Characteristics of Adolescents and Youth with Recent-Onset Type 2 Diabetes: The TODAY Cohort at Baseline

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Context: The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) cohort represents the largest and best-characterized national sample of American youth with recent-onset type 2 diabetes.

Objective: The objective of the study was to describe the baseline characteristics of participants in the TODAY randomized clinical trial.

Design: Participants were recruited over 4 yr at 15 clinical centers in the United States (n = 704) and enrolled, randomized, treated, and followed up 2–6 yr.

Setting: The study was conducted at pediatric diabetes care clinics and practices.

Participants: Eligible participants were aged 10–17 yr inclusive, diagnosed with type 2 diabetes for less than 2 yr and had a body mass index at the 85th percentile or greater.

Interventions: After baseline data collection, participants were randomized to one of the folllowing groups: 1) metformin alone, 2) metformin plus rosiglitazone, or 3) metformin plus a lifestyle program of weight management.

Main Outcome Measures: Baseline data presented include demographics, clinical/medical history, biochemical measurements, and clinical and biochemical abnormalities.

Results: At baseline the cohort included the following: 64.9% were female; mean age was 14.0 yr; mean diabetes duration was 7.8 months; mean body mass index Z-score was 2.15; 89.4% had a family history of diabetes; 41.1% were Hispanic, 31.5% were non-Hispanic black; 38.8% were living with both biological parents; 41.5% had a household annual income of less than $25,000; 26.3% had a highest education level of parent/guardian less than a high school degree; 26.3% had a blood pressure at the 90th percentile or greater; 13.6% had a blood pressure at the 95th percentile or greater; 13.0% had microalbuminuria; 79.8% had a low high-density lipoprotein level; and 10.2% had high triglycerides.

Conclusions: The TODAY cohort is predominantly from racial/ethnic minority groups, with low socioeconomic status and a family history of diabetes. Clinical and biochemical abnormalities and comorbidities are prevalent within 2 yr of diagnosis. These findings contribute greatly to our understanding of American youth with type 2 diabetes. **(*J Clin Endocrinol Metab* 96: 159–167, 2011)**

The worldwide epidemic of childhood obesity has been accompanied by an increase in the incidence of type 2 diabetes in youth, which now accounts for 8–45% of new pediatric cases in urban diabetes centers (1–4). In youth over 10 yr of age, type 2 diabetes is increasingly common, especially in minority populations, representing 46.1% of newly diagnosed cases of diabetes in Hispanics, 57.8% in non-Hispanic blacks (NHBs), 69.7% in Asian/

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Abbreviations: A1C, Hemoglobin A1C; ADA, American Diabetes Association; AI, American Indian; ALT, alanine transaminase; ATPIII, Adult Treatment Panel III; BMI, body mass index; BP, blood pressure; DAA, diabetes autoantibody; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LFT, liver function test; NHB, non-Hispanic black; NHW, non-Hispanic white; SEARCH, SEARCH for Diabetes in Youth Study; TG, triglyceride; TODAY, Treatment Options for Type 2 Diabetes in Adolescents and Youth; ULN, upper limit of normal.

Pacific Islanders, and 86.2% in American Indians (AIs), but 14.9% in non-Hispanic whites (NHWs) (5). Because the development of long-term microvascular and macrovascular complications of type 2 diabetes in adults is related to duration of diabetes and control of glycemia (6), the increase in numbers of children diagnosed with type 2 diabetes becomes a major public health concern. Such concerns are compounded by the fact that the most effective approaches to treatment of this relatively new pediatric disease have not been defined. Only one oral pharmacological agent, metformin, has been tested and approved (in 2000) for use by the U.S. Food and Drug Administration for the treatment of type 2 diabetes in youth (7).

There are substantial limitations in knowledge of treatment paradigms in youth based on considerations unique to youth, including the influence of puberty and to the patient population, including socioeconomic challenges. The known waning effectiveness of oral hypoglycemic agents in adults over time is of particular concern for youth with type 2 diabetes, who will have a longer duration of diabetes over the course of a lifetime. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial was designed to address these limitations and will provide important information about this population upon completion of the intervention phase of the trial in February 2011.

