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Complications and comorbidities of T2DM in adolescents: findings from the TODAY clinical trial

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Summary

With the rise in childhood obesity, type 2 diabetes mellitus (T2DM) has been recognized to occur in adolescents with increasing frequency. Although much is known about T2DM in adults, few studies have examined the treatment and complications of T2DM in youth. The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study was designed to evaluate the efficacy of various treatments and provided a unique opportunity to study the disease progression and appearance of complications in a pediatric cohort with recent onset of the disease. In the TODAY study, hypertension was present in 11.6% of the population at baseline and increased to 33.8% by the end of the study. Prevalence of high-risk LDL-cholesterol rose from 4.5% at baseline to 10.7% at the end of the study. Microalbuminuria was found in 6.3% of the cohort at baseline and increased to 16.6%. Retinopathy was not assessed upon entry into TODAY, but was present in 13.9% of the TODAY cohort at the end of the study. Experience to date indicates that these complications and comorbidities are similar to that seen in adults, but occur on an accelerated timeline. The early manifestation of diabetes complications in youth-onset T2DM suggests that this group will be burdened with the tangible consequences of cardiovascular disease, nephropathy, and retinopathy in the third and fourth decades of life. It is hoped that through an early, aggressive approach to treatment and prevention, we may be able to curb the onset and progression of these potentially devastating outcomes.

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Introduction

The prevalence of obesity has rapidly increased in the last century (1), and now ranks as one of the major causes of morbidity and mortality in the industrialized world.(2) Based on CDC criteria, obesity has risen among children to its current prevalence of ~17% (this is slightly higher then WHO criteria), and disproportionately affects ethnic minorities.(3) The upsurge in childhood obesity is paralleled by an increase in diseases previously seen almost exclusively in adult populations, such as hypertension, dyslipidemia, and type 2 diabetes (T2DM).(4) In the SEARCH for Diabetes in Youth study, the prevalence of T2DM in 2009 was estimated to be 0.46 per 1000, a 35% increase compared to 2001 data.(5) Analysis of the prevalence of T2DM by ethnicity was estimated to be 0.17, 0.79, 1.06, and 1.20 per 1000 among 10- to 19-year old non-Hispanic (NH) whites, Hispanics, NH blacks and American Indians, respectively.(5) Based on the most current data, T2DM accounts for 3% of all diabetes cases among white youth, but 23% among Hispanics, 25% among NH blacks and 64% among American-Indians in the United States.(5)

Although numerous studies have addressed management of diabetes and its comorbidities in adults, few studies have examined the impact of T2DM in youth. The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) was designed to begin to address these issues. The primary goal of the study was to examine the effect of three different treatments (metformin alone, metformin plus rosiglitazone, and metformin plus intensive lifestyle modification) on the durability of glycemic control.(6) The primary outcome of the TODAY study was time to treatment failure defined as either HbA1c ≥ 8% over a 6-month period or the inability to wean from insulin therapy within 3 months after an acute metabolic decompensation.(6)

The study included 699 participants 10–17 years of age diagnosed with T2DM using the prevailing ADA criteria with illness duration of 2 years or less at the time of enrollment.(6) Other inclusion criteria were a BMI ≥ 85% and fasting C-peptide > 0.6 ng/mL with absence of pancreatic autoantibodies.(6) Exclusion criteria included renal or hepatic insufficiency, uncontrolled hypertension, and hypercholesterolemia despite appropriate therapy.(6) The occurrence of comorbidities such as cardiovascular risk factors, microvascular complications, and quality of life were assessed at standard intervals throughout the study to determine the impact of diabetes control as well as other factors on their prevalence and severity.(6)

Of the 699 participants in the TODAY study, 319 (45.6%) reached the primary endpoint (glycemic failure) over an average follow-up time of 3.86 years.(7) Failure rates for all of the treatment arms were high (51.7% in the metformin only group, 38.6% in the metformin plus rosiglitazone group, and 46.6% in the metformin plus intensive lifestyle group), demonstrating the aggressive nature of youth-onset T2DM.(7) Metformin plus rosiglitazone was superior to metformin alone, while metformin plus lifestyle modification was not different from either of the other two groups, suggesting that multiple drug therapy may be necessary early in the disease process for youths with T2DM.(7)

The goal of this review is to describe the complications and comorbidities of T2DM observed during the TODAY study. Although the incidence of various complications and comorbid conditions has been established in adults (8–12), very few studies have examined comorbidities in youth-onset type 2 diabetes, and none have done so in the context of a randomized treatment trial. The following is a comprehensive review of these findings from the study.

