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Annu Rev Med. Author manuscript; available in PMC 2022 April 21.

Published in final edited form as:

Annu Rev Med. 2022 January 27; 73: 501–515. doi:10.1146/annurev-med-042120-012033.

Spectrum of Phenotypes and Causes of Type 2 Diabetes in Children

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Abstract

Several factors, including genetics, family history, diet, physical activity, obesity, and insulin resistance in puberty, appear to increase the risk of type 2 diabetes in youth. Youth-onset type 2 diabetes is often thought of as a single entity but rather exists as a spectrum of disease with differences in presentation, metabolic characteristics, clinical progression, and complication rates. We review what is currently known regarding the risks associated with developing type 2 diabetes in youth. Additionally, we focus on the spectrum of phenotypes of pediatric type 2 diabetes, discuss the pathogenic underpinnings and potential therapeutic relevance of this heterogeneity, and compare youth-onset type 2 diabetes with type 1 diabetes and adult-onset type 2 diabetes. Finally, we highlight knowledge gaps in prediction and prevention of youth-onset type 2 diabetes.

Keywords

type 2 diabetes; pediatrics; obesity; complications

INTRODUCTION

The rates of youth-onset type 2 diabetes continue to rise globally (1–3), portending a significant burden to healthcare systems. The rise in type 2 diabetes largely parallels the rise in childhood obesity, and in 2012 the estimated incidence of type 2 diabetes in the United States was 12.5 per 100,000 children (3). It is expected that by 2050 rates of type 2 diabetes

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DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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will quadruple in the United States, with an increase in prevalence of 178% from 0.27 per 1,000 to 0.75 per 1,000 youth (4).

Precision medicine aims to find strata of individuals who share characteristics that can be used to optimize disease prediction, prevention, diagnosis, prognosis, and treatment. Understanding the spectrum of phenotypes and causes of type 2 diabetes in children will bring us closer to that goal. In this review, we present what is known regarding predisposing influences that increase the risk of developing type 2 diabetes in youth, describe the heterogeneity of phenotypes that have been observed to date in pediatric type 2 diabetes and how they differ from children with type 1 diabetes or adults with type 2 diabetes, discuss gaps in our current understanding, and draw attention to potential future directions for research in precision medicine in youth-onset type 2 diabetes.

IDENTIFIED RISK FACTORS

Weight

Obesity predisposes to type 2 diabetes by decreasing insulin sensitivity in multiple tissues. However, not all obese children go on to develop type 2 diabetes, and some children develop type 2 diabetes at a relatively lower body mass index (BMI) percentile than others, demonstrating the involvement of additional factors beyond obesity in the disease pathogenesis. The location of obesity appears to be important; hepatic steatosis and visceral adiposity are strong risk factors associated with type 2 diabetes development (5, 6). Literature suggests that obesity-induced inflammation starting in childhood (7) may increase the risk of type 2 diabetes (8).

Diet

A diet high in calories, saturated or trans fat, and carbohydrates has been implicated in the development of type 2 diabetes. The standard American diet, characterized by a high proportion of processed starches, high glycemic load, and added sugars, stresses the physiological processes that regulate glucose metabolism. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, a multicenter randomized clinical trial of 699 youth aged 10 to 17 years, assessed diet quality among teens with recent-onset diabetes following a run-in period that included standard diabetes education (9). The study found that dietary intake consistently fell short of recommendations across age, racial/ethnic and sex groups, with a high percentage of energy from saturated fat (13–14%). Only 1% of TODAY study participants met American Diabetes Association recommendations for intake of <7% of energy from saturated fat, only 11% met fruit consumption goals, and only 5% met vegetable consumption goals. Similarly, the SEARCH for Diabetes in Youth (SEARCH) study found that total fat intake among youth with type 2 diabetes (n = 186) was 37–38% and saturated fat intake was 13–14% (10).

