Youth-Onset Type 2 Diabetes
Consensus Report: Current Status, Challenges, and Priorities

Type 2 diabetes is a significant and increasing burden in adolescents and young adults. Clear strategies for research, prevention, and treatment of the disease in these vulnerable patients are needed. Evidence suggests that type 2 diabetes in children is different not only from type 1 but also from type 2 diabetes in adults. Understanding the unique pathophysiology of type 2 diabetes in youth, as well as the risk of complications and the psychosocial impact, will enable industry, academia, funding agencies, advocacy groups, and regulators to collectively evaluate both current and future research, treatment, and prevention approaches. This Consensus Report characterizes type 2 diabetes in children, evaluates the fundamental differences between childhood and adult disease, describes the current therapeutic options, and discusses challenges to and approaches for developing new treatments.

Youth-onset type 2 diabetes is an emerging disorder in children, adolescents, and young adults with unique challenges in both research and clinical care. Type 2 diabetes has a disproportionate impact on youth of ethnic/racial minorities and from disadvantaged backgrounds (Fig. 1) and occurs in complex psychosocial and cultural environments that make durable lifestyle change elusive and adherence to medical recommendations a struggle. Furthermore, these complexities hinder successful recruitment into and completion of research programs (1), leaving large gaps in knowledge on pathophysiology and treatment optimization.

Type 2 diabetes in youth clearly differs from type 1 diabetes and more closely resembles the pathophysiology in adults: insulin resistance and nonautoimmune β-cell failure. However, youth-onset type 2 diabetes displays unique aspects, such as rapidly progressive β-cell decline (Fig. 2) and accelerated development of diabetes complications. Treatment options for youth-onset type 2 diabetes are inadequate, limited to two approved drugs (insulin and metformin) and the promotion of healthy lifestyles. Comprehensive, coordinated, and innovative strategies for the investigation, prevention, and treatment of youth-onset type 2 diabetes are urgently needed.

OBJECTIVES
The American Diabetes Association, in collaboration with the American Academy of Pediatrics, International Society for Pediatric and Adolescent Diabetes, and Pediatric Endocrine Society, conducted a consensus conference. The goal was to review the current state of knowledge and controversies surrounding youth-onset type 2 diabetes, including similarities and differences between childhood and adult disease, current therapeutic options, and unmet clinical and research needs, in order to make specific recommendations regarding research priorities.
and creation of a sustainable clinical research infrastructure that supports treatment development.

A CASE STUDY: THE FACE OF YOUTH-ONSET TYPE 2 DIABETES

R.Y., an 11-year-old youth of American Indian heritage, was diagnosed with type 2 diabetes during a routine school physical exam. Her mother had recently moved the family from a stressful urban environment of domestic violence, financial distress, frequent school changes, unstable housing, and lack of consistent parental supervision back home to her childhood community. Before the move, R.Y. had developed poor school performance, oppositional behavior, and severe weight gain. R.Y.’s mother wondered if R.Y.’s diabetes diagnosis was due to gestational diabetes mellitus, witnessing physical abuse, or social inequalities. The return to the Native American community benefitted R.Y., with improvements in R.Y.’s school performance, relationships, and disciplinary issues, as well as improvement in family cohesion. However, the family continued to face barriers to adopting a healthy lifestyle: long drives to school, a health clinic, or grocery store; financial strains; and few safe outdoor areas. R.Y. exemplifies the complexity of the social milieu common to youth with type 2 diabetes (2).

EPIDEMIOLOGY

The incidence of type 2 diabetes in youth has increased dramatically over the past 20 years. In the U.S., estimates are as high as 5,000 new cases per year (3). Prevalence increases with age, tripling from age 10–14 years to 15–18 years (4). Although rates in adult men and women are similar, adolescent girls, for reasons that remain unclear, have a 60% higher prevalence rate than boys (4). Disadvantaged racial/ethnic groups are at higher risk of disease at all ages, but the association is especially strong in youth (4) (Fig. 1).

Indigenous children around the world bear the greatest burden of youth-onset type 2 diabetes (5). American Indians have the highest rates of youth-onset type 2 diabetes in the U.S. (6). Moreover, in the SEARCH for Diabetes in Youth (SEARCH) study, a population-based registry of youth with diabetes from five representative U.S. catchment sites, nearly half of American Indian youth with diabetes had an A1C >9.5% (7). Available global data indicate considerable variation in incidence and prevalence, depending on ethnicity and geographical region. Rates of youth-onset type 2 diabetes are lowest in Europe. The increasing incidence reported in China and India is of particular concern, given their large populations (8,9).

