disease duration was 5.7 years (0.1–19.9), mean current A1C was 9.1%, and 69.6% were receiving an intensive insulin regimen. Only six probands were overweight/obese (one NHW, four NHB, and one other/mixed). A large proportion had complications including dyslipidemia (53.2%) and hypertension (21.5%). More than two-thirds had at least one obese parent, and 14.5% had at least one parent who self-reported diabetes. Mean eGDR was 9.05 mg · kg^{-1} · min^{-1} (1.44–12.81).

Current age had an inverse association with eGDR: eGDR (mg · kg^{-1} · min^{-1}) = 12.51 − [0.26 × age (years)] ($P < 0.0001$). Diabetes duration also had an inverse association with eGDR: eGDR (mg · kg^{-1} · min^{-1}) = 10.15 − [0.19 × duration (years)] ($P = 0.004$). However, the relationship with diabetes duration was not significant after adjusting for age. eGDR did not differ by sex (Table 2). Race/ethnicity was significantly associated with eGDR even after adjustment for age; compared with NHW, eGDR was significantly lower among nonwhites [mean difference (Δ) = −1.83, $P = 0.0006$].

With adjustment for age, eGDR had a significant negative association with percent body fat (Table 2). Probands with at least one obese parent had significantly lower eGDR levels than those with no obese parent ($\Delta = -2.42$, $P = 0.0001$); further adjustment for probands' percent body fat did not attenuate this association. Probands with at least one insulin-resistant parent also had significantly lower eGDR than those with no insulin-resistant parent ($\Delta = -1.79$, $P = 0.03$);

however, parental self-reported diabetes status was not associated with proband eGDR. eGDR was positively associated with HDL and negatively associated with triglycerides and albumin-to-creatinine ratio. Total cholesterol, LDL, and neuropathy were not related to eGDR. Participants with acanthosis nigricans and those with elevated C-reactive protein had significantly lower eGDR compared with those without ($\Delta = -2.06$, $P = 0.0002$, and $\Delta = -1.84$, $P = 0.04$, respectively). In those with body fat determined (≥10 years old, $n = 57$), the association of eGDR with C-reactive protein was also significant, but the relationship became nonsignificant after adjustment for body fat.

Both leptin and adiponectin were negatively associated with eGDR, but after controlling for age, adiponectin was no longer significant (Table 2). Further, for the subgroup of probands with body fat determined ($n = 51$), leptin was negatively associated with eGDR, but subse-

Table 1—Description of probands with type 1 diabetes

	All	NHW	Nonwhite	P
n	79	26	53	
Demographics				
Current age (years)	13.5 ± 5.7	13.3 ± 6.4	13.6 ± 5.4	0.81
Age range (years)	3.2–32.5	4.4–32.5	3.2–27.0	
Female sex (%)	53.2	38.5	60.4	0.07
Head of household education ≤high school (%)	27.9	7.7	37.7	0.005
Anthropometrics				
BMI Z score (SD units)	−0.7 ± 0.8	−1.0 ± 0.5	−0.6 ± 0.9	0.04
Waist circumference (cm)	70.9 ± 15.0	67.7 ± 10.9	72.4 ± 16.5	0.20
Body fat (percentage unit) ($n = 57$)*	27.1 ± 10.2	21.5 ± 7.6	30.1 ± 10.2	0.002
1 or 2 obese parents (%) ($n = 61$)†	67.2	44.0	83.3	0.001
Diabetes				
Duration (years)	5.7 ± 4.5	5.3 ± 4.6	5.8 ± 4.5	0.66
Duration range (years)	0.1–19.9	0.4–19.9	0.1–17.7	
Intensive insulin therapy (%)	69.6	96.2	56.6	0.0003
A1C (percentage unit)	9.1 ± 2.2	7.9 ± 1.7	9.7 ± 2.2	0.0004
1 or 2 parents with insulin resistance (%) ($n = 51$)†	27.5	17.4	35.7	0.15
1 or 2 parents with diabetes (%) ($n = 76$)†	14.5	19.2	12.0	0.40
Clinical measures				
Dyslipidemia (%)	53.2	34.6	62.3	0.02
Hypertension (%)	21.5	11.5	26.4	0.13
Nephropathy (%)	11.4	3.9	15.1	0.14
Neuropathy (%)	17.7	23.1	15.1	0.38
Any acanthosis (%)	29.1	7.7	39.6	0.003
Elevated C-reactive protein (%)	10.1	3.9	13.2	0.20
eGDR (mg · kg^{-1} · min^{-1})	9.05 ± 2.71	10.34 ± 2.16	8.42 ± 2.74	0.003

