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Update on Youth-Onset Type 2 Diabetes: Lessons Learned from the TODAY Clinical Trial

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INTRODUCTION

Type 2 diabetes mellitus (T2D) in children and adolescents has become increasingly prevalent in parallel with rising rates of childhood obesity. Prior to the late 1990s, T2D was a rare entity in children and an increase in prevalence was first described in urban minority youth in 1996 [1, 2]. At the present time, youth-onset T2D spans across continents and affects children of all ethnicities and socioeconomic backgrounds. However, youth-onset T2D disproportionately affects disadvantaged families of minority, indigenous, or migrant communities. The SEARCH for Diabetes in Youth, a registry-based study in the US, has shown that the overall prevalence of T2D in 2009, the latest year for which data are available, was 0.46 per 1000 youth under age 18, a 30.5% increase in comparison with 2001 [3, 4]. Yet, despite the increase over time, T2D remains much less prevalent in adolescents than in adults; T2D is present in 120–140 per 1000 adults in the United States, based on National Health and Nutrition Examination Survey (NHANES) data.[5]. Between 2001 and 2009, a significant increase in childhood T2D was seen in non-Hispanic whites, African Americans, and Hispanics, but not among Asian Pacific Islanders and American Indians [3, 4], who already had high rates of T2D. In children ten years of age or older, T2D is now responsible for 3% of all cases of diabetes among Caucasians, 23% in Hispanics, 25% in African Americans, and 64% in American Indians [4].

The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) Study cohort consists of racially/ethnically diverse participants with youth-onset T2D who have been rigorously characterized and followed longitudinally to better understand the clinical course of complications and comorbidities of diabetes[6]. The initial results of the TODAY intervention trial have been published and reviewed in many publications and are

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summarized in the next few paragraphs. The remainder of this chapter will focus on the more recent findings from the TODAY study.

TODAY TRIAL RESULTS

The TODAY trial began recruiting subjects in 2004 [6]. Subjects eligible for participation were 10–17 years old with T2D (based on established ADA criteria) for less than two years. They also had a BMI $\geq 85\%$ and a fasting c peptide $> 0.6\text{ng/mL}$ without demonstrable pancreatic islet autoantibodies [6]. Exclusion criteria included renal insufficiency, uncontrolled hypertension, liver disease, and uncontrolled hyperlipidemia [6]. 699 subjects were randomized to receive one of three treatments: metformin monotherapy, metformin plus rosiglitazone, and metformin plus an intensive lifestyle intervention [6]. The primary outcome was the length of time to glycemic failure, defined as a hemoglobin A1c (HbA1c) $\geq 8\%$ for at least six months or the inability to wean from insulin injections for at least three months after acute metabolic decompensation [6].

Nearly half (45.6%) of all TODAY participants reached glycemic failure over an average time of 3.86 years [7]. Failure rates for each of the three treatment arms were: 51.7% in the metformin monotherapy group, 46.6% for the metformin plus lifestyle group, and 38.6% for the metformin plus rosiglitazone group (See Figure 1). The difference between the metformin monotherapy and metformin plus rosiglitazone arms was statistically significant, suggesting that adding a second oral medication early in the disease process of youth-onset T2D may help to promote durable glycemic control [7]. These differences were not the result of differences in medication adherence. The metformin plus lifestyle arm did not differ significantly from the other two treatment arms, illustrating the challenges in delivering an intensive lifestyle intervention as a supplement to metformin monotherapy in this patient population [7].

Sex and racial differences were also noted in the subgroup analyses of the TODAY study. The combination of metformin plus rosiglitazone proved to be more effective at preventing glycemic failure in girls (65% of the cohort) than in boys [7]; among girls, those in the metformin plus rosiglitazone group did better than girls in the other two treatment arms, while there were no treatment group differences in the boys. [7]. Race/ethnicity had an impact on glycemic failure rates as well (See Figure 2). Non-Hispanic blacks had the highest rates of glycemic failure (52.8%), followed by Hispanics (45%) and Non-Hispanic whites (36.6%) [7]. Metformin monotherapy was least effective in non-Hispanic blacks compared to other racial/ethnic groups, whereas no significant differences were found in other treatment arms [7].