PATHOPHYSIOLOGY

The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study was a multicenter trial that examined the durability of glycemic control in 699 U.S. youth randomized to metformin, metformin plus rosiglitazone, or metformin plus an intensive lifestyle intervention for up to 6 years, while also providing pathophysiological insight into the disease (10,11). Surprisingly, loss of glycemic control was rapid in many of the participants, despite a mean baseline diabetes duration of only 7.8 months. Lower initial β-cell reserve and higher A1C following initiation of metformin were significant independent predictors of loss of glycemic control (12,13).

A decline in β-cell function also occurs in adults with type 2 diabetes, though not as rapidly as in youth (Fig. 2) (11,14–16). In particular, the rate of loss of
glycemic control on either metformin monotherapy or combination therapy with rosiglitazone in TODAY appears to be three- to fourfold higher than published rates in adults. Although the studies in Fig. 2 had different primary end points and lacked head-to-head prospective evaluations, the outcomes suggest that β-cell failure may be more rapid in youth than in adults. Thus, efforts are needed to preserve β-cell function in youth before significant deterioration occurs.

PUBERTY

Puberty is associated with significant changes in physiology, including a transient reduction in insulin sensitivity by ~50% in lean, healthy children as they enter puberty (17). To compensate, insulin secretion must increase reciprocally, which may lead to hyperglycemia in youth with limited β-cell capacity due to genetic, epigenetic, and/or lifestyle factors. Thus puberty, similar to pregnancy, creates a high-risk time for diabetes development in susceptible individuals. Furthermore, reminiscent of gestational diabetes mellitus, diabetes onset during puberty may be reversible in some youth due to the dynamic nature of the underlying insulin resistance. Other potentially modifiable risk factors influencing insulin sensitivity include adiposity, diet, physical activity, sleep, and stress—all markedly abnormal in youth-onset type 2 diabetes (18,19).

COMPLICATIONS

Diabetes duration and glycemic control are closely associated with the development of microvascular complications in type 1 diabetes and in adult-onset type 2 diabetes. However, evidence of microvascular complications and risk markers for macrovascular complications are often present at the time of diagnosis of type 2 diabetes in youth. At enrollment into the TODAY study, 14% of participants had a blood pressure at the 95th percentile or greater, 13% had microalbuminuria, 80% had a low HDL cholesterol level, and 10% had high triglycerides (18). Similarly, in Canadian First Nations youth with type 2 diabetes, 37% had elevated triglycerides and apolipoprotein B levels and 12% and 14% of male and female youth, respectively, had systolic blood pressure greater than the 95th percentile (20).

Rapid progression of complications is also seen; current evidence in First Nations youth with type 2 diabetes shows that renal and neurological complications begin to appear within 5 years of diagnosis, and major complications (dialysis, blindness, or amputation) start to manifest 10 years after diagnosis (21,22).

In the TODAY study, 10% of female adolescents became pregnant during the first 6 years of the study despite an aggressive program of preconception counseling and access to birth control (23). When adolescents with type 2 diabetes become pregnant, fetuses are exposed to the metabolic consequences of diabetes that likely contribute to an increased risk of type 2 diabetes and earlier age of diagnosis in the offspring (24,25). Moreover, in the TODAY study ~30% of pregnancies were complicated by preterm birth or fetal malformation.

PSYCHOSOCIAL ASPECTS AND CARE DELIVERY

The World Health Organization defines the social determinants of health as “the conditions in which people are born, grow, work, live, and age,” which are “the fundamental drivers” of many health conditions (26). Socioeconomic status (SES), as determined by income, education, and employment, among other factors, is the primary social determinant of health impacting youth and families living with type 2 diabetes. Egerter et al. (27) documented how parental educational attainment affects the health of all family members through impacts on the parents’ insurance options, the safety and social support available, choices for housing, and opportunities for healthy eating and physical activity in the neighborhood. In 50% of the TODAY study families, the highest educational level attained by a parent was a high school diploma or less (18). Globally, many populations at high risk for youth-onset type 2 diabetes also have high rates of poverty and low parental educational attainment (28).

McEwen and Stellar (29) introduced the concept of “allostatic load” to describe how chronic exposure to social and environmental stressors negatively impact body weight, metabolism, blood pressure, and the sympathetic nervous system. Genetics also plays a role in individual vulnerability or resilience to SES adversity, and, conversely, social factors can alter whether a gene is expressed or suppressed through epigenetic pathways (30,31).

Youth with type 2 diabetes and their family members experience multiple stressors in their daily lives. However, stress and other social determinants are poorly addressed in standard medical care (32). Alternate models of care delivery are likely needed to address stress and will require broad and intensive intervention (33).