Cardiovascular Risk Factors

Previous studies have established T2DM as a major independent risk factor for cardiovascular disease.(13) According to the Framingham cardiovascular risk assessment, T2DM is equivalent in risk to an increase in age of 10 years in adults, and when combined with other risk factors (e.g., dyslipidemia, hypertension), T2DM increases the risk of cardiovascular disease by an additional three to four fold above that predicted for each risk factor alone.(14) Cardiovascular disease is a major contributor to morbidity and mortality in the United States, and the leading cause of death among people with T2DM. In a small Australian cohort of adolescents with T2DM, Ruhayel and colleagues found that 15 out of 27 (56%) met the criteria for dyslipidemia defined as total cholesterol ≥ 5.2mmol/L (15) and/or triglycerides ≥ 1.7 mmol/L (16).(17) In a study of 153 youth with T2DM in Canada, 60% had elevated total cholesterol, 41% had elevated LDL-cholesterol, and 51% had elevated triglycerides defined as a level >75%ile.(18) From the SEARCH for Diabetes in Youth study, about 2/3 of the youth with T2DM had elevated triglycerides and low HDL. (19) Each of the studies used a different method to define dyslipidemia. The TODAY study assessed risk factors using lipid profiles, inflammatory markers, and echocardiograms as described below.

Lipid Profiles

After an overnight fast of at least 10 hours, blood was collected for measurement of total plasma cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, and apoB. Lipid profiles were assessed at baseline (N=699), 6 and 12 months (N=512) and then annually (N=404 at 24 months and N=264 at 36 months). The lipid goals defined by the study protocol were LDL cholesterol <100 mg/dL and triglycerides <150 mg/dL. Elevated LDL (≥130 mg/dL) and triglycerides (300–599 mg/dL) were treated by study staff with a dosage escalation of atorvastatin, if 6 months of nutrition counseling and intensified diabetes management were unsuccessful. For triglycerides ≥600mg/dL a fibrate could be added.(6)

At baseline 4.5% of participants had LDL ≥130mg/dL or were using lipid-lowering drugs, and this rose to 10.7% by 36 months. Although 47 (6.7%) subjects began lipid-lowering medications during the trial, only 21% of those treated (10) achieved the LDL goal. Only 55.9% of the 517 participants with complete lipid profiles were always at the goal LDL. Across the entire cohort, diabetes treatment assignment did not have an impact on LDL cholesterol, but LDL rose with HbA1c independent of treatment group.

Similar trends were observed in LDL, triglycerides, apoB, LDL particle size and non-HDL cholesterol, all of which rose over time across the cohort with a few notable treatment effects. Triglycerides were lower in the group receiving intensive lifestyle intervention

(N=234), and small, dense LDL was more common in the metformin only group (N=232) than in either of the combined treatment groups. Triglycerides rose with HbA1c in the metformin and metformin plus rosiglitazone groups (N=233), but HbA1c was not associated with triglycerides in the group receiving intensive lifestyle intervention.(20) When considering differences in lipid profiles based on race, non-Hispanic black (N=227) (NHB) had lower triglycerides than the Hispanic (N=278) (H) or non-Hispanic white (N=142) (NHW) groups, and NHB had significantly lower percent with small dense LDL than H and NHW. Finally, the percent of females (N=452) (87.6%) who had HDL levels below the high-risk cut-off of 50 mg/dL was greater than the percent of males (N=247) with high-risk levels (65.6%), similar to what is reported in the SEARCH study.(19, 20) This difference may be attributed to the lower cut off in males (<40 mg/dL).(20)

Inflammatory Markers

Plasma was collected at the same time points as lipid profiles (N for each time point is the same as above) for measurement of inflammatory factors [high-sensitivity c-reactive protein (hsCRP), homocysteine, and plasminogen activator inhibitor-1 (PAI-1)], which generally rose across the cohort throughout the trial. Forty-one percent of participants had high-risk hsCRP levels at baseline (defined as >0.3mg/dL) and this proportion increased slightly but significantly at 36 months (41.2% at baseline and 46.3% at 36 months; P=0.0217).(20) In contrast to these other inflammatory markers, non-esterified fatty acids (NEFA) initially dropped at 12 months but returned to near baseline levels at 24 and 36 months.(20)