LESSONS FROM THE TODAY RUN-IN

After subjects were screened for participation in the TODAY trial, they entered a run-in phase. The objectives of the run-in phase were to: provide standard diabetes education, assess subjects' tolerance to metformin and adherence to study protocol, wean off other diabetes medications while achieving a HbA1c $< 8\%$ for at least two months, and establish a uniform study cohort before randomization.

Of the 927 participants who entered the run-in phase, 35.6% had an HbA1c $\geq 8\%$ and 38% were on insulin; the mean HbA1c was 7.7% [8, 9]. Of note, 90.9% of these subjects achieved an HbA1c $< 8\%$ and nearly all subjects who had been on insulin at screening were able to lower their A1c on metformin to $< 8\%$ after insulin discontinuation [8, 9]. After the completion of the run-in phase, 223 were not eligible for randomization. The most common reasons for ineligibility were: inability to lower HbA1c to $< 8\%$, failure to wean off insulin, and metformin intolerance [9]. The group of participants who were unable to be randomized had a mean HbA1c of 8.5% at screening, were more likely to be non-Hispanic Black and gain weight during the run-in phase. C peptide levels were not significantly different in the non-randomized group [9].

DURABLE CONTROL

Given the high rate of loss of glycemic control on oral therapy in youth-onset T2D, the TODAY study examined whether specific clinical markers identified early in a patient's disease may be useful in predicting which subjects were more likely to develop glycemic failure on oral agents [10]. Participants were divided into two categories: those who met the primary outcome of glycemic failure in less than 48 months and those who achieved durable control and did not exhibit glycemic failure over this period of time. Table 1 highlights the differences between these two groups [10].

In multivariate analysis, HbA1c at screening and at randomization (after treatment with metformin for two to six months during Run-in) and baseline insulinogenic index (the change in insulin in response to change in glucose during the oral glucose tolerance test) were the two metabolic factors that were significantly different between the group that had glycemic failure and the group that achieved metabolic goals over 48 months [10]; baseline HbA1c was lower (figure 3) and insulinogenic index higher in the group with durable control. Since HbA1c is more clinically accessible, HbA1c as a potential marker for risk was examined more closely. In receiver-operator curve analysis, an HbA1c of 6.3% or more after initiation of metformin was shown to be a predictor of eventual loss of glycemic control; for every 0.1% increase in HbA1c there was a 16% increase in risk of loss of glycemic control, with a median time to loss of control of approximately 11 months, irrespective of treatment arm [10]. Therefore, patients who do not lower their HbA1c to a "non-diabetes range" on metformin monotherapy are at increased risk for loss of glycemic control and should be followed closely for a more rapid decline in glucose control.

METABOLIC SYNDROME

Metabolic syndrome in patients with T2D heightens cardiovascular disease risk. In the LOOK Ahead trial, 94% of adults with T2D had metabolic syndrome and lifestyle interventions in these adults did not reduce cardiovascular events [11, 12]. Metabolic syndrome in the TODAY study was defined using the adult ATP III definition [13] and because all subjects had diabetes, required at least 2 of the following four criteria: abdominal obesity (> 102 cm in males and > 88 cm in females), triglycerides > 150 mg/dL or on lipid-lowering treatment, low HDL cholesterol (< 40 in males and < 50 in females), and high blood pressure ($\geq 130/85$ or on anti-hypertensive treatment).

The TODAY study found the prevalence of metabolic syndrome to be 75.8% at randomization [14]. Neither the overall prevalence nor incidence of metabolic syndrome significantly changed in first two years of the trial. Further there were no differences in the prevalence of metabolic syndrome among the three treatment arms[14]. Table 2 displays the prevalence of metabolic syndrome in TODAY subjects by sex, race/ethnicity, and glycemic status. Metabolic syndrome was more common in female subjects (83.1%) compared to their male counterparts (62.3%) and this difference persisted over time. The factors contributing to the difference between sexes were a higher likelihood of abdominal obesity and low HDL cholesterol in female subjects[14]. The prevalence of metabolic syndrome among subjects with different racial/ethnic backgrounds was similar at baseline and 6 months after the study began. However after two years, 82.7% of Hispanics had metabolic syndrome, which was significantly higher than the rate observed in non-Hispanic blacks (72.7%) and non-Hispanic whites (67.5%). Low levels of triglycerides in non-Hispanic blacks and low HDL cholesterol levels in Hispanics contributed to these differences[14]. Subjects who reached glycemic failure in the study were more likely to have metabolic syndrome at 6 months and had higher rates of hypertriglyceridemia and hypertension[14].

