Adiponectin, Insulin Sensitivity, β-Cell Function, and Racial/Ethnic Disparity in Treatment Failure Rates in TODAY

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OBJECTIVE

The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study demonstrated that glycemic failure rates in the three treatments combined—metformin plus rosiglitazone, metformin alone, and metformin plus lifestyle—were higher in non-Hispanic blacks (NHB; 52.8%) versus non-Hispanic whites (NHW; 36.6%) and Hispanics (H; 45.0%). Moreover, metformin alone was less effective in NHB versus NHW versus H youth. This study describes treatment-associated changes in adiponectin, insulin sensitivity, and β-cell function over time among the three racial/ethnic groups to understand potential mechanism(s) responsible for this racial/ethnic disparity.

RESEARCH DESIGN AND METHODS

TODAY participants underwent periodic oral glucose tolerance tests to determine insulin sensitivity, C-peptide index, and oral disposition index (oDI), with measurements of total and high-molecular-weight adiponectin (HMWA).

RESULTS

At baseline NHB had significantly lower HMWA than NHW and H and exhibited a significantly smaller increase (17.3% vs. 33.7% vs. 29.9%, respectively) during the first 6 months overall. Increases in HMWA were associated with reductions in glycemic failure in the three racial/ethnic groups combined (hazard ratio 0.61, $P < 0.0001$) and in each race/ethnicity separately. Over time, HMWA was significantly lower in those who failed versus did not fail treatment, irrespective of race/ethnicity. There were no differences in treatment-associated temporal changes in insulin sensitivity, C-peptide index, and oDI among the three racial/ethnic groups.

CONCLUSIONS

HMWA is a reliable biomarker of treatment response in youth with type 2 diabetes. The diminutive treatment-associated increase in HMWA in NHB (∼50% lower) compared with NHW and H may explain the observed racial/ethnic disparity with higher therapeutic failure rates in NHB in TODAY.

The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study of 699 obese youth with type 2 diabetes randomly assigned to metformin, metformin plus rosiglitazone, or metformin plus lifestyle showed that the overall failure rates (loss of glycemic control defined as HbA_{1c} ≥8% [≥64 mmol/mol] for 6 months

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**A complete list of the members of the TODAY Study Group can be found in the Supplementary Data online.*

or sustained metabolic decompensation requiring insulin) were higher in non-Hispanic blacks (NHB; 52.8%) versus non-Hispanic whites (NHW; 36.6%) and Hispanics (H; 45.0%) (1). Race/ethnicity alone had a significant effect (P = 0.0060) beyond the treatment effect. Metformin alone was significantly less effective in NHB with failure rates of 66.2% versus NHW (44.9%) versus H (44.0%), with no differences for the other treatments (1).

NHB youth, normal or with diabetes, have lower peripheral insulin sensitivity, an upregulated β-cell function, and lower insulin clearance compared with their NHW counterparts (2–5). Moreover, adiponectin, an insulin-sensitizing adipokine predictive of glycemic efficacy in adult type 2 diabetes (6), is lower in NHB versus NHW youth (7,8) and adults (9). We therefore hypothesized that the higher glycemic failure rates in NHB could stem from these differences in the pathophysiological components of type 2 diabetes and/or differences in adiponectin levels. In this report we describe treatment-associated changes in adiponectin, insulin sensitivity, and β-cell function relative to insulin sensitivity (oral disposition index [oDI]) over time among the three racial/ethnic groups in an effort to probe the potential metabolic mechanism(s) responsible for the observed racial/ethnic disparity in therapeutic failure rates.

RESEARCH DESIGN AND METHODS

Detailed descriptions of the TODAY protocol and the primary outcome results were previously published (1,10,11). Briefly, the TODAY trial consisted of a screening phase and a 2- to 6-month run-in phase, after which 699 overweight youth, 10–17 years old, with a mean duration of type 2 diabetes of 7.8 months, were randomly assigned to receive metformin alone, metformin plus rosiglitazone, or metformin plus lifestyle intervention (1,10,11). Demographic and anthropometric data were collected at randomization (10). Race/ethnicity was determined by self-report on two separate items: *1*) participants checked Hispanic/Latino ethnicity (yes or no) and *2*) checked as many racial categories as needed. Participants were categorized as NHB, NHW, H, or "other." Only the three main racial/ethnic groups are reported here (647 of 699 [92.6%] of the randomized participants) as a result of heterogeneity and small numbers in the "other" racial/ethnic group (10). Oral medication adherence was based on pill count and collected throughout TODAY. TODAY defined adequate adherence as mean adherence ≥80% (1). HbA_{1c} was obtained at screening, randomization, and at every study visit thereafter. Oral glucose tolerance tests (OGTT) were performed, after a 10- to 14-h overnight fast, at randomization, 6 months, 24 months, and annually thereafter, and blood samples were analyzed for glucose, insulin, and C-peptide. Total and high-molecular-weight adiponectin (HMWA) were measured at the same times. This report uses temporal data related to adiponectin, HMWA, and measures of insulin sensitivity and insulin secretion among the three main racial/ethnic groups.

Assays and Calculations

All assays, including HbA_{1c} (high performance liquid chromatography), C-peptide (two-site immunoenzymatic assay), and insulin (double-antibody radioimmunoassay) were performed at the TODAY central laboratory (Northwest Lipid Research Laboratory, University of Washington, Seattle, WA), as previously described (11).