LIFESTYLE, COMMUNITY, AND COORDINATED INTERVENTIONS FOR THE PREVENTION AND TREATMENT OF YOUTH-ONSET TYPE 2 DIABETES

Lifestyle intervention is considered the first-line treatment for type 2 diabetes in adults. However, most pediatric lifestyle intervention studies have focused on youth affected by obesity or prediabetes (34–36), not specifically on youth with type 2 diabetes. The majority of interventions have examined individual-level behavior modification, targeting diet and/or physical activity with classic health education and social-cognitive models. The TODAY study is the only trial to date combining lifestyle and drug therapy in youth with type 2 diabetes (11).

Bright Bodies Weight Management Program for Children, an intensive 12-month behavior modification intervention in obese youth without diabetes, demonstrated significant treatment-induced reductions in BMI, total cholesterol, and insulin resistance estimated by HOMA of insulin resistance; results were sustained at 12-month postintervention (37). In addition, when applied over 6 months to youth with prediabetes, Bright Bodies showed significantly more reduction in 2-h glucose compared with standard care participants (38). However, among children already diagnosed with type 2 diabetes, the evidence for lifestyle intervention effects is limited and less clear. In the TODAY study, lifestyle strategies in combination with metformin therapy did not perform better than metformin alone in delaying progression of hyperglycemia (11).

Given the complex social and environmental context surrounding youth with
type 2 diabetes, individual-level lifestyle interventions may not be sufficient to target the complex interplay of family dynamics (39), mental health (40,41), community readiness (42), and the broader environmental system (43). The few pediatric obesity interventions to date with psychosocial outcomes have reported mixed findings, including decreased anxiety (44) and improved psychosocial functioning and social performance (45) but no change in perceived or measured stress (46). One alternate model of pediatric care delivery, the patient-centered medical home, is designed specifically to address the social context of patient care (32) by including three key components—comprehensive, interdisciplinary care; patient/family-centered care; and coordinated care—with all health and community resources housed under one roof. A related approach is to increase community readiness by assessing a community’s self-identified needs, mobilizing community leaders and internal and external resources, increasing public knowledge, and cultivating a sense of priority in the community (47). Environmental strategies could target community access to healthy foods, physical activity, and health care (48,49). Importantly, community engagement and cocreation of both the content and implementation of interventions may be key to effective and sustained impact (50,51).

ADDITIONAL KNOWLEDGE GAPS IN YOUTH-ONSET TYPE 2 DIABETES

Further limiting the development of best practices for evaluating and treating youth-onset type 2 diabetes are gaps in our understanding of normal and abnormal glucose metabolism during adolescence and development of complications and the long-term outcomes of youth-onset type 2 diabetes (Table 1). Indeed, even the definitions of prediabetes and type 2 diabetes in youth are not evidence based, as they have simply been extrapolated from glycemic indices predicting microvascular complications in adults. Dysglycemia appears to be transient in some youth, who may not need long-term drug treatment, and others rapidly lose glycemic control on oral monotherapy and require multiple-drug treatment (52). Given this heterogeneity, algorithms to predict disease trajectory would enable customized approaches to patients.

Research is needed to better understand what diabetes complications may require pediatric-specific approaches. Nonalcoholic fatty liver disease occurs in both youth and adults with type 2 diabetes (53), but the pathological phenotype is unique and appears more aggressive in youth. The kidney function measures for adults are inappropriate for youth (54), and little is known about the long-term outcomes for youth-onset dyslipidemia, hypertension, kidney disease, nonalcoholic fatty liver disease, and cardiovascular dysfunction (55). The impact on glycemic control of the sleep abnormalities endemic among adolescents is also unknown (56).

RECRUITMENT CHALLENGES IN CLINICAL AND TRANSLATIONAL RESEARCH

Despite the development of more than 10 different classes of antidiabetes medications since the U.S. Food and Drug Administration (FDA) approval of sulfonylurea agents in 1984, metformin remains the only oral medication approved for use in children today (57,58). Although numerous formulations of insulin are commonly used in youth-onset type 2 diabetes, they have not been studied for the specific indication of pediatric type 2 diabetes. FDA regulations require a commitment from pharmaceutical sponsors to complete an assessment of safety and efficacy in pediatric patients for all new active ingredients, indications, or dosage forms as a condition of new drug approval (with similar mandates in Europe) (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079756.pdf). Therefore, numerous new drug pharmacokinetic studies and safety and efficacy trials in youth-onset type 2 diabetes are currently under way or are committed by pharmaceutical sponsors as a prerequisite for new drug approval in adults. However, the mandated pediatric trials are having substantial difficulty completing enrollment. As a consequence, individuals with youth-onset diabetes have benefitted minimally, if at all, from the development of new therapeutic agents. Barriers to study execution include the small number of available study participants, restrictive study eligibility criteria, small number of research sites with dedicated resources for pediatric type 2 diabetes trials, socioeconomic challenges inherent in the affected population, and growing number of trials competing for the limited pool of available patients (Fig. 3).