PARENTAL DIABETES

Other studies have shown that having a parent with self-reported T2D greatly increases a child's risk for development of the disorder; exposure to T2D during pregnancy results in a three-fold increased risk of diabetes in offspring compared to a sibling who was not exposed to high blood sugars in utero [15]. The maternal influence is known to be stronger than the paternal effect[16–20]. In addition to genetic factors, in utero exposure to diabetes may also affect offspring through an epigenetic process [21].

In the TODAY study, 50% of participants had a mother with diabetes, whereas 32% of the subjects' fathers were reported to have diabetes at the randomization visit [22]. Table 3 contrasts the effect of maternal versus paternal diabetes on demographic, anthropometric, parental, and metabolic measures. Participants with a maternal history of T2D and who were exposed to diabetes in utero were younger by 0.6 years at the time of diagnosis, more likely to be male, and were heavier at birth by approximately 400 grams. Neither BMI z score, percent body fat, nor waist circumference were associated with parental diabetes history[22]. Subjects whose mothers had diabetes during their pregnancy had a significantly higher (by 0.3%) hemoglobin A1c at baseline and a maternal history of diabetes (either diagnosed during or after pregnancy) was also associated with a higher fasting and 2 hour glucose at the time of randomization. Insulin secretion (as measured by the c-peptide oral disposition index) was lower in subjects with a maternal history of diabetes; the lower oral disposition index was significant regardless of whether the mother's diabetes was diagnosed before, during, or after the pregnancy. Conversely, markers of insulin sensitivity were not associated with parental diabetes status[22].

PREGNANCY

Teen pregnancy carries a heightened risk to the mother and neonate. Pregnancy in individuals with diabetes poses additional risks to mother and baby, particularly when the

mother's glycemic control is not optimal. The TODAY study provided an opportunity to assess the additional risks that face teens with T2D who become pregnant. 46 (10.8%) of the 452 female TODAY participants became pregnant during the study, a proportion in line with rates of pregnancy in the general teen population[23]. All female TODAY participants were counseled to use birth control at each visit, were advised against pregnancy because of the possible exposure to rosiglitazone, a Pregnancy Class C medication, and received a video based program regarding pregnancy planning developed for girls with diabetes. However, only 13% of the participants who became pregnant recalled the recommendation to avoid pregnancy during the study [23].

Compared to the girls without pregnancy, subjects who became pregnant were more likely to be older, live outside of parental home, and have a lower annual household income[23]. There was no difference in parental education, diabetes duration, BMI, smoking history, TODAY treatment group, HbA1c at baseline, or the percent losing glycemic control. Of all pregnancies in TODAY, 26.4% ended in a miscarriage, stillbirth, or intrauterine fetal demise. Of the live-born offspring, 20.5% had a major congenital anomaly – 50% with cardiac defects and the remaining with congenital kidney, intestinal, brain, or palate malformations. Maternal prenatal complications included 8.7% with preeclampsia, 10.9% with nephrotic-range proteinuria, and 21.7% with hypertension. In the women who had been pregnant and who had retinal photography after delivery (63% of total), 27.6% had mild non-proliferative diabetic retinopathy, compared to an overall rate of non-proliferative retinopathy of 13.7% in the cohort [23].

COMPLICATIONS

Microvascular and macrovascular complications of T2D are a main source of morbidity and mortality in adults, but less is known about youth-onset disease. Previous case series in children with T2D show higher rates of hypertension and microalbuminuria compared with youth with type 1 diabetes mellitus of similar age and duration of disease [24–26]. The TODAY trial provided an opportunity to examine the longitudinal prevalence of hypertension, microalbuminuria, retinopathy, and cardiovascular disease risk in children and adolescents with T2D.

