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Youth-Onset Type 2 Diabetes: What We've Learned From Key Youth-Onset Type 2 Diabetes Studies, What We Still Don't Know, and Why It Is Important

Kristen J. Nadeau, Elizabeth J. Mayer-Davis, Rose Gubitosi-Klug, Philip S. Zeitler, Steven E. Kahn, and Dana Dabelea, on behalf of the SEARCH, TODAY, RISE, and DISCOVERY study groups

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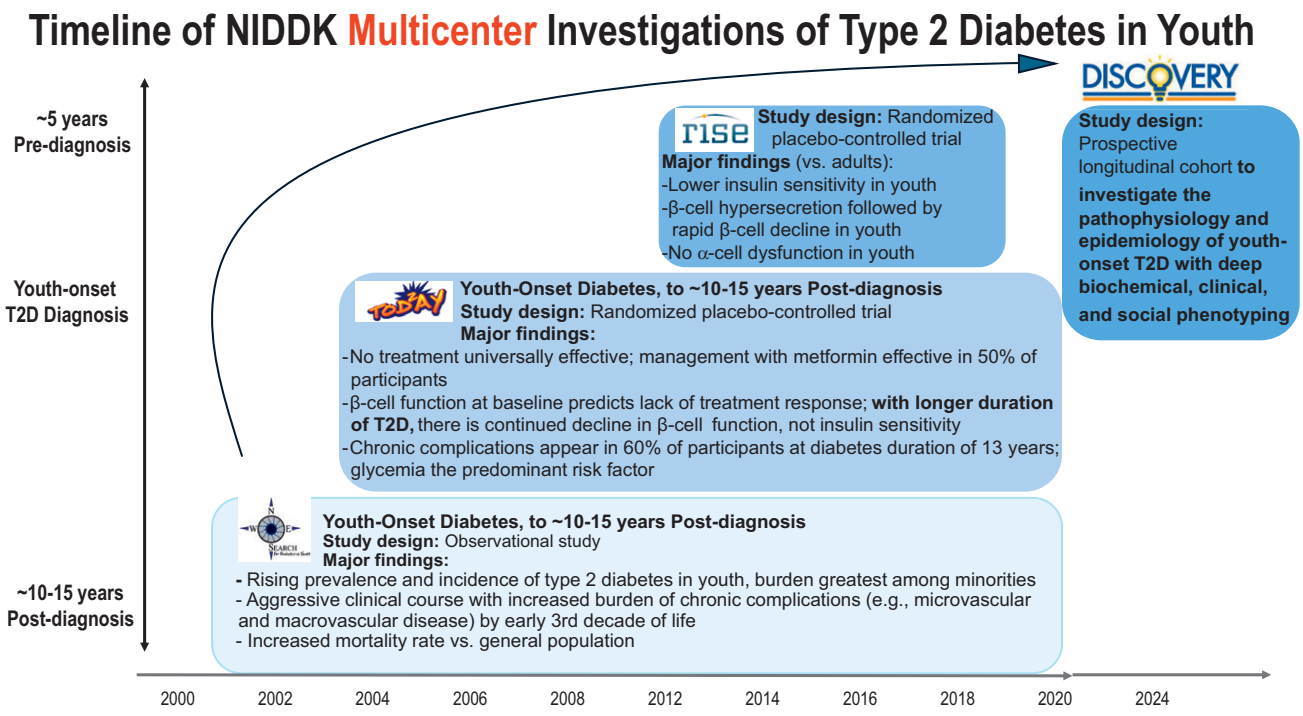

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  To review landmark National Institute of Diabetes and Digestive and Kidney Diseases–funded youth-onset type 2 diabetes studies, beginning when type 2 diabetes was first recognized as a new pediatric condition.
- **What is the specific question(s) we wanted to answer?**
  What is unique about youth-onset type 2 diabetes, and how can these findings inform current best practice and help with identification of knowledge gaps to direct future research?
- **What did we find?**
  Youth-onset type 2 diabetes is increasingly common, especially among girls and underserved racial and ethnic groups, and is tied to pubertal insulin resistance; there is rapid onset of β-cell failure; and there is poorer response to lifestyle and medication interventions and higher burden of complications in comparison with those in adult-onset and youth-onset type 1 diabetes.
- **What are the implications of our findings?**
  A better understanding of the pathophysiology and triggers of youth-onset type 2 diabetes is needed.

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Kristen J. Nadeau,[1] Elizabeth J. Mayer-Davis,[2] Rose Gubitosi-Klug,[3] Philip S. Zeitler,[1] Steven E. Kahn,[4] and Dana Dabelea,[5] on behalf of the SEARCH, TODAY, RISE, and DISCOVERY study groups

In this review, we describe the epidemiology, pathophysiology, pediatric-specific treatment response data, morbidity, and mortality of youth-onset type 2 diabetes. In recognition of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) 75th anniversary, the focus is primarily on data from three landmark youth-onset type 2 diabetes studies funded by the NIDDK in the last 20+ years. We discuss the now-recognized aggressive clinical course of youth-onset type 2 diabetes, which only recently became appreciated as a pediatric disease among health care providers. We highlight the similarities and differences between youth-onset and adult-onset type 2 diabetes, in particular how type 2 diabetes in youth appears to have an accelerated clinical course with earlier onset of complications in comparison with adult-onset type 2 diabetes; how these findings influenced the care and treatment recommendations for youth with type 2 diabetes; and how the many lessons from these studies, in turn, highlight remaining unanswered questions. We feature recent findings regarding long-term follow-up of diabetes complications in these youth, and how they differ from youth with type 1 diabetes. Finally, we conclude with an overview of emerging studies and topics in type 2 diabetes research that have potential to inform effective preventive action strategies.

YOUTH-ONSET TYPE 2 DIABETES: A NEW DISEASE

Until the 1980s, pediatric diabetes was considered almost exclusively type 1, autoimmune-mediated, insulin-dependent diabetes (1). However, a novel form of diabetes resembling "adult-onset type 2 diabetes" increasingly was noted among youth (2–5). Recognizing fundamental knowledge gaps regarding the epidemiology, pathophysiology, and clinical course of this new form of pediatric diabetes, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) launched several multicenter studies: *1*) the SEARCH for Diabetes in Youth (SEARCH) study (collaboratively developed and funded by the Centers for Disease Control and Prevention [CDC]), to describe the epidemiology, monitor trends, develop projections, and evaluate complication risks (6); *2*) the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study (7), to understand the pathophysiology and identify best treatment options; and *3*) Restoring Insulin Secretion (RISE), to directly compare pathophysiology and treatment responses of youth-onset and adult-onset type 2 diabetes (8). A brief description of these studies can be found in Table 1. Over

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the past 22 years, these landmark studies advanced our understanding of the disease, shaped current care guidelines, identified further knowledge gaps, and informed the recently-launched NIDDK-funded DISCOVERY of Risk Factors for Type 2 Diabetes in Youth (DISCOVERY) study, to identify and follow high-risk children and inform targeted preventive approaches. On the NIDDK's 75th anniversary, we review the major findings and goals of these studies, which collectively address the NIDDK's mission of improving health for youth with type 2 diabetes in the U.S.