Remission of type 2 diabetes in adults is reported with a very low calorie diet (11). There are limited data to support the safety of this approach in growing children, and severe caloric restriction is unlikely to be practical in youth. In adults, short-term studies show that changes in diet composition, achieved by reducing added sugars, high-glycemic grains, and fructose,

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can lead to weight loss and improved insulin sensitivity (12, 13). A low-carbohydrate diet also resulted in a greater decrease in HbA1c in adults compared with a low-fat diet, despite similar weight loss (14). Similar studies are lacking in children.

Physical Inactivity

Physical activity promotes glucose use for energy and improves insulin sensitivity. The recommendations for physical activity from the American Academy of Pediatrics include 60 min of moderate to vigorous physical activity per day for all children (15). Youth with obesity and those with obesity and type 2 diabetes rarely meet these targets (16). At the time of enrollment in the TODAY study, males were engaging in less than 40 min per day of moderate to vigorous physical activity and females less than 30 min per day. The mean time of sedentary behavior was >500 min, or 8 h, per day in these youth when assessed by accelerometer (16).

Puberty

Puberty is associated with a transient physiological decrease in insulin sensitivity, even in lean, healthy children, and is normally associated with an increase in insulin secretion, a phenomenon that is impaired in children with type 2 diabetes relative to their degree of insulin resistance. The decrease in insulin sensitivity in puberty is believed to be related in part to higher levels of growth hormone, a counterregulatory hormone to insulin. Puberty seems to be an important inciting factor insofar as most youth are diagnosed with type 2 diabetes after the onset of puberty, although rare cases of prepubertal onset of type 2 diabetes have been reported (17–19). Adolescent females are more likely to develop type 2 diabetes than are adolescent males. Earlier onset of pubertal insulin resistance in females, along with greater adiposity and lower insulin sensitivity and physical activity, may explain the higher incidence of youth-onset type 2 diabetes in females (20).

Genetics

Genome-wide association studies have identified more than 65 genetic variants that increase the risk of developing type 2 diabetes. These genetic loci include genes involved in the production of glucose, β cell function, insulin sensitivity, insulin signaling, pancreatic development, and monogenic diabetes (21–25; for a summary, see 26). While most genetic studies on type 2 diabetes have been conducted in adults, data in children are becoming available. Recently, Giannini et al. (27) showed that in a multiethnic cohort of obese children, a genetic risk score of five type 2 diabetes risk variants was associated with higher risk of impaired glucose tolerance (IGT), lower insulin secretion, and increased risk of progressing from normal glucose tolerance to IGT or diabetes. The ProDiGY Gene Consortium was formed to identify genetic variants predisposing to youth-onset type 2 diabetes. ProDiGY is a collaboration of three studies (TODAY, SEARCH, and T2D-GENES) with 3,006 multiethnic youth-onset type 2 diabetes cases (mean age at the time of study, 15.1 ± 2.9 years) and 6,061 diabetes-free adult controls (mean age, 54.2 ± 12.4 years) (28). Six previously described genome-wide significant loci, *TCF7L2*, *MC4R*, *CDC123*, *KCNQ1*, *IGF2BP2*, and *SLC16A11*, as well as a novel locus in *PHF2*, were associated with an increased risk of type 2 diabetes in youth (28). However, most of the

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single-nucleotide polymorphisms identified showed only a small effect in causing type 2 diabetes and are likely modulated by other genes and environmental factors.

Race and Ethnicity

Type 2 diabetes is disproportionately prevalent among certain racial/ethnic groups, such as Native American, Hispanic, and African American populations (18, 29). This finding provides evidence for racial/ethnic differences in susceptibility to type 2 diabetes in youth, though why certain groups are at higher risk remains unclear. The SEARCH study reported an average 4.8% annual increase of youth-onset type 2 diabetes in the United States between 2002 and 2012, with an estimated overall incidence in the United States of 12.5 per 100,000 children (3). The largest increases in incidence were observed in non-Hispanic black, Native American, and Asian/Pacific Islander youth, followed by Hispanic youth, with a low and stable incidence in non-Hispanic white youth from 2002 to 2012 (3). The rate of complications related to type 2 diabetes in youth also differs by race and ethnicity, with higher rates of diabetic kidney disease (DKD) in Canadian First Nations youth versus non–First Nations groups (30) and a lower prevalence of nonalcoholic fatty liver disease in African American youth, intermediate prevalence in Caucasian and Asian youth, and highest prevalence in Hispanic youth (31, 32).