Hypertension in the TODAY study was defined as either a blood pressure $\geq 130/80$ mmHg or $\geq 95^{\text{th}}$ percentile for age, sex, and height on three separate visits [27]. Dietary counseling restricting sodium consumption was initiated when high blood pressures first became apparent. Microalbuminuria was identified as an albumin-to-creatinine ratio ≥ 30 $\mu\text{g}/\text{mg}$ in at least two urine samples collected over a three month time period[27]. Treatment for both hypertension and microalbuminuria began with an ACE-inhibitor followed by the sequential addition of antihypertensive agents (using a predefined algorithm) in order to reach goal blood pressure and urinary albumin excretion parameters[27].

The overall prevalence of hypertension increased from 11.6% at baseline to 33.8% by the end of the study [27]. These prevalences compare with $<5\%$ in the similarly aged non-diabetic, general population [28]. The factors associated with risk of hypertension were: male sex, older age at baseline, and higher BMI. Boys were 81% more likely to be

hypertensive compared to girls. Each year older at baseline conferred an additional 14% risk of hypertension. Each additional kg/m² in BMI added an additional 6% risk of hypertension[27]. Neither treatment arm, race/ethnic background, HbA1c, nor incidence of glycemic failure affected hypertension risk in the TODAY study.

Microalbuminuria among all participants increased from an overall prevalence of 6.3% at the start of the study to 16.6% by the end of the study [27]. Baseline and subsequent annual incidence rates of microalbuminuria were similar to those found in the adult UKPDS study [29]. TODAY study participants who met criteria for glycemic failure were more likely to develop microalbuminuria compared to those who did not (16% and 5.5%, respectively). HbA1c over time was significantly related to the risk of developing microalbuminuria; for every 1% rise in A1c, the risk increased by 17%[27]. However, rates of microalbuminuria did not differ among the TODAY study treatment arms, sex, or race/ethnic backgrounds.

In the final year of the TODAY trial, retinal exams, including digital fundus photography, were obtained and read at a dedicated reading center at the University of Wisconsin. Retinopathy was defined as the minimum amount of retinal disease including a microaneurysm, retinal hemorrhage or cotton wool spot in at least one eye. The overall prevalence of retinopathy in TODAY participants with a mean diabetes duration of 4.5 +/– 1.5 years was 13.7% [30]. All subjects with retinopathy were classified as mild nonproliferative diabetic retinopathy (NPDR); there were no participants with more advanced disease (i.e., macular edema, advanced NPDR, proliferative retinopathy). Subjects who developed NPDR were older (19.1 versus 17.9 years), had higher A1c (8.3% versus 6.9%), and had diabetes for a longer duration (5.6 versus 4.7 years)[30]. The onset of retinopathy did not correlate with sex, ethnicity, TODAY treatment arm, blood pressure, smoking, pregnancy, microalbuminuria, or hyperlipidemia. Participants with the highest BMIs were least likely to develop retinopathy, suggesting that obesity and perhaps insulin resistance may play a protective role in the evolution of retinopathy in these patients[30]. Similar associations between obesity and lower risk for retinopathy have been reported in adults[31–34].

Cardiovascular disease is the leading cause of death in adults with T2D [2]. In the TODAY study there were no cardiovascular events. Lipid parameters (LDL, non-HDL, apolipoprotein B, LDL particle density, triglycerides, and HDL) and inflammatory markers (high-sensitivity c-reactive protein, homocysteine, plasminogen activator inhibitor-1, and nonesterified fatty acids) were assessed at baseline and then annually. Lipid goals were defined as LDL<100 mg/dL and triglycerides <150 mg/dL, and if LDL was >130 mg/dL and triglycerides >300 mg/dL, nutrition counseling and dietary changes were attempted for six months before starting statin therapy [6]. The percentage of total subjects with an LDL>130 mg/dL or who were taking a prescribed statin increased from 4.5% at baseline to 10.7% three years later [35]. Around half (55.9%) of the TODAY subjects remained at target LDL levels for the first three years of the study. Among the three TODAY treatment arms, LDL, triglycerides, apolipoprotein B, and non-HDL rose significantly in the first year after diagnosis and then stabilized for the next two years of observation. One notable exception was that triglycerides were considerably lower in the group receiving metformin plus an intensive lifestyle intervention [35]. Triglycerides levels were also significantly lower in the

non-Hispanic Blacks compared to the Hispanic and non-Hispanic White cohorts. Inflammatory markers hs-CRP, homocysteine, and PAI-1 all steadily rose throughout the first three years of the TODAY study[35].