DIAGNOSTIC DILEMMA

Type 2 diabetes is considered clinically among pubertal youth with hyperglycemia plus obesity, a family history of diabetes, and/or metabolic syndrome–associated comorbidities (e.g., low HDL cholesterol, high triglycerides, polycystic ovary syndrome, or metabolic dysfunction–associated steatotic liver disease) (7). However, with rising obesity in all youth, and shared symptomatology between type 1 and type 2 diabetes, initial definitive diabetes typology is challenging, necessitating measurement of diabetes-related autoantibodies (9). For example, among the 1,206 participants considered clinically to have type 2 diabetes screened for TODAY, 9.8% had GAD65 or IA-2 antibodies and 3.9% had both (10,11), and of the 687 TODAY participants screened for ZnT8 antibodies, 0.59% were positive.

The American Diabetes Association (ADA) classification framework (12) was operationalized in SEARCH, to provide standard case definitions for large observational studies, with use of two etiologic markers: autoimmunity (type 1 diabetes–related autoantibodies) and insulin sensitivity (estimated with an equation including HbA_{1c}, triglycerides, and waist circumference, validated against hyperinsulinemic-euglycemic clamps) (13,14). Type 1 diabetes was defined as autoimmune diabetes, regardless of degree of obesity or insulin resistance, and type 2 diabetes as absence of diabetes autoantibodies, plus obesity or markers of insulin resistance (13,15). However, when gold standard measures of insulin sensitivity are performed, youth with type 1 and type 2 diabetes of similar BMI are both markedly and similarly insulin resistant, but those with type 1 usually lack metabolic syndrome features (16–19). Findings of SEARCH showed that provider-assigned diabetes type agreed strongly enough with the etiological phenotype for epidemiologic surveillance but insufficiently for individual-level use; future work is required to allow individual precision medicine approaches.

PREVALENCE ACROSS POPULATIONS

In 2017, SEARCH identified 1,230 youth with type 2 diabetes among 1,848,899 youth ages 10–19 years. The estimated prevalence of 0.67/1,000 represented a 95.3% relative increase over 16 years (20). Minoritized populations carried the largest burden, with the highest prevalence among non-Hispanic Black youth, followed by American Indian, Hispanic White, and Asian/Pacific Islander and then non-Hispanic White youth. Across all race and ethnicity groups, prevalence increased with age and was higher among females than males (0.82 vs. 0.51/1,000) (20). The TODAY cohort reflected similar demographics (21). Figure 1 displays selected worldwide prevalence estimate rankings by region and ethnicity, comprising data from the International Diabetes Federation 2021 IDF Diabetes Atlas (22) and SEARCH (20). Although direct comparisons between countries are difficult, given different diagnostic criteria across studies, these estimates place the U.S. among countries with the highest burden of youth-onset type 2 diabetes.

INCIDENCE TRENDS AND PROJECTIONS

Between 2002 and 2018, SEARCH identified 5,293 youth with newly diagnosed type 2 diabetes aged 10–19 years, in 44 million person-years (23). Few youth age $<$10 years with type 2 diabetes were identified (4% [approximately half of whom were 9 years old]), likely because the insulin resistance of puberty catalyzes disease development. A significant upward trend in age-, sex-, and race- and ethnicity-adjusted incidence rates was observed, from 9.0 cases/100,000/year in 2002–2003 to 17.9 in 2017–2018. The annual rate of increase was 5.3%, highest for the combined Asian/Pacific Islander group (8.92%), followed by Hispanic White (7.17%) and non-Hispanic Black (5.99%) youth (Fig. 2). Peak incidence occurred at age 16 years, with no differences by sex; however, the incidence in non-Hispanic Black youth peaked earlier at 13 years.

With use of SEARCH estimates, a six-fold increase in U.S. youth-onset type 2 diabetes prevalence is predicted by 2050, accounting for anticipated demographic changes, with the greatest increases among minoritized populations—particularly those of non-Hispanic Black or Indigenous backgrounds (24,25). These groups also have the highest overweight and obesity prevalence, portending future trends in other populations, should the obesity epidemic continue (26).

PATHOPHYSIOLOGY OF GLUCOSE METABOLISM IN YOUTH: SIMILAR TO OR DIFFERENT FROM THAT IN ADULTS?

Our understanding of the pathophysiology underlying dysglycemia in youth originates from smaller cross-sectional studies and two large longitudinal studies: TODAY, designed to test whether an aggressive approach to reducing insulin resistance early in the course of youth-onset type 2 diabetes would prolong glycemic control and improve associated risk factors (27), and RISE, with comparison of the effects of matched treatments in youth and adults with prediabetes and recent-onset type 2 diabetes on β-cell function (8).

One common feature in youth and adults with type 2 diabetes is lower insulin sensitivity in muscle, liver, and adipose tissue than in age- and BMI-matched peers without dysglycemia (18). Another shared trait is ectopic fat accumulation that correlates with insulin resistance, including visceral, intramyocellular, and hepatic lipid, and increased circulating nonesterified fatty acids (18). Additional similarities include muscle mitochondrial dysfunction, markers of systemic inflammation, and low cardiorespiratory fitness level and adiponectin (28–31).

However, a prominent feature unique to youth-onset type 2 diabetes, demonstrated by TODAY and RISE, is markedly lower insulin sensitivity than in adult-onset type 2 diabetes. Increased growth hormone secretion is likely a key trigger of this pubertal insulin resistance (akin to pregnancy) (32,33). In pubertal youth with normoglycemia, the hyperbolic relationship between insulin sensitivity and secretion is retained (34–36). However, when pubertal insulin resistance is overlaid on obesity-associated insulin resistance (akin

Table 1—Summary of key NIDDK studies on youth-onset type 2 diabetes

	SEARCH	TODAY	RISE	DISCOVERY
Years of study	2000–2020	2004–2020	2013–2018	2024–in progress
No. of sites	5	15	4 for pediatric, 4 for adult	15
Sample size	7,525 youth with type 1 or type 2 diabetes (1,083 with type 2 diabetes; 428 with longitudinal follow up)	699 youth with type 2 diabetes (~500 participants with longitudinal follow-up)	91 youth (37 type 2 diabetes, 54 prediabetes), 355 adults (251 prediabetes, 104 type 2 diabetes)	3,600 youth
Age-group at enrollment	<20 years	10–17 years	10–19 years for youth, 20–65 years for adults	9–14 years
Pubertal status	Tanner stage 1–5	Tanner stage ≥2	Tanner stage ≥2	Tanner stage ≥2–4
Disease group	Youth-onset type 2 diabetes and youth-onset type 1 diabetes diagnosed clinically and according to etiologic definition	Youth-onset type 2 diabetes, BMI ≥85th percentile, fasting C-peptide >0.6 ng/mL, absence of pancreatic autoimmunity, and negative MODY testing	Youth: BMI ≥85th percentile, youth-onset type 2 diabetes treated with only metformin or prediabetes. Adults: BMI 25–40 kg/m^2, treatment-naive adult-onset type 2 diabetes or prediabetes. Absence of pancreatic autoimmunity for all ages	Youth with overweight and obesity and HbA_{1c} 5.5%–6.4%
Diabetes duration	Prevalent cohort of any duration and inception cohort	<2 years' duration at enrollment	At enrollment: youth, <6 months' duration with or without metformin treatment; adults, duration of <1 year and drug naive	Any duration of high-normal glucose/ prediabetes
Study design	Observational study to assess incidence, prevalence, natural history, and risk factors for acute and chronic diabetes-related complications; quality of care; and quality of life	Randomized placebo-controlled trial to assess effects of glucose-lowering treatments followed by long-term observational study to assess the natural history of insulin sensitivity and secretion and risk factors for acute and chronic diabetes-related complications	Randomized placebo-controlled trial to assess effects of glucose-lowering treatments on insulin sensitivity and secretion	Prospective longitudinal cohort to investigate the pathophysiology and epidemiology of youth-onset type 2 diabetes with deep biochemical, clinical, and social phenotyping
Duration of follow-up	Average 14 years for inception cohort	Average 3.9 years in the clinical trial, average 10.2 years overall	21 months	≥2.5 years
Intervention	n/a	Metformin vs. metformin plus intensive lifestyle vs. metformin plus rosiglitazone	12 months of metformin vs. 3 months of glargine insulin followed by 9 months of metformin	n/a
Key outcomes	Prevalence and incidence of diabetes, chronic complications (retinopathy, nephropathy, neurocognitive function, cardiac echocardiography, cardiac autonomic and peripheral neuropathy, arterial stiffness), acute	Primary outcome: time to glycemic failure (HbA_{1c}). Secondary outcomes: OGTT-based metabolism, psychosocial measures, habitual physical activity, BMI, medications, genetic testing, chronic complications including	Primary outcome: hyperglycemic clamp–based β-cell function. Secondary outcomes: hyperglycemic clamp– and OGTT-based metabolism, HbA_{1c}, BMI	Primary outcome: development of type 2 diabetes (HbA_{1c}). Secondary outcomes: OGTT-derived insulin sensitivity, secretion and clearance, β-cell function, glucose excursions, free fatty acids and lactate flux, and incretin responses;