Analysis of plasma total adiponectin was performed using latex beads–based adiponectin assay reagents (Otsuka Pharmaceutical Co., Tokyo, Japan; distributed by MedTest DX, Cortland Manor, NY) on a Modular P Chemistry analyzer (Roche Hitachi, Inc., Indianapolis, IN). The assay is linear in the 500–25,000 ng/mL range, and the sensitivity is 500 ng/mL. The intra- and interassay coefficients of variation were 1.6% and 1.2%, for the low and high adiponectin level controls were 1.6% and 1.2%, and 2.5% and 1.9%, respectively. Analysis of plasma HMWA was performed by a commercially available ELISA (R&D Systems, Inc., Minneapolis, MN). The quantikine assay uses two HMWA-specific monoclonal antibodies to capture and measure HMWA. The measurement range is 0–250 ng/mL, and plasma samples were diluted 1:100 for analysis. The assay sensitivity is 0.195 ng/mL. The intraassay coefficients of variation for the low, medium, and high HMWA concentrations were 2.6%, 3.7%, and 2.8%, respectively, and for the interassay were 8.5%, 8.2%, and 7.6%, respectively.

Given that HMWA complexes have demonstrated the most profound examples of the prometabolic potential of adiponectin (12,13) and have been shown to provide a biological advantage over total adiponectin in prediction of insulin resistance, the development of type 2 diabetes, and the response to thiazolidinediones (14,15), HMWA data are presented as the main focus in this report. Surrogate markers of insulin sensitivity (1/fasting insulin [$1/I_F$]), β-cell function (C-peptide index [$\triangle Cpep_{30}/\triangle G_{30}$] as the ratio of the incremental C-peptide and glucose responses over the first 30 min of the OGTT), and oDI (product of insulin sensitivity multiplied by the C-peptide index [$1/I_F \times \triangle Cpep_{30}/\triangle G_{30}$]), a measure of β-cell function relative to insulin sensitivity, were calculated as previously reported (16–18). In obese youth, the oDI correlates strongly with clamp-derived disposition index (DI) and has analogous predictive power to that of clamp-derived DI for the 2-h glucose concentration of the OGTT (18). As reported before (16), we used the C-peptide index of insulin secretion ($\triangle Cpep_{30}/\triangle G_{30}$) because some participants had received insulin before screening/enrollment in TODAY, which could potentially result in circulating insulin antibodies interfering with the insulin assay. In addition, differences in insulin clearance in different racial/ethnic groups (2) could confound the circulating insulin data. Metabolic assessments performed after participants reached treatment failure are not reported because accurate assessment of β-cell function is hindered by the effect of exogenous insulin therapy on parameters of insulin secretion. Thus, treatment group differences in the above measures over time may be influenced by the successive removal of subjects who reached treatment failure. Sensitivity analyses were used to assess the potential effect of this bias.

Statistical Methods

Outliers, suspected nonfasting values, and values for C-peptide index of ≤0 were set to missing for analysis purposes. Of the 1,734 C-peptide index values obtained during the 3 years, 16 (0.9%) were ≤0. Although mathematically possible, such values were judged biologically implausible and were treated as missing values similar to our prior TODAY publication (16).

These improbable responses were observed in 16 subjects (average of 1 per such subject), of whom 6 had a response ≤0 at baseline necessitating their exclusion from the longitudinal analyses.

Variables not normally distributed were log-transformed before testing, and analyses included all available data from participants before reaching the primary outcome (i.e., while the participants were still in glycemic control per study criteria). Kruskal-Wallis tests or *F* tests were used to compare baseline variables among the racial/ethnic groups for continuous variables and the χ^2 test for categorical variables. If the overall test was significant, pairwise comparisons were performed. Baseline differences in the metabolic parameters were assessed before and after adjustment for sex, baseline BMI, and baseline age. Similar analyses were repeated to make comparisons of baseline factors between participants who failed versus those who did not fail treatment within each racial/ethnic group.

Longitudinal data were analyzed using generalized linear mixed models to account for the multiple observations per participant (SAS PROC MIXED) and used to estimate mean levels of the parameters over time within groups over the follow-up period using all available data. Models examining racial/ethnic differences in insulin sensitivity, β-cell function, adiponectin, and HMWA over time were adjusted for the baseline value of the outcome and included a term for sex, baseline BMI, baseline age, treatment group, medication adherence, racial/ethnic group, time, and the interaction of time with race/ethnicity. If racial/ethnic differences over time were found, pairwise comparisons were performed. To evaluate whether treatment group or treatment failure influenced insulin sensitivity, β-cell function, adiponectin, and HMWA differently across the three racial/ethnic groups, subgroup analyses were conducted including appropriate main effect and interaction terms of race/ethnicity by treatment or race/ethnicity by treatment failure.

Data in the figures are model-adjusted geometric means ± SE asymmetric limits (obtained as exp[mean ± SE] of the log values). Longitudinal analyses were performed on the log-values, allowing model-derived estimates to be presented as percent change over time. The mean percent change from baseline to 6 months and the average rate of change from 6 months to 36 months were estimated from linear contrast of the model-estimated means over time (16).