Echocardiography was also performed on TODAY subjects during the last year of the trial. Mean left ventricular (LV) mass was high/normal in these subjects and 16.2% of them had adverse LV geometry (8.1% concentric geometry, 4.5% LV hypertrophy and 3.6% both) [36]. Factors that were positively associated with higher LV mass were male sex, non-Hispanic Black race, BMI, systolic blood pressure, use of blood pressure medication, absence of glycemic failure, and smoking[36]. Longitudinal changes in BMI and blood pressure adversely affected LV mass, suggesting that control of these risk factors plays an important role in cardiovascular disease risk reduction in youth-onset T2D.

FUTURE RESEARCH

Youth-onset T2D has become more common, carries a high disease burden and is associated with increased short term and long-term morbidity and risk for earlier mortality. In 2013, Constantino et. al. compared rates of diabetes-related morbidity and mortality between 354 young adult subjects with T2D (average age of onset 25.6 years and average duration 11.6 years) and 470 type 1 diabetes (T1D) subjects of similar diabetes duration [37]. Subjects with T2D had 3 times the rate of albuminuria, 4 times the rate of stroke (4.3% vs. 0.7%), nearly 6 times the rate of ischemic heart disease (12.6% vs 2.5%), and nearly 3 times the rate of any macrovascular disease [37]. T2D subjects had a mortality excess of 11% (vs. 6.8% in T1D subjects) and a hazard ratio for death of 2.0 (95% CI 1.2–3.2). Death occurred at a shorter disease duration of 27 years in T2D subjects compared to 36.5 years in T1D subjects [37]. However, although documenting the significant morbidity and mortality associated with youth-onset T2D, the study's cross-sectional and retrospective design limits our understanding of the causal relationships among treatment, metabolic control, β -cell function, and diabetes complications and comorbidities. The longitudinal follow-up of the well-characterized TODAY cohort in TODAY2, a long-term observational study of outcomes in the TODAY cohort, is well suited to help answer these questions.

The TODAY2 post-intervention follow-up study will continue collecting data on diabetes outcomes on these subjects through the year 2021. To date, the retention rate in TODAY2 is high, as 72.1% of the original TODAY participants have consented to continue in TODAY2 and adherence to annual visits has been greater than 90%. Individuals in the cohort have been comprehensively characterized, including measures of glycemic control, insulin sensitivity, β -cell secretory capacity, body composition, fitness, physical activity, dietary intake, quality of life, hypertension, dyslipidemia, urinary albumin excretion, peripheral neuropathy, arterial stiffness (pulse wave velocity), cardiac function (echocardiography), retinal status, depression indicators, and eating disorders since soon after diagnosis. DNA has also been collected on these subjects to help determine what other genetic factors may contribute to the pathogenesis of youth-onset T2D. By following these well-characterized individuals as they transition to emerging adults, TODAY2 will expand our understanding of the nature and determinants of long-term outcomes in youth-onset T2D.

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Materials developed and used for the TODAY standard diabetes education program and the intensive lifestyle intervention program are available to the public at <https://today.bsc.gwu.edu/>

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Figure 1.
 TODAY Primary Outcome Results (M= Metformin alone treatment arm; M+R= Metformin plus rosiglitazone treatment arm; M+L= Metformin plus intensive lifestyle changes treatment arm)

Figure 2.
Primary Outcome Results Accordingly to Race, Ethnicity, Sex

Figure 3. Distribution of Baseline HbA1c in Group 1 (no glycemic failure within 48 months) and Group 2 (glycemic failure within 48 months)

Table 1

Demographics and Baseline Characteristics Affecting Durability of Glycemic Control