Data are means ± SD or percentages. $n = 79$. Racial/ethnic groups were compared using t and χ^2 tests. *Subgroup ≥10 years old. †Subgroups with respective data for parents available.

Table 2—*Associations of eGDR with demographic, anthropometric, diabetes, clinical, and hormonal characteristics in probands with type 1 diabetes*

	Unadjusted		Age-adjusted	
	Regression coefficient	$P*$	Regression coefficient	P
Demographic				
Tanner stage (pubic hair; vs. 1)		<0.0001†		
2	−0.27		0.35	
3	−2.62	0.001	−1.79	
4	−2.13	0.004	−1.14	
5	−3.96	<0.0001	−2.30	
Female sex (vs. male)	−0.63		0.01	
Nonwhite (vs. NHW)	−1.92	0.003	−1.83	0.0006
Head of household education (vs. <high school)		0.01†		0.007†
High school graduate	−0.14		−0.15	
Some college	1.37		1.67	0.04
College graduate	2.67	0.01	2.36	0.008
Professional school	2.28		1.88	
Head of household working (vs. not working)	0.58		−0.29	
Anthropometric				
Body fat (10 percentage units) ($n = 57$)‡	−0.90	0.01	−0.76	0.03
1 or 2 obese parents ($n = 61$)§	−3.01	<0.0001	−2.42	0.0001
Diabetes				
Age at diagnosis (years)	−0.24	0.0005	−0.05	
Intensive insulin therapy	0.71		0.70	
1 or 2 parents with insulin resistance ($n = 51$)§	−2.52	0.004	−1.79	0.03
1 or 2 parents with diabetes ($n = 76$)§	−1.90	0.03	−1.32	
Clinical				
Total cholesterol (10 mg/dl)	−0.14	0.04	−0.08	
LDL (10 mg/dl; $n = 61$)	−0.15		−0.12	
HDL (10 mg/dl; $n = 68$)	0.50	0.008	0.38	0.02
Triglycerides (mg/dl; log transformed)	−2.58	0.0002	−1.60	0.01
Dyslipidemia present	−0.79		−0.71	
Albumin-to-creatinine ratio (mg/g; log-transformed)	−1.05	0.001	−0.73	0.01
Nephropathy present	−2.92	0.002	−1.64	0.04
Neuropathy present	−1.17		−0.28	
Any acanthosis present	−2.54	<0.0001	−2.06	0.0002
Elevated C-reactive protein	−3.20	0.001	−1.84	0.04
Positive cotinine	−2.66	0.01	−1.13	
Average sleep duration (hours)	0.45	0.007	0.19	
Hormonal				
Leptin (ng/ml; log-transformed) ($n = 71$)	−1.16	<0.0001	−0.57	0.04
Adiponectin (10 μg/ml) ($n = 45$)	0.34	0.03	0.17	
Total testosterone (10 ng/dl)‡				
Female subjects ($n = 31$)	0.10		0.10	
Male subjects ($n = 24$)	−0.03		0.00	
Free testosterone (10 pg/ml)‡				
Female subjects ($n = 31$)	0.07		0.04	
Male subjects ($n = 24$)	−0.14		−0.05	
SHBG (10 nmol/l)‡				
Female subjects ($n = 31$)	0.86	0.02	1.10	0.004
Male subjects ($n = 24$)	1.04	0.008	0.68	

$N = 79$. eGDR in milligrams per kilogram per minute. *P values are specified if <0.05. †P value for overall effect. ‡Subgroup ≥10 years old. §Subgroups with respective data for parents available.

quent adjustment for percent body fat attenuated this association. In stratified analyses, SHBG was positively associated with eGDR in both sexes and remained significant in women after controlling for age. Among all probands, there was a significant age- and sex-adjusted positive association between eGDR and SHBG (regression coefficient = 0.96 mg · kg^{-1} min^{-1} rise in eGDR per 10 nmol/l increase in SHBG, $P = 0.0001$); additional adjustment for proband percent body fat did not change this association.

