Rapid Rise in Hypertension and Nephropathy in Youth With Type 2 Diabetes

The TODAY clinical trial

TODAY Study Group*

OBJECTIVE—Among adolescents with type 2 diabetes, there is limited information regarding incidence and progression of hypertension and microalbuminuria. Hypertension and microalbuminuria assessments made during the TODAY clinical trial were analyzed for effect of treatment, glycemic control, sex, and race/ethnicity.

RESEARCH DESIGN AND METHODS—A cohort of 699 adolescents, 10–17 years of age, <2 years duration of type 2 diabetes, BMI ≥85%, HbA_{1c} ≤8% on metformin therapy, controlled blood pressure (BP), and calculated creatinine clearance >70 mL/min, were randomized to metformin, metformin plus rosiglitazone, or metformin plus intensive lifestyle intervention. Primary study outcome was loss of glycemic control for 6 months or sustained metabolic decompensation requiring insulin. Hypertension and microalbuminuria were managed aggressively with standardized therapy to maintain BP <130/80 or <95th percentile for age, sex, and height and microalbuminuria <30 μg/mg.

RESULTS—In this cohort, 319 (45.6%) reached primary study outcome, and 11.6% were hypertensive at baseline and 33.8% by end of study (average follow-up 3.9 years). Male sex and higher BMI significantly increased the risk for hypertension. Microalbuminuria was found in 6.3% at baseline and rose to 16.6% by end of study. Diagnosis of microalbuminuria was not significantly different between treatment arms, sex, or race/ethnicity, but higher levels of HbA_{1c} were significantly related to risk of developing microalbuminuria.

CONCLUSIONS—Prevalence of hypertension and microalbuminuria increased over time among adolescents with type 2 diabetes regardless of diabetes treatment. The greatest risk for hypertension was male sex and higher BMI. The risk for microalbuminuria was more closely related to glycemic control.

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Adults with type 2 diabetes and poor glycemic control are at increased risk for the development of microvascular complications involving the kidney that are exacerbated by comorbid hypertension. In the U.S. and Puerto Rico, over 116,000 adults began treatment for end-stage renal disease (ESRD) in 2009, and the two leading causes were diabetes and hypertension, with incident rates of ESRD increased among African American, Native American, and Hispanic populations (1). Data from the UK Prospective Diabetes Study (UKPDS) and other adult studies have addressed the impact of intensive treatment of hyperglycemia and hypertension on the development and progression of diabetic nephropathy (2–5).

The natural history of diabetic nephropathy and hypertension in youth with type 2 diabetes has not been established. Cross-sectional studies in high-risk adolescent type 2 diabetes populations have found microalbuminuria in 18–72% of patients within 10 years of diabetes (6). Youth with type 2 diabetes have significantly higher rates of microalbuminuria as well as increased incidence and progression of nephropathy when compared with type 1 diabetic patients with similar diabetes duration (7). It is likely that a higher degree of insulin resistance contributes both to a diagnosis of type 2 diabetes at a younger age and to early microalbuminuria and hypertension. Predictors of susceptibility to nephropathy as well as longitudinal data on renal disease occurrence and progression in youth with type 2 diabetes are needed. The multicenter Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial recruited youth from a wide cross-section of geographic and ethnic populations to provide a cohort representative of the target population. The large and well-characterized cohort of adolescents with type 2 diabetes participating in TODAY provided an opportunity to examine the prevalence, incidence, and risk factors associated with the development of incident hypertension and microalbuminuria. The associations of hypertension and microalbuminuria with diabetes treatment, glycemic control, BMI, sex, and race/ethnicity were analyzed.

RESEARCH DESIGN AND METHODS

TODAY randomized clinical trial

Rationale, design, and methods have been reported in detail (8). Beginning in July 2004 and ending in February 2009, 699 participants were randomly assigned to metformin monotherapy (M), metformin plus rosiglitazone 4 mg twice daily (M+R), or metformin plus an intensive lifestyle intervention program (M+L). Eligibility criteria included 10–17 years of age with type 2 diabetes according to American Diabetes Association criteria for <2 years,

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A slide set summarizing this article is available online.
*A complete list of the members of the TODAY Study Group can be found in the Supplementary Data online. The members of the writing group are listed in the APPENDIX.
The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the respective Tribal and Indian Health Service Institutional Review Boards or their members.