An additional analysis was performed to probe the significant racial/ethnic difference in the 6-month change in HMWA and total adiponectin in the longitudinal mixed-models analyses. Cox proportional hazards models run for the total cohort and for each race/ethnicity separately were used to assess the effect of early change in HMWA and total adiponectin in the first 6 months on the progression to glycemic failure (19). Unless otherwise specified, hazard ratios are reported for convenient increments approximating 1 SD of measure to facilitate comparisons of effects across variables. Models were adjusted for sex, race/ethnicity (overall model only), baseline age, medication adherence, baseline BMI, and treatment group. Area under the curve (AUC) measures were estimated to assess and compare the predictive ability of the Cox models. SAS 9.2 software (SAS Institute Inc., Cary, NC) was used for statistical analyses. All analyses were considered exploratory, and

Table 1—Demographic and metabolic characteristics of TODAY participants (*n* = 647) by race/ethnicity at baseline

	NHB	H	NHW	*P* value*	
	n = 227	*n* = 278	*n* = 142	Unadjusted	Adjusted
Demographic characteristics					
Age at randomization (years)	13.9 ± 2.0	14.0 ± 2.0	14.1 ± 2.1	NS	—
Female (%)	69.6	61.1	60.6	NS	—
Months since diagnosis	6 (4, 10)	5 (4, 10)	5 (4, 9)	NS	—
Tanner stage (%)					
4–5	92.1	88.8	85.9	NS	—
<4	7.9	11.2	14.1		
BMI (kg/m^2)	36.6 ± 8.1	34.5 ± 7.4	33.5 ± 7.0	0.0004[a,b]	—
BMI Z-score	2.32 ± 0.40	2.22 ± 0.46	2.12 ± 0.51	0.0002[a,b,c]	—
Waist circumference (cm)	111.4 ± 17.5	108.9 ± 16.1	106.2 ± 16.3	0.0149[b]	—
Metabolic characteristics					
HbA_{1c} (%)	6.2 ± 0.8	6.0 ± 0.7	5.9 ± 0.7	<0.0001[a,b]	0.0003[a,b]
HbA_{1c} (mmol/mol)	44 ± 8.7	42 ± 7.7	41 ± 7.7	<0.0001[a,b]	0.0003[a,b]
Fasting glucose (mg/dL)	111.5 ± 25.6	110.2 ± 25.1	112.5 ± 23.6	NS	NS
Fasting insulin (μU/mL)†	34.4 ± 23.7	30.0 ± 20.2	27.7 ± 21.5	0.0020[a,b]	NS
Fasting C-peptide (ng/mL)†	3.7 ± 1.6	3.9 ± 1.5	3.8 ± 1.6	NS	0.0006[a,b]
Insulin sensitivity [$1/I_F$] (mL/μU)†	0.041 ± 0.025	0.050 ± 0.039	0.052 ± 0.033	0.0015[a,b]	NS
C-peptide index [$\Delta C_{30}/\Delta G_{30}$] (ng/mL per mg/dL)†	0.083 ± 0.074	0.077 ± 0.067	0.066 ± 0.070	0.0174[b]	NS
oDI [$1/I_F \times \Delta C_{30}/\Delta G_{30}$]†	0.003 ± 0.003	0.003 ± 0.003	0.003 ± 0.003	NS	NS
Total adiponectin (ng/mL)†	5,003 ± 2,190	5,825 ± 2,502	5,738 ± 2,305	<0.0001[a,b]	<0.0001[a,b]
HMWA (ng/mL)†	2,411 ± 1,474	3,083 ± 1,867	3,124 ± 1,681	<0.0001[a,b]	<0.0001[a,b]
HMWA–to–total adiponectin ratio	0.46 ± 0.13	0.50 ± 0.13	0.53 ± 0.14	<0.0001[a,b,c]	<0.0001[a,b]

Continuous data are presented as mean ± SD or median (first, third quartile) and categorical data as indicated. NS, not significant ($P > 0.05$). *Unadjusted *P* values were calculated from *F* tests and/or Kruskal-Wallis tests for continuous variables and from χ^2 tests for categorical variables. Adjusted *P* values are adjusted by sex, baseline BMI, and age at randomization. Pairwise comparisons were performed when an overall difference by race/ethnicity was found; significant comparisons ($P < 0.05$) between racial/ethnic groups are indicated as follows: [a]NHB vs. H; [b]NHB vs. NHW; and [c]H vs. NHW. †Variables were log-transformed before testing.

P values <0.05 were considered to be statistically significant.

RESULTS

Demographic and Metabolic Characteristics

Age, sex, pubertal stage, and duration of diagnosed diabetes were similar among the three racial/ethnic groups at randomization (Table 1). BMI, BMI Z-scores, and waist circumference were significantly different among the three groups, highest in NHB. HbA_{1c} was significantly different and highest in NHB before and after adjustment for sex, age, and BMI at randomization. The significant differences among the three racial/ethnic groups in fasting insulin, insulin sensitivity, and C-peptide index disappeared after adjusting for BMI, age, and sex. The oDI was not different before and after adjustment. Total adiponectin, HMWA, and the HMWA–to–total adiponectin ratio were significantly different among the three racial/ethnic groups before and after adjustment for BMI, age, and sex, being lowest in NHB compared with NHW and H. HMWA was lower in male versus female patients in the total cohort (2,669 ± 1,881 vs. 2,965 ± 1,625 ng/mL, *P* = 0.0026), in NHB