Continued on p. 1139

Table 1—Continued

	SEARCH	TODAY	RISE	DISCOVERY
	complications (hypoglycemia, DKA), medications, behavioral, psychosocial, medical care, socio-cultural factors, quality of life	microvascular and macrovascular disease (retinopathy, nephropathy, cardiac autonomic and peripheral neuropathy, echocardiography, arterial stiffness, cardiac echocardiography), acute complications (hypoglycemia, DKA), pregnancy complications		CGM results; and BMI. Samples also stored for additional analyses

DKA, diabetic ketoacidosis; HbA_{1c}, glycosylated hemoglobin; MODY, maturity-onset diabetes of the young; n/a, not applicable.

to gestational diabetes mellitus), some youth cannot increase insulin secretion sufficiently and glucose rises into ranges currently defined as prediabetes or type 2 diabetes.

In TODAY, youth were randomized to one of three interventions (metformin alone, metformin plus intensive lifestyle, or metformin plus rosiglitazone) for determination of whether one approach was superior in avoiding sustained hyperglycemia (HbA_{1c} ≥8.0% for >6 months) (21). Disappointingly, none were unequivocally effective, although adding rosiglitazone to metformin reduced the occurrence of sustained hyperglycemia by 23%. Regardless of the intervention, low baseline β-cell function, not insulin sensitivity, predicted rising glucose. Further, over time, a relentless decline in β-cell function, not insulin sensitivity, was observed (37,38).

Given the high rates of β-cell deterioration seen in TODAY, NIDDK funded the RISE

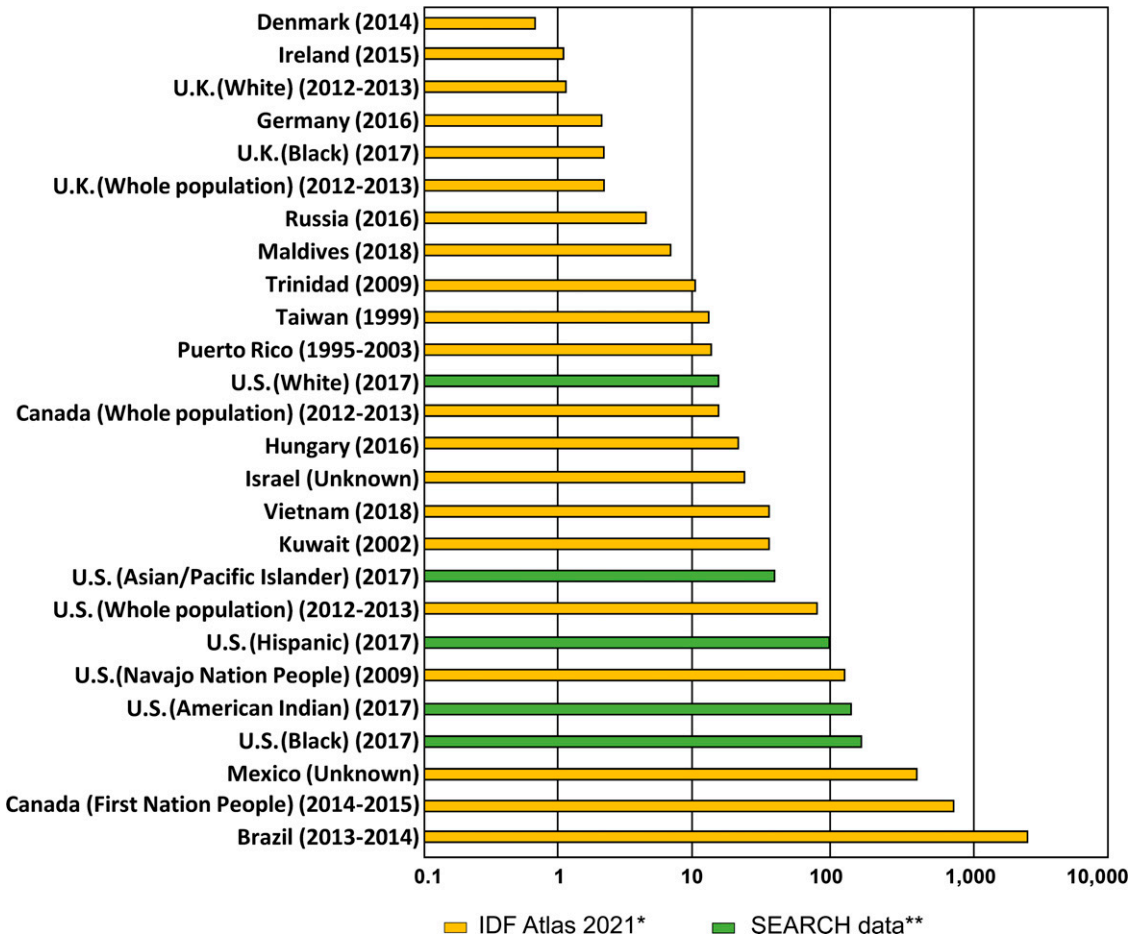

Figure 1—Global prevalence of type 2 diabetes among children and adolescents (age <20 years), per 100,000 (135). *Reproduced with permission from the International Diabetes Foundation (22). **SEARCH data from Lawrence et al. (20).