To date, information regarding the demographics and clinical characteristics of youth with type 2 diabetes has come primarily from case series (4). Although these reports have provided a relatively consistent description of this population, the total numbers of patients included have been small. Recently population-based data have emerged from the SEARCH for Diabetes in Youth Study (SEARCH) study (5). However, the 704 youth enrolled in the TODAY trial represent the largest ethnically and geographically diverse group of pediatric patients with type 2 diabetes ever assembled. In this report, we describe the characteristics of this cohort upon entry into TODAY.

Materials and Methods

The TODAY study rationale, design, and methods have been reported (8). In brief, TODAY is a multicenter randomized clinical trial funded by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health. The collaborative study group includes 15 clinical centers and a data coordinating center (see on-line appendix). Clinical centers were selected for their ability to recruit from the patient population representative of pediatric type 2 diabetes.

The primary objective was to compare three treatment arms on time to treatment failure, *i.e.* loss of glycemic control defined as either a hemoglobin A1C (A1C) of 8% or greater over a 6-month period or inability to wean from temporary insulin therapy within 3 months after metabolic decompensation. The major secondary aims were to compare the three treatment arms on safety, insulin sensitivity and secretion, body composition, nutrition, physical activity and aerobic fitness, cardiovascular risk factors, microvascular complications, quality of life, psychological outcomes, and relative cost-effectiveness. The three treatment arms were the following: 1) metformin alone, 2) metformin plus rosiglitazone, and 3) metformin plus the TODAY lifestyle program, a program of family-based behavioral lifestyle change aimed at promoting weight loss (9). Treatment assignment to the two medication arms (groups 1 and 2) was masked to investigators, study personnel, and participants (8).

Potential participants were identified from within the clinical populations of the participating centers or by referral from other health care providers within the geographic area. Eligible individuals were aged 10–17 yr inclusive, were diagnosed with type 2 diabetes for less than 2 yr according to American Diabetes Association (ADA) diagnostic glucose criteria operative at the time of randomization (10), had a body mass index (BMI) at the 85th percentile or greater at the time of diagnosis or screening, had negative diabetes autoantibody (DAA) for glutamic acid decarboxylase-65 and tyrosine phosphatase autoantibodies (11), and had an adult caregiver who was closely involved in the participant's daily activities and willing to support the youth's study participation. Eligible subjects entered a 2- to 6-month run-in period with goals of weaning from nonstudy diabetes medications, tolerating metformin up to a dose of 1000 mg twice daily but no less than 500 mg twice daily, attaining glycemic control (A1C $<8\%$ for at least 2 months) on metformin alone, mastering standard diabetes education, and demonstrating adherence to study medication and visit attendance. Enrollment started in July 2004 and ended in February 2009 with a total of 704 participants randomized. The randomization scheme was designed so that the three treatment arms were equally represented at each clinical center. After randomization, data collection and medical monitoring were performed every 2 months in the first year and quarterly thereafter. Participants were followed up for a minimum of 2 yr to a maximum of 6 yr, depending on when they were randomized (8).

Samples were processed following standardized procedures, shipped on dry ice, and analyzed at the Northwest Lipid Metabolism and Diabetes Research Laboratories (University of Washington, Seattle, WA), which served as the central biochemistry laboratory for the study (8).

Data collected included demographics, physical examination, anthropometrics, laboratory values, psychosocial measures and quality of life, nutrition and eating behaviors, physical activity and fitness, dual-energy x-ray absorptiometry, and resource use costs. Tanner stage was determined by physical ex-

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amination of breasts and pubic hair for girls and testicles and pubic hair for boys. Blood pressure was measured using appropriate cuff size, and percentiles were determined using a program from the Centers for Disease Control and Prevention that adjusted for sex, age, and height (12). Participants were provided monetary and other incentives to promote visit attendance and adherence to medication and monitoring. Microalbuminuria (MA) was defined according to the guidelines of the ADA (10) and required two of three independent albumin/creatinine measurements of 30 or greater collected over a 3-month period.