Why have so many diabetes drugs been studied, yet none approved for use in children? The answer is as complex as the environment in which youth-onset type 2 diabetes occurs. Clinical trial recruitment for youth with type 2 diabetes is a relatively new endeavor and has had limited success (59–61). As an

Table 1—Gaps in knowledge in youth-onset type 2 diabetes

| Question                                                                 | Comment |
|-------------------------------------------------------------------------|---------|
| How do insulin resistance and insulin secretion differ between youth and adults? | Differences in glucose/insulin physiology require a different approach to prevention and treatment? |
| What are the definitions of prediabetes and diabetes in youth-onset type 2 diabetes? | Current definitions are based on extrapolation from adults and are not evidence based. |
| What are the implications of transient hyperglycemia seen in some youth and the rapid progression of β-cell dysfunction seen in others? | |
| What are the implications of physiological barriers (cardiac, vascular, autonomic, muscle mitochondrial dysfunction) to exercise seen in obese youth and youth with type 2 diabetes? | |
| What are the best approaches to understanding kidney function in youth with obesity and type 2 diabetes and what is the natural history of the renal hyperfiltration characteristic of these youth? | |
| How do the unique physiology of adolescent sleep and endemic poor sleep patterns of youth contribute to development of type 2 diabetes and associated disorders? | |
| What is the optimal approach to management of comorbidities and complications in youth-onset type 2 diabetes, including lipids, blood pressure, and microalbuminuria? | |
| What is the impact of stress and historical trauma on the development, presentation, and management of youth-onset type 2 diabetes? | |
| What are effective ways to increase compliance with lifestyle interventions and medication in adolescents with type 2 diabetes? | |
**Total pediatric T2D population (~20,000–25,000 U.S.; 100%)**

| Socioeconomically challenged population with many inherent barriers to participation |
|---|
| Patients out of reach of study PIs |
| - Receiving care at clinical care—only facilities |
| - Receiving care at research sites without dedicated pediatric T2D teams (e.g., T1D focused) |

**# of patients at sites active in T2D clinical (~5,000–6,000; 20%) trials**

- Unlikely to be eligible
  - Controlled on metformin or insulin
  - A1C or liver enzymes too high
  - Age >17 years
- Unable to reach

**“Pre-Screen” Failure**

- No show
- Unwilling to participate
- Cannot comply with study visits
- Inclusion/exclusion criteria not met

**# of patients approached for screening (~1,000–1,500; <5%)**

**Screen Failure**

- Eligible subjects for pediatric T2D trials (~500–600; 2%)**

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**Figure 3**—Few patients with youth-onset type 2 diabetes are available to participate in clinical trials. The population of youth-onset type 2 diabetes is small, approximately 20,000–25,000 in the U.S., compared with the approximately 20 million adults. Barriers to clinical trial participation include the paucity of centers with dedicated resources for pediatric type 2 diabetes trials, SES challenges inherent to the population, and the many study entry requirements that exclude study eligibility before and after formal study screening procedures (69). T2D, type 2 diabetes.

*N*umbers are from Imperatore et al. (69).

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Example of the challenges in recruitment in youth-onset type 2 diabetes, the SEARCH study aimed to register pediatric patients with both type 1 and type 2 diabetes. Yet, despite the same well-funded, full-time, dedicated research staff, the case ascertainment time from diagnosis was two times longer in youth-onset type 2 diabetes than in type 1 diabetes (62). Similarly, the duration of the TODAY study recruitment had to be extended substantially, and although the well-funded, full-time TODAY research staff were ultimately successful in randomizing 699 youth, recruitment took 5.5 years (18).