In multivariable analysis (Table 3), lower eGDR was significantly associated with older age, nonwhite race/ethnicity, and acanthosis. When HDL was included, resulting in a smaller sample size, these associations remained significant. In addition, lower eGDR was significantly associated with lower HDL. The potential confounding effects of probands' percent body fat, parental obesity, and parental insulin resistance on these associations were examined and found not to occur nor did race/ethnicity modify the associations of eGDR with these factors. The independent variables in the multivariable models explained 46–50% of the variance in eGDR.

Whether the racial/ethnic variation in eGDR was driven by differences in the components used to calculate eGDR was explored. With adjustment for age, compared with NHW participants, nonwhites had significantly higher A1C and a trend for larger waist circumference (9.7 vs. 7.9%, $P = 0.0005$, and 72.2 vs. 68.2 cm, $P = 0.10$, respectively; estimates at mean age of 13.5 years), and a trend toward a higher prevalence of hypertension (26.4 vs. 11.5%, odds ratio 3.1, $P = 0.10$).

CONCLUSIONS — Insulin resistance is an important component of type 1 diabetes (2). To our knowledge, this is the first study to show that racial/ethnic differences in insulin resistance, as measured by eGDR, exist in this group. Furthermore, this variation was observed in a sample of young individuals with short diabetes duration and normal adiposity, suggesting that racial/ethnic differences are present early in the disease course.

The current results are consistent with previous research in healthy individuals and in those with type 2 diabetes of whom nonwhite groups were generally more insulin resistant. Specifically, nondiabetic African American and Hispanic adults were more insulin resistant than nondiabetic NHW adults, using a fre-

Table 3—Multivariable model for eGDR in probands with type 1 diabetes

	Regression coefficient	P
Model 1: $n = 79$, $R^2 = 0.46$		
Current age (years)	−0.23	<0.0001
Nonwhite (vs. NHW)	−1.33	0.01
Any acanthosis present	−1.60	0.004
Model 2: $n = 68$, $R^2 = 0.50$		
Current age (years)	−0.21	<0.0001
Nonwhite (vs. NHW)	−1.60	0.006
Any acanthosis present	−1.30	0.03
HDL (10 mg/dl)	0.39	0.009

$N = 79$. eGDR in milligrams per kilogram per minute. Variables entered into the model: current age, race/ethnicity, head of household education, percent body fat, parental obesity, parental insulin resistance, HDL, triglycerides, albumin-to-creatinine ratio, acanthosis, elevated C-reactive protein, positive cotinine, sleep duration, and SHBG.

quently sampled intravenous glucose tolerance test with minimal model analysis (8). For adults with type 2 diabetes, African Americans, but not Hispanics, were more insulin resistant than NHW (1). The picture may be more complicated in adolescence, because puberty is an insulin-resistant state (10). One study demonstrated that Mexican American, but not black, children were more insulin-resistant than NHW youth as measured by homeostasis model assessment (9), whereas another study using the clamp method found that insulin resistance was increased in black but not white participants between 11 and 19 years of age (10).

Our results demonstrating trends for racial/ethnic differences in the eGDR components are also consistent with the literature, with minorities demonstrating poorer outcomes. For example, African American children with type 1 diabetes have worse glycemic control than white children with diabetes (18). With regard to adiposity, a higher percentage of Mexican-American and black adolescents are overweight/obese compared with NHW adolescents (9). The National Health and Nutrition Examination Survey III also found that African American adult women with type 2 diabetes have a higher BMI than NHW women with diabetes (19). Last, hypertension is more prevalent in African American adults than in NHW and Mexican American adults, both with and without type 2 diabetes (20).