The Adult Treatment Panel III (ATPIII) guidelines were used to characterize lipid abnormalities (13). The patient population was late pubertal or fully mature and of sufficient weight and height to more closely resemble adults than children in most ways except for chronologic age. In addition, there are no universally accepted cutoffs for lipid abnormalities in youth. It should be noted, however, that the adult cutoffs used in this trial are more conservative than proposed pediatric guidelines and therefore reduce the risk of overdiagnosing lipid abnormalities in these children.

Race/ethnicity was determined by self-report on two separate items. For data analysis, 25 (3.6%) who reported belonging to more than one racial group were assigned to a racial/ethnic group according to the following priority of risk for type 2 diabetes in youth: AI greater than Hispanic greater than NHB greater than NHW (14).

The Data and Safety Monitoring Board convened twice a year to review progress and safety and was available as needed; at their initial meeting, they developed rules for interim review of treatment success or futility. The protocol was approved by an external evaluation committee convened by the National Institute of Diabetes and Digestive and Kidney Diseases and the institutional review boards of each participating institution. All participants provided both informed parental consent and minor child assent (8).

Descriptive statistics reported are median, mean, SD, quartiles, or percents. Subgroup comparisons used ANOVA or the Kruskal-Wallis test for continuous variables, depending on normality of distribution, and the χ^2 test for categorical variables. $P < 0.05$ is noted as statistically significant; no correction was made for multiple comparisons and results should be considered descriptive and exploratory.

Results

A total of 1211 patients were screened and 927 (76.6%) entered the run-in phase of the trial. Of those who failed to enter the run-in, 118 (9.7%) were determined to be DAA positive, 58 (4.8%) were excluded based on other laboratory criteria (*i.e.* fasting C-peptide <0.6 ng/ml, transaminanses ≥2.5 upper limit of normal (ULN), estimated creatinine clearance of 70 ml/min or greater, abnormal reticulocyte count or A1C chromatogram), 52 (4.3%) elected not to proceed with the study, 27 (2.2%) did not meet ADA criteria for the diagnosis of type 2 diabetes on review of records, and 29 (2.4%) were excluded for other reasons. In particular, 1.4% of our screened participants had a transaminase value greater than 2.5 ULN and thus were excluded from further participation. This rate for screened participants is comparable with or slightly higher than published reports that approximately 1% of obese adolescents have alanine transaminase (ALT) levels more than twice normal (15). Subjects entering and completing the run-in were representative of those screened in race/ethnicity, gender, age, degree of obesity, and diabetes duration, with the only difference observed being a higher mean A1C value for those not completing the run-in (data not shown). During the run-in, 55 participants (5.9%) were unable to maintain glycemic control on metformin alone, 49 (5.3%) elected not to proceed with randomization, and 119 (12.8%) were excluded for other reasons (8), including less than 80% compliance with study medication, persistent gastrointestinal symptoms that prevented administration of at least 500 mg metformin twice daily, failure to complete the standard diabetes education modules, or failure to keep study appointments. A cohort of 704 (76% of those entering the run-in and 58% of those screened) successfully completed the run-in period, were randomized, and provided baseline data.

Table 1 gives baseline descriptive statistics for the overall sample and by treatment group. The cohort was 64.9% female, with a mean age of 14.0 yr and mean time since diagnosis of 7.8 months. More than 80% of participants were in Tanner stage 4 or 5; no boys and less than 1% of girls were prepubertal. Although inclusion criteria required that BMI be at the 85th percentile or greater for age and gender at diagnosis or screening, randomized participants were substantially more obese than this threshold, with mean BMI Z-score of 2.15. The ethnic composition of the cohort was 41.1% Hispanic, 31.5% NHB, 19.6% NHW, 6.1% AI, and 1.7% Asian. Almost 60% reported at least one parent, full sibling, or half-sibling with diabetes, which rose to almost 90% when grandparents were included. Notably, 85.6% of the entire cohort had acanthosis nigricans, determined by examination of the neck. For the 76.8% of participants born within 2 wk of their due date, 9.0% were small for gestational age (<2500 g), and 17.2% were large for gestational age (>4000 g). A third of the participants were born after a pregnancy complicated by diabetes.