Recruitment for pharmaceutical trials has been even less successful due to the interaction between specific regulatory requirements, need to demonstrate reduction in the glycemic surrogate A1C, and realities of youth-onset type 2 diabetes (18). For example, entry criteria, such as the typical 7–10% A1C ranges, often do not reflect the trajectory of youth-onset type 2 diabetes. As noted previously, the population of youth with type 2 diabetes appears to be heterogeneous, with two large subsets and a bimodal distribution. One subset has durable normalization of glycemia on initial monotherapy with A1C in the nondiabetic range, while another group has a rapidly progressing course and very elevated values requiring insulin treatment. Thus, only a small number of individuals remain in the range typical of pharmaceutical trial inclusion criteria, an A1C >7.0% on treatment with diet/exercise or metformin monotherapy. The Pediatric Diabetes Consortium Type 2 Diabetes Registry (63) demonstrated that this criteria alone excludes ~87% of potentially eligible participants. More recently, some trials have changed the criteria to allow participants on a stable dose of basal insulin who have an A1C ≥6.5% and ≤10.5%. Although an improvement, these eligibility criteria still exclude ~53% of potential participants, as 38% of patients included in the registry have an A1C <6.5% and 15% have an A1C ≥10.5% (63). Exclusion criteria seen in some trials, such as elevated liver enzymes, prior ketoacidosis, or common comorbid conditions, can further restrict the eligibility pool.

The rationale for excluding participants with an A1C <6.5% in pharmaceutical trials is a consequence of the glucocentric A1C-lowering design and the recognition that it may be difficult to lower A1C further in patients with already well-controlled diabetes, as well as outstanding questions regarding the benefit of further lowering of A1C. However, this approach fails to take into consideration the observation that a substantial proportion of youth initially in good glycemic control ultimately often fail to maintain glycemic control (11,64) within a relatively short time period. Therefore, studies of add-on therapy could include adolescents with A1C <6.5% on metformin because many would be expected to show an abrupt increase in A1C over time while on metformin alone. The superiority of an add-on medication could then be tested in its ability to prevent the loss of glycemic control.

U.S. (FDA) and European (European Medicines Agency) pediatric type 2 diabetes investigation plans historically required a stand-alone pharmacokinetics/pharmacodynamics (PK/PD) study and a phase III efficacy and safety study. This approach substantially increases both the number of participants and the time to completion required. However, the results of stand-alone PK/PD studies to date indicate that the PK properties of diabetes drugs in adolescent patients with type 2 diabetes are not significantly different from those in adults (64). As a result, more recent pediatric study plans have waived the need for a stand-alone PK study and instead confirmed exposure of the predicted dose through sparse sampling of PK parameters embedded within the pivotal pediatric safety and efficacy study, allowing for more rapid progress. However, some recent phase III study plans continue to require the analysis of the safety and efficacy of different doses of the experimental drug, again increasing the number of required participants.

The clinical presentation of new-onset type 2 diabetes is another barrier. Youth with new-onset type 1 diabetes typically require urgent attention and families eagerly seek opportunities to participate...
In clinical research in hopes of finding a cure. In contrast, the majority of youth with type 2 diabetes have subtler initial symptoms; many families express relief at what is perceived as a familiar and less severe form of diabetes. Insulin, if started initially, is often stopped, adding to the perception of a milder disease. As a result, families may be less likely to accept the potential risks of an experimental medication. Furthermore, studies must recruit youth quickly to stay within the pediatric age range of <18 years for eligibility yet may also have to wait for the youth to fail initial metformin monotherapy.

As mentioned previously, the SES challenges (65,66) of families of youth with type 2 diabetes decrease the ability to obtain clinical care or prioritize research participation. In addition, families with an existing high burden of diabetes-related disease often have fatalistic beliefs regarding the inevitable progression of diabetes. This perception further decreases the motivation to sustain consistent medical care or participate in research, and youth are often lost to follow-up within a year of diagnosis. Past history of ethical maltreatment creates attitudes of distrust and apprehension among family members. The high risk for losing contact, combined with early rapid deterioration of β-cell function, creates missed opportunities to recruit youth who meet study eligibility criteria.

**SOLUTIONS**

Given the realities of the epidemiology, biology, and SES characteristics of youth-onset type 2 diabetes, as well as the experience of clinical research to date, progress in understanding the pathophysiology of the disease in youth and successful completion of clinical trials for this population will require

1. Prioritization of clinical and translational research addressing the gaps in knowledge regarding the apparently unique physiological features of youth-onset type 2 diabetes. In addition to the importance of understanding the fundamental biology, a fuller understanding of the similarities and differences between youth-onset and adult-onset type 2 diabetes will be critical to potential creative regulatory approaches to new drug approval based on extrapolation from adult trials.

2. Increased exploration of the psychological and SES aspects of youth-onset type 2 diabetes. An improved understanding of the ways in which the environment contributes to the pathophysiology of the disorder, as well as to challenges in treatment and research recruitment, will be necessary for development and delivery of feasible and successful interventions.