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BMI ≥85th percentile, negative diabetes autoantibodies, fasting C-peptide >0.6% ng/mL, and an adult caregiver willing to support study participation. Subjects were excluded for refractory hypertension, defined as blood pressure (BP) ≥150/95 mmHg despite appropriate medical therapy, or a calculated Cockcroft and Gault creatinine clearance <70 mL/min (9). Study medication arms were masked to investigators, study personnel, and participants. The primary objective was to compare treatment arms on time to treatment failure, i.e., loss of glycemic control defined as HbA_{1c} ≥8% for 6 months or sustained metabolic decompensation requiring insulin. Secondary aims included comparison of hypertension and microvascular complications. Participants received standardized treatment for confirmed hypertension and/or microalbuminuria. The protocol was approved by the institutional review boards of all participating institutions, and informed consent was obtained.

Measurement procedures, diagnostic criteria, and treatment

BP (using a CAS 740 monitor with standardized oscillometric cuff sizes) was measured at baseline and at study visits every 2 months in the first year and quarterly thereafter, and BP percentile was calculated based on age, sex, and height (10). All participants received initial standardized dietary education provided by trained staff. Participants with BP ≥90th percentile for age, sex, and height on two consecutive visits were instructed to eliminate added salt to cooked foods and to reduce foods high in sodium content. Hypertension was defined as an average systolic or diastolic BP ≥130/80 mmHg or ≥95th percentile for age, sex, and height measured on at least two consecutive study visits and one interim visit. Once hypertension was confirmed, pharmacologic treatment with a single ACE inhibitor began. Additionally, the elimination of added salt to cooked foods and the reduction of foods high in sodium content were reinforced with a recommendation to decrease caloric intake by 500 kcal/day and to increase activity. Diagnostic testing for new-onset hypertension included routine urinalysis, blood urea nitrogen, and creatinine to screen for renal-related disease. Coarctation of the aorta was excluded by palpation of femoral pulses and measurement of BP in both legs. Treatment of hypertension with initial lisinopril ACE therapy was titrated according to standardized algorithms to achieve BP <130/80 mmHg or <95th percentile for age, sex, and height.

Urine microalbumin was measured and GFR was calculated at baseline and annually thereafter unless a result was abnormal. Microalbuminuria was defined as an albumin-to-creatinine ratio of ≥30 μg/mg on two of three urine samples collected over a 3-month minimal period (9). Confirmed repeat urine albumin-to-creatinine ratios ≥30 μg/mg were required to initiate ACE therapy using the study protocol for lisinopril ACE therapy with protocol-driven dosage adjustments made until the albumin-to-creatinine ratio fell to <30 μg/mg at a consecutive visit. Annual microalbumin measurements were obtained thereafter on ACE therapy.

Additional medications were added as needed after maximal ACE therapy at the discretion of the local study clinician, applying a TODAY study treatment–recommended algorithm for adding calcium channel blocker, diuretic, and/or angiotensin receptor blocker therapy. Treatment was monitored by a safety oversight process using central data to enhance study site compliance and consistency with treatment protocols.

Treatment was altered for elevation of liver enzymes or pregnancy. Study investigators blinded to the treatment arm reviewed all BP and urine results and tracked their treatment to assure adherence to the standardized algorithms. Safety and risk management were monitored by an independent data and safety monitoring board appointed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Laboratory methods

Samples were processed immediately according to standardized procedures and shipped on dry ice for analysis at the TODAY central biochemical laboratory (8).