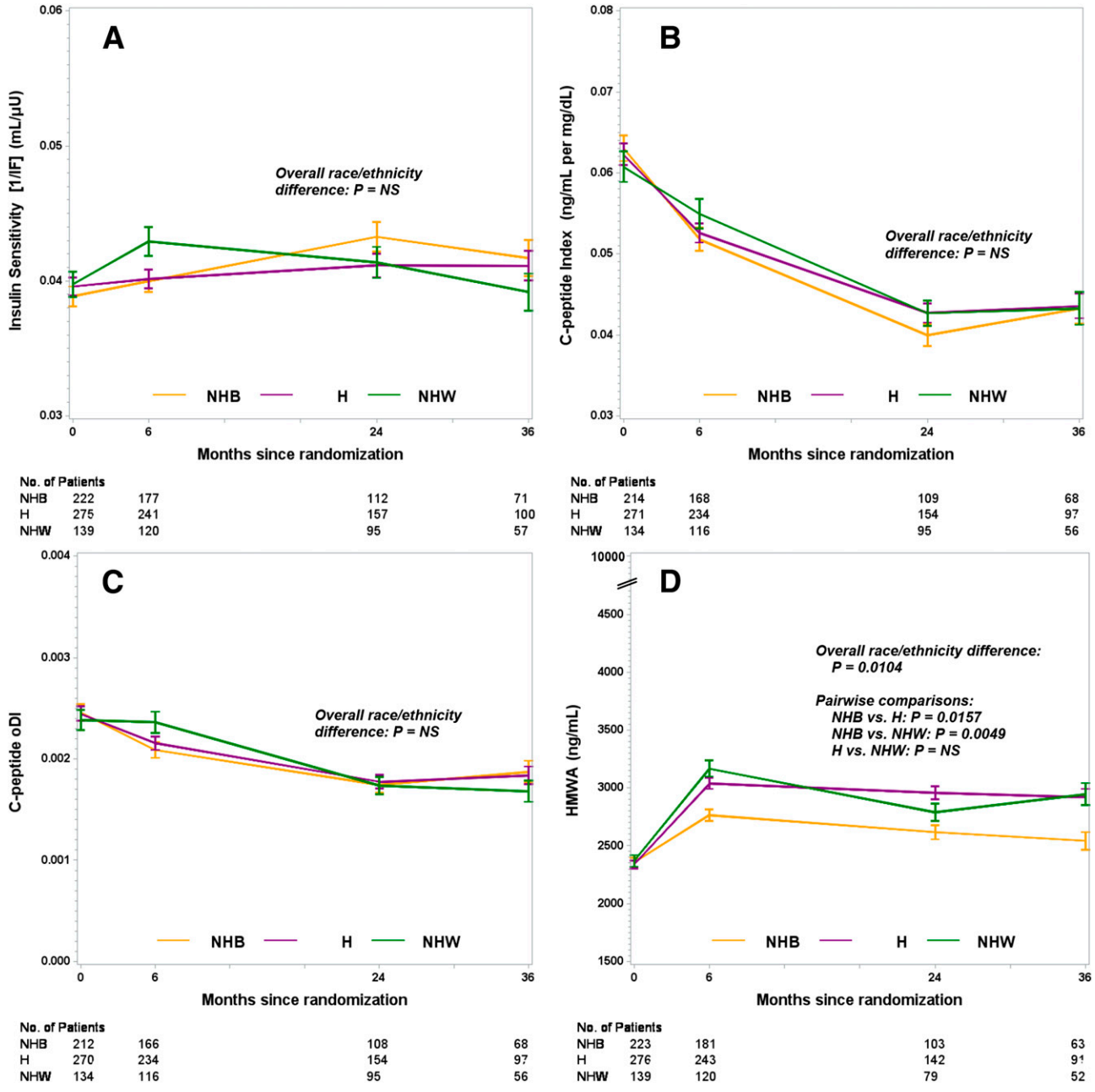

Figure 1—Temporal patterns of insulin sensitivity (*A*), C-peptide index (*B*), C-peptide oDI (*C*), and HMWA (*D*) in the three racial/ethnic groups with the three treatments combined. Model-adjusted geometric mean ± SE asymmetric limits (obtained as exp[mean ± SE of log values]) of insulin sensitivity ($1/I_F$) (*A*), C-peptide index ($\Delta C_{30}/\Delta G_{30}$) (*B*), C-peptide oDI ($1/I_F \times \Delta C_{30}/\Delta G_{30}$) (*C*), and HMWA (*D*) in the three racial/ethnic groups (NHB, H, NHW) over 36 months of follow-up in TODAY, analyzed using log-transformed values. *P* values refer to the overall effect of race/ethnicity in the longitudinal models, adjusted for the baseline value of the outcome, sex, baseline BMI, age at randomization, medication adherence, and treatment group. The geometric mean is a good approximation of the median as the log-transformed data are approximately symmetric. NS, not significant ($P > 0.05$).

(2,093 ± 1,512 vs. 2,550 ± 1,439 ng/mL, $P = 0.0146$), and in H (2,732 ± 1,866 vs. 3,309 ± 1,838 ng/mL, $P = 0.0412$), but not in NHW (3,248 ± 2,130 vs. 3,041 ± 1,301 ng/mL, P = NS).

Temporal Patterns of Insulin Sensitivity, C-Peptide Index, oDI, and HMWA in the Three Racial/Ethnic Groups

Only patients with a baseline and follow-up evaluation of each outcome measure contributed data to the longitudinal analyses of the measures in Fig. 1. The longitudinal models present data for 36 months of follow-up within each racial/ethnic group for insulin sensitivity (Fig. 1*A*), C-peptide index (Fig. 1*B*), oDI (Fig. 1*C*), HMWA (Fig. 1*D*), and total adiponectin (Supplementary Fig. 1). Temporal patterns were similar among the three racial/ethnic groups in insulin sensitivity, C-peptide index, oDI, and total adiponectin, except for HMWA ($P = 0.0104$). During the first 6 months, HMWA increased significantly in all three groups, with no significant change thereafter in all groups (Fig. 1*D* and Supplementary Table 1). NHB had significantly lower HMWA than NHW ($P = 0.0157$) and H ($P = 0.0049$) during the 3 years (Fig. 1*D*). Figure 2 shows the short-term effect of therapy as the mean percent change from baseline to 6 months for insulin sensitivity, C-peptide index, oDI, and HMWA in each race/ethnicity with the three treatments combined. The 0–6 month mean percent change in HMWA was lowest in NHB versus H versus NHW (17.3% vs. 29.9% [$P = 0.0281$] vs. 33.7% [$P = 0.0190$], respectively). The 0–6 month mean percent change in total adiponectin was lower in NHB versus NHW (15.4% vs. 25.0%, $P = 0.0376$). After the first 6 months, no further racial/ethnic difference was found at in the longer-term (6–36 months) for any of the outcomes (Supplementary Table 1).