Demographic and Baseline Characteristics by Analysis Group – mean (SD) or n (%) –				
Characteristic		Group 1 no PO* <48 mo (n=172)	Group 2 PO* <48 mo (n=305)	p - value
Treatment	M	53 (30.8%)	116 (38.0%)	0.2453
	M+R	58 (33.7%)	86 (28.2%)	
	M+L	61 (35.5%)	103 (33.8%)	
Sex	Female	111 (64.5%)	193 (63.3%)	0.7845
	Male	61 (35.5%)	112 (36.7%)	
Age (years)		13.8 (1.9)	14.1 (2.1)	0.1825
Race-ethnicity	NHB	47 (27.3%)	117 (38.3%)	0.0323
	H	70 (40.7%)	119 (39.0%)	
	NHW	43 (25.0%)	48 (15.7%)	
	Other	12 (7.0%)	21 (6.9%)	
Months since diagnosis		8.1 (6.2)	8.7 (6.2)	0.3752
Depressive symptoms	No	154 (91.1%)	251 (83.4%)	0.0217
	Yes	15 (8.9%)	50 (16.6%)	
Tanner stage	4	155 (90.1%)	271 (88.9%)	0.6682
	3	17 (9.9%)	34 (11.1%)	
Household income	Low (<\$25,000)	62 (39.7%)	120 (45.0%)	0.0512
	Mid (\$25,000–49,999)	46 (29.5%)	93 (34.8%)	
	High (≥ \$50,000)	48 (30.8%)	54 (20.2%)	
Household education	Less than high school	46 (27.1%)	80 (26.5%)	0.4529
	HS, GED, bus or tech	37 (21.8%)	85 (28.1%)	
	College no degree	57 (33.5%)	93 (30.8%)	
	College degree	30 (17.6%)	44 (14.6%)	
1 st degree family history of diabetes	No	86 (50.6%)	100 (33.3%)	0.0003
	Yes	84 (49.4%)	200 (66.7%)	
BMI (kg/m ²)		34.0 (7.6)	35.1 (7.5)	0.1189
Waist circumference (cm)		107.1 (16.2)	109.2 (17.0)	0.1940
HbA1c at screening (%) (mmol/mol)		6.79 (1.64)	8.05 (2.07)	< .0001
		51 (17.9)	64 (22.6)	< .0001
HbA1c at randomization (%) (mmol/mol)		5.68 (0.55)	6.39 (0.80)	<.0001
		39 (6.0)	46 (8.7)	<.0001

Demographic and Baseline Characteristics by Analysis Group – mean (SD) or n (%) –			
Characteristic	Group 1 no PO* <48 mo (n=172)	Group 2 PO* <48 mo (n=305)	p - value
C-peptide (ng/mL)	3.71 (1.55)	3.91 (1.64)	0.1921
DXA fat mass (kg)	32.9 (10.0)	33.0 (9.8)	0.9453
DXA lean mass (kg)	55.6 (12.4)	54.0 (11.0)	0.2299
Insulin inverse (mL/μU)	0.045 (0.027)	0.047 (0.037)	0.7956
Insulinogenic index (μU/mL per mg/dL)	2.04 (2.18)	1.12 (2.08)	<.0001

Table 2

Prevalence of Metabolic Syndrome (MetS) by Sex, Race/Ethnicity, and Glycemic Status

	Baseline (N=679)		6 Months (N=625)		24 Months (N=545)	
	N and (%)	p-value	N and (%)	p-value	N and (%)	p-value
Overall	515 (75.8%)		472 (75.5%)		418 (76.7%)	
Sex		<.0001		<.0001		<.0001
Female	368 (83.1%)		331 (81.5%)		293 (81.8%)	
Male	147 (62.3%)		141 (64.4%)		125 (66.8%)	
Race/Ethnicity		0.7036		0.4198		0.0038 [#]
Non-Hispanic Black	172 (76.4%)		153 (75.7%)		125 (72.7%)	
Hispanic	205 (76.8%)		190 (77.2%)		187 (82.7%)	
Non-Hispanic White	101 (73.2%)		91 (71.1%)		77 (67.5%)	
Glycemic Status ^{##}						
For those not reaching primary outcome by end of trial [*]						
HbA1c<6.0 %	188 (74.6%)		173 (72.1%)		130 (70.7%)	
HbA1c< 7%	264 (74.4%)		228 (70.8%)		204 (74.2%)	
HbA1c 6.0% – 7.9%	89 (75.4%)		59 (68.6%)		86 (83.5%)	
Reached primary outcome at visit [*]	N/A ^{**}	N/A ^{**}	56 (83.6%)		136 (79.5%)	
Reached primary outcome by end of trial [*]	238 (77.0%)		237 (80.3%)		195 (78.3%)	