Statistical methods

The proportion of participants with hypertension or microalbuminuria was computed overall and by study treatment arm, sex, and racial/ethnic group; effects were analyzed using a χ^2 test. The minimal differences in incidence rates of hypertension or microalbuminuria between treatment groups during the study allowed for further analysis of other factors contributing to these complications (Fig. 1*A* and Fig. 2*A*). Risk of developing hypertension or microalbuminuria was assessed in separate models using time-to-event analysis with the log-rank test. Participants were considered at risk from study enrollment until either diagnosis (hypertension or microalbuminuria) or the last visit date on which a measurement (BP or urine microalbumin) was collected; data for six participants who elected to undergo bariatric surgery were included up to the day of surgery. Participants with hypertension or microalbuminuria at baseline were excluded from all time-to-event analyses. A multivariate Cox proportional hazards model analysis was applied to assess the simultaneous effects of time-dependent and fixed covariates. HbA_{1c}, BMI, and glycemic failure were analyzed as time-dependent covariates, baseline age as a continuous variable, and other covariates (treatment arm, sex, and race/ethnicity) as categorical variables. There was too little variation in pubertal status to use as a factor in the model (at baseline, 89% had Tanner stage ≥4); age, sex, and race/ethnicity were included as surrogates. The proportional hazards assumption in the Cox model was assessed with graphical methods and with models including time-by-covariate interactions. Madalla's likelihood ratio R^2 was used to estimate the proportion of variation in risk of hypertension or microalbuminuria over time explained by each covariate in the model. $P < 0.05$ is noted as statistically significant; no correction was made for multiple comparisons and results should be considered exploratory. Statistical Analysis Software was used for all analyses (SAS version 9.2, 2008; SAS Institute Inc., Cary, NC).

RESULTS

Participant characteristics

The demographic and baseline clinical characteristics of this cohort have been reported in detail (8). In brief, mean age was 14.0 (SD 2.0), 64.7% were female, 32.5% were non-Hispanic black (NHB), 39.7% were Hispanic (H), 20.3% were non-Hispanic white (NHW), and mean time since diagnosis of type 2 diabetes was 7.8 months (SD 5.8). At baseline, distribution across treatment arms was equally balanced with respect to sex, race/ethnicity, age, BMI, and HbA_{1c}. After an average follow-up of 3.9 years (range 2–6.5), 319 (45.6%) reached the primary outcome; median time to treatment failure was 11.5 months. M+R was superior to M (failure rates 38.6 and 51.7%, respectively; $P = 0.006$), and M+L was intermediate (46.6%) but not