There was also an overall treatment group difference (i.e., overall temporal patterns among the three different treatments) for total adiponectin and HMWA. Irrespective of race/ethnicity, those in the metformin plus rosiglitazone group had larger increases over time compared with those in the metformin alone and metformin plus lifestyle group (Supplementary Fig. 2*A* and *B* and Supplementary Table 2).

Cox Proportional Hazards Models Evaluating Early Change in HMWA and Progression to Glycemic Failure

Because of the significant difference in the percent change in HMWA in the first 6 months among the three racial/ethnic groups, we used Cox proportional hazards models to predict progression to glycemic failure in relation to the percent change in HMWA in the first 6 months, with and without adjustment for baseline demographics (baseline age, sex, baseline BMI, medication adherence, treatment group, and race/ethnicity in the total cohort) (Table 2). Because baseline HMWA was not a predictor for failure in all racial/ethnic groups combined, the first variable entered in the model was the percent change in HMWA. An increase in HMWA during the first 6 months was a significant predictor of reductions in future glycemic failure in the total cohort and in each race/ethnicity analyzed separately. An increase in HMWA of 1 SD in the first 6 months was associated with a 39% reduction in progression to glycemic failure (Table 2, model 2). Results were similar for total adiponectin (data not shown).

In TODAY, significant determinants of glycemic failure were randomization HbA_{1c} and oDI (16). Adding HbA_{1c} (Table 2, model 3) or oDI (Table 2, model 4) individually or together (Table 2, model 5) to the models predicting glycemic failure did not remove the significant contribution of the 6-month change in HMWA ($P < 0.0001$). Although randomization HbA_{1c} alone had the highest discrimination ability to predict glycemic failure after 6 months (AUC 0.65, SE 0.01), the addition of the 6-month change in HMWA in the model increased the AUC significantly by 4% (AUC 0.69; SE 0.01, 95% CI 0.03–0.07).

Temporal Patterns of Total Adiponectin and HMWA by Treatment Failure in the Three Racial/Ethnic Groups

No significant racial/ethnic differences were found in the temporal pattern in total adiponectin (Fig. 3*A*) and HMWA (Fig. 3*B*) in those who failed treatment and those who did not. However, irrespective of race/ethnicity, those who did not fail treatment had overall higher total and HMWA over time and greater treatment-related increases than those who failed ($P < 0.0001$).

Baseline/Randomization Characteristics of TODAY Patients by Race/Ethnicity Who Failed Treatment Versus Those Who Did Not

In each racial/ethnic group, baseline total and HMWA levels were not different

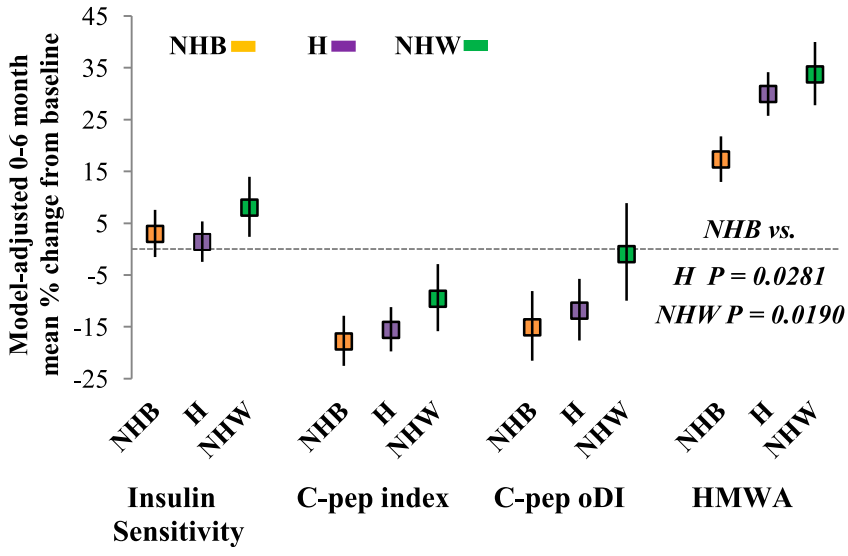

Figure 2—Short-term effect of therapy as the mean percent change (± SE) from baseline to 6 months for insulin sensitivity, β-cell function, and HMWA in each race/ethnicity with the three treatments combined. The log-transformed value of insulin sensitivity and other β-cell function biomarkers (HMWA) are modeled and results are presented as the mean percent change from baseline (± SE). Differences by race/ethnicity (NHB, H, NHW) in the 0–6 month percent change was examined in models adjusted for the baseline value of the outcome, sex, baseline BMI, age at randomization, medication adherence, and treatment group.