Only 38.7% of the participants lived with both biological parents, whereas 47.0% lived with the mother only, 5.1% with the father only, and 9.2% with neither biological parent. A household annual income less than $25,000 was reported by 41.5%, and the highest level of education attained by a parent/guardian in the household was less than a high school graduate for 26.3%.

At baseline (Table 1), treatment groups did not differ according to age, BMI Z-score, duration of diabetes, gen-

TABLE 1. Baseline characteristics of 704 participants, overall and by treatment group[a]

Demographic characteristics and clinical/medical history	Overall (n = 704)	Treatment group[b]			*P* value
		Metformin (n = 233)	Met+Rosi (n = 236)	Met+TLP (n = 235)	
Age at randomization (yr)	14.0 (2.0)	14.1 (1.9)	14.1 (2.1)	13.8 (2.0)	0.28
BMI Z-score	2.15 (0.44)	2.2 (0.4)	2.1 (0.5)	2.1 (0.4)	0.29
Duration of diabetes (months)	7.8 (5.8)	7.8 (6.0)	8.0 (5.7)	7.6 (5.7)	0.82
Acanthosis present at neck	85.6%	88.3%	85.7%	82.9%	0.26
Female sex	64.9%	63.1%	65.7%	66.0%	0.77
Race/ethnicity					0.78
NHW	19.6%	20.1%	19.5%	19.2%	
NHB	31.5%	32.2%	27.1%	35.3%	
Hispanic	41.1%	40.8%	44.1%	38.3%	
AI	6.1%	5.6%	7.2%	5.5%	
Asian	1.7%	1.3%	2.1%	1.7%	
Household income					0.18
<$25,000	41.5%	39.2%	41.8%	43.4%	
$25,000–49,999	33.5%	39.7%	29.8%	31.1%	
>$49,999	25.0%	21.1%	28.4%	25.5%	
Parent/guardian highest level education					0.55
12th grade or less	26.3%	26.1%	26.0%	27.0%	
High school graduate/GED/business/technical	25.2%	25.2%	21.6%	28.7%	
Some college/associates degree	31.7%	33.5%	34.2%	27.4%	
Bachelors degree or higher	16.8%	15.2%	18.2%	16.9%	
Presence of biological parent(s)					0.46
Youth lives with both mother and father	38.7%	36.7%	38.7%	41.0%	
Youth lives with mother only	47.0%	49.1%	47.4%	44.4%	
Youth lives with father only	5.1%	7.1%	3.5%	4.7%	
Youth lives with neither mother or father	9.2%	7.1%	10.4%	9.9%	
Tanner stage 4 or 5	83.9%	85.4%	85.6%	80.9%	0.28
Size at on-time birth (within 2 wk of due date)					0.03
Small (<2500 g)	9.0%	13.3%	7.9%	5.7%	
Normal (2500–4000 g)	73.8%	72.7%	69.7%	79.2%	
Large (>4000 g)	17.2%	14.0%	22.4%	15.1%	
Mother had gestational diabetes with participant	33.3%	28.5%	35.8%	35.7%	0.17
Nuclear family history of diabetes	59.6%	57.2%	59.0%	62.6%	0.48
Nuclear family + grandparents history of diabetes	89.4%	92.6%	88.2%	87.4%	0.15

Met, Metformin; Rosi, rosiglitazone.

[a] Values are expressed as mean (SD) or percent.

[b] The three treatment arms are metformin alone, metformin plus rosiglitazone, and metformin plus the TODAY Lifestyle Program (TLP).

der, or race/ethnicity, Tanner stage, gestational diabetes, or family history of diabetes, although the distribution across small, normal, and large birth size was different among the three treatment groups ($P = 0.03$).