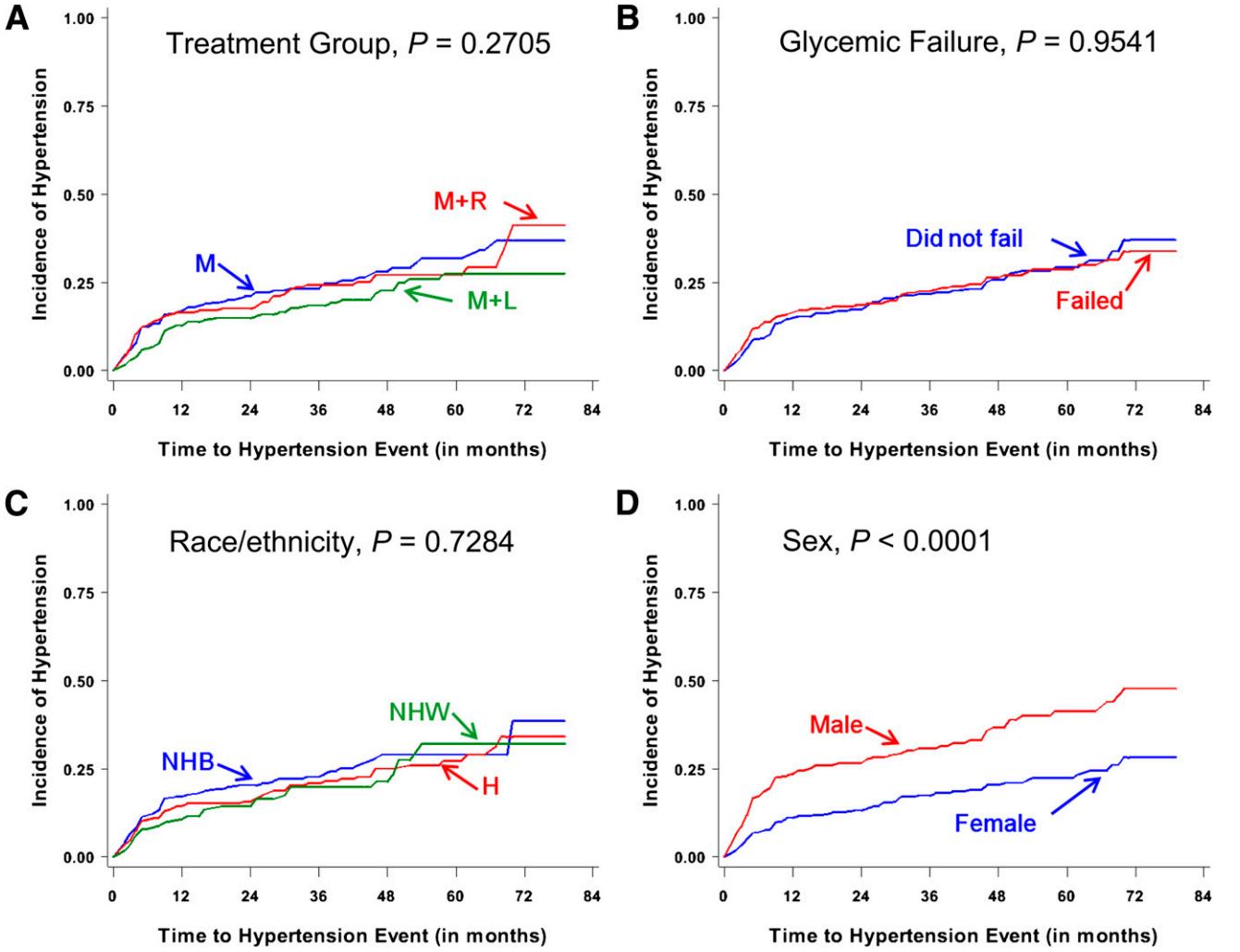

Figure 1—*Cumulative incidence curves for time to diagnosis of hypertension during TODAY by treatment group* (A)*, occurrence of glycemic failure* (B)*, race/ethnicity* (C)*, and sex* (D)*.*

different from M (11). BMI was equivalent among treatment groups at baseline, with the greatest increase in M+R and the smallest in M+L.

The prevalence of hypertension and microalbuminuria at baseline and new incident cases diagnosed over equivalent person-years of follow-up are shown in Table 1.

Hypertension

Overall, the prevalence of hypertension increased from 11.6% at baseline to 33.8% by end of study; 155 of the 618 participants who had normal BP at baseline developed hypertension during the study. There was no significant difference at baseline in the prevalence of hypertension across treatment arms. The lowest baseline prevalence of hypertension was in H (7.9%) compared with 13.7% in NHB (P = 0.0480) and 17.6% in NHW (P = 0.0039). The percentage of new cases of hypertension diagnosed was significantly increased in males versus females (P = 0.0001). Figure 1 shows cumulative incidence curves by subgroups; the sexes were significantly different ($P < 0.0001$) but not treatment, race/ethnicity, or occurrence of glycemic failure.

In multivariate analysis of hypertension (Table 2), male sex, age at baseline, and BMI significantly affected risk of hypertension. On average, males were at 81% greater risk than females of developing hypertension (P = 0.0005). A participant 1 year older than another at baseline was at 14% greater risk on average (P = 0.0038). A participant with a 1 kg/m^2 greater BMI than another at any point in time was at 6% greater risk on average ($P <$ 0.0001). Treatment, race/ethnicity, HbA_{1c}, and occurrence of glycemic failure were not associated with development of hypertension. The proportion of variation explained in the model (R^2) reflects the contribution of the three significant factors.

Microalbuminuria

At baseline, there were no significant differences in prevalence of microalbuminuria by sex or race/ethnicity; baseline cases of microalbuminuria were significantly different between M and M+R (9.1 and 3.4%, respectively; P = 0.0126). Overall the prevalence of microalbuminuria increased from 6.3 to 16.6% by the end of the study, and incidence of new cases was equivalent across treatments, sex, and race/ethnicity (Table 1 and Fig. 2). Figure 2 shows a significant difference between the group that experienced glycemic failure versus the group that did not (overall incident rates 16.0 and 5.5%, respectively; $P < 0.0001$).