With regard to the impact of treatment group, hsCRP decreased in the group that received metformin plus rosiglitazone (N=233) between baseline and 12 months (P<0.0001) and remained lower than the other two treatment arms (N=232 in the metformin group and N=234 in the metformin plus lifestyle intervention).(20) Homocysteine was higher (P=0.0002) in the metformin plus rosiglitazone group compared with the other two treatment arms.(20)

Sex and racial-ethnic difference were also observed. hsCRP rose in females (N=452) from baseline to 36 months (P=0.0059), as opposed to males (N=247) who did not have a significant change from baseline. NHW (N=142) had lower hsCRP than Hispanic (N=278) (P=0.0171) and NHB (N=227) (P=0.0059).(20) Homocysteine was higher in males (P<0.0001), and PAI-1 was higher in Hispanic than NHB (P<0.0001) and NHW (P=0.0480). (20) NEFA was higher in females compared to males (P=0.0114) and in NHW than NHB (P=0.0034) and Hispanic (P=0.0150).

Echocardiography

Echocardiography assessing left ventricular and atrial dimensions, left ventricular mass and left ventricular ejection fraction was performed at the end of the study on the 455 participants still actively involved in the study. The majority (83.8%) of this young cohort (mean age = 18 years) had normal left ventricular architecture, while 8.1% had increased left ventricular wall thickness, 4.5% had increased left ventricular mass, and 3.6% had both. In regression analysis, changes in left ventricular architecture were related to obesity and systolic blood pressure as they are in the non-diabetic population. Baseline HbA1C was

related to higher left ventricular mass and left ventricular wall thickness. Age, diabetes control, and treatment group assignment were not associated with left ventricular structure. (21)

Renal Complications and Hypertension

The leading causes of end-stage renal disease in the United States are diabetes and hypertension, and diabetic kidney disease continues to increase in prevalence in concert with the increasing prevalence of diabetes.(22)

Hypertension (defined as blood pressure ≥ 130/80 mmHg or ≥ 95% for age, height, and sex on at least three confirmed blood pressure reading) at presentation in adolescents with T2DM has been reported to be between 10–32%.(23) In a study Australian youths with T2DM, 9 out of 30 (30%) had hypertension at diagnosis.(17) In a cohort of children from New South Wales, 21 out of 58 (36%) of subjects had a blood pressure >95th percentile for age and sex as defined by the U.S. Task Force Report.(24) From the SEARCH for Diabetes in Youth study, of the 95 participants with T2DM, 65.63% had hypertension.(19)

Although the pathogeneses of T1DM and T2DM differ, the renal manifestations are very similar. In the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC), the cumulative incidence of nephropathy in individuals with T1DM was 25% in the conventional treatment group and 9% in the intensive treatment group after diabetes duration of 30 years, reflecting the impact of intensive therapy over time.(25) The natural history of nephropathy in adults with T2DM suggests about 2% progress from normal renal function to microalbuminuria each year and 2% progress from microalbumnuria to clinical grade proteinuria.(9) As is the case for T1DM, where the DCCT demonstrated a 59% reduction in risk for microalbuminuria and 86% reduction in the risk for new albuminuria by intensive therapy (26, 27), tight blood glucose control also significantly reduces the risk of developing nephropathy in T2DM, as demonstrated by 33% reduction in nephropathy over a 12-year period in the UKPDS.(9) In a cohort of 1148 patients in the UKPDS trial, tight blood pressure control (defined as below target blood pressure of 150/85 mmHg) using captopril or atenolol also delayed the development of renal disease in T2DM.(9)

Cross-sectional data from children with T2DM suggest that 18–72% of these patients have microalbuminuria within 10 years of diagnosis and that the incidence and progression of nephropathy is increased relative to progression rates observed in T1DM.(28) In an Australian cohort of adolescents, 9 out of 20 (45%) were found to have abnormally high microalbumin.(17) In another group of 68 adolescents in Australia with T2DM, 7% had microalbuminuria at presentation which increased to 28% over about a 2 year period.(24) In a cohort of 105 children with T2DM in New Zealand, 72% developed microalbuminuria after a three year period.(29) From the SEARCH study, 22% of T2DM subjects (average age 16.2 years and diabetes duration of 1.9 years) had abnormal albumin to creatinine ratios compared to 9.2% in the T1DM population (average age 11.9 years and diabetes duration 3.7 years).(30) Although these cross-sectional data are alarming, very few studies have assessed the longitudinal progression of renal disease in children diagnosed with T2DM.