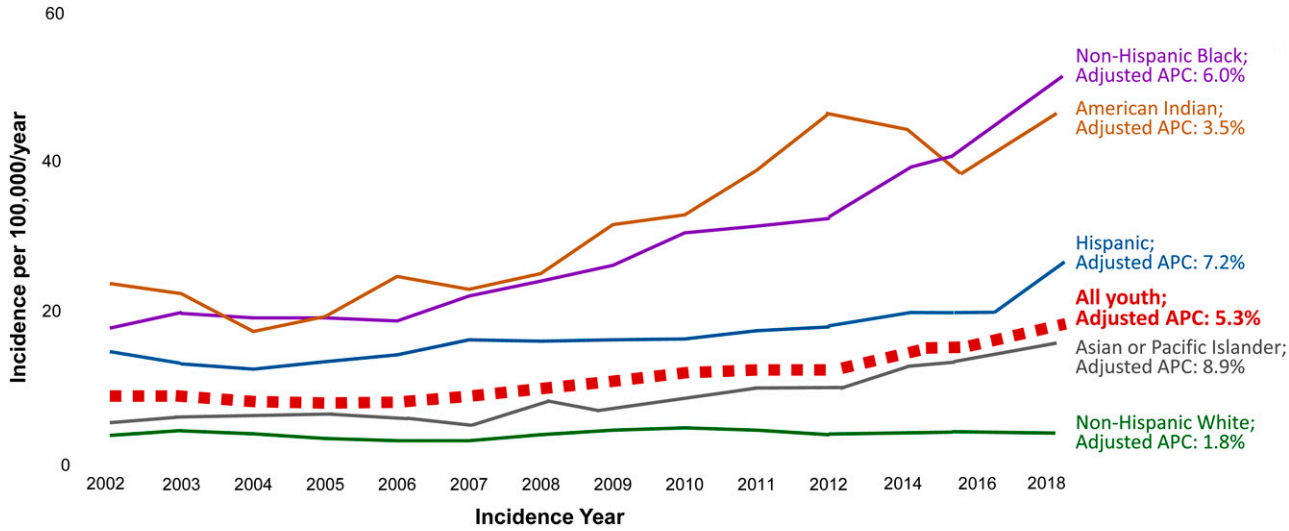

Figure 2—Temporal trends and annual percent change (APC) in incidence of type 2 diabetes among multiethnic U.S. youth between ages 10 and <20 years in the SEARCH study from 2002 to 2018. Annual percent change estimates for all youth are adjusted for age, sex, and race and ethnicity; estimates within racial and ethnic strata are adjusted for age and sex (23,136,137).

Consortium to interrogate earlier interventions designed to preserve or improve β-cell function, in both adults and youth with prediabetes or recently diagnosed type 2 diabetes (8). Both age-groups received either *1*) 3 months of insulin glargine treatment followed by 9 months of metformin or *2*) 12 months of metformin treatment, with a primary outcome of β-cell function assessed with the gold standard hyperglycemic clamp and oral glucose tolerance test (OGTT) at baseline, after 12 months of treatment, and 3 and 9 months following treatment washout. Adults were also randomized to placebo, the glucagon-like peptide 1 receptor agonist (GLP-1RA) liraglutide, or gastric banding. In using the same methodology in both age-groups, RISE allowed direct comparisons between youth and adults, providing novel insights into type 2 diabetes physiology and intervention responses.

At baseline, youth had lower insulin sensitivity and insulin clearance and much greater β-cell secretory responses (acute, steady-state, and maximal C-peptide and insulin responses) than adults (39,40) (Fig. 3*A*–*C*). OGTT-response modeling demonstrated that youth have higher insulin secretion rates and β-cells that are more responsive to glucose than adults, even after adjustment for differences in insulin sensitivity (41), raising the question of whether adolescent β-cells are healthier or whether hypersecretion is pathologic, contributing to more rapid loss of function. In response to both interventions, β-cell function in youth declined markedly over 12 months of treatment, in contrast to adults (Fig. 3*E*), without any significant treatment group differences (42,43), underscoring that youth-onset type 2 diabetes is more aggressive than adult-onset, as hypothesized based on TODAY and SEARCH. This progressive loss of β-cell function in youth was seen in response to glucose secretagogues, affecting both first- and second-phase responses, and nonglucose secretagogues (43). In addition, glycemia worsened, defined according to a HbA_{1c} increase ≥0.5% from baseline, more in youth versus adults in RISE (17.8% and 36% of youth at months 12 and 21 vs. 7.5% and 20% of adults, respectively) (44). Predictors of glycemic worsening included lower β-cell responses in both age-groups, whereas insulin resistance was only predictive in adults, supporting an argument that adults have more phenotypic heterogeneity in predominance of insulin resistance versus β-cell dysfunction, whereas the youth's uniformly high degree of insulin resistance does not contribute to the prediction.

Beyond the β-cells, hyperglucagonemia was also explored in RISE as an explanation for the age-group differences in insulin sensitivity and secretion. Interestingly, there was no evidence of α-cell dysfunction, and if anything, α-cell glucagon release was more effectively suppressed in youth (45). Thus, the age-related differences in type 2 diabetes pathophysiology remain unexplained, with differential loss of β-cell mass or de-differentiation unexplored areas.

Given the differences noted between adult-onset and youth-onset diabetes, investigators from TODAY, SEARCH, and Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic Samples (T2D-GENES) established the Progress in Diabetes Genetics in Youth (ProDiGY) consortium to explore genetic underpinnings (46). Comparison among 3,006 youth with type 2 diabetes, 6,061 diabetes-free adults, and 856 diabetes-free youth identified six known loci and two novel loci (*PHF2* and *CPEB2*), with a stronger association with loci associated with BMI in youth than in adults.

EVOLUTION OF THERAPEUTIC STRATEGIES

Lifestyle and Behavioral

SEARCH and TODAY demonstrated activity and dietary levels below recommended guidelines for youth with type 2 diabetes. SEARCH uncovered low levels of moderate-to-vigorous physical activity and high levels of electronic media use (47) and saturated fat intake (48), and co-occurrence of inactivity and unhealthy diet (49). TODAY revealed higher levels of sedentary behavior than identified among youth from the National Health and Nutrition Examination Survey (NHANES) who had similar BMI but did not have diabetes (50), along with high saturated fat intake (only 1% met ADA guidelines of <7% of calories from saturated fat) (51).

Obesity in young children portends adolescent and adult obesity, necessitating prevention and early intervention, but