Multivariate analysis of microalbuminuria (Table 2) showed that HbA_{1c} as a time-dependent covariate was the only

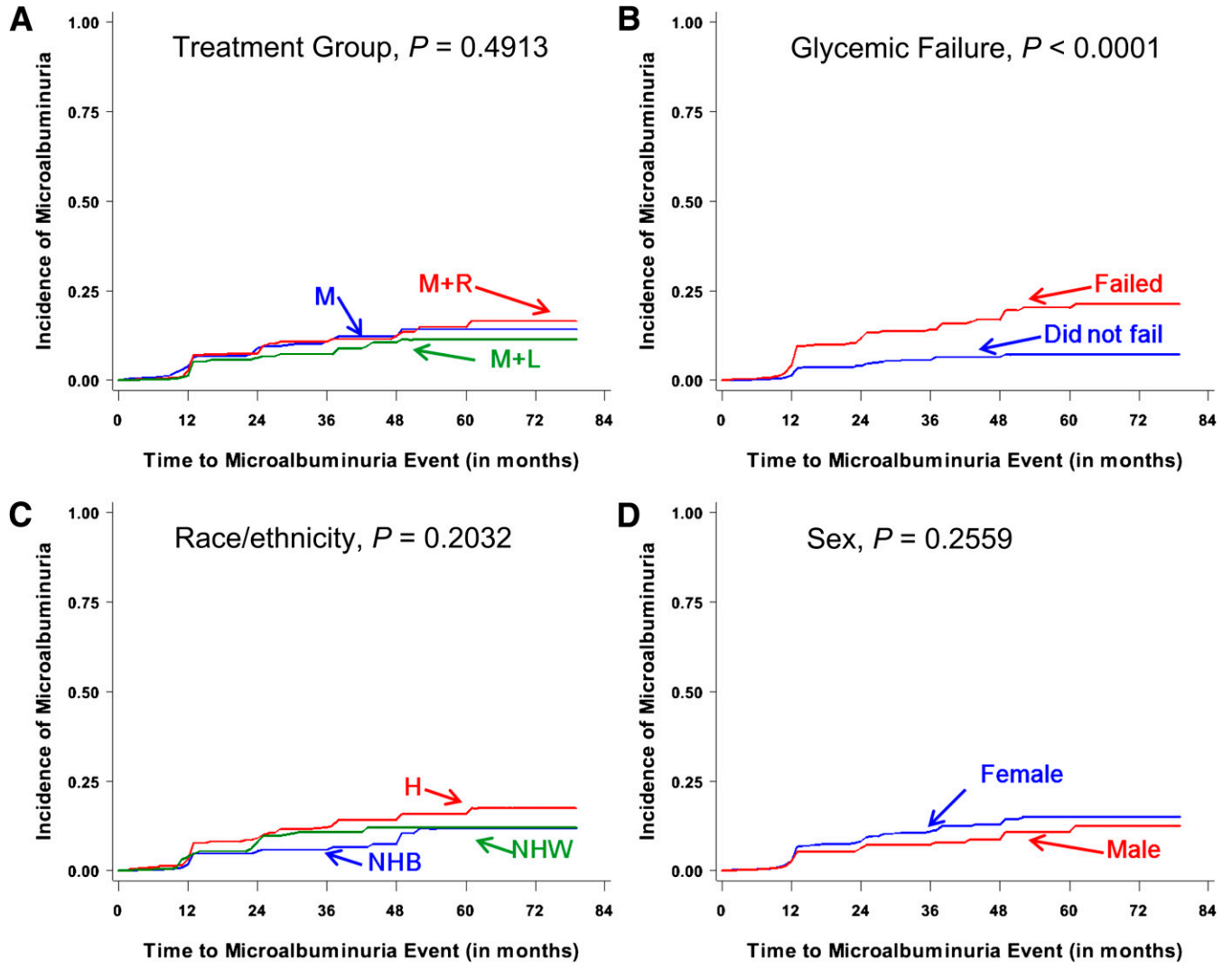

Figure 2—*Cumulative incidence curves for time to diagnosis of microalbuminuria during TODAY by treatment group* (A)*, occurrence of glycemic failure* (B)*, race/ethnicity* (C)*, and sex* (D).