To address this knowledge gap, the TODAY study assessed the progression of nephropathy over the course of the trial by measuring blood pressure, serum creatinine (to calculate glomerular filtration rate (GFR) using the Cockcroft-Gault equation), and urine protein excretion.

Hypertension and Treatment in TODAY

Blood pressure was measured at baseline, every 2 months during the first year of the study, and quarterly thereafter. Hypertension was defined as blood pressure ≥ 130/80 mmHg or ≥ 95% for age, height, and sex consistently over at least three confirmed blood pressure readings meeting the above criteria with additional evaluation to rule-out other etiologies. Once the diagnosis of hypertension was confirmed, dietary intervention consisting of elimination of added salt to cooked foods and reduction in foods high in sodium content was implemented. In addition, a dose escalation scheme for the ACE inhibitor, lisinopril (supplied by the study), was used to achieve a blood pressure goal of < 130/80 mmHg or < 95% for age, height, and sex whichever was the lower value. Additional medications (e.g., calcium channel blockers, diuretics, and/or angiotensin receptor blockers) were employed when lisinopril was ineffective at 80 mg/day.(31)

The prevalence of hypertension at baseline (N=699) was 11.6% and increased to 33.8% after approximately 3.9 years of follow-up, similar to the reports in Australian youth with T2DM.(17, 24, 31) Males (N=247) had an 81% higher risk of developing hypertension than females (N=452).(31) Hispanic race (N=278) had the lowest prevalence of hypertension compared to NHB (N=227) (P=0.0480) and NHW (N=142) (P=0.0039).(31) Sex, BMI and age at baseline (but not treatment group, glycemic failure or race/ethnicity) were associated with the development of hypertension.(31) Of 205 subjects starting lisinopril for hypertension, 79 (38.5%) required the maximum dose and over one-third required additional medications.(31)

Microalbuminuria and Treatment in TODAY

Urine microalbumin and creatinine were measured on a random urine sample and GFR was calculated using the Cockcroft-Gault equation at baseline and annually thereafter. Microalbuminuria was defined as a microalbumin-to-creatinine ratio of ≥30μg/mg on 2 of 3 consecutive urine samples collected over a period of at least three months. Once microalbuminuria was confirmed, lisinopril was initiated and titrated to achieve an albumin-to-creatinine ratio of < 30μg/mg.(31)

The prevalence of microalbuminuria at baseline (6.3%) was similar to that reported in large adult cohorts soon after diagnosis.(31) The metformin treatment group (N=232) had more microalbuminuria (9.1%) at baseline than to the treatment group with metformin and rosiglitazone (N=233) (3.4%, P=0.0126).(31) The incidence of newly diagnosed microalbuminuria during TODAY was 10.3% over an average follow-up of 3.9 years, for a rate of 2.6% per year, which is comparable to that seen in adults.(9, 32) By the end of the study, the prevalence of microalbuminuria was 16.6%, with incidence increasing disproportionately in the participants experiencing glycemic failure compared to those who did not (16.0% vs. 5.5%, respectively; p< 0.0001), but was not different with regard to treatment group, sex or race.(31) The only identified risk factor for the development of

microalbuminuria was HbA1c, analyzed as a time-dependent covariate.(31) Overall, 57 subjects developed macroalbuminuria (≥ 300mcg/mg creatinine), and of these 1/3 progressed to frank proteinuria (≥ 1,000mcg/mg creatinine).(31)

Ophthalmologic Complications

Diabetic retinopathy (the leading cause of blindness in Americans age 20–74) is characterized by gradual alterations in the microvasculature that disrupt retinal perfusion by increasing vascular permeability. Diabetic retinopathy has four stages: mild nonproliferative retinopathy, moderated nonproliferative retinopathy, severe nonproliferative retinopathy, and proliferative retinopathy. The ultimate consequence of this process when unchecked is vascular proliferation that disrupts retinal function resulting in vision loss.(33) Approximately 4.1 million of the 10.1 million adults 40 years and older with diabetes have some form of retinopathy, with 1 in 12 of those having advanced disease.(34)

During the UKPDS study of T2DM in adults, 63% of subjects without pre-existing retinopathy developed microaneurysms and 29% of those already with retinopathy showed progression within 6 years.(12) The incidence and progression of retinopathy in these adults with T2DM were related to HbA1c, systolic blood pressure, and smoking history.(12)

In a subset of the SEARCH study, 42% out of 43 individuals with T2DM (average age 21.1 years and time since diagnosis 7.2 years) had some form of retinopathy compared to 17% of 222 individuals with T1DM (average age 16 years and time since diagnosis 6.8 years).(35) However, in a smaller study of Australian youths (average age 15.3 years and duration of diabetes 1.3 years), only 1 out of 25 assessed had retinopathy.(24) Another study from Australia found that 4 out of 16 children (25%) with T2DM had abnormal findings on a retinopathy scan.(17) The disparate prevalence of retinopathy between these studies may be related to the subjects' age and disease duration. Heretofore, no studies have evaluated the prevalence of retinopathy in the first several years after youth-onset T2DM. The TODAY study provided a unique opportunity to examine this crucial time period, and assess the impact of intensive management of T2DM in youth on the development of retinopathy.