Maternal Diabetes and Obesity

Low birth weight and being born to a mother who had gestational diabetes increase the risk of developing obesity, IGT, and type 2 diabetes later in life (33). The SEARCH Case-Control Study found that exposure to both maternal gestational diabetes and maternal prepregnancy obesity was associated respectively with 5.7-fold-higher odds (95% CI, 2.4–13.4) and 2.8-fold-higher odds (95% CI, 1.5–5.2) of type 2 diabetes in the offspring. Combined exposure to maternal diabetes and obesity in utero accounted for 47% of the type 2 diabetes risk in this study (33).

Data from the TODAY study demonstrated that youth exposed to maternal diabetes during pregnancy (whether the mother was diagnosed with diabetes prior to pregnancy or had gestational diabetes mellitus), were diagnosed with diabetes at a younger age by more than 7 months, had ~0.3%-higher HbA1c at study enrollment, and had worse β cell function, as measured by the C-peptide oral disposition index, than youth who were not exposed to diabetes (34). The metabolic changes as a result of in utero exposure to maternal diabetes may be evident in infancy. Short et al. (35) reported that 1-month-old infants born to mothers with type 2 diabetes or gestational diabetes have 14%-lower resting energy expenditure and 26%-lower fat oxidation compared with controls, potentially implicating the diabetic milieu in metabolic reprogramming.

Breastfeeding

In observational studies, breastfeeding appears protective against later development of obesity and type 2 diabetes. In the SEARCH Case-Control Study, the prevalence of breastfeeding (any duration) was associated with significantly lower odds of type 2 diabetes (odds ratio, 0.26; 95% CI, 0.15–0.46) (36). However, when current BMI *z*-score was considered, the odds ratio was attenuated, suggesting that breastfeeding may protect against

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the development of type 2 diabetes in childhood but that the effect is mediated in part by current weight status (36). Additionally, poor maternal diet and shorter duration and intensity of breastfeeding may contribute to the risk of diabetes and obesity (37, 38).

Family History

There is a high concordance rate of type 2 diabetes in identical twins (29). Most adolescents with type 2 diabetes have a family member with the disease. In the TODAY study, almost 60% of participants reported at least one parent, full sibling, or half-sibling with diabetes, and almost 90% had an affected grandparent with diabetes (29). The increased risk of type 2 diabetes associated with family history reflects a shared genetic burden and environmental exposures, including maternal diabetes and obesity.

SPECTRUM OF DISEASE (HETEROGENEITY)

Type 2 diabetes is typically considered in pubertal youth with obesity, a family history of type 2 diabetes, features of the metabolic syndrome, and/or absent islet autoantibodies (39). Polydipsia and polyuria are observed in ~67% of youth with type 2 diabetes at presentation, while ~33% are diagnosed through routine screening of asymptomatic youth with obesity (17). Diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar state is present at diagnosis in 6–11% and 2% of youth with type 2 diabetes, respectively (17, 40). The median age of presentation with type 2 diabetes is 13.5 years, coinciding near the peak of pubertal physiological insulin resistance. The disease presents earlier in girls versus boys, possibly because of sex differences at the age of pubertal onset (17, 39, 41). In the following subsections, we discuss the progression to type 2 diabetes in youth, its phenotypic spectrum, and how it differs from that in youth with type 1 diabetes and adult-onset disease.

Progression of Type 2 Diabetes

Insulin resistance is thought to be the primary cause of type 2 diabetes development, leading to compensatory hyperinsulinemia and eventual failure of pancreatic β cells to produce adequate insulin relative to the degree of insulin resistance. Insulin resistance in adolescents is typically induced by a combination of obesity, inactivity, growth and pubertal hormones, and genetic factors, as discussed above. The presence of insulin resistance in muscle, adipose, and hepatic tissue in youth with type 2 diabetes has been demonstrated using hyperinsulinemic euglycemic clamps following tracer infusions (42). However, while obesity and insulin resistance are critical initial factors, progression to diabetes is not predicted by the degree of insulin resistance or by BMI. Instead, as found by both the TODAY study (43) and the Restoring Insulin Secretion (RISE) study of youth with recently diagnosed type 2 diabetes (44), glycemic failure is predicted by evidence of impaired β cell function. This finding argues for interventions aimed at preservation or improvement of β cell health.