3. Development of formalized collaborative networks of investigators and centers with recognized expertise in clinical studies of youth-onset type 2 diabetes. Progress in studying, understanding, and treating this rare disorder cannot be achieved by sole investigators who are unlikely to have access to sufficient numbers of affected individuals. Rather, consortia, such as the Children’s Oncology Group, have promoted remarkable progress in addressing other rare disorders and should be looked to as models.

4. Collaboration among academic leaders, government and charitable sponsors, industry, and regulatory agencies to delineate research priorities and strategies. This should include consideration for treatment strategy trials that clarify how to approach treatment of affected youth rather than only individual drug registration trials. There is also a need to prioritize outcomes other than glycemic control, including preservation of β-cell function, improvement in insulin sensitivity, weight control, lowering cardiovascular disease risk, and reduction of other diabetes complications.

5. Increasing research and infrastructure capacity for youth-onset type 2 diabetes through the development of purpose-built research centers of excellence that are uniquely staffed and maintained. Such centers will more successfully address the recruitment and retention obstacles characteristic of the population than current models consisting of short-term trials that enroll a few patients per site.

6. Promote development of appropriate study design, monitoring of recruitment and retention, and a central coordinating center to support the research teams (e.g., institutional review board and convening logistics, budgeting, supplies, certification, data management, and stakeholder engagement). These consortia could use a hybrid approach to funding: a modest amount of committed support at each site to build and maintain the research team, supplemented by payment for the number of participants enrolled in active treatment trials.

7. Increasing the proportion of youth with type 2 diabetes who participate in clinical drug trials through

a. More flexible enrollment criteria, including wider A1C and age ranges (i.e., allowing a participant who is over 18 years but who developed diabetes prior to age 18 years) and fewer exclusion criteria (i.e., concomitant medications, hypertension, elevated liver enzymes);

b. Trial designs appropriate for the typical youth with type 2 diabetes, including flexibility of scheduling, minimization of visit number and burden, and parent and participant reimbursement, including recognition of the sacrifices of school and work time these studies require; and

c. Creative strategies to overcome barriers to care and research, including telemedicine, mobile or community-based research sites, and engagement of affected youth, their families, and communities in the research process to identify outcomes that are important and relevant to the population.

8. Increasing efficiency of pharmaceutical registration studies by focusing on high-impact trials of novel agents and exploration of innovative trial designs, such as multi-agent studies to eliminate duplicative placebo control groups (60), and elimination of low-priority trials, such as fixed-dose combinations or new dosage formulations.

9. Harmonization of national and international regulatory guidelines to ensure inclusion of diverse populations, broad relevance of the results, and improved efficiency in protocol approval.
SUMMARY

Not only is it essential for health care providers to understand the pathophysiological differences in youth versus adults but also it is imperative that the biology and environment of youth-onset type 2 diabetes continue to be studied due to the urgent need for targeted treatments and patient-centered care in what appears to be a more aggressive disease in youth. Therefore, a focus on improving the knowledge base regarding the pathophysiology of youth-onset type 2 diabetes, finding the most effective approach to working with this population, and using more realistic and efficient study designs and intervention types appropriate to this population is required to help improve the care of youth with type 2 diabetes worldwide.