Table 2—Cox proportional hazards modeling predicting progression to glycemic failure, overall and by racial/ethnic group*

Variables	Overall				NHB				H				NHW			
	Unadjusted		Adjusted†		Unadjusted		Adjusted†		Unadjusted		Adjusted†		Unadjusted		Adjusted†	
(unit increase)	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Model 1																
Baseline HMWA (per 1 SD)	1.01 (0.88–1.16)	0.9066	1.10 (0.94–1.27)	0.2366	0.97 (0.78–1.21)	0.7850	1.00 (0.79–1.27)	0.9844	1.04 (0.85–1.27)	0.6982	1.09 (0.89–1.35)	0.3956	1.31 (0.86–2.00)	0.2151	1.61 (1.03–2.50)	0.0347
Model 2																
0–6 month % change HMWA (per 1 SD)	0.66 (0.57–0.77)	<0.0001	0.61 (0.51–0.73)	<0.0001	0.68 (0.54–0.87)	0.0021	0.64 (0.49–0.85)	0.0019	0.72 (0.58–0.90)	0.0044	0.62 (0.47–0.82)	0.0007	0.52 (0.35–0.79)	0.0019	0.51 (0.32–0.81)	0.0043
Model 3																
0–6 month % change HMWA (per 1 SD)	0.63 (0.54–0.74)	<0.0001	0.56 (0.46–0.67)	<0.0001	0.62 (0.48–0.80)	0.0002	0.57 (0.42–0.76)	0.0001	0.67 (0.53–0.85)	0.0009	0.57 (0.42–0.76)	0.0001	0.55 (0.35–0.86)	0.0081	0.53 (0.32–0.87)	0.0113
Baseline HbA_{1c} (per 1 unit)	2.55 (2.12–3.08)	<0.0001	2.63 (2.16–3.21)	<0.0001	2.86 (2.06–3.97)	<0.0001	3.25 (2.25–4.70)	<0.0001	2.45 (1.86–3.22)	<0.0001	2.52 (1.90–3.33)	<0.0001	2.34 (1.48–3.70)	0.0003	2.56 (1.53–4.28)	0.0003
Model 4																
0–6 month % change HMWA (per 1 SD)	0.66 (0.56–0.78)	<0.0001	0.60 (0.50–0.72)	<0.0001	0.65 (0.50–0.84)	0.0010	0.55 (0.41–0.74)	<0.0001	0.70 (0.56–0.89)	0.0032	0.64 (0.49–0.85)	0.0022	0.64 (0.42–0.99)	0.0427	0.63 (0.38–1.05)	0.0767
Baseline C-peptide oDI (per 1 unit)	0.59 (0.51–0.69)	<0.0001	0.58 (0.49–0.67)	<0.0001	0.67 (0.53–0.84)	0.0007	0.61 (0.47–0.78)	<0.0001	0.53 (0.41–0.67)	<0.0001	0.54 (0.42–0.69)	<0.0001	0.50 (0.33–0.75)	0.0010	0.40 (0.25–0.64)	0.0001
Model 5																
0–6 month % change HMWA (per 1 SD)	0.63 (0.53–0.74)	<0.0001	0.55 (0.46–0.66)	<0.0001	0.61 (0.47–0.79)	0.0002	0.52 (0.38–0.70)	<0.0001	0.65 (0.51–0.84)	0.0007	0.58 (0.43–0.78)	0.0003	0.65 (0.42–1.02)	0.0632	0.63 (0.37–1.06)	0.0842
Baseline HbA_{1c} (per 1 unit)	2.13 (1.70–2.66)	<0.0001	2.18 (1.73–2.75)	<0.0001	2.68 (1.77–4.05)	<0.0001	2.95 (1.90–4.59)	<0.0001	1.93 (1.38–2.70)	0.0001	2.03 (1.46–2.85)	<0.0001	1.85 (1.06–3.22)	0.0298	2.21 (1.16–4.23)	0.0161
Baseline C-peptide oDI (per 1 unit)	0.78 (0.65–0.93)	0.0068	0.76 (0.64–0.91)	0.0030	0.97 (0.73–1.29)	0.8231	0.86 (0.64–1.17)	0.3448	0.70 (0.53–0.93)	0.0154	0.73 (0.55–0.98)	0.0342	0.58 (0.37–0.91)	0.0170	0.46 (0.28–0.75)	0.0017

*Hazard ratios (95% CI) are expressed per SD increase within the population for HMWA, per 1% (10.9 mmol/mol) increase for baseline HbA_{1c}, and per 1-unit increase for baseline C-peptide oDI (mL/μU × ng/mL per mg/dL). Modeling examining 0–6 month change is based on the log difference to provide estimates of the percent change from baseline to 6 months. †Unadjusted models include variables specifically listed in the far left column; in addition, adjusted models include sex, race/ethnicity (overall model only), treatment group, baseline BMI, and age at randomization and medication adherence during the first 6 months.

between those who failed treatment vs. those who did not (Supplementary Table 3). However, irrespective of treatment failure group, total adiponectin and HMWA were significantly lower in NHB compared with NHW and H (Supplementary Table 3). Irrespective of race/ethnicity, patients who failed treatment compared with those who did not had significantly higher HbA_{1c} and lower β-cell function relative to insulin sensitivity at randomization. In addition, NHB who failed treatment versus those who did not had significantly lower insulin sensitivity, but this was not the case for H and NHW. However, H and NHW who failed treatment compared with those who did not fail had significantly longer duration of diabetes, which was not the case in NHB (Supplementary Table 3).

At baseline HMWA correlated with $1/I_F$, oDI, and HbA_{1c} (r = 0.27, 0.10, and −0.11, respectively, $P < 0.01$ all) before and after adjustment for age, sex, and baseline BMI. These correlations did not persist when each race/ethnicity was analyzed separately, except for $1/I_F$ in NHB and H (r = 0.30 and 0.27, $P <$ 0.001) and for oDI in H (r = 0.13, P = 0.036).