Early-Onset Type 2 Diabetes

Age at diagnosis varies among patients within pediatric type 2 diabetes. Although type 2 diabetes is uncommon in children younger than 10 years, representing between 2.4% and 8% of cases in youth (17, 18), it is more frequent in populations with higher background

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prevalence of type 2 diabetes, such as Pima Indians (45) or Canadian First Nations (46). A study found that children diagnosed at this young age are more likely to be female and obese and have lower HbA1c than youth who present older than 10 years (17). Similarly, children with prepubertal type 2 diabetes have higher BMI, greater insulin resistance, and more frequent dyslipidemia than those presenting after the start of puberty (47–49). These findings support the hypothesis that, in the absence of the diabetogenic influence of growth and sex hormones at the levels observed during adolescence, other factors also contribute importantly to the development of type 2 diabetes before the onset of puberty. Increased fat accumulation in liver and skeletal muscle also correlates with and likely contributes to insulin resistance in the prepubertal years (20). Additionally, in Aboriginal youth with type 2 diabetes, an *HNF1A* G319S mutation is associated with early-onset type 2 diabetes despite lower frequencies of obesity and acanthosis nigricans and lower insulin levels, related to insulin secretion defect (50). The sum of and interactions between genetics and early-life exposures (33, 51), many of them possibly facilitated by social determinants of health, seem to underpin the development of early-onset type 2 diabetes. Further research in this area is needed to identify children at highest risk and implement targeted preventive strategies (52).

Sex Differences

As opposed to type 1 diabetes, which is slightly more common in males (53), type 2 diabetes is more prevalent in females, especially at younger ages (54–56). Genetic, environmental, and lifestyle causes, as mentioned above, have been proposed to explain the sex differences in type 2 diabetes incidence (reviewed in 57). In a cohort of 722 children with recent-onset type 2 diabetes, females were found to be younger at diagnosis and had more advanced pubertal stage, after adjustment for race/ethnicity, BMI, HbA1c, and glucose (58). These findings may be related to the earlier pubertal development that occurs in girls compared with boys. In addition, the trajectory of insulin sensitivity through pubertal development differs by sex; in girls, insulin sensitivity is lower during the prepubertal and early pubertal years and then increases in the last stages of pubertal development, while in boys, insulin sensitivity starts to diminish in late adolescence (20). Girls with type 2 diabetes frequently have elevated testosterone concentrations (59), whereas boys with type 2 diabetes have lower testosterone concentrations than similarly obese boys of the same Tanner stage (60, 61). Girls with type 2 diabetes are also less physically active than boys (16) and have lower cardiorespiratory fitness (62).

Sex differences also exist in response to diabetes medications. The TODAY study found that an HbA1c value above 6.3% following 2–6 months of metformin treatment alone distinguished girls who went on to lose glycemic control in follow-up, but for boys an HbA1c value above 5.6% predicted failure. These findings argue for earlier escalation of additional therapies in boys (63). In addition, girls in the TODAY study responded significantly better than boys to a combination of rosiglitazone and metformin versus metformin alone or metformin plus intensive lifestyle intervention (64). In contrast, boys in the TODAY study responded better than girls to the metformin–plus–intensive lifestyle intervention (64); however, this observation could be explained by the fact that boys had significantly higher levels of adherence to the exercise sessions (65).

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There also appear to be sex differences in the risk and type of diabetes complications in adults (reviewed in 66), but these are less well studied in children. Sex differences regarding diabetes complications reported in youth include a greater degree of cardiac left ventricular hypertrophy and increased left atrial dimension (67), a greater prevalence of cardiac autonomic dysfunction (68) and arterial stiffness (69), and a greater degree of nonalcoholic fatty liver disease in boys with type 2 diabetes versus girls (70). In contrast, girls with type 2 diabetes are disproportionally affected by DKD and have a threefold-higher risk of developing renal hyperfiltration in comparison to boys (71).