Table 2 shows clinical and fasting biochemical measures overall and by race/ethnicity. At baseline, 45.6% of participants had normal fasting blood glucose and an A1C less than 6.5% on metformin alone. Median values for other biochemical measures in the cohort were normal except for mildly elevated fasting insulin, C-peptide, and glucose concentrations, low high-density lipoprotein (HDL), and mildly elevated fibrinogen (Esoterix range is 180–420 mg/dl). Racial/ethnic groups did not differ in total cholesterol, fasting glucose, fasting C-peptide, proinsulin, apolipoprotein B, or C-reactive protein. However, NHBs had higher A1C, HDL, vitamin B-12, and homocysteine values and lower triglycerides (TGs) and ALT values relative to the other racial/ethnic groups. Although fasting C-peptide levels did not differ across groups, NHWs had lower fasting insulin levels compared with the other racial/ethnic groups. None of these racial/ethnic differences, however, was of a magnitude considered clinically significant.

More importantly, Table 2 shows that, at baseline, a large percentage of the cohort had clinical and/or biochemical abnormalities as determined by cutoff values. Approximately one fourth had a blood pressure (BP) value (either systolic or diastolic or both) at the 90th percentile or greater, 13.6% had a BP value at the 95th percentile or greater, almost 13% had microalbuminuria (*i.e.* urine albumin/creatinine ≥30 mg/g), 79.8% had low HDL, and 10.2% had high TGs. NHBs were less likely to have high TGs. Individuals with a liver function test (LFT) greater than 2.5 × ULN at screening were excluded, but 3.3% of participants had LFT 1.5–2.5 × ULN at baseline.

Among hypertensive (BP value ≥95th percentile) participants (n = 92), 21.7% also had microalbuminuria,

TABLE 2. Baseline clinical and biochemical abnormalities and measurements, overall and by race/ethnicity[a]