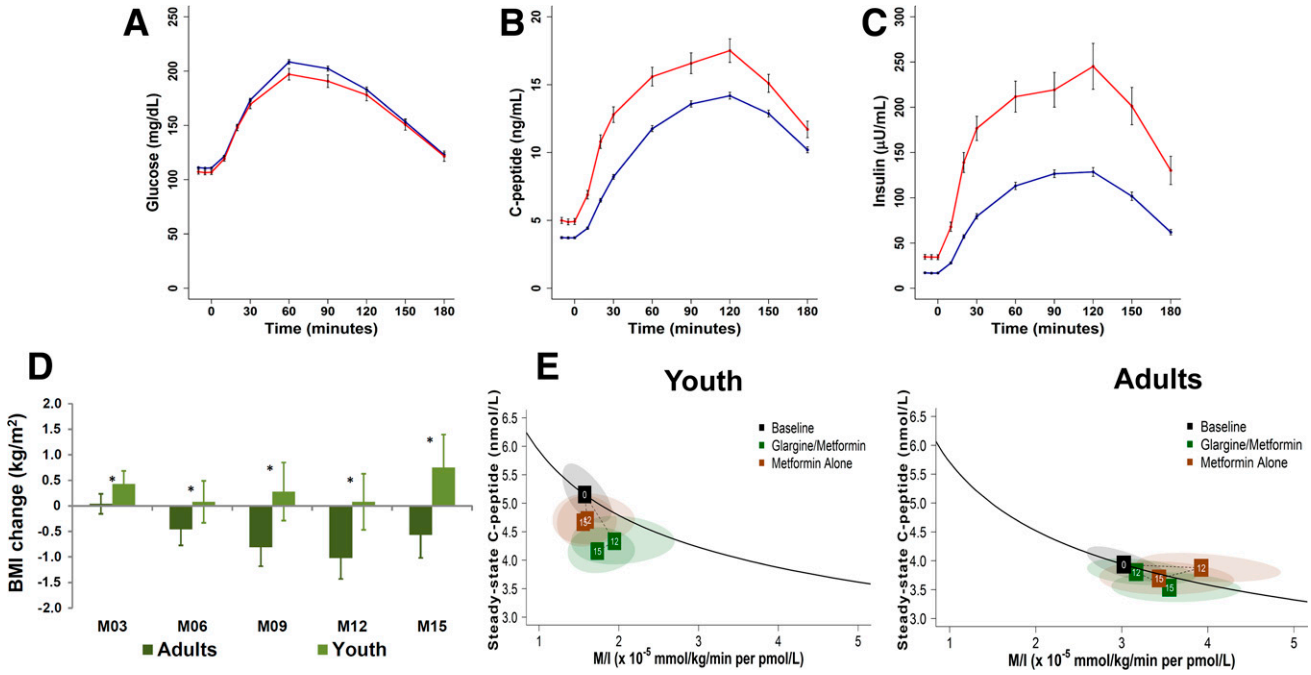

Figure 3—*A–E*: Youth-onset type 2 diabetes differs from type 2 diabetes in adults at baseline and in response to treatments in RISE. *A–C*: Baseline plasma glucose (*A*), C-peptide (*B*), and insulin (*C*) concentrations during OGTT in youth and adults in RISE. Red, youth; blue, adults. Data are means ± SEM. In youth and adults, following glucose ingestion, baseline glucose concentrations were similar, but C-peptide and insulin were higher in youth at all time points ($P \leq 0.009$) (40). *D*: Comparison in changes in BMI from baseline in youth vs. adults in RISE from the insulin glargine followed by metformin arm (dark green, adults; light green, youth). The bars indicate 95% CI. *Significantly different changes in youth vs. adults ($P < 0.05$): weight gain with insulin in youth not seen in adults that persisted despite replacement of insulin with metformin at 3 months. M03 = month 3 (3 months after medication start), M06 = month 6 (6 months after medication start), M09 = month 9 (9 months after medication start), M12 = month 12 (12 months after medication start), M15 = month 15 (3 months after medication withdrawal) (43). *E*: Vector plots illustrating the treatment effects with model-based changes from baseline to 12 and 15 months in hyperglycemic clamp–derived insulin sensitivity (M/I) paired with β-cell response (steady-state C-peptide) from a hyperglycemic clamp in youth and adults in RISE (green, insulin glargine followed by metformin group; brown, metformin alone group). The black line depicts the joint relationship between β-cell response and M/I at baseline for the full cohort within each study, with the mean value at baseline for the full cohort indicated by the black box with a 0. The dotted lines to boxes for months 12 and 15 show the trajectory of values from baseline to 12 months of intervention and then to 3 months after discontinuation of the intervention (15 months). Positioning above the black line represents improved β-cell function and below the line poorer β-cell function. The ellipses depict the 95% confidence bands around the points at months 12 and 15 (43). M/I = glucose infusion rate/serum insulin concentration.

pediatric health education and activity promotion studies to date have shown limited long-term beneficial effects (52,53). TODAY participants received lifestyle education, and one treatment group also underwent an intensive family-based lifestyle intervention. Despite improved 6-month BMI, after an average follow-up of 3.9 years, the intensive lifestyle intervention had no glycemic benefit, similar to results of other lifestyle modification studies in youth-onset type 2 diabetes, and had a weaker effect in girls than in boys (54,55). Males with improved cardiovascular fitness at 6 months had lower HbA_{1c}, but overall lifestyle intervention attendance was only ∼60%, driven by lower exercise participation for girls (21). In contrast, improved 24-month HbA_{1c} occurred among females who reduced saturated fat intake or increased dietary fiber. Thus, evidence suggests potential glycemic benefit from lifestyle changes, with important sex differences; yet, broadly effective and durable intervention strategies remain elusive.

Metformin and Insulin

Metformin remains the first-line treatment for youth-onset type 2 diabetes (56). TODAY's initial run-in phase showed that nearly all recently diagnosed youth tolerate rapid discontinuation of insulin and initially achieve glycemic targets on metformin alone, regardless of initial HbA_{1c} (57). However, sustained hyperglycemia eventually occurred in 51.7% of youth in TODAY on metformin alone (21). While A Diabetes Outcome Progression Trial (ADOPT) was not designed as a direct comparison, meaning caution should be applied in interpretation, in ADOPT, performed in drug-naïve adults with type 2 diabetes with the same duration of metformin as in TODAY, only 12% developed sustained hyperglycemia (21,58)—again suggesting a more aggressive process in youth despite shorter diabetes duration. The incidence of sustained hyperglycemia in TODAY plateaued over time, suggesting the existence of subgroups with rapidly deteriorating glycemia and others who maintain glycemic stability. TODAY also demonstrated that metformin monotherapy is less effective in non-Hispanic Black youth (66.2% with sustained hyperglycemia).

HbA_{1c} foreshadows different outcomes in youth versus adults. $HbA_{1c} \geq 6.3\%$ after initiation of metformin monotherapy predicted sustained hyperglycemia over the first 48 months in TODAY (59), suggesting that treatment escalation was needed earlier in youth, in comparison with the historical ADA target ($HbA_{1c} \geq 7\%$) (60–62). Based on TODAY's findings, the 2025 ADA guidelines now recommend an HbA_{1c} target $<6.5\%$ in youth-onset type 2 diabetes (63). Only a modest improvement in HbA_{1c} ($<0.5\%$) was

observed 6 months after initiation of insulin for sustained hyperglycemia in TODAY, with no significant improvement after a year (mean HbA_{1c} 10.0%) (64), highlighting difficulties in achieving glycemic targets in youth with only metformin and insulin, once β-cell function has declined severely.

In RISE, transient HbA_{1c} reductions occurred in both the metformin plus insulin and metformin monotherapy groups, but HbA_{1c} returned to baseline by 12 months, with no effect on fasting or 2-h glucose. Despite initially more robust β-cell responses in youth than in adults (Fig. 3*A*–*C*), youth had β-cell decline even on treatment (Fig. 3*E*) and weight gain with insulin treatment that persisted despite adding metformin (Fig. 3*D*). In contrast, adults in RISE showed stable β-cell responses (Fig. 3*E*) and HbA_{1c} and weight loss (Fig. 3*D*) with metformin. Thus, RISE extended the findings of TODAY, illustrating that in youth, in contrast to adults, metformin treatment and insulin plus metformin were ineffective in preventing β-cell deterioration in prediabetes or early type 2 diabetes, even when initiated early (41,42,65). Given the weight gain with insulin in RISE youth (66) and its ineffectiveness in correcting hyperglycemia in TODAY (64), early initiation of other glucose-lowering approaches is needed (60–62).

Thiazolidinediones

Adding rosiglitazone to metformin slowed progression to sustained hyperglycemia in the adult Department of Defense (DOD) study (67), similar to rosiglitazone's improvement when added to metformin in youth in TODAY (21). However, sustained hyperglycemia with the combination was still 38.6% in TODAY, versus only 14.3% in DOD (21). In contrast to lifestyle intervention, which preferentially benefited boys, rosiglitazone preferentially benefited girls in TODAY. As expected, subcutaneous adipose tissue increased more with rosiglitazone than with other treatments in TODAY, but surprisingly, visceral adipose tissue also increased more with rosiglitazone (68)—the opposite of reported effects in adults, in whom thiazolidinediones typically decrease visceral adipose tissue despite increasing subcutaneous adipose tissue (69–71). Rosiglitazone is not currently recommended for youth-onset type 2 diabetes due to increased fracture, heart failure, and macular edema risks reported in adults (72) and the diminished rise in bone mineral content and density with rosiglitazone in TODAY (73). However, because rosiglitazone may have improved β-cell function during the first 6 months of TODAY (37), the thiazolidinedione pioglitazone is increasingly now used off-label in youth, with the rationale that the improvement in insulin sensitivity and/or β-cell function observed in adults outweighs theoretical risks (60,74), but more data are needed.