Retinopathy in TODAY

During the last year of the TODAY study, digital fundus photographs with seven standard stereoscopic fields that were readable in at least one eye were obtained from 517 participants (average age = 18.1 ± 2.5 years; diabetes duration = 4.9±1.5 years).(36) Of these, 71 (13.7%) had early retinopathy, with 64 having very mild nonproliferative retinopathy (defined by the presence of either microaneurysms, or intraretinal hemorrhage, or cotton wool infarct), and 7 participants had nonproliferative retinopathy with both microaneurysms and intraretinal hemorrhage or cotton wool infarct.(36) None of the participants had macular edema, advanced nonproliferative retinopathy, or proliferative retinopathy.(36) Not surprisingly, those with retinopathy were older, had longer duration of diabetes and higher mean HbA1c (8.3 ± 1.8% vs. 6.9 ± 1.6%) compared to participants without retinopathy.(36) Retinopathy was not affected by treatment group, sex or ethnicity.(36)

Psychosocial Functioning

Psychosocial functioning has been shown to have an impact on one's ability to self-manage a chronic disease, such as diabetes.(37) Studies in adults with T2DM have shown that major depression is associated with increased risk of microvascular complications, even after controlling for disease severity and self-care activities.(11) In a meta-analysis of 20 adult studies (3 with T1DM only, 8 with T2DM only, and 9 with both T1DM and T2DM subjects), the odds of depression in people with diabetes were twice that found in a non-diabetic comparison group.(8) There is cause for heightened concern about depression in youth-onset type 2 diabetes, as 20% of adolescents will have a depressive disorder before they are 20 years old and early-onset depression is associated with a chronic, episodic course of illness.(38) As is the case with depression, eating disturbances have also been associated with poor metabolic control and early onset of diabetes complications, specifically retinopathy, in women and adolescents with T1DM.(39) Although the most common eating disorders reported in individuals with T1DM are anorexia nervosa and purging behaviors (39, 40), binge eating disorders are more common in T2DM.(41, 42) In one study of adults with T2DM, 8.3–11.9% of women and 4.6–5.8% of men suffered from an eating disorder, with the most common being binge eating disorder.(42) Very few previous studies have examined the prevalence of depression or disordered eating in youth with T2DM. The TODAY study cohort provides a unique opportunity to address the unanswered questions regarding psychosocial functioning in this at-risk group.

Depression Symptoms in TODAY

To assess depressive symptoms in the TODAY cohort at baseline, 687 participant completed the Children's Depression Inventory (CDI) for those 15 years and younger and the Beck Depression Inventory II (BDI-II) for those 16 years and older. The CDI evaluates the presence and severity of depressive symptoms by self-report. A cutoff score of ≥ 13 identified clinically significant depressive symptoms.(43) The BDI-II is a 21-item self-report measuring the severity of depression. A cutoff score of ≥ 14 identifies clinically significant depression and a score ≥ 29 is suggestive of "severe" depression.(44) Subjects were excluded from participation in the TODAY study if they had a clinical diagnosis of major depressive disorder or were taking psychotropic medications.(45) From these two inventories, 14.8% of the cohort reported depressive symptoms above the threshold for clinical significance at baseline, with significantly more females (N=452) reporting depressive symptoms than males (N=235). The sex difference was marked in the group over age 15 (22.8% in females vs. 4.1% in males; $p<0.001$).(45) There were no apparent differences in these trends across race/ethnicity, and depression scores were inversely correlated with quality of life as assessed by the Pediatric Quality of Life inventory.(45)