Biochemical measurements	Overall (n = 704)	Race/ethnicity[b] NHW (n = 138)	NHB (n = 222)	Hispanic (n = 289)	AI (n = 43)	*P* value
A1C (%)	5.9 (5.5, 6.5)	5.7 (5.3, 6.3)	6.2 (5.7, 6.5)	5.8 (5.4, 6.4)	5.7 (5.3, 6.2)	<0.01
Total cholesterol (mg/dl)	144 (126, 165)	146 (125, 169)	143 (124, 165)	144 (127, 164)	144 (124, 156)	0.89
LDL (mg/dl)	83 (68, 101)	82 (68, 103)	87 (70, 107)	80 (66, 98)	79 (67, 96)	0.05
HDL (mg/dl)	38 (33, 43)	36 (33, 42)	40 (34, 45)	37 (32, 43)	37 (34, 44)	<0.01
TGs (mg/dl)	94 (66, 136)	110 (70, 147)	72 (54, 98)	110 (78, 160)	104 (75, 155)	<0.01
AST (U/liter)	22 (17, 27.5)	21 (18, 27)	21 (17, 25)	22 (18, 29)	24 (19, 34)	<0.01
ALT (U/liter)	24 (17, 38)	26 (18, 40)	20 (15, 28)	27 (18, 44)	34 (20, 55)	<0.01
Urine albumin/creatinine (mg/g)	7 (5, 14)	7 (4, 14)	6 (4, 11)	7 (5, 15)	8 (5, 15)	0.01
Fasting glucose (mg/dl)	103 (93, 123)	109 (94, 126)	103 (94, 122)	103 (92, 124)	102 (94, 115)	0.57
Fasting insulin (μU/ml)	25.7 (16.7, 37.8)	21.5 (14.8, 34.0)	28.1 (18.2, 44.1)	25.8 (17.3, 36.7)	26.0 (16.4, 35.6)	<0.01
Fasting C-peptide (ng/ml)	3.6 (2.7, 4.7)	3.5 (2.7, 4.8)	3.4 (2.6, 4.6)	3.8 (2.9, 4.7)	3.8 (2.9, 5.4)	0.13
Proinsulin (pM)	25.6 (14.1, 46.3)	22.7 (13.5, 41.2)	28.2 (16.6, 51.1)	24.6 (13.6, 45.6)	27.5 (11.2, 52.0)	0.11
Apolipoprotein-B (mg/dl)	75 (62, 90)	73 (60, 94)	75 (61, 86)	76 (63, 92)	75 (64, 88)	0.72
Estimated creatinine clearance (ml/min)	147 (128, 175)	146 (130, 174)	144 (123, 167)	154 (130, 183)	144 (121, 168)	<0.01
Free fatty acid (mEq/liter)	0.59 (0.45, 0.72)	0.64 (0.49, 0.76)	0.57 (0.43, 0.71)	0.59 (0.45, 0.69)	0.60 (0.45, 0.75)	0.02
Fibrinogen (mg/dl)	425 (366, 483)	400 (360, 451)	437 (382, 501)	428 (369, 491)	415 (334, 495)	<0.01
Homocysteine (μmol/liter)	6.0 (4.8, 7.2)	5.9 (5.2, 7.1)	6.5 (5.6, 7.7)	5.5 (4.6, 7.0)	4.8 (4.1, 6.9)	<0.01
Vitamin B-12 (pg/ml)	378 (297, 491)	350 (283, 441)	437 (328, 573)	367 (291, 464)	340 (287, 410)	<0.01
C-reactive protein (mg/dl)	0.2 (0.1, 0.5)	0.2 (0.0, 0.5)	0.2 (0.1, 0.5)	0.2 (0.1, 0.5)	0.2 (0.1, 0.5)	0.36
Clinical and biochemical abnormalities	**Overall (n = 704)**	**NHW (n = 138)**	**NHB (n = 222)**	**Hispanic (n = 289)**	**AI (n = 43)**	***P* value**
Blood pressure ≥90th percentile	26.3%	26.1%	28.8%	24.2%	30.2%	0.63
Blood pressure ≥95th percentile	13.6%	16.7%	15.3%	10.7%	16.3%	0.27
Urine albumin/creatinine ≥30 mg/g	13.0%	14.6%	11.2%	14.1%	7.9%	0.57
Liver function test 1.5–2.5 × ULN	3.3%	4.3%	1.4%	3.8%	7.0%	0.16
LDL (mg/dl)[c]						<0.01
Optimal (<100)	72.4%	73.2%	64.4%	76.8%	81.4%	
Near optimal (100–129)	23.6%	23.2%	30.2%	20.8%	9.3%	
Borderline (130–159)	3.6%	3.6%	4.0%	2.4%	9.3%	
High (160–189)[d]	0.4%	0.0%	1.4%	0.0%	0.0%	
HDL (mg/dl)[c]						0.42
High (≥60)	2.3%	1.5%	3.6%	1.7%	0.0%	
Normal (females 50–59, males 40–59)	17.9%	18.1%	20.3%	17.7%	11.6%	
Low (females <50, males <40)	79.8%	80.4%	76.1%	80.6%	88.4%	
TGs (mg/dl)[c]						<0.01
Optimal (<150)	79.1%	75.4%	94.1%	70.6%	72.1%	
Borderline (150–199)	10.7%	8.7%	5.4%	14.5%	18.6%	
High (≥200)	10.2%	15.9%	0.5%	14.9%	9.3%	

AST, Aspartate transaminase.

[a] Biochemical measurements expressed as median (25th, 75th percentiles); clinical and biochemical abnormalities expressed as percent.

[b] Data not shown for n = 12 classified as Asian race/ethnicity.

[c] Cutoffs according to ATPIII guidelines.

[d] Very high (≥190) category had 0 count and is not shown.

TABLE 3. Clinical and biochemical characteristics by sex[a]