factor significantly associated with risk of microalbuminuria ($P = 0.0300$); on average, there was a 17% increase in risk for every 1% increase in HbA_{1c}. Glycemic failure, which by itself was significantly related to MA, was not significant in the presence of HbA_{1c}, which largely defined the study outcome of glycemic failure.

There were 57 participants who developed confirmed macroalbuminuria (≥300 μg/mg creatinine), and one-third (12) of those progressed to proteinuria (≥1,000 μg/mg creatinine). Overall, less than 1% of the participants progressed to a calculated Cockcroft and Gault creatinine clearance <70 mL/min.

Treatment of hypertension and microalbuminuria

A smaller percentage of females than males in the TODAY cohort required initial ACE inhibitor for hypertension (27.7 and 45.0%, respectively). In contrast, a slightly higher percentage of females than males required initial ACE therapy for microalbuminuria (17.7 and 14.6%, respectively). The median lisinopril dosage requirements at month 24 of the study were 20 mg/day in females and 30 mg/day in males (80 mg/day maximum dose per study algorithm). Of 205 on ACE therapy for hypertension and/or microalbuminuria, 79 (38.5%) required maximal therapy.

CONCLUSIONS—In TODAY, more than 1 in 10 participants had hypertension very early in the course of type 2 diabetes, and this rose to one-third of participants over an average of only 3.9 years in the study. As has been reported in adolescents without diabetes, male sex and increasing BMI were the primary factors that correlated with the development of hypertension (13). Neither poor metabolic control nor race/ethnicity or study treatment arm was significantly associated with the development of hypertension in this cohort.

Over one-third of those initially treated with ACE inhibitor required multiple medications. Hypertension may be particularly resistant to treatment in youth with type 2 diabetes as it is secondary to obesity and may be worsened by progressive vascular injury due to diabetes (14). Although pharmacologic treatment of obesity (e.g., metformin) can address insulin resistance, successful weight management needed to manage hypertension was rare in the TODAY cohort. In contrast, better glycemic control reduced the risk of developing microalbuminuria.

A little over 6% of the participants had microalbuminuria at the start of the study (within 2 years of type 2 diabetes diagnosis), and the prevalence of microalbuminuria nearly tripled after an average follow-up of less than 4 years.

The relationship between glycemic control and microalbuminuria in recently diagnosed TODAY participants is consistent with the findings of the adult UKPDS cohort. The prevalence of microalbuminuria in TODAY at baseline was 6.3%, with an average HbA_{1c} of 5.9%. The UKPDS enrolled adults with newly diagnosed type 2 diabetes and had a similar baseline prevalence of 6.5% microalbuminuria (urinary albumin concentration of 50–299 mg/L) but higher HbA_{1c} of 7.08% (2,3). The incidence of newly diagnosed microalbuminuria in TODAY was 10.3% within an average follow-up of 3.9 years, or an approximate annual rate of 2.6%. The UKPDS participants had an annual rate of progression from microalbuminuria to proteinuria of 2.8%, progression from proteinuria to end-stage renal failure of 2.3%, and a 33% reduction in relative risk of microalbuminuria or proteinuria with more intensive blood glucose control (2,3). In contrast to the 81% white European UKPDS cohort, the TODAY cohort had a multiethnic composition reflecting the known disproportionately higher risk of type 2 diabetes in minority children (15–17). However, despite reported ethnic variances in diabetic nephropathy, the TODAY results do not suggest a major role of race/ethnicity in the early development of microalbuminuria in youth with type 2 diabetes (18).