Other Diabetes Medications

While not the focus of the studies highlighted in this article, other medications will be briefly discussed to highlight future directions needed. The sulfonylurea glipizide was found to have glycemic effects similar to those of metformin, but sulfonylureas are currently avoided in youth due to associated hypoglycemia, weight gain (75), and potential β-cell decline (76). No glycemic improvement was shown with dipeptidyl peptidase 4 inhibitors in youth (77–80). Data to date on sodium–glucose cotransporter 2 inhibitors in youth-onset type 2 diabetes show potential renoprotection, but no improvements in BMI or blood pressure, and conflicting short-term glycemic effects (77,78,81). When added to metformin/insulin versus placebo in youth-onset type 2 diabetes, the daily GLP-1RA liraglutide lowered HbA_{1c} by 1.3 percentage points (%-points) (roughly a doubling in achieving HbA_{1c} <7%) (82), weekly exenatide by 0.85%-points (83), and weekly dulaglutide by 1.4%-points (84). Retrospective analyses of real-world GLP-1RA use confirm their glycemic efficacy in youth (85), leading to their designation as the second-line therapy of choice where metformin monotherapy fails to achieve glycemic targets in some pediatric type 2 diabetes guidelines (61,62). However, despite similar effectiveness of weekly semaglutide for weight loss in adolescents without diabetes as adults (86) (16.1% weight loss at 68 weeks vs. 0.6% with placebo), GLP-1RA studies to date in youth-onset type 2 diabetes show minimal BMI improvement (82–84,87), potentially due to more severe insulin resistance or lower medication adherence (76). Enrollment has now been completed for trials in youth-onset type 2 diabetes with weekly semaglutide and the GLP-1RA/gastric inhibitory polypeptide (GIP) receptor agonist tirzepatide, with outcomes pending. Maximal follow-up in pediatric studies to date is also only 68 weeks, leaving remaining questions regarding whether cardiovascular and renoprotective benefits occur in youth, as seen in adults (76).

Metabolic Bariatric Surgery

The NIDDK-funded Teen–Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study demonstrated 27% absolute weight loss with metabolic bariatric surgery (MBS) at 5 years in youth with obesity (88), similar to weight loss rates in adults (89). The limited glycemic data in youth with type 2 diabetes from Teen-LABS are encouraging, with 95% experiencing diabetes remission 3 years post-MBS (88), waning to 55% by 10 years (90), but higher than the 18% and 12% remission rates recently reported among adults at 7 and 12 years post-MBS (89). In the overall Teen-LABS cohort, including youth without diabetes, at 3 years postsurgery there was remission of abnormal kidney function in 86% (57% at 10 years), prediabetes in 76%, elevated blood pressure in 74%, and dyslipidemia in 66% (54% at 10 years) (88,90).

For comparison of effects of MBS with those of medical therapy, youth with type 2 diabetes from Teen-LABS and TODAY were retrospectively examined, with acknowledgments of limitations inherent to retrospective comparisons. During 5 years of follow-up, BMI decreased by 11 units in Teen-LABS versus increasing by 1 unit in TODAY; HbA_{1c} decreased from 6.8% to 5.9% in Teen-LABS versus increasing from 6.2% to 8.8% in TODAY; insulin sensitivity, triglycerides, renal hyperfiltration, and urinary albumin excretion improved in Teen-LABS versus worsening in TODAY (91,92); and there was a suggestion of CVD event reduction in Teen-LABS.

Few data exist for adolescents regarding impacts of MBS on insulin sensitivity and secretion in youth with type 2 diabetes, and most Teen-LABS participants did not have diabetes, were non-Hispanic White, and received gastric bypass (88). Vertical sleeve gastrectomy is overwhelmingly now the most common MBS procedure in youth due to its superior safety profile (93). Moreover, TODAY occurred prior to GLP-1RA, GIP receptor agonist, and sodium–glucose cotransporter 2 inhibitor use. Therefore, study of vertical sleeve

Table 2—Burden of microvascular complications and cardiovascular comorbidities and rate of major diabetes-related events in youth and young adults with type 2 diabetes from SEARCH and TODAY

	SEARCH		TODAY	
	First follow-up	Second follow-up	Follow-up phase 1	Follow-up phase 2
Average disease duration (years)	~8 (94)	~12	~12	~14–15
Kidney disease	19.9% (any albuminuria or low eGFR)			54.8% (any albuminuria or low or high eGFR) (95)
Any retinopathy	31% (9.1% pre- and proliferative)	55.7% at 12 years (3.1% proliferative) (128)	49% (3.8% proliferative) (96)	
Peripheral neuropathy	17.7% (MNSI exam)			38.5% males vs. 27.2% females, MNSI exam; 14.0% males vs. 5.1% females, monofilament (95)
Cardiac autonomic neuropathy	15.7% (abnormal HRV)	HRV worse: SDNN by 11.9 m/s and PNN50 by 9.1% (129)		HRV worse by median change of 10.1%–50.0% in 5 years (130)
High blood pressure	21.6% (≥95th percentile or medication)			59.2% (≥95th percentile or medication) (95)
Arterial stiffness	47.4% (PWV ≥90th percentile in control group)	Carotid-radial PWV worse by 1.2 ± 2.0 (mean ± SD) m/s (129)		PWV increased by 0.15–0.24 m/s per year (130)
Cardiac hypertrophy/ dysfunction			Mean LV mass high/normal, 16.2% had adverse LV geometry, mean LA internal dimension high/ normal (131), arterial stiffness related to LV mass and diastolic function (132)	EF <52% in 11.7% of males; diastolic function declined during follow-up (mitral valve lateral E/Em increased 0.72 ± 0.12 in women and 0.50 ± 0.17 in men [mean ± SD]) (133)

Data are percentages of the no. of participants unless otherwise indicated. EF, ejection fraction; eGFR, estimated glomerular filtration rate; E/Em, the ratio of the early transmitral flow velocity (E) to the early diastolic tissue velocity at the mitral annulus (Em); HRV, heart rate variability; LA, left atrium; LV, left ventricle; MNSI, Michigan Neuropathy Screening Instrument; PNN50, the percentage of adjacent N-N intervals with a difference >50 ms; PWV, pulse wave velocity; SDNN, the SD of the N-N intervals.

gastrectomy in youth-onset type 2 diabetes is currently underway in direct comparison with contemporary medical treatment in the NIDDK-funded Surgical or Medical Treatment for Pediatric Type 2 Diabetes (ST_2OMP) study, including outcomes beyond glycemia and weight (β-cell function, insulin sensitivity, metabolic dysfunction–associated steatotic liver disease, and cognitive, renal, and cardiovascular end points).

COMPLICATIONS AND COMORBIDITIES

Both SEARCH and TODAY documented a more aggressive course of diabetes-related complications in youth-onset type 2 versus type 1 diabetes or adult-onset type 2 diabetes. Estimates of prevalence or cumulative incidence of complications and comorbidities in each study are shown in Tables 2 and 3, alongside joint analysis of incidence rates for major events. Prevalence in SEARCH of early diabetes-related complications was reported among 272 youth/young adults with type 2 vs. 1,746 with type 1 diabetes (94). With exclusion of cardiovascular autonomic neuropathy, prevalence of all complications was significantly higher among those with type 2 diabetes, even with adjustment for sociodemographic factors. Additional adjustments for differences in clinical factors (especially waist-to-height ratio) negated

Table 3—Combined SEARCH and TODAY incidence of major events

	Eye	Kidney	Nerve	Peripheral vascular	Cerebrovascular	Cardiac
Major events (per 100,000/year) (134)	40.0	6.2	21.2	10.0	5.0	21.2

the increased odds of arterial stiffness and hypertension but not microvascular complications. At an average age of only 21 years and diabetes duration of 8 years, almost 75% of young adults with youth-onset type 2 diabetes had at least one complication or comorbidity.