Characteristic	Female (n = 457)	Male (n = 247)	*P* value
Age at randomization (yr)	13.7 (2.1)	14.5 (1.9)	<0.01
Duration of diabetes (months)	6 (4, 10)	5 (4, 9)	0.24
BMI Z-score	2.2 (0.4)	2.1 (0.5)	0.50
Nuclear family history of diabetes	60.2%	58.4%	0.65
BP ≥90th percentile	21.9%	34.4%	<0.01
BP ≥95th percentile	11.4%	17.8%	0.02
Urine albumin/creatinine ≥30 mg/g	14.3%	10.6%	0.18
Liver function test 1.5–2.5 × ULN	3.5%	2.8%	0.63
LDL (mg/dl)[b]			0.99
Optimal (<100)	72.7%	72.1%	
Near optimal (100–129)	23.4%	23.5%	
Borderline (130–159)	3.5%	4.0%	
High (160–189)[c]	0.4%	0.4%	
HDL (mg/dl)[b]			<0.01
High (≥60)	2.6%	1.6%	
Normal (females 50–59, males 40–59)	10.1%	32.4%	
Low (females <50, males <40)	87.3%	66.0%	
TGs (mg/dl)[b]			0.21
Optimal (<150)	80.3%	76.9%	
Borderline (150–199)	10.9%	10.1%	
High (≥200)	8.8%	13.0%	
Size at on-time birth (within 2 wk of due date)			<0.01
Small (<500 g)	9.9%	7.3%	
Normal (2500–4000 g)	76.8%	67.9%	
Large (>4000 g)	13.3%	24.8%	
Mother had gestational diabetes with participant	29.8%	40.1%	<0.01

[a] Age and BMI Z-score expressed as mean (SD), duration of diabetes as median (25th to 75th percentile), all other as percent.

[b] Cutoffs according to ATPIII guidelines.

[c] Very high (≥190) category had 0 count and is not shown.

compared with only 11.5% of the normotensive (n = 541) participants, whereas coexistent dyslipidemia was unrelated to blood pressure status (79.1% hypertensive *vs.* 80.7% normotensive). Microalbuminuria and dyslipidemia together were present in 18.5% of the participants who were hypertensive but in only 9.8% of the participants who were normotensive. In our sample, microalbuminuria and dyslipidemia (without regard to hypertension) were not significantly correlated (r = 0.04, $P = 0.30$).

Table 3 gives clinical characteristics and laboratory abnormalities by gender. There were no differences by gender for diabetes duration, BMI Z-score, or family history. Males were approximately 1 yr older than females at the time of randomization despite similar diabetes duration. Males were statistically more likely to have been born to a pregnancy complicated by diabetes and to be large for gestational age than females. In addition, males were more likely to be hypertensive and to have normal HDL compared with females. As expected from previous reports, approximately two thirds of the cohort were female. This varied by race/ethnicity, being higher for AI and NHB participants (74.4 and 70.3%, respectively) and lower for NHW and Hispanic participants (59.4 and 61.6%, respectively).

Discussion

The TODAY trial cohort represents the largest group of well-characterized American children and adolescents with rigorously defined type 2 diabetes ever assembled. Despite rigorous eligibility criteria and limitation to the sociodemographic environments of the 15 participating clinical centers, the resulting gender, age, racial/ethnic, and socioeconomic distributions of the cohort are very similar to that of other recent population-based studies (5, 14), suggesting that the TODAY cohort is representative of the population of youth with type 2 diabetes in the United States. As such, the description of this cohort provides more detailed insight into this population than previously possible. Furthermore, randomization resulted in three comparable treatment groups at baseline (Table 1). This baseline homogeneity across treatment groups will allow reliable comparisons of treatment responses and safety on completion of the intervention phase of the study.

We found that approximately 10% of participants with clinically diagnosed type 2 diabetes referred for screening were DAA positive and were thus excluded from further participation in TODAY. This rate of antibody positivity is lower than previously described for newly diagnosed

youth with type 2 diabetes (5). The lower rate of antibody positivity may be due, in part, to the increased practice of measuring antibodies in this patient population as part of routine clinical evaluation, which would lead to some obese DAA-positive patients not being referred to TODAY for screening. It may also reflect the use of newer assay methodologies with lower false-positive rates. However, the persistent presence of antibody-positive participants in the screening population emphasizes the overlap in clinical characteristics between DAA-positive and DAA-negative obese youth with new-onset diabetes and the difficulty in distinguishing these patients on clinical grounds, even for experienced pediatric endocrinologists. A detailed comparison of antibody negative and positive youth presenting for screening for TODAY has been reported (11).