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References

1. Zeitzer P, Chou HS, Copeland KC, Geffner M. Clinical trials in youth-onset type 2 diabetes: needs, barriers, and options. Curr Diab Rep 2015;15:28.
2. Berends LM, Ozanne SE. Early determinants of type-2 diabetes. Best Pract Res Clin Endocrinol Metab 2012;26:569–580.
3. Lawrence JM, Imperatore G, Pettitt DJ, et al. Incidence of diabetes in United States youth by diabetes type, race/ethnicity, and age, 2008–2009 (Abstract). Diabetes 2014;63(Suppl. 1):A409.
4. Dabelea D, Mayer-Davis EJ, Saydah S, et al.; SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA 2014;311:1778–1786.
5. Fazeli Farsani S, van der Aa MP, van der Vorst MMJ, Knibbe CA, de Boer A. Global trends in the incidence and prevalence of type 2 diabetes in children and adolescents: a systematic review and evaluation of methodological approaches. Diabetologia 2013;56:1471–1488.
6. Pettiti DB, Klingensmith GJ, Bell RA, et al.; SEARCH for Diabetes in Youth Study Group. Glycemic control in youth with diabetes: the SEARCH for Diabetes in Youth Study. J Pediatr 2009;155:668–672.e1–e3.
7. Hamman RF, Bell RA, Dabelea D, et al.; SEARCH for Diabetes in Youth Study Group. The SEARCH for Diabetes in Youth study: rationale, findings, and future directions. Diabetes Care 2014;37:3336–3344.
8. Fu J, Prasad HC. Changing epidemiology of metabolic syndrome and type 2 diabetes in Chinese youth. Curr Diab Rep 2014;14:447.
9. Prasad AN. Type 2 diabetes mellitus in young need for early screening. Indian Pediatr 2011;48:683–688.
10. Kelsey MM, Geffner ME, Guandalini C, et al.; Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) Study Group. Presentation of findings from the PREVENT intervention in type 2 diabetes in youth: lessons from the TODAY study. Pediatr Diabetes 2016;17:212–221.
11. Zeitler P, Hirsh K, Pyle L, et al.; TODAY Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med 2012;366;2247–2256.
12. TODAY Study Group. Effects of metformin, metformin plus lifestyle, and metformin plus lifestyle on insulin sensitivity and β-cell function in TODAY. Diabetes Care 2013;36:1749–1757.
13. Zeitler P, Hirsh K, Copeland KC, et al.; TODAY Study Group. HbA1c after a short period of monotherapy with metformin identifies durable glycemic control among adolescents with type 2 diabetes. Diabetes Care 2015;38:2285–2292.
14. Rascati K, Richards K, Lopez D, Cheng L-I, Wilson J. Progression to insulin for patients with diabetes mellitus on dual oral antidiabetic therapy using the US Department of Defense Surveillance Database. Diabetes Obes Metab 2013;15:903–905.
15. Kahn SE. Clinical review 135: The importance of beta-cell failure in the development and progression of type 2 diabetes. J Clin Endocrinol Metab 2001;86:4047–4058.
16. Kahn SE, Lachin JM, Zinman B, et al.; ADOPT Study Group. Effects of rosiglitazone, glyburide, and metformin on β-cell function and insulin sensitivity in ADOPT. Diabetes 2011;60:1552–1560.
17. Hannon TS, Janosky J, Arslanian SA. Longitudinal study of physiologic insulin resistance and metabolic changes of puberty. Pediatr Res 2006;60:759–763.
18. Copeland KC, Zeitler P, Geffner M, et al.; TODAY Study Group. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. J Clin Endocrinol Metab 2011;96:159–167.
19. Klingensmith GJ, Connor CG, Ruedy KJ, et al.; Pediatric Diabetes Consortium. Presentation of youth with type 2 diabetes in the Pediatric Diabetes Consortium. Pediatr Diabetes 2016;17:266–273.
20. Sellers EAC, Yung G, Dean HJ. Dyslipidemia and other cardiovascular risk factors in a Canadian First Nation pediatric population with type 2 diabetes mellitus. Pediatr Diabetes 2007;8:384–390.
21. Hannon TS, Arslanian SA. The changing face of diabetes in youth: lessons learned from studies of type 2 diabetes. Ann N Y Acad Sci 2015;1353:113–137.
22. Dart AB, Martens PJ, Rigatto C, Brownell MD, Dean HJ, Sellers EA. Earlier onset of complications in youth with type 2 diabetes. Diabetes Care 2014;37:436–443.
23. Klingensmith GJ, Pyle L, Nadeau KJ, et al.; TODAY Study Group. Pregnancy outcomes in youth with type 2 diabetes: the TODAY study experience. Diabetes Care 2016;39:122–129.
24. Dabelea D, Hanson RL, Lindsay RS, et al. Intratherine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes 2000;49:2208–2211.
25. Mendelson E, Cloutier J, Spence L, Sellers E, Taback S, Dean H. Obesity and type 2 diabetes mellitus in a birth cohort of First Nation children born to mothers with pediatric-onset type 2 diabetes. Pediatr Diabetes 2011;12:219–228.
26. World Health Organization. Social Determinants of Health. The Solid Facts. 2nd edition. Wilkinson R, Marmot M, Eds. [Internet]. Available from http://www.euro.who.int/en/publications/abstracts/social-determinants-of-health--the-solid-facts. Accessed 21 December 2015.