Prospective evaluation of complications in TODAY demonstrated that ∼60% of participants developed one or more and 28% two or more microvascular complications at average age of only 26 years and diabetes duration of 13 years (95). The 15-year cumulative incidence of any diabetes-related kidney disease was 54.8%, nerve disease 32.4%, and retinal disease 49% (95,96) (Table 2). In contrast, only 25% of UK Prospective Diabetes Study (UKPDS) participants with adult-onset type 2 diabetes experienced moderately increased albuminuria after ∼10 years of diabetes duration (97). TODAY also highlighted the severity of these complications and comorbidities, with 17 serious cardiovascular events reported in addition to 60 vision-threatening events and 6 deaths after only 15 years of diabetes. An excess mortality risk was also described for youth-onset type 2 diabetes in SEARCH (98), with an overall standardized mortality ratio of 2.3 (1.7–3.0), versus a geographically representative U.S. population sample regarding age, sex, and race.

Risk factor analyses highlighted that a primary driver of early eye, kidney, and nerve complications is glycemia, with additional risk imparted by race, ethnicity, blood pressure, insulin resistance, and dyslipidemia (94,96,99–101). Moreover, the prevalence of baseline hypertension (19.2%), dyslipidemia (20.8%), and early kidney disease (8.0%) in TODAY is important (21), underscoring the compounding risk factors beginning prior to type 2 diabetes diagnosis and the critical need for investigation in younger children and determination of the timing, risk factors, and targets to prevent development of this pathologic metabolic milieu.

Youth-onset type 2 diabetes also intersects with social determinants of health and psychosocial well-being (6). More than 40% of TODAY participants had an annual household income below $25,000 USD (7). In SEARCH, compared with that of youth with type 1 diabetes, health-related quality of life was worse for youth with type 2 diabetes, and parents of youth with type 2 diabetes had lower household income and were much less likely to have a bachelor's degree or private health insurance (102). Fifty percent of youth with type 2 diabetes in SEARCH had disordered eating, which correlated with depressive symptoms and poorer health-related quality of life (103). Household food insecurity was nearly twice as prevalent, and participation in the Supplemental Nutrition Assistance Program (SNAP) three times as prevalent, among youth with type 2 versus type 1 diabetes (102). Youth with type 2 diabetes in food insecure households had three times the odds of diabetic ketoacidosis versus those in food secure households (104).

PREGNANCY COMPLICATIONS

Rising youth-onset type 2 diabetes rates result in growing numbers of females entering their reproductive years with diabetes, with potential adverse impacts on maternal, perinatal, and offspring health. Of girls in TODAY, 10% became pregnant, with a mean age at first pregnancy of 18.4 years, and 30% of those had another pregnancy, with 22% of newborns born large for gestational age, 6% small for gestational age, and 23% preterm (105). Of great concern, 21% of newborns in TODAY had major congenital anomalies, most commonly cardiac, a rate fourfold higher than that reported among adult women with type 2 diabetes. At post-TODAY follow-up into adulthood (maximum of 15 years), 260 pregnancies were reported, 31.9% with HbA_{1c} ≥8% (106). Pregnancy complications were reported in 65%: pregnancy loss in 25.3%, stillbirth 3%, preterm birth 32.6%, small for gestational age 7.8%, large for gestational age 26.8%, macrosomia 17.9%, neonatal hypoglycemia 29.4%, respiratory distress 18.6%, cardiac anomalies 10%, and preeclampsia 20.1%. Complications were also more frequent among those with higher glycemia.

CHALLENGES AND OPPORTUNITIES FOR THE FUTURE

Need for Ongoing Surveillance

Continued surveillance of youth-onset obesity and type 2 diabetes is critical to monitor disease burden and inform public health resource allocation. Monitoring trends in prevalence and/or incidence of youth-onset type 2 diabetes can provide clues about harmful or beneficial environmental changes (such as the rise during the recent coronavirus disease 2019 pandemic), identify scalable interventions, and provide evidence to support policy changes to decrease risk. With many providers using electronic health records for patient care, electronic health record–based surveillance of chronic diseases provides new opportunities (107–109), including linking registries to clinical care (6). Data from SEARCH over the past 20 years informed a new NIDDK and CDC-funded initiative, Diabetes in Children, Adolescents and Young Adults (DiCAYA), for surveilling diabetes burden by

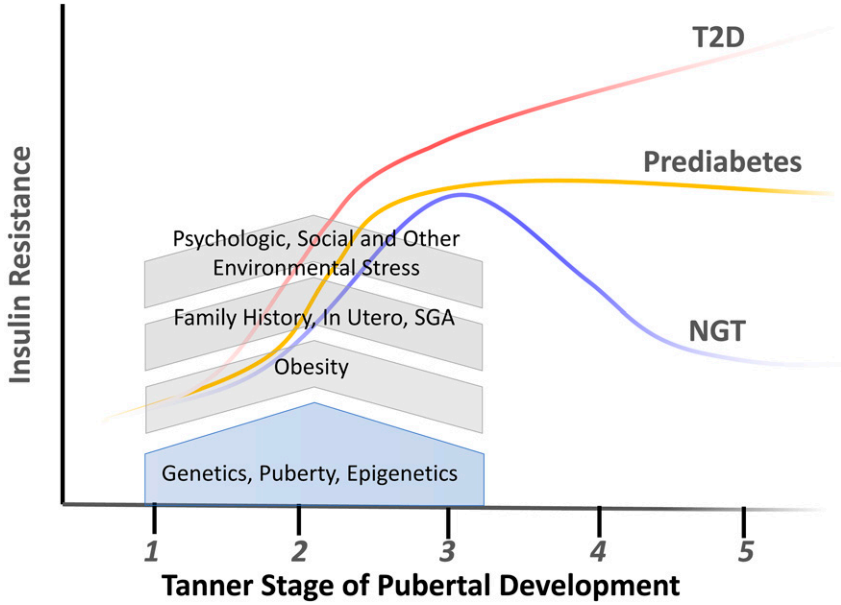

Figure 4—DISCOVERY: theoretical trajectories of the temporal impact of risk factors on the progression to youth-onset type 2 diabetes, a window of "physiologic" opportunity to prevent type 2 diabetes in youth? NGT, normal glucose tolerance; SGA, small for gestational age; T2D, type 2 diabetes.

type in youth and young adults (110), now underway at several U.S. sites. Continued NIDDK investment in youth-onset type 2 diabetes surveillance, interrogation of underlying mechanisms, and intervention in contemporary cohorts is crucial, since these populations will bear the consequences of chronic diseases for much of their life.

Predicting and Preventing Type 2 Diabetes in High-risk Youth: DISCOVERY

Multiple risk factors for youth-onset type 2 diabetes are known, including race and ethnicity, adiposity, family history of diabetes, in utero exposure to diabetes, and intrauterine growth restriction. Yet, gaps remain in our understanding of the unique pathophysiology of prediabetes and type 2 diabetes in youth and their interrelationship with pubertal physiology, psychological factors, social determinants of health, and unknown factors affecting early onset and progression (Fig. 4).