Phenotypic Type 2 Diabetes with Positive Islet Autoantibodies

Although islet autoantibody positivity supports a diagnosis of type 1 diabetes, it is found in only a small percentage (<10%) of children with a clinical diagnosis of type 2 diabetes (72). Positive islet autoantibodies in youth who phenotypically appear to have type 2 diabetes predict higher rates of ketosis and progression to insulin dependence (73), highlighting the importance of measuring islet autoantibodies (72). Some children with type 2 diabetes may also develop DKA at presentation of their diabetes or during their course of treatment (74). It is still unclear whether these children represent a pathophysiologically different subset, as has been described in adults, some of whom develop ketosis and DKA and have rapid loss of β cell function (75, 76).

At the other end of the spectrum of diabetes are children with autoimmune type 1 diabetes and obesity-related morbidities that are increasingly posing a challenge for diagnosis and treatment as obesity rates rise in type 1 diabetes (77). Youth with type 1 diabetes who are obese have higher heart rate, blood pressure, leptin, high-sensitivity C-reactive protein, hypertension prevalence, and arterial stiffness as well as a lower VO_2 peak in comparison to youth with type 1 diabetes of normal BMI. Their hypertension prevalence and resting heart rate exceed even those of youth with type 2 diabetes with similar BMI (77). Several randomized clinical trials with metformin in adolescents with type 1 diabetes and overweight or obesity demonstrated no effect on HbA1c but did improve measures of BMI, adiposity (78), insulin resistance (79), aortic stiffness, wall shear stress, and carotid intima-media thickness.

Maturity-Onset Diabetes in the Young

The classical features of type 2 diabetes, type 1 diabetes, and maturity-onset diabetes in the young (MODY) overlap considerably. Negativity for islet autoantibodies and detectable C-peptide levels support a diagnosis of MODY over type 1 diabetes, but both characteristics can be observed in individuals with otherwise indistinguishable type 1 diabetes. Manifestations consistent with insulin resistance, such as obesity or acanthosis nigricans, are typical of type 2 diabetes but do not exclude a diagnosis of MODY and are absent in so-called lean type 2 diabetes. As a result, MODY is often misdiagnosed as type 2 or type 1 diabetes. The SEARCH study found that 8% of youth with autoantibody-negative diabetes and C-peptide values of 0.8 ng mL^{-1} or higher had a known MODY mutation, and it estimated the prevalence of MODY in the overall pediatric diabetes population as 1.2% (80). However, among children with autoantibody-negative diabetes and C-peptide values at or above 0.8 ng mL^{-1}, only 6% had been correctly diagnosed with MODY by their

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clinician, whereas 36% received a diagnosis of type 1 diabetes and 51% of type 2 diabetes. Therefore, a diagnosis of MODY should be considered in children with atypical diabetes. A MODY probability calculator has been developed to help clinicians decide whether to conduct genetic testing for MODY (81). Further contributing to the overlap between diabetes types is the finding that some of the mechanisms in monogenic diabetes play a role, albeit a smaller one, in type 2 diabetes. For instance, the E23K variant in *KCNJ11*, mutation of which causes permanent neonatal diabetes mellitus (82), increases type 2 diabetes risk (83, 84), possibly via reduced glucose-induced insulin secretion (85).