27. Egert S, Braveman P, Sadegh-Nobari T, Grossman-Kahn R, Dekker M, Robert Wood Johnson Foundation Commission to Build a Healthier America. Exploring the Social Determinants of Health. Education and Health, Issue Brief 5 [Internet]. 2011. http://www.rwjf.org/en/library/research/2011/05/education-matters-for-health.html. Accessed 21 December 2015.
28. Gracey M, King M. Indigenous health part 1: determinants and disease patterns. Lancet 2009;374:65–75.
29. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med 1993;153:2093–2101.
30. Braveman P, Gottlieb L. The social determinants of health: it’s time to consider the causes of the causes. Public Health Rep 2014;129 Suppl. 2:19–31.
31. Duncan AE, Auslander WF, Bucholz KK, Hudson DL, Stein RI, White NH. Relationship between abuse and neglect in childhood and diabetes in adulthood: differential effects by sex.
national longitudinal study of adolescent health. Prev Chronic Dis 2015;12:E70.
32. Garg A, Jack B, Zuckerman B. Addressing the social determinants of health within the patient-centered medical home: lessons from pediatrics. JAMA 2013;309:2001–2002
33. Glazier RH, Bajcar J, Kennie NR, Willson K. A systematic review of interventions to improve diabetes care in socially disadvantaged populations. Diabetes Care 2006;29:1675–1688
34. Brackney DE, Cutshall M. Prevention of type 2 diabetes among youth: a systematic review, implications for the school nurse. J Sch Nurs 2015;31:6–21
35. Ho M, Garnett SP, Baur LA, et al. Impact of dietary and exercise interventions on weight change and metabolic outcomes in obese children and adolescents: a systematic review and meta-analysis of randomized trials. JAMA Pediatr 2013;167:759–768
36. McGavock J, Dart A, Wicklow B. Lifestyle therapy for the treatment of youth with type 2 diabetes. Curr Diab Rep 2015;15:568
37. Savoye M, Nowicka P, Shaw M, et al. Long-term results of an obesity program in an ethnically diverse pediatric population. Pediatrics 2011;127:402–410
38. Savoye M, Caprio S, Dziura J, et al. Reversal of early abnormalities in glucose metabolism in obese youth: results of an intensive lifestyle randomized controlled trial. Diabetes Care 2014;37:317–324
39. Protudjer JLP, Dumontet J, McGavock JM. My voice: a grounded theory analysis of the lived experience of type 2 diabetes in adolescence. Can J Diabetes 2014;38:229–236
40. Hood KK, Beavers DP, Yi-Frazier J, et al. Effects of a twelve-week randomized intervention of exercise and/or diet on weight loss and weight maintenance, and other metabolic parameters in obese preadolescent children. Horm Res 2009;72:287–301
41. Weigensberg MJ, Lane CJ, Ávila Q, et al. Imagine HEALTH: results from a randomized pilot lifestyle intervention for obese Latino adolescents using Interactive Guided ImagerySM. BMC Complement Altern Med 2014;14:28
42. Edwards RW, Jumper-Thurman P, Pliested BA, Yetting ER, Swanson L. Community readiness: research to practice. J Community Psychol 2000;28:291–307
43. Committee on Accelerating Progress in Obesity Prevention, Institute of Medicine. Accelerating Progress in Obesity Prevention: Solving the Weight of the Nation. 1st ed. Washington, D.C., National Academies Press, 2012, 478 pp
44. The Oxford Handbook of the Social Science of Obesity. 1st ed. Oxford, U.K., Oxford University Press, 2011
45. Shalitin S, Ashkenazi-Hoffnung L, Yackobovitch-Gavan M, et al. Insulin sensitivity is an important determinant of early abnormalities in glucose metabolism in obese preadolescents. Horm Res 2015;83:277–284
46. Nambam B, Silverstein J, Cheng P, et al. Pediatric Diabetes Consortium. A cross-sectional view of the current state of treatment of youth with type 2 diabetes in the USA: enrollment data from the Pediatric Diabetes Consortium Type 2 Diabetes Registry. Pediatr Diabetes. 11 March 2016 [Epub ahead of print]. DOI: 10.1111/pedi.12377
47. Tamborlane WV, Hammity MW, Dunger D, et al.; NICHD Diabetes Working Group. Expanding treatment options for youth with type 2 diabetes: current problems and proposed solutions: a white paper from the NICHD Diabetes Working Group. Diabetes Care 2016;39:323–329
48. Anderson BJ, McKay SV. Barriers to glycemic control in youth with type 1 diabetes and type 2 diabetes. Pediatr Diabetes 2011;12:197–205
49. Song SH. Complication characteristics between young-onset type 2 versus type 1 diabetes in a UK population. BMJ Open Diabetes Res Care 2015;3:e000044
50. Kahn SE, Haffner SM, Heise MA, et al.; ADOPt Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–2434
51. Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC; UK Prospective Diabetes Study (UKPDS) Group. UKPDS 26: Sulphonylurea failure in non-insulin-dependent diabetic patients over six years. Diabet Med 1998;15:297–303
52. Imperatore G, Boyle JP, Thompson TJ, et al.; SEARCH for Diabetes in Youth Study Group. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. Diabetes Care 2012;35:2515–2520