CONCLUSIONS

The present investigation of racial/ethnic contrast in adiponectin, insulin sensitivity, and β-cell function in TODAY at randomization and over time demonstrates that:

1. NHB had significantly lower total adiponectin, HMWA, and HMWA–to–total adiponectin ratio at baseline compared with the other two groups.
2. Treatment-associated change in HMWA over time was significantly different among the three racial/ethnic groups, with a lower percentage increase over the first 6 months in NHB.
3. Early change in HMWA, in the first 6 months of treatment, was a significant independent predictor of progression to glycemic failure.
4. Baseline HMWA did not predict glycemic failure nor was it different between those who failed versus those who did not fail treatment.
5. Treatment-associated change in total and HMWA was significantly lower in those who failed treatment versus those who did not fail irrespective of race/ethnicity.

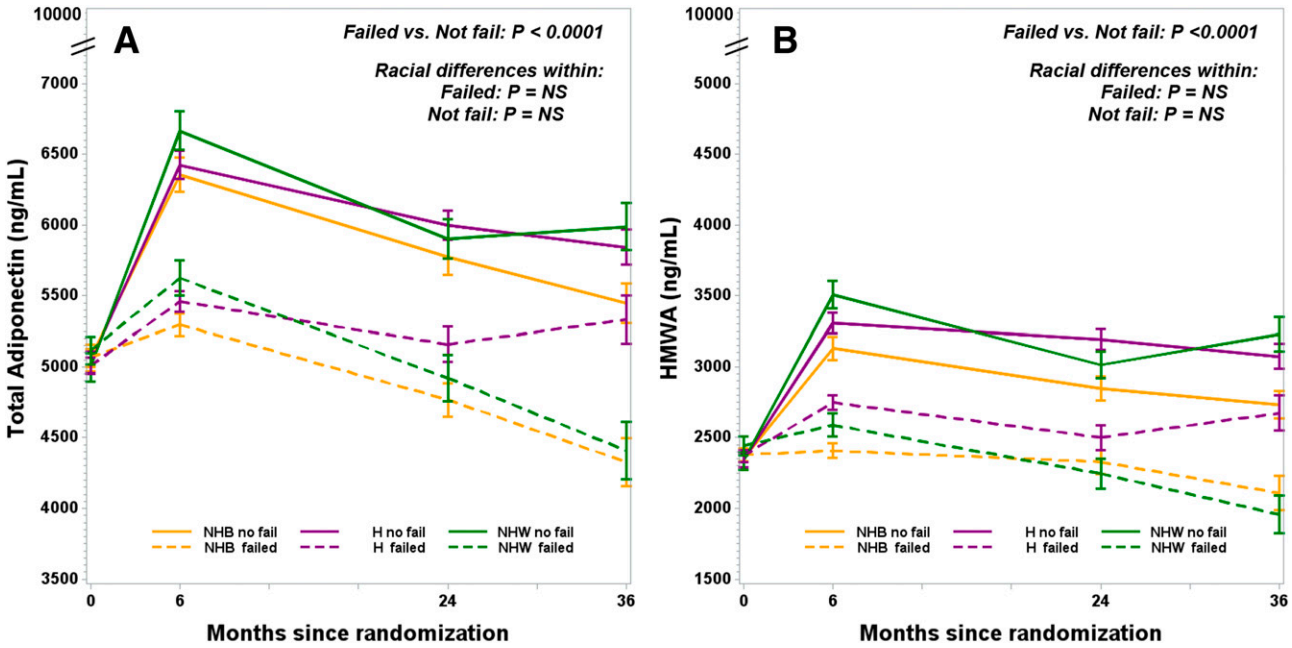

Figure 3—Temporal patterns of total adiponectin (*A*) and HMWA (*B*) by treatment failure in the three racial/ethnic groups with the three treatments combined. Model-adjusted geometric mean ± SE asymmetric limits (obtained as exp[mean ± SE of log values]) of measures total adiponectin (*A*) and HMWA (*B*) in the three racial/ethnic groups (NHB, H, NHW) over 36 months of follow-up in TODAY and by treatment failure/loss of glycemic control (failed: dashed lines vs. not fail: solid lines), analyzed using log-transformed values. *P* values from longitudinal models adjusted for the baseline value of the outcome, sex, baseline BMI, age at randomization, medication adherence, treatment group, race/ethnicity, treatment failure, and the interaction of race/ethnicity with treatment failure. The geometric mean is a good approximation of the median as the log-transformed data are approximately symmetric. NS, not significant ($P > 0.05$).

6. There were no racial/ethnic-related differences in insulin sensitivity and β-cell function at baseline and over time.

The TODAY study of obese youth with type 2 diabetes randomly assigned to metformin alone, metformin plus rosiglitazone, or metformin plus lifestyle showed that glycemic failure rates were higher in NHB (52.8%) versus NHW (36.6%) and H (45.0%), with race/ethnicity alone having a significant effect beyond the treatment effect (1). Similar racial/ethnic disparity, with higher HbA_{1c} in black versus white youth with type 2 diabetes, was reported from a pediatric diabetes clinic (20).

To probe the metabolic/hormonal mechanism(s) potentially responsible for the racial/ethnic disparity in therapeutic failure rates in TODAY, we targeted *1*) adiponectin because it is known to vary by race/ethnicity (7–9,21) and *2*) insulin sensitivity and β-cell function because of the well-established racial/ethnic contrast (2–5,22).

Adiponectin has antidiabetic properties (12,13,23,24): it suppresses hepatic glucose output, lowers systemic glucose concentrations (13,25), stimulates skeletal muscle glucose uptake, and promotes β-cell function and survival (13,25). Adiponectin concentrations are low in obesity, and in states of insulin resistance, type 2 diabetes, and cardiovascular disease (26). Adiponectin levels in youth with type 2 diabetes are significantly lower compared with equally obese peers without diabetes and correlate positively with insulin sensitivity and first-phase insulin response and negatively with the proinsulin-to-insulin ratio in youth with and without diabetes (7,27,28). Therefore, adiponectin levels may carry prognostic value for diabetes course beyond the currently recognized set of risk factors.

Racial/ethnic differences in adiponectin have been previously described in youth and adults (7–9,29). NHB youth have significantly lower adiponectin concentrations compared with their white peers irrespective of adiposity (7,8,29). Studies of HMWA reveal similar racial/ethnic contrasts in adults (21). In line with these observations, the current study showed that NHB youth with type 2 diabetes had significantly lower total adiponectin and HMWA concentrations at the time of randomization in TODAY even after adjusting for the higher BMI in NHB. An additional novel finding was that the HMWA–to–total adiponectin ratio was significantly lower in NHB than in the other two groups. Contrary to our postulate, however, baseline adiponectin did not provide any prognostic value with respect to glycemic failure. Baseline adiponectin was neither a predictor of glycemic failure in Cox proportional hazards analysis (Table 2) nor were baseline adiponectin levels different between those who failed versus did not fail (Supplementary Table 3).

Adiponectin levels in adults increase with treatment of diabetes, and this effect is most pronounced with thiazolidinediones (30–32). With rosiglitazone treatment at 4 or 8 mg/day, adiponectin levels increase by ∼50–200% after 3–6 months in adults with type 2 diabetes, with improvements in glycemic control and insulin sensitivity (30–32). With respect to metformin treatment in adults with type 2 diabetes, most studies (33,34)—but not all (35,36)—show no change in adiponectin levels. In the Diabetes Prevention Program (DPP), however, metformin intervention in impaired glucose tolerant adults was associated with a significant increase in adiponectin from baseline to year 1 (24).

Results on the effect of metformin treatment on adiponectin concentrations in youth are contradictory. Some studies show no change in obese insulin-resistant normoglycemic adolescents (37,38), whereas others demonstrate increases after 3 months of metformin at 850 mg twice daily in youth with impaired glucose tolerance (39). Trials combining metformin with lifestyle intervention in obese children with normal glucose tolerance showed an increase in adiponectin levels after 3 (40) and 6 months (41,42). Studies in youth with type 2 diabetes examining change in adiponectin associated with metformin or thiazolidinedione are lacking. In the present investigation, total adiponectin and HMWA increased during the first 6 months in the three racial/ethnic groups (Fig. 1*D*). However, those in the metformin plus rosiglitazone group had significantly larger increases over time compared with those in the metformin alone and metformin plus lifestyle groups (Supplementary Fig. 2 and Supplementary Table 2). This is in agreement with observations in adult type 2 diabetes showing consistent increases in adiponectin with rosiglitazone or thiazolidinedione treatment (30–32), which is not necessarily the case with metformin (33,34).

An important observation that emerged from this investigation is that treatment-associated changes in HMWA were proportional to the effectiveness of treatment in preventing glycemic failure (hazard ratio 0.55 in the total cohort, 0.52 in NHB, 0.58 in H, and 0.63 in NHW) (Table 2, model 5). In proportional hazards modeling, changes in total adiponectin and HMWA remained significant determinants of progression to glycemic failure even after adjusting for baseline HbA_{1c} and oDI, important determinants of glycemic failure (16). Moreover, treatment-associated change in total adiponectin and HMWA was significantly lower in those who failed treatment versus those who did not (Fig. 3). Lastly, our finding that the metformin plus rosiglitazone group had larger increases in HMWA over time compared with those in the metformin alone and the metformin plus lifestyle groups lends further support for the TODAY main outcome, which showed that the combination of metformin plus rosiglitazone was superior to metformin in sustaining durable glycemic control, with glycemic failure rates of 38.6% compared with 51.7% for metformin and 46.6% for metformin plus lifestyle (1). Collectively, these novel observations underscore the utility of adiponectin in youth type 2 diabetes as a biomarker of treatment response predictive of glycemic efficacy consistent with adult data (6). This combined with the discovery that the increase in HMWA was significantly lower in NHB than in H and NHW (Fig. 1*D*) provides a possible explanation for the higher therapeutic failure rates in NHB than in the other two racial/ethnic groups. The question remains though whether the lower increase in HMWA in NHB is a biological/genetic phenomenon or consequent to inadequate treatment adherence. However, adherence to the medication regimen, defined by pill count, did not differ by race/ethnicity in TODAY (1) nor did the current results differ when the analyses were performed with or without adjustment for medication adherence. There is no current literature addressing whether adiponectin response to pharmacotherapy of youth type 2 diabetes differs by race/ethnicity.

With respect to the postulated racial/ethnic-related contrast in the pathophysiological components of type 2 diabetes as a potential explanation for the racial/ethnic disparity in therapeutic failure rates, surrogate estimates did not differ by race/ethnicity at baseline or over time (Table 1 and Fig. 1). This divergent observation from the existing literature (4) may stem from the use of surrogate estimates that are not as sensitive as the gold standard of the clamp method. In addition, before enrollment in TODAY, patients were treated with a variety of modalities, insulin, and/or other medications, which may have modified insulin sensitivity and secretion.

In summary, these observations support the validity and the value of HMWA as a biomarker predictive of glycemic response to treatment in youth with type 2 diabetes. The significantly lower increase in HMWA in the first 6 months in NHB may explain the higher therapeutic failure rates in NHB compared with the other two racial/ethnic groups. Therapeutic modalities that more effectively increase adiponectin levels may yet prove beneficial in NHB as well as all youth with type 2 diabetes.

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the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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