DIFFERENCES FROM YOUTH-ONSET TYPE 1 DIABETES

Type 1 diabetes is typically characterized by insulin deficiency and is thought to result when an environmental trigger initiates an autoimmune response to pancreatic β cells in a genetically susceptible individual (86). Differences in prevalence, age at onset, presentation, and disease progression of youth with type 1 diabetes compared with type 2 diabetes have been reviewed in depth (87). Data from the SEARCH study consistently show a higher prevalence of comorbidities in young adults with type 2 versus type 1 diabetes despite similar duration of diabetes and even after adjusting for established cardiovascular risk (88, 89). At age 21 years, patients with type 2 versus type 1 diabetes showed higher rates of DKD, retinopathy, peripheral neuropathy, arterial stiffness, and hypertension (90, 91). There are also some comorbidities, including low levels of high-density lipoprotein cholesterol and adiponectin; elevated triglycerides, hepatic fat (62), and liver transaminases (92); and nonalcoholic steatohepatitis (6) that are observed in youth with type 2 diabetes but are not typically seen in youth with type 1 diabetes, especially in those with a normal BMI. Moreover, blindness and amputation by early adulthood have been reported only in youth-onset type 2 diabetes (88, 93), and rates of DKD, neuropathy, retinopathy, and cardiovascular death are currently higher in young adults with type 2 versus type 1 diabetes. These differences in complication rates highlight the heterogeneity in diabetes type with onset in youth.

DIFFERENCES FROM ADULT-ONSET TYPE 2 DIABETES

Pathophysiology

Youth with type 2 diabetes typically are more obese than older adults with type 2 diabetes (94). Studies have consistently shown that youth-onset type 2 diabetes is more common in females (3), whereas diabetes is more common in males later in life (95). Youth with type 2 diabetes are also less likely to be white than adults with type 2 diabetes (96), and youth are more likely to have a family history of type 2 diabetes and exposure to maternal diabetes in utero (94). The RISE study found that, in comparison to adults with similar BMI and HbA1c with recently diagnosed type 2 diabetes, youth with recently diagnosed type 2 diabetes were more insulin resistant; had lower insulin clearance and higher acute, steady-state, and maximal insulin secretion by oral glucose tolerance test (97) and by hyperglycemic clamp (96); and had hyperreactive β cells (98). In addition, in the RISE study, glycemic failure over time in youth was predicted by worse baseline first-phase, steady-state, and maximal β cell function measures and worse glycemia, whereas glycemic failure in adults given identical

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treatments was predicted by insulin resistance and by only first-phase, but not steady-state or maximal, β cell function (44).

The TODAY study reported a 20–35% annual decline in β cell function in youth aged 10–19 years with type 2 diabetes; as in the RISE study, this decline was predicted by lower baseline β cell function and higher HbA1c but not insulin sensitivity (64). The SEARCH study showed that β cell decline among youth with negative diabetes autoantibodies was predicted by age at diagnosis, race/ethnicity, HLA risk status, baseline HbA1c, and BMI *z*-score, with rates that varied between 6% and 30% annually (99). Both the TODAY and SEARCH studies showed that while some youth have a rapid decline in β cell function compared with adult-onset type 2 diabetes, where the annual decline is reported to be 7% (94), other youth appear to have a very mild form of diabetes with limited progression and excellent response to medical therapy (64, 99).

Complications

At diagnosis, patients with youth-onset type 2 diabetes had similar or worse metabolic risk profiles compared with those of patients with adult-onset type 2 diabetes (100). More rapid progression of complications also appear to be prominent in youth-onset type 2 diabetes; renal and neurological complications begin to appear within 5 years of type 2 diabetes diagnosis in First Nations youth, with major complications (dialysis, blindness, or amputation) starting to emerge 10 years after diagnosis (101). Risk of nonfatal cardiovascular disease is higher in early- versus late-onset type 2 diabetes (102), and the risk of myocardial infarction is higher in youth-onset type 2 diabetes than in patients presenting in middle or later life (103).Nonalcoholic fatty liver disease is twice as common in adolescent versus older patients with type 2 diabetes (103) and youth-onset disease is associated with a significantly higher incidence of end-stage renal disease and mortality in middle age– versus adult-onset type 2 diabetes (104). A large retrospective study in Asia found that diabetes-related eye disease is more common in early-onset (i.e., onset before age 30 years) versus late-onset type 2 diabetes (105), and recently the TODAY study showed nearly 60% of young adults with youth-onset diabetes have at least one microvascular complication (106).

Medication Responses

According to the TODAY study, the rate of loss of glycemic control on either metformin monotherapy or combination therapy with rosiglitazone appears to be three- to fourfold higher in youth than published rates of glycemic failure on these same medications in adults (107). The RISE study found that, despite their higher insulin secretion and higher β cell responsiveness, youth responded worse to metformin monotherapy or insulin followed by metformin treatment, and had a more rapid decline in β cell function and loss of glycemic control than adults given the same treatments (108).

Rosiglitazone is known to increase subcutaneous adipose tissue and decrease visceral adipose tissue in adults (109). However, in youth in the TODAY study, despite providing superior glycemic control, the addition of rosiglitazone to metformin caused greater visceral and subcutaneous adipose deposition in comparison to either metformin alone or

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metformin plus an intensive lifestyle intervention (110), arguing for different responses to thiazolidinediones in youth versus adults. The recent ELLIPSE (Evaluation of Liraglutide in Pediatrics with Diabetes) study of liraglutide in youth with type 2 diabetes demonstrated encouraging short-term improvements in glycemia and BMI (111), arguing for studies of the impact of glucagon-like peptide 1 agonists on β cell function and diabetes complications in youth. Sulfonylureas are not recommended in youth because of their lack of benefit in glycemic control over metformin, higher degrees of weight gain and hypoglycemia, and potential for accelerating β cell failure.

SUMMARY AND FUTURE DIRECTIONS

Type 2 diabetes in youth is influenced by a combination of risk factors, resulting in heterogeneity in the presentation and progression of disease. The current classification of type 2 diabetes in youth as a single entity does not capture this spectrum of the disease and, importantly, does not help guide individualized clinical management. Alternative classifications using insulin resistance/sensitivity status and autoimmunity have been proposed (112, 113), but unfortunately, they are not yet widely employed in clinical practice.

Few studies focus on the unique phenotypic presentations of type 2 diabetes. For example, positivity for islet autoantibodies is often an exclusion criterion in clinical trials for youth with type 2 diabetes (39, 111). Similarly, children with type 2 diabetes diagnosed before age 10 are often excluded from trials. There are also gaps in our knowledge of the preclinical evolution and pathophysiology of youth-onset type 2 diabetes, including insulin clearance and glucose effectiveness, which can only be provided by large longitudinal cohort studies starting early in life (at or before birth) and continuing through clinical onset of type 2 diabetes. In addition, there are important unknowns in our knowledge about the responses to medications in this unique patient group. The RISE study included a head-to-head comparison of youth and adults with similar disease duration and BMI in order to determine how youth-onset disease differs from adult-onset type 2 diabetes, but because of the lack of US Food and Drug Administration approval at the time of the study, the effects of longer-term liraglutide use on β cell function and disease progression in youth are currently unknown (111). Similarly, we lack data on youth response to sodium-glucose cotransporter 2 inhibitors or to vertical sleeve gastrectomy, a treatment increasingly used in adults with type 2 diabetes (114).

We need to enhance our understanding of how to use a combination of genetics, islet autoantibodies, β cell function, clinical phenotype, environmental factors, and social determinants to apply precision to the prediction, prevention, diagnosis, treatment, and prognosis of type 2 diabetes in youth (115–117). For example, should preventive strategies focus on altering insulin sensitivity, β cell insulin secretion, insulin clearance, or non-insulin-mediated glucose uptake? Should healthy lifestyle modification focus on genetically at-risk youth or be offered to the entire population, or would a combination of approaches be most successful? When should prevention start, at what stage during the preclinical evolution of youth-onset type 2 diabetes, and during which life stage (in utero, infancy, before or during puberty)? Once type 2 diabetes is diagnosed, should treatments differ according to age, sex, and race, given that the TODAY study showed different responses

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to medication by sex and by race/ethnicity? Similarly, should specific genes, if present, dictate therapy or add-on therapy? Finally, should specific therapies be chosen on the basis of clinical presentation, BMI at disease onset, or β cell response over time? In the field of monogenic diabetes, identification of unique molecular defects that cause a phenotype has allowed the design of targeted treatments. Describing novel mutations and expanding our knowledge about the molecular mechanisms underpinning disease, associated phenotypes, and interactions with environmental factors and lifestyle are areas of current research.

Over the last few decades, significant progress has been made in our knowledge about and treatment of type