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Determinants of Glycemic control in Youth with Type 2 diabetes at randomization in the TODAY study

The TODAY Study Group

Abstract

Objective—To investigate insulin sensitivity and secretion indices and determinants of glycemic control in youth with recent-onset type 2 diabetes at randomization in the TODAY study, the largest study of youth with type 2 diabetes to date.

Research Design and Methods—We examined estimates of insulin sensitivity [$1/\text{fasting insulin (1/I}_F)$], fasting glucose/insulin (G_F/I_F), $1/\text{fasting C-peptide (1/C}_F)$, G_F/C_F], β -cell function [insulinogenic index ($\Delta I_{30}/\Delta G_{30}$), and $\Delta C_{30}/\Delta G_{30}$], and disposition index (DI) in the TODAY cohort of 704 youth (14.0 \pm 2.0 yr; diabetes duration 7.8 \pm 5.8 mo; 64.9% female; 41.1% Hispanic, 31.5% Black, 19.6% White, 6.1% American Indian, and 1.7% Asian) according to HbA1c quartiles at study randomization. The randomization visit followed a run-in period (median 71 days) during which glycemic control (HbA1c \leq 8% for at least 2 months) was achieved with metformin alone. These measures were also examined in relation to screening HbA1c levels prior to run-in.

Results—Insulin secretion indices declined with increasing HbA1c quartiles, at randomization and screening, (at randomization: $\Delta C_{30}/\Delta G_{30}$: 0.11 \pm 0.09, 0.10 \pm 0.19, 0.07 \pm 0.06, and 0.03 \pm 0.03 ng/ml per mg/dl, $p < 0.0001$; DI: 0.03 \pm 0.03, 0.03 \pm 0.05, 0.02 \pm 0.02, and 0.01 \pm 0.01 mg/dl $^{-1}$, $p < 0.0001$) with no significant difference in insulin sensitivity. There were no significant differences in estimates of insulin sensitivity or secretion between genders or across the different racial groups. At randomization and screening, HbA1C correlated with DI ($r = -0.3$, $p < 0.001$), with $\Delta C_{30}/\Delta G_{30}$, but not with insulin sensitivity estimates.

Conclusions—In youth with recent-onset type 2 diabetes treated with metformin, glycemic control, as measured by HbA1c, appears to be associated with residual β -cell function, and not insulin sensitivity.

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Keywords

Insulin secretion; Insulin sensitivity; Disposition Index; Glycemic control; youth type 2 diabetes

Introduction

The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study is the first large multi-center trial examining treatment for youth with type 2 diabetes (1). Between May 2004 and August 2008, 1,211 young people between 10–17 years of age with type 2 diabetes of less than 2 years duration were screened for enrollment. Of those screened, 704 were randomized into a three-arm controlled clinical trial. The three arms consisted of treatment with metformin alone, metformin plus rosiglitazone or metformin plus an intensive lifestyle intervention program (1). This cohort represents the largest and most ethnically and geographically diverse group of pediatric patients with type 2 diabetes ever studied (2).

Using sensitive *in vivo* techniques to measure insulin sensitivity and secretion, youth with type 2 diabetes are reported to have impairments in both insulin sensitivity and secretion (3–6). In a previous investigation using the hyperinsulinemic-euglycemic and the hyperglycemic clamp, HbA1C correlated inversely with disposition index (DI) and first phase insulin, but not insulin sensitivity (7). In the present investigation, we aimed to examine if the latter observations hold true for a large population of youth with type 2 diabetes, uniformly treated with only metformin at randomization, using surrogate estimates of insulin sensitivity and secretion.

Research Methods and Design

Eligible individuals were 10–17 years of age, diagnosed with type 2 diabetes for <2 years at time of randomization in TODAY, had a body mass index (BMI) \geq 85th percentile at the time of diagnosis or screening, and did not have laboratory evidence of β -cell autoimmunity. After screening, potentially eligible subjects entered a run-in period of 2–6 months with the goal to discontinue all diabetes medications except metformin, tolerate metformin at a dose of between 500 to 1000 mg twice daily, and maintain HbA1c \leq 8% for at least 2 months on this regimen. Enrollment ended in February, 2009. Of the 1,211 subjects screened, 1091 (90%) did not have β -cell autoimmunity, 927 (76%) entered the run-in phase, and 704 (58%) successfully completed run-in and were randomized (2).

This report utilizes data obtained at randomization and screening to compare surrogate estimates of insulin sensitivity and secretion, glycemic control, and body composition from the 704 randomized participants. Measures obtained at the randomization visit included anthropometrics (height, weight, and waist circumference), total and percent body fat (by DEXA), fasting lipid profile, and a 2-hour oral glucose tolerance test (OGTT) with fasting and stimulated glucose, insulin, and C-peptide levels. Blood testing, including the OGTT, was performed after an overnight fast and before 10 AM. If an OGTT was not performed (n=10), fasting glucose, insulin, and C-peptide levels were utilized for the respective estimates of insulin sensitivity and secretion. DEXA scans were obtained on all subjects except those whose weight was above 300 pounds (n=40). Glucose, insulin and C-peptide levels from fasting samples and the 2-hour OGTT were used to calculate estimates of insulin sensitivity (7–9), including 1/fasting insulin ($1/I_F$), fasting glucose to insulin ratio (G_F/I_F) (9), 1/fasting C-peptide ($1/C_F$), fasting glucose to C-peptide ratio (G_F/C_F) and estimates of insulin secretion: insulinogenic index ($\Delta I_{30}/\Delta G_{30}$), C-peptide index ($\Delta C_{30}/\Delta G_{30}$), and OGTT area under the curve (AUC) index: AUC C-peptide/AUC glucose (7–9). Disposition index (DI), an expression of β -cell function relative to insulin sensitivity, was calculated as

$1/I_F \times \Delta I_{30}/\Delta G_{30}$ (9) and $1/C_F \times \Delta C_{30}/\Delta G_{30}$. These estimates of insulin sensitivity derived from fasting measures have been previously validated against hyperinsulinemic-euglycemic clamps in individuals with impaired glucose regulation (10–11) and type 2 diabetes (11, 12). Estimates of insulin secretion (insulinogenic index) and disposition index derived from the OGTT have proven to be good surrogate measures of β -cell function even in the setting of impaired glucose regulation and type 2 diabetes (9). They are also useful in predicting the risk of future type 2 diabetes and are particularly suitable for large epidemiologic studies (9). We preferentially utilized C-peptide derived measures of insulin sensitivity and secretion because some participants had received insulin before their enrollment in the TODAY study (screening visit) and because of differences in insulin clearance in different racial groups (13,14).

Randomization and screening HbA1c levels were divided into quartiles with the 1st quartile the lowest 25% of the HbA1c levels, and the 4th quartile- the highest (>75th percentile) of the total study population. Randomization HbA1c quartiles were: 1st quartile 5.5% (mean \pm SD: 5.2 \pm 0.2, n=176); 2nd quartile 5.5 to 5.9% (5.7 \pm 0.1, n=193); 3rd quartile 5.9–6.5% (6.2 \pm 0.2, n=188); and 4th quartile >6.5% (7.2 \pm 0.4, n=147). Screening HbA1c quartiles were: 1st quartile 5.9% (5.5 \pm 0.3, n=176); 2nd quartile 5.9 to 6.8% (6.4 \pm 0.3, n=181); 3rd quartile 6.9 to 8.5% (7.6 \pm 0.5, n=172); and 4th quartile >8.5% (10.5 \pm 1.4, n=173). Anthropometric and insulin sensitivity and secretion estimates were examined according to HbA1c quartiles at randomization and at the screening visit.

The protocol was approved by an External Evaluation Committee convened by the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) and by the Institutional Review Boards of each participating institution. All participants provided informed consent and minor children confirmed assent according to local guidelines. A Data and Safety Monitoring Board convened by NIDDK reviews progress and safety regularly throughout the study.

Laboratory Methods

HbA1c levels were determined by an automated high-performance liquid chromatography system (G7, Tosoh Bioscience, San Francisco, CA). C-peptide was measured by a two-site immunoenzymatic assay (Tosoh, Bioscience, San Francisco, CA). The assay sensitivity is 0.05 ng/mL. Insulin was measured by a double-antibody radioimmunoassay developed by the Immunoassay Core Laboratory of the Diabetes Endocrinology Research Center, University of Washington, Seattle. All laboratory tests were performed at the Northwest Lipid Research Laboratory, University of Washington (Seattle, WA).

Statistical Methods

Data reported in this manuscript include descriptive statistics of the participants at the time of randomization. Group comparisons were made by ANOVA in the case of normally distributed continuous variables, the Kruskal-Wallis test for non-normally distributed continuous variables, and the chi-square test for categorical variables, with adjustments made as indicated in each table. When continuous outcome variables were significantly different by group, post-hoc tests were performed using the Tukey adjustment for multiple comparisons. Simple linear regression analysis was performed to evaluate the determinants of HbA1c as a dependent variable. Data are presented as mean \pm SD.

Results

Description of the TODAY cohort

Screening and entry criteria have previously been described in detail (1). Median screening HbA1c was 6.8%. The cohort of 704 randomized participants consisted of 457 females (65%) and 247 males (Table 1). At the time of randomization, the age of participants was 14.0 ± 2.0 years, time since diagnosis 7.8 ± 5.8 months, and HbA1c $6.0 \pm 0.8\%$. Most participants were in Tanner stage 4 or 5 of puberty. Participants were significantly obese with weight 95.6 ± 25.3 kg, BMI 34.9 ± 7.6 kg/m² and BMI Z-score $+2.2 \pm 0.4$. The ethnic composition of the cohort was 41.1% Hispanic, 31.5% Non-Hispanic Black (NH Blacks), 19.6% Non-Hispanic White (NH Whites), 6.1% American Indian (AI), and 1.7% Asian. There were no significant differences in percent body fat among ethnic groups. Because of the small sample size of the Asian group (n=11), this group was not included in subsequent analyses that compared variables of interest across the different racial groups.

Surrogate Estimates of insulin sensitivity and secretion by racial/ethnic groups (Table 1)

Racial/ethnic groups did not differ with respect to fasting glucose levels. After adjustment for sex and BMI, there were no significant differences in the fasting or OGTT-derived surrogate estimates of insulin sensitivity, secretion or DI across racial/ethnic groups except that $1/C_F$ and G_F/C_F as measures for insulin sensitivity were higher in NH Blacks compared with the Hispanic group ($1/C_F = 0.34 \pm 0.01$ vs. 0.30 ± 0.01 ng/ml⁻¹, post-hoc $p = 0.015$ and $G_F/C_F = 37.4 \pm 1.1$ vs. 32.8 ± 1.0 mg/dl per ng/ml, $p = 0.014$ in NH Blacks vs Hispanics, respectively).

Anthropometric characteristics and surrogate estimates of insulin sensitivity and secretion by gender

There were no gender differences in diabetes duration, BMI z-score, or HbA1c. Males had a larger waist circumference (112 ± 18 cm vs. 107 ± 16 cm, $p < 0.01$), but lower percent body fat ($33.9 \pm 6.7\%$ vs. $40.0 \pm 4.9\%$, $p < 0.01$) than females. Among the 40 subjects too heavy to obtain DEXA scans, 65% were males. Females were approximately one year younger than males (13.7 ± 2.1 years vs. 14.5 ± 1.9 years, $p < 0.01$) at the time of randomization despite similar diabetes duration. After adjusting for BMI as a reasonable measure of adiposity in this population (since not all participants had DEXA scans), females had lower insulin sensitivity than males estimated by G_F/I_F (5.1 ± 4.1 vs. 6.1 ± 7.6 mg/dl per μ u/ml, $p = 0.012$) and $1/I_F$ (0.047 ± 0.038 vs. 0.053 ± 0.053 μ u/ml⁻¹, $p = 0.03$), but not by $1/C_F$ (0.3 ± 0.1 vs. 0.3 ± 0.2 ng/ml⁻¹, $p = 0.2$). There were no gender differences in measures of β -cell function $\Delta I_{30}/\Delta G_{30}$ (1.5 ± 2.0 vs. 1.4 ± 2.3 μ u/ml per mg/dl, $p = 0.3$) or $\Delta C_{30}/\Delta G_{30}$ (0.56 ± 0.07 vs. 0.08 ± 0.14 ng/ml per mg/dl, $p = 0.4$). There was no difference between females and males in DI calculated as $1/I_F \times \Delta I_{30}/\Delta G_{30}$ (5.8 ± 10.2 vs. 5.4 ± 6.1 mg/dl⁻¹, $p = 0.5$) or as $1/C_F \times \Delta C_{30}/\Delta G_{30}$ (0.02 ± 0.04 vs. 0.02 ± 0.02 mg/dl⁻¹, $p = 0.3$).

Relationship of surrogate estimates of insulin sensitivity and secretion to HbA1c levels

Estimates of insulin sensitivity and secretion were assessed across HbA1c quartiles at randomization and at screening to evaluate the association between glycemic control and insulin sensitivity and β -cell function estimates in the TODAY participants.

At randomization (Figure 1A–C) and at screening (Figure 1D–F), $\Delta C_{30}/\Delta G_{30}$ and DI decreased significantly with increasing quartiles of HbA1c with no difference in insulin sensitivity ($1/C_F$).

These trends persisted after adjusting for BMI, race, and sex. There were no significant differences in age and BMI or BMI Z-scores across the HbA1c quartiles.

Correlations between randomization HbA1c and surrogate estimates of insulin secretion and disposition index (DI)

At randomization, HbA1c and β -cell function correlated inversely (albeit weakly), with the highest correlation with DI ($r=-0.30$, $p<0.0001$), followed by AUC C-peptide ($r=-0.20$, $p<0.0001$), and $\Delta C_{30}/\Delta G_{30}$ ($r=-0.11$, $p=0.003$); there was no correlation with measures of insulin sensitivity. Similarly, screening HbA1c correlated inversely with DI ($r=-0.1$, $p=0.009$). In a multiple regression analysis, with HbA1c as the dependent variable and DI, BMI, Tanner stage, sex, and race as independent variables ($R^2=0.1233$, $p<0.0001$), all variables except Tanner stage contributed to the variance in HbA1c (p-values for individual covariates: DI $p<0.0001$; BMI $p=0.05$; sex $p=0.02$; and race $p=0.0008$), and DI explained 8% of the variance in HbA1c.

Discussion

This study describes surrogate indices of insulin sensitivity and secretion in the largest multi-ethnic cohort of youth with type 2 diabetes studied to date. The main findings of this report are: 1) residual β -cell function is the major determinant of glycemic control in pediatric patients with recent-onset type 2 diabetes treated with metformin; and 2) glycemic control in youth with type 2 diabetes is related to β -cell function relative to insulin sensitivity.

Studies on the pathophysiology of type 2 diabetes in adults (15) demonstrate reduced insulin sensitivity as well as decreased β -cell function. Longitudinal studies in adults indicate that worsening metabolic control over time is associated with decreasing β -cell function irrespective of the mode of therapy (16). A limited number of cross-sectional pediatric studies (3–6) similarly revealed that the pathophysiology of type 2 diabetes involves both a decrease in insulin action (3,5) as well as a β -cell secretory defect (3–6). The TODAY cohort study confirms the findings from adult studies and the limited clinical studies in children of a defect in both insulin sensitivity and secretion in youth with type 2 diabetes. Moreover, our findings demonstrate that, in youth with type 2 diabetes treated with metformin, residual β -cell function, and not insulin sensitivity, appears to be the major determinant of glycemic control as measured by HbA1c. Indeed, when the TODAY participants are evaluated according to screening or randomization HbA1c quartiles, insulin sensitivity indices were not significantly different, but insulin secretion parameters were worse, with increasing HbA1c quartiles. The disposition index (DI), which reflects insulin secretion relative to insulin sensitivity (9,15), showed a significantly declining pattern with increasing HbA1c quartiles suggesting that the β -cell defect (loss of insulin secretion) relative to the severity of insulin resistance determines the level of glycemic control. This is consistent with findings from other pediatric studies (3,5). On the other hand, one might argue that the glycemic control could be modulating β -cell function through glucotoxicity. However, this seems unlikely since all participants in this report had HbA1c levels under 8% for at least 2 months prior to randomization.

A limitation of this report is that participants at the screening visit were on different treatment regimens, including insulin therapy or no pharmacotherapy. A higher HbA1c at screening may reflect exposure to less intensive therapy and/or a higher degree of glucotoxicity (17) resulting in lower insulin secretion. However, the finding of decreased insulin secretion indices across HbA1c quartiles was observed not only at screening, but also at the randomization visit, at which time all participants were treated uniformly with metformin only (1) and all had relatively good metabolic control (HbA1c < 8%) for at least two consecutive months. During this early stage of type 2 diabetes, some recovery of β -cell function is expected (18) and glucotoxicity is unlikely to be the major determinant responsible for our findings. Females in our study were a year younger than males at

randomization in the study despite similar diabetes duration. This suggests earlier age of onset of type 2 diabetes in females, likely related to earlier onset of puberty and its associated insulin resistance (19). To what degree this earlier onset of puberty-related insulin resistance contributes to earlier decompensation of β -cell function is unclear.

In conclusion, our data demonstrate that in youth with type 2 diabetes treated with metformin, residual β -cell function, and not insulin sensitivity, is the major determinant of glycemic control as measured by HbA1c. Future reports from the TODAY study will further contribute to our understanding of the natural history and efficacy of different treatment modalities in maintaining glycemic control and preserving β -cell function in youth with type 2 diabetes.

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Appendix

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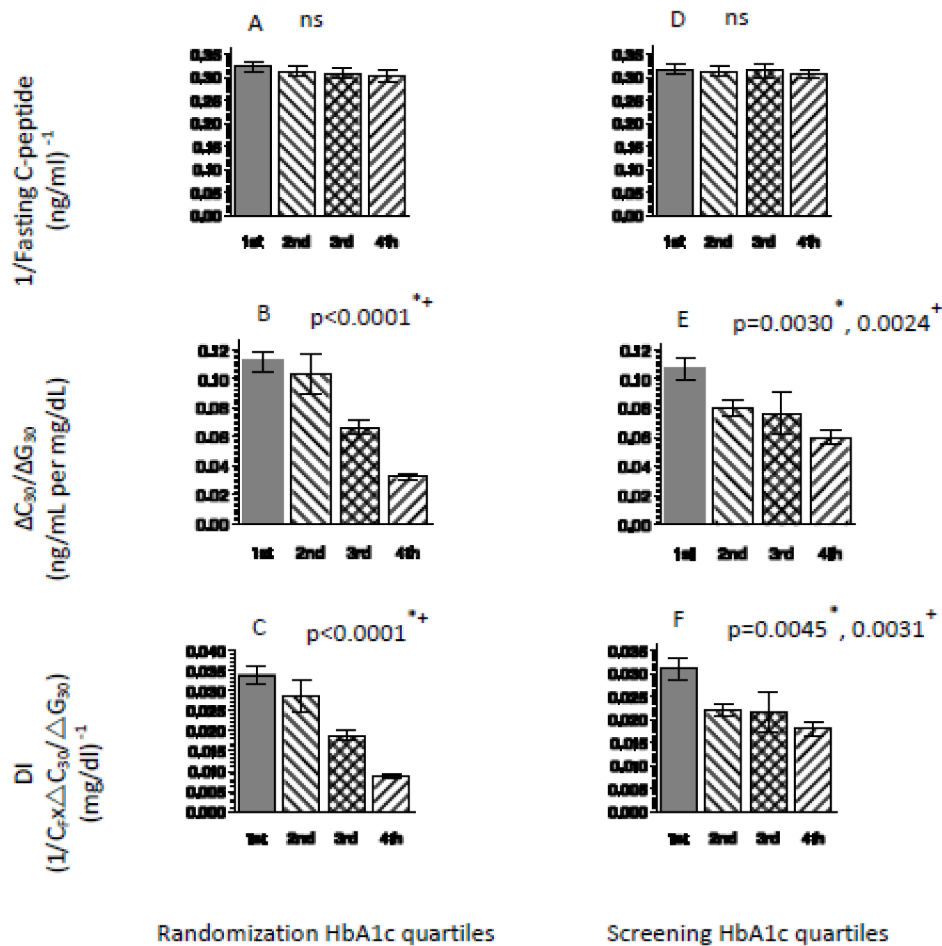


Figure 1. (A)- 1/Fasting C-peptide (C_F), (B)- $\Delta C_{30}/\Delta G_{30}$, (C)- DI across randomization HbA1c quartiles (left panel); (D)- 1/Fasting C-peptide (C_F), (E)- $\Delta C_{30}/\Delta G_{30}$, (F)- DI across screening HbA1c quartiles (right panel). Unadjusted p-value, + adjusted for BMI, race and sex.

Table 1

Anthropometric characteristics and surrogate estimates of insulin sensitivity and secretion of TODAY participants at randomization: total cohort and by race/ethnicity. All data are presented as mean±SD.

Characteristic	Total Cohort (n=704)	Hispanic (n=290)	Non-Hispanic Black (n=221)	Non-Hispanic White (n=138)	American Indian (n=43)	Unadjusted p-value	BMI and Sex Adjusted p-value
Age (years)	14.0± 2.0	14.0± 2.0	13.8± 2.0	14.1± 2.1	14.1± 2.2	0.54	-
Months since diagnosis	7.8± 5.8	7.6± 5.7	8.2± 6.0	7.8± 6.0	6.3± 4.3	0.25	-
Female (n, %)	457 (64.91%)	178 (61.59%)	156 (70.27%)	82 (59.42%)	32 (74.42%)	0.05	-
BMI (kg/m ²)	34.9± 7.6	34.5± 7.5 ^c	36.4± 8.1 ^{b,c}	33.7± 6.9 ^b	34.9± 7.7	<0.05	-
BMI Z-score	2.2± 0.4	2.1± 0.4 ^c	2.3± 0.4 ^{b,c}	2.1± 0.5 ^b	2.1± 0.5	.0001	-
Percent body fat	38.1± 6.2	39.0± 6.1	37.4± 6.2	37.6± 6.4	38.0± 6.8	0.09	-
Waist circumference (cm)	108.6± 16.7	108.7± 16.1	111.2± 17.6 ^a	106.8± 16.2	102.4± 14.1 ^a	<0.01	-
HbA1c (%)	6.0± 0.8	6.0± 0.7 ^c	6.2± 0.7 ^{b,c}	5.9± 0.7 ^b	5.9± 0.8	<0.001	-
Fasting glucose (mg/dL)	111.3± 25.7	110.8± 25.0	110.9± 26.9	113.1± 23.5	113.9± 32.0	0.71	-
Insulin Sensitivity Estimates							
1/I _F (mL/μU)	0.05± 0.04	0.05± 0.05	0.04± 0.05	0.05± 0.05	0.05± 0.03	0.28	0.80
G _F A _F (mg/dL per μU/mL)	5.5± 5.6	5.7± 5.0	5.0± 7.4	5.8± 3.8	5.6± 4.7	0.50	0.92
1/C _F (ng/mL) ⁻¹	0.31± 0.14	0.30± 0.13 ^c	0.32± 0.14 ^c	0.31± 0.16	0.32± 0.22	0.37	<0.01
G _F C _F (mg/dL per ng/mL)	34.2± 18.0	33.1± 16.0 ^c	35.1± 16.4 ^c	35.0± 18.6	36.8± 32.6	0.44	0.03
Insulin Secretion Estimates							
ΔC ₃₀ /ΔG ₃₀ (ng/mL per mg/dL)	0.08± 0.12	0.09± 0.16	0.08± 0.07	0.06± 0.07	0.09± 0.12	0.34	0.40
AUC C-peptide (ng/mL/min)	2890± 2081	3027± 2480	2813± 1826	2686± 1692	3045± 1647	0.40	0.20

Characteristic	Total Cohort (n=704)	Hispanic (n=290)	Non-Hispanic Black (n=221)	Non-Hispanic White (n=138)	American Indian (n=43)	Unadjusted p-value	BMI and Sex Adjusted p-value
$1/I_F \times \Delta I_{30}/\Delta G_{30} \text{ (mg/dl)}^{-1}$	0.06±0.08	0.05±0.08	0.06±0.08	0.04±0.05	0.06±0.11	0.16	0.18
$1/C_F \times \Delta C_{30}/\Delta G_{30} \text{ (mg/dl)}^{-1}$	0.02±0.03	0.02±0.04	0.03±0.02	0.02±0.02	0.03±0.05	0.22	0.18

Superscript pairs reflect statistically significantly different groups in Tukey post hoc comparison

^a p<0.05 for post hoc comparison of American Indian vs Black Non Hispanic

^b p<0.05 for post hoc comparison of Black Non Hispanic vs White Non Hispanic

^c p<0.05 for post hoc comparison of Black Non Hispanic vs Hispanics