Binge Eating in TODAY

Eating disorder symptoms were assessed in TODAY study participants at baseline using the Youth Eating Disorder Examination Questionnaire (YEDE-Q). The YEDE-Q was designed to assess eating disorder psychopathology, particularly binge eating.(46) Subjects were placed into one of four eating categories based upon their response to two questions ("How many times [over the past 28 days] have you eaten what other people would think was a

really big amount of food, given the situation?" and "On how many of these times did you feel like you had lost control while eating?") assessing objective overeating episodes and loss of control during those episodes.(46) Binge eaters were those reporting ≥ 4 overeating episodes with a loss of control, while subclinical binge eaters reported 1–4 episodes of binge eating, and overeaters reported ≤ 1 episode of overeating with no loss of control. Of the 678 respondents, 24% reported binge eating 1–4 times during the previous 28 days, and 6% reported 4 or more episodes during the previous 28 days.(47) Clinical binge eaters (N=42) were more obese, as measured by BMIz-score and percent overweight, than overeaters (N=164) and non-overeaters (N=337) and had greater global eating, weight, and shape concerns.(47) Clinical binge eaters also had more depressive symptoms, while clinical and subclinical binge eaters (N=135) had lower quality of life than non-overeaters.(47) No significant differences were found with regard to sex, race, or glycemic control.(47)

Summary of Findings

The TODAY study is the first and only large-scale, randomized trial to assess the impact of intensive therapy on youth-onset T2DM. Metformin alone resulted in durable glycemic control in only half of the participants over a 5-year period, but a combination of metformin and rosiglitazone improved the durability of glycemic control.(7) From the ADOPT trial in adults, the treatment failure on metformin and rosiglitazone monotherapy over a 5-year period were 21% and 15%, respectively.(48) This suggests that progression of youth-onset T2DM has a more aggressive course than when diagnosed in later life. As the future role of rosiglitazone as a treatment option for T2DM is unclear, the less durable effect of metformin alone on glycemic control raises tangible concern over the development of comorbidities in patients presenting with type 2 diabetes at a young age.

TODAY was among the first efforts to assess the complications and comorbidities of T2DM in an adolescent population. Given the known link between diabetes complications and glycemic control, the design of the TODAY study (with the primary outcome being durability of glycemic control) was well suited to assess complications in youth with T2DM. The prevalence of microalbuminuria tripled in an average follow-up of less than 4 years.(31) Retinopathy was present in 13.9% of the TODAY study cohort.(36) Over an average of 3.9 years follow-up in the study, one-third of the TODAY participants had a medical diagnosis of hypertension with one-third of those requiring more than one medication for control.(31) The cohort also reported depression and disordered eating which, in turn, adversely affect weight and diabetes control.(41, 45) (See Table 1) The treatment group had an impact on triglycerides, hsCRP and homocysteine, but none of the other complications or comorbidities.(20, 26, 31, 36, 45, 47) While some of the complications and comorbidities may have been affected by treatment options during the trial, the overall frequency and progression of diabetes complications and comorbidities observed in the TODAY study cohort portend an ominous fate for children and adolescents diagnosed with T2DM.

Gregg and colleagues recently reported an overall decline in diabetes-related complications in adults.(49) While rates of complications in adults may be declining, prevalence of diabetes is increasing, resulting in a continued burden of disease related to diabetes. It is known that complications increase with duration of disease and decline in metabolic control.

From SEARCH data, 27% of youth with T2DM were found to have poor glycemic control (A1C ≥ 9.5%) and longer disease duration was associated with poor control.(50) Despite the individualized attention the youth received in the TODAY study, metabolic decompensation and treatment failure occurred in less than for 4 years for one-third to one-half of the cohort depending on treatment group.(7) Given this, along with the potential for longer disease duration in this population, a secular trend toward increasing complications arising from youth onset T2DM seems inevitable. From projections based on SEARCH data, by the year 2050, T2DM in persons under the age of twenty could increase by 49% to 178%, depending on the model used, resulting in increased health care needs and costs.(51) T2DM can be prevented with appropriate lifestyle modification. Although the TODAY study has shown that in youth-onset T2DM, a combination of therapies may be required early in the disease progression to maintain glycemic control (7), emphasis must also be placed on primary prevention of obesity in an attempt to bypass progression to T2DM and its seemingly inevitable complications.

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Table 1

Complications and Comorbidities during TODAY

	Baseline	End of Study
Elevated LDL	4.5	10.7
Elevated Triglycerides	21	23.3
Elevated hsCRP	41.2	46.3
Hypertension	11.6	33.8
Microalbuminuria	6.3	16.6
Retinopathy		13.7
Depression	14.8	
Binge Eating	6.2	

Percentage of TODAY study participants experiencing complications and comorbidities at baseline and end of study. All numbers are reported as percentages.