The current definition of diabetes, and thus prediabetes, originated from glucose ranges predicting development of diabetes complications in adults, but data are lacking on what criteria should be used to define abnormal glycemia for pubertal adolescents. With use of adult criteria, estimates from NHANES 2005–2016 data show an 18.0% prevalence of HbA_{1c}-based prediabetes among youth 12–18 years of age (111); 9.2% had impaired glucose tolerance, 2.8% impaired glucose tolerance, and 0.7% both. After age, race and ethnicity, and BMI were accounted for, prediabetes prevalence was higher among males (22.5% vs. 13.4% among females), yet type 2 diabetes prevalence is higher among adolescent females, possibly suggesting a more "harmful" effect of puberty on metabolic health in females. However, age rather than the more physiologically relevant pubertal stage was adjusted for and girls are usually further into puberty than boys at the same age (112). Importantly, a substantial proportion (~70%) of youth categorized with "prediabetes" under rigorous criteria revert to normoglycemia after puberty (113,114), a phenomenon analogous to gestational diabetes mellitus, thought to reflect recovery of insulin sensitivity postpubertally. Whether this group has increased risk for future gestational diabetes mellitus or type 2 diabetes remains unknown; investigation is called for of whether extrapolation of adult prediabetes or diabetes criteria is appropriate for youth, to assess clinical relevance of current definitions and to identify determinants of progression versus reversion to normoglycemia.

Collectively, these gaps inspired the NIDDK-funded, multicenter DISCOVERY study, with recruitment of at-risk youth prior to type 2 diabetes diagnosis, for identification of "who, when, and how."

1. Who: Which youth with overweight or obesity are at highest risk? Answering this question can inform risk prediction models for future clinical practice implementation. DISCOVERY is recruiting 3,600 diverse high-risk youth across 15 U.S. clinical centers, who are pubertal (ages 9–14 years) and have overweight or obesity (BMI ≥85th percentile) and high-normal glucose (HbA_{1c} 5.5%–5.6%) or prediabetes (HbA_{1c} 5.7%–6.4%), to be followed up every 6 months for 2–4 years. β-Cell physiology and psychological and social risk factors will be studied as trajectories of glycemic worsening (i.e., progression to type 2 diabetes) versus improvement (i.e., reversion to normoglycemia) emerge (Fig. 4) for determination of who is at highest risk.
2. When: When is the ideal window of opportunity for intervention based on the timing of early physiologic changes in glucose homeostasis relative to sex, pubertal maturation, psychological factors, and social context? Investigating HbA_{1c} trajectories in youth during pubertal progression will help confirm or redefine pediatric HbA_{1c} cutoffs for prediabetes and diabetes. DISCOVERY will include longitudinal surveillance of laboratory (OGTT) and free-living (continuous glucose monitoring [CGM]) glucose-insulin homeostasis and exploration of additional outcome measures for translation to clinical practice. Analogous to growth velocity charts that change dramatically during puberty, charts can be envisioned of normal HbA_{1c}, insulin sensitivity, β-cell responses, and/or CGM time in range, for identification of abnormal trajectories.
3. How: What are the intervention targets, from molecular mechanisms to public health initiatives, to restore healthy physiology? DISCOVERY will include collection and storage of biospecimens (i.e., blood, urine, and stool) longitudinally to create a repository to fuel future investigations of novel mechanisms and therapeutic targets. Resulting predictive models for youth-onset type 2 diabetes from nos. 1 and 2 will also inform clinical and public health interventions.

Navigating the Path to Personalized Care

Current data demonstrate that the treatments most widely used for youth-onset type 2 diabetes are insufficient for maintenance of glycemic stability or prevention of diabetes complications. Moreover, the prominent psychosocial comorbidities in youth-onset type 2 diabetes (115) influence adherence (116) and likely physiology. Thus, achieving personalized care will require integrating medical, behavioral, and social factors. The multiphase optimization strategy (MOST) (117) (a framework for optimizing and evaluating multicomponent biobehavioral interventions) and sequential multiple-assignment randomized trials (SMART) (118) (trials with personalized adaptive interventions) or other novel clinical trials designs may aid the development of new treatments in youth, allowing personalized approaches.

Economic Burden and Impact on the Workforce

Given the aggressive nature of youth-onset type 2 diabetes, direct expenditures will occur for medical care, and as these youth enter the workforce, secondary costs will occur related to presenteeism, reduced employment due to disability, and premature death resulting in lost productivity, contributing to the ever-increasing economic expenses of diabetes (119). Thus, improvements in prevention, treatment, and outcomes of youth-onset type 2 diabetes are critical to reduce the economic burden and impact on the workforce.

Health Equity: Primary and Secondary Prevention

Ideally, the future will bring concerted efforts to prevent youth-onset type 2 diabetes and, thus, its complications. Youth-onset obesity (120), prediabetes, and type 2

diabetes occur differentially across population groups (20,23). Prevention will require comprehensive combinations of clinical and public health efforts to fully address individual and community-level risk factors, beginning with primordial prevention during the perinatal period, as both obesity and type 2 diabetes have origins in utero (121). Prevention efforts should include *1*) societal measures to modify the diabetogenic environment; *2*) tools for earlier identification of at-risk youth by primary care providers to easily select which children with overweight or obesity will progress to prediabetes or diabetes; *3*) determination of early windows of opportunity for interventions to avoid irreversible pathophysiology; *4*) targeted, personalized interventions to address the diversity of risk factors affecting glucose homeostasis in youth including social determinants of health; and *5*) collaboration among health care providers and public health leaders to broaden awareness and implement strategies.

Recent reviews reinforce that there are substantial limitations in our understanding and capacity to design and implement effective, individually targeted behavioral interventions for treating obesity in youth (122,123), again reinforcing that interventions much earlier in life, and taking a broad public health perspective, will be required. In the home environment, availability of electronic media is most consistently associated with child adiposity and is an important target. School-based interventions may be useful, although to date, effectiveness has been modest (124,125). Recently, drawing on the premise of complexity science and deploying systems mapping methods focusing on positive or negative feedback loops, Hagenaars et al. (126) provided insights into how broad public health policy might be designed and deployed to reduce excess adiposity, beginning with reframing obesity from an individual problem to a societal problem. Accordingly, public health policies should be designed to address the wide array of social determinants of health in communities most at risk, particularly Black, Hispanic, and Indigenous communities (127).

SUMMARY AND CONCLUSION

Understanding of youth-onset type 2 diabetes would not have been possible without the sustained, outstanding support by NIDDK during its 75 yearslong legacy. NIDDK-funded studies to date, specifically TODAY, SEARCH, RISE, and DISCOVERY, provide invaluable insight into pathophysiology, epidemiology, and the vast array of clinical and psychosocial impacts of youth-onset type 2 diabetes. Identification of high-risk populations, elucidation of specific metabolic pathways in relation to disease risk and to response to longstanding and emerging pharmacological treatments, and ongoing efforts to address behavioral strategies in support of risk reduction and advancing understanding of the role of social determinants of health—all converge to enhance our capacity to address the epidemic of youth-onset type 2 diabetes. In summary, of paramount importance is a focus on comprehensive prevention strategies for high-risk communities, in parallel with targeted prevention efforts for individual youth at high risk of type 2 diabetes and its complications, with the intention of addressing the psychosocial impacts of the disease. This will require the efforts and insights of current and future investigators with diverse expertise and perspectives, and continued funding investment.

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