As expected, a female preponderance was present but variable across race/ethnicity (14, 16). This interaction between gender and race/ethnicity has not been reported previously in cohorts of youth with type 2 diabetes, likely because no previous sample of youth with type 2 was sufficiently large or ethnically diverse to allow this analysis. Although a very similar interaction was observed among children with diabetes in the SEARCH study (14), the SEARCH prevalence estimates included both type 1 and type 2 cases and may have been strongly influenced by the greater proportion of type 1 cases among the NHW and Hispanic youth. This confounding is not present in the TODAY cohort. Although TODAY is not a population-based cohort, there is no obvious manner in which the selection criteria would favor males in certain racial/ethnic groups but not in others. Thus, the finding raises intriguing questions regarding possible racial/ethnic influences on the pathophysiology of type 2 diabetes in youth and, in particular, interactions between sex steroids and insulin resistance.

Median values of metabolic and biochemical parameters were normal in this cohort, except for slight elevations of fasting insulin, glucose, and fibrinogen concentrations and low HDL. However, the cohort at baseline had a high prevalence of metabolic abnormalities, particularly low HDL, elevated TGs, and hypertension. Abnormal low-density lipoprotein (LDL), elevated LFT, and microalbuminuria were uncommon, possibly as a consequence of the improvement in glycemic control and lifestyle changes accomplished during the run-in period.

Several racial/ethnic differences were observed in physical and biochemical markers. In particular, NHB participants had lower TGs and higher HDL but higher LDL, A1C, vitamin B-12, and homocysteine values relative to the other ethnic groups. In addition, ALT was lowest in NHBs, as reported previously in this population (17–19).

Previous epidemiological studies have identified important relationships between exposure to pregnancy complicated by diabetes and early onset of obesity, insulin resistance, and type 2 diabetes (20–22). However, we report here novel findings regarding apparent gender differences in this relationship, with males with type 2 diabetes being more likely than females to have been born to a mother with gestational diabetes and to have been born large for gestational age. Again, it is likely that these gender differences have not been previously reported due to the small size of previous cohorts. The reasons for this gender difference are not clear but are not likely due to recruitment or selection criteria and may suggest an important interaction between gender and neonatal or early-life risk factors.

These data also reveal several additional observations about youth with type 2 diabetes that confirm and extend previous reports in smaller cohorts. First, a large percentage of participants had comorbidities present at baseline (13.0% microalbuminuria, 80.5% dyslipidemia, 13.6% hypertension), similar to previous, smaller reports (23). Furthermore, these metabolic abnormalities were present despite good glycemic control at the time of randomization. Second, microalbuminuria is noted to be closely linked to hypertension, whereas dyslipidemia was not (24). Finally, almost half of the participants achieved good glycemic control and had an A1C at target on metformin alone after the run-in period, confirming the efficacy of metformin in this cohort of youth with recent-onset diabetes. Indeed, few screened participants were excluded for inability to wean off insulin, indicating that metformin is effective monotherapy in the vast majority of these youth.

One limitation of this study may be that TODAY participants met inclusion and exclusion criteria based in part on rigid adherence and safety considerations. These strict criteria were imposed because the research subjects for this trial were considered vulnerable, in terms of both age and high minority representation. In addition, as in most large clinical trials, recruitment procedures varied across clinical centers. For example, some clinical centers performed prescreening that included local testing for antibody status, whereas others did not. The cohort also excluded potential participants if their diabetes was not of recent onset, if they were only mildly overweight, if they were on psychotropic medications (25), or if they were over 18 yr of age at the time of recruitment. Despite these potential biases, the cohort at baseline was found to be remarkably similar both to prior reports (5, 14) and to those screened for entry into TODAY, except for evidence of autoimmunity, an *a priori* exclusion criterion for the trial. The baseline characteristics of the TODAY cohort can be interpreted as representative of youth with type 2 diabetes throughout the United States in general. Likewise, final

outcome data will yield insights applicable to the treatment of youth with type 2 diabetes.

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In this trial, ethnicity was determined by self-report. Because ethnicity by self-report does not indicate blood quantum, American Indian ethnicity in this trial may or may not represent American Indians in the United States.

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