Microalbuminuria may precede the development of type 2 diabetes in insulin-resistant obese adolescents, with increasing evidence for obesity/metabolic syndrome–related glomerulopathy (11,19,20). Complex type 2 diabetes kidney milieu alterations associated with type 2 diabetes underlie the initial hyperfiltration and glomerular basement membrane thickening seen in patients at risk for nephropathy progression (21,22). Growth factors and insulin resistance during adolescence may accelerate this process (23,24). Identifying and better understanding the factors that increase nephropathy risk or progression are crucial to improving outcomes in youth diagnosed with type 2 diabetes (25–29). A recent comprehensive review of adult randomized controlled trials between 1960 and 2012 reporting major cardiovascular or renal outcomes reinforced the importance of renin-angiotensin system blocker therapy in patients with type 2 diabetes who have an enhanced risk for cardiovascular disease (30). Similar reports regarding early hypertension and renal comorbidities associated with type 2 diabetes in youth are limited (9,11,26).

The TODAY cohort is the largest and most carefully studied group of youth and adolescents with type 2 diabetes to date. The strengths of the TODAY clinical trial were enrollment of participants soon after diagnosis of type 2 diabetes, administration of early aggressive therapy for type 2 diabetes, hypertension, and microalbuminuria, and the careful, comprehensive, prospective monitoring of subjects over 2–6.5 years of follow-up. Initial observations in this longitudinal study suggest differences in the risks for hypertension and microalbuminuria in this cohort. Treatment outcomes of youth and adolescents with type 2 diabetes are confounded by challenges of dietary and medication adherence, insulin resistance, and the pubertal hormonal milieu that contribute to the anticipation of increased lifetime diabetes complication risks in this population. These data underscore the worrisome prognosis for developing complications of hypertension in youth with type 2 diabetes, especially in light of a "best case" scenario of study-provided comprehensive diabetes care delivered in a clinical setting without interruptions of medical resources or barriers to care.

The TODAY trial provided generous staff support that helped to address the anticipated challenges of adherence and other therapy barriers in this psychosocially challenged cohort of youth and adolescents (31). Without these advantages, higher rates of hypertension and microalbuminuria might have been observed. Even with the resources to encourage consistent early lifestyle modification and the provision of medications for glycemic control and aggressive ACE therapy, there was a progressive threefold increase in the prevalence of both hypertension and microalbuminuria. Limitations of this study were the practical need to accept urine specimens that were not always collected as first morning samples. Study medication adherence did not differ across treatment arms or by sex, but specific data regarding adherence to ACE inhibitor therapy were not collected.

In view of high rates of hypertension (33.8%) and microalbuminuria (16.6%) in youth with new-onset type 2 diabetes

Table 1—*Hypertension and microalbuminuria at baseline and during study by treatment group, sex, and race/ethnicity*

	Overall (n = 699)	Treatment group				Sex			Race/ethnicity			
		M (n = 232)	M+R (n = 233)	M+L (n = 234)	P	Female (n = 452)	Male (n = 247)	P	NHB (n = 227)	H (n = 278)	NHW (n = 142)	P
Hypertension												
At baseline	11.6% (81)	12.1% (28)	11.6% (27)	11.1% (26)	0.9492	10.0% (45)	14.6% (36)	0.0682	13.7% (31)	7.9% (22)	17.6% (25)	0.0102[a]
During study	22.2% (155)	24.6% (57)	22.7% (53)	19.2% (45)	0.3697	17.7% (80)	30.4% (75)	0.0001	22.9% (52)	21.9% (61)	19.0% (27)	0.6678
Microalbuminuria												
At baseline	6.3% (44)	9.1% (21)	3.4% (8)	6.4% (15)	0.0444[b]	6.4% (29)	6.1% (15)	0.8583	6.6% (15)	7.2% (20)	5.6% (8)	0.8312
During study	10.3% (72)	10.8% (25)	11.6% (27)	8.5% (20)	0.5343	11.3% (51)	8.5% (21)	0.2475	7.9% (18)	12.2% (34)	9.9% (14)	0.2799

[a]Pairwise comparison showed NHB vs. H P = 0.0480 and H vs. NHW P = 0.0039. [b]Pairwise comparison showed M vs. M+R P = 0.0126 was the only significant difference.