^{*} Primary outcome: HbA1c > 8.0% over 6 months or inability to wean from temporary insulin therapy following acute metabolic decomposition^{**} HbA1c<8.0% during pre-randomization run-in period was an eligibility criteria so no possibility for having primary outcome at baseline[#] Non-Hispanic Black vs. Hispanic p-value=0.0164, Hispanic vs. Non-Hispanic White p-value=0.0017, Non-Hispanic Black vs. Non-Hispanic White p-value=0.3514^{##} Only statistically significant difference is for the prevalence of MetS in those who did not reach the primary outcome with HbA1c values of 6.0% – 7.9% versus other HbA1c values at 24 months (p=0.0174)

Table 3

Parental Diabetes

	Maternal Diabetes Status (n=632)			Paternal Diabetes Status (n=494)		
	During pregnancy (D, n=215, 34%)	After pregnancy (A, n=103, 16%)	Never (N, n=314, 50%)	Ever (n=157, 32%)	Never (n=337, 68%)	<i>P-value*</i>
Demographic						
Age at diagnosis (years)	13.3 ± 2.2	14.0 ± 2.1	13.9 ± 2.1	13.6 ± 2.1	13.7 ± 2.2	0.5978
Duration of diabetes (months)	7.6 ± 5.7	8.4 ± 6.3	7.7 ± 5.8	8.4 ± 6.3	7.6 ± 5.8	0.1638
% Male	42.3%	29.1%	31.8%	28.0%	40.4%	0.0073
Race/ethnicity (%) [†]						
Non-Hispanic Black	31.6%	30.1%	33.8%	30.6%	31.2%	0.8833
Hispanic	40.5%	43.7%	37.3%	40.1%	38.9%	
Non-Hispanic White	20.5%	17.5%	23.2%	21.0%	23.1%	
Other	7.4%	8.7%	5.7%	8.3%	6.8%	
Parental (self-report)						
Maternal BMI (kg/m ²)	34.5 ± 9.6	36.0 ± 9.6	33.6 ± 8.7	35.2 ± 9.7	33.6 ± 8.8	0.0777
Maternal age at birth (years)	28.7 ± 6.0	26.3 ± 5.8	25.8 ± 5.7	27.9 ± 6.1	26.7 ± 5.7	0.0302
Paternal age at birth (years)	31.7 ± 7.4	29.5 ± 6.8	28.6 ± 6.5	31.7 ± 8.0	29.1 ± 6.3	0.0001
Anthropometric						
Birth weight at term (g) ‡	3678 ± 788	3386 ± 660	3269 ± 629	3247 ± 765	3351 ± 820	0.3190
BMI z-score	2.3 ± 0.5	2.2 ± 0.5	2.2 ± 0.5	2.2 ± 0.5	2.2 ± 0.5	0.2543
% body fat from DXA	37.5 ± 6.6	38.2 ± 6.2	37.6 ± 5.9	37.9 ± 6.3	37.4 ± 6.3	0.6285
Waist circumference (cm)	107.5 ± 16.4	109.1 ± 15.3	109.5 ± 17.4	109.8 ± 18.2	107.9 ± 15.4	0.0892
Metabolic						
HbA1c (%)	6.2 ± 0.8	6.1 ± 0.7	5.9 ± 0.7	6.1 ± 0.8	6.0 ± 0.7	0.0241
(mmol/mol)	44.2 ± 8.5	42.6 ± 7.8	40.8 ± 7.6	43.3 ± 8.2	41.5 ± 7.8	
Fasting blood glucose (mg/dL)	116.1 ± 26.8	114.6 ± 25.9	105.4 ± 21.7	111.4 ± 25.4	110.1 ± 24.9	0.5071
2-hour blood glucose (mg/dL)	217.3 ± 66.8	213.4 ± 60.5	190.4 ± 60.6	209.7 ± 61.7	199.2 ± 64.2	0.1076