Several clinical characteristics are associated with insulin resistance in type 1 diabetes. For example, higher insulin resistance is related to older age and longer disease duration (6). The authors found similar relationships, but the association with age was stronger and duration was no longer significant after adjustment for age. Family history of type 2 diabetes has been shown to be associated with greater insulin resistance in those with type 1 diabetes (5). In the current study, there was no association with parental history of diabetes, which was based on self-report. However, parental obesity and parental insulin resistance, which were directly measured in the current study and are risk factors for diabetes, were related to greater proband age-adjusted insulin resistance. This association was independent of the probands' adiposity, indicating that other familial characteristics in addition to factors affecting probands' body composition (e.g., genetic predisposition) may influence their insulin resistance.

As may be expected, acanthosis nigricans was related to greater insulin resistance. Lower levels of SHBG were also significantly associated with greater insulin resistance in age-adjusted analysis. This finding is consistent with basic science (21) and clinical research (22) demonstrating a negative association between insulin and SHBG levels, such that the greater the level of insulin resistance in an individual with type 1 diabetes is, the higher is the insulin dose required to meet physiological requirements and the lower the hepatic production of SHBG. These results suggest that the derived measure of insulin resistance, eGDR, is indeed measuring insulin resistance in those with type 1 diabetes.

The risk of micro-and macrovascular complications is elevated for individuals with type 1 diabetes who have insulin resistance. For example, greater insulin resistance is associated with the development of nephropathy (3,6), neuropathy (7), and elevated lipids (6). In the current study, higher insulin resistance was associated with prevalent dyslipidemia and nephropathy. It could be argued that these relationships may be capturing the well-established associations of diabetes complications with the components used to calculate eGDR, specifically suboptimal glycemic control and/or hypertension. However, previous research in NHW adults with long-standing type 1 diabetes showed that insulin resistance as measured by eGDR more strongly predicted overt diabetic nephropathy than did glycemia or blood pressure (23). There were no differences in insulin resistance by prevalent neuropathy.

eGDR is a derived measure of insulin resistance, and clamp techniques are needed to confirm our results. However, because eGDR is noninvasive and strongly correlated with clamp-measured insulin resistance, it is useful for population-based studies, similar to the numerous surrogate measures of insulin resistance that are commonly used in studies of type 2 diabetic and nondiabetic groups. We demonstrated for the first time associations of proband insulin resistance with parental obesity and parental insulin resistance, although there may have been limited power to confirm the associations in the multivariable model. Limited sample size may also explain the lack of a significant difference in insulin resistance by neuropathy status, although the magnitude of the difference was small. Last, because we combined nonwhite groups owing to small sample sizes and similar eGDR, we may have limited the ability to detect interactions by race/ethnicity. The research had a number of strengths, most importantly that it is the first study of type 1 diabetes, to our knowledge, to examine insulin resistance using a racially/ethnically diverse sample. We were also able to evaluate and adjust for confounders in the multivariable model to estimate the independent association of race/ethnicity with insulin resistance.

The greater insulin resistance observed in nonwhites with type 1 diabetes may help clarify the well-documented gaps in diabetes outcomes for underserved minorities. Insulin resistance is associated with a spectrum of poor health outcomes; thus, the greater insulin resistance in minorities with type 1 diabetes may explain their higher incidence of diabetes-related complications compared

with NHW (24). Future research is needed to determine which factors contribute to racial/ethnic differences in insulin resistance in this group, such as disparities in diabetes care, differences in behaviors, environmental factors, or physiological processes, or simply residual confounding. Understanding which modifiable factors prevent insulin resistance and then targeting interventions to those groups most at risk will help address the public health burden of type 1 diabetes and its complications in minority populations.

In summary, insulin resistance as estimated by eGDR was greater in minorities with type 1 diabetes than in NHW probands. Because there exists a strong association between insulin resistance and poor health outcomes in diabetes, the search for effective interventions to improve insulin resistance in minorities with type 1 diabetes must become a priority.

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