Table 2—*Multivariate model hazard ratios for hypertension and microalbuminuria*

Characteristics (reference group or unit change[a])	Hypertension				Microalbuminuria			
	HR[b]	95% CI	*P*	R^{2c}	HR[b]	95% CI	*P*	R^{2c}
Treatment group (M)								
M+R	1.00	(0.68–1.46)	0.9816	<0.1%	1.07	(0.61–1.87)	0.8199	<0.1%
M+L	0.89	(0.59–1.33)	0.5559	0.1%	0.77	(0.42–1.41)	0.3939	0.1%
Male	1.87	(1.34–2.60)	0.0002	2.2%	0.68	(0.40–1.15)	0.1502	0.3%
Race/ethnicity (NHW)								
NHB	1.06	(0.65–1.73)	0.8147	<0.1%	0.54	(0.26–1.12)	0.0983	0.4%
H	0.93	(0.59–1.49)	0.7774	<0.1%	1.13	(0.59–2.15)	0.7084	<0.1%
Age at baseline (1 year)	1.13	(1.04–1.24)	0.0050	1.3%	0.98	(0.87–1.11)	0.7694	<0.1%
HbA_{1c} (1%)[d]	1.05	(0.93–1.18)	0.4274	0.1%	1.17	(1.03–1.33)	0.0150	0.9%
BMI (1 kg/m^2)[d]	1.06	(1.04–1.08)	<0.0001	4.5%	1.02	(0.99–1.05)	0.2356	0.2%
Glycemic failure (did not fail)[d]	1.09	(0.60–1.97)	0.7784	<0.1%	1.94	(0.95–3.97)	0.0685	0.5%

[a]Reference groups are specified for categorical covariates and unit changes are given for continuous ones. [b]Hazard ratio (HR) for specified unit change or respective to reference group, where <1 indicates less risk at follow-up and >1 indicates more risk at follow-up. [c]R^2 indicates the proportion of variance explained by a covariate in estimating the diagnosis. For hypertension, the model R^2 = 10.6%, and for microalbuminuria R^2 = 5.5%. [d]HbA_{1c}, BMI, and glycemic failure were analyzed as time-dependent covariates.

in the TODAY study, the long-term impact of type 2 diabetes and its comorbidities on the future progression to clinically important diabetic nephropathy, cardiovascular disease, and ESRD is of great concern. The epidemic of youth with type 2 diabetes is an emerging global issue with many unanswered questions and minimal guidance for evidence-based clinical strategies. The continued longitudinal follow-up of this multiethnic, young, type 2 diabetes cohort will provide much needed data on the natural history and trajectory of progression to proteinuria and the development of associated cardiovascular and renovascular disease. More importantly, these data highlight the malignant effect of developing youth-onset type 2 diabetes and emphasize the need for primary prevention of obesity starting at a very young age.

APPENDIX—The members of the writing group are as follows: Jane Lynch (chair), MD, University of Texas Health Science Center at San Antonio; Laure El ghormli, MS, George Washington University Biostatistics Center; Lynda Fisher, MD, Children's Hospital Los Angeles; Samuel S. Gidding, MD, Nemours Cardiac Center; Lori Laffel, MD, Joslin Diabetes Center; Ingrid Libman, MD, PhD, Children's Hospital of Pittsburgh; Laura Pyle, PhD, George Washington University Biostatistics Center; William V. Tamborlane, MD, Yale University School of Medicine; Sherida Tollefsen, MD, St. Louis University Health Sciences Center; Ruth S. Weinstock, MD, PhD, State University of New York Upstate Medical University; and Phil Zeitler, MD, PhD, University of Colorado Denver.

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J.L., L.P., and P.Z. researched data, contributed to the discussion, and wrote, reviewed, and edited the manuscript. L.E. researched data and reviewed and edited the manuscript. S.S.G., L.L., and W.V.T. researched data, contributed to the discussion, and reviewed and edited the manuscript. I.L. contributed to the discussion and reviewed and edited the manuscript. S.T. and R.S.W. reviewed and edited the manuscript. L.F. researched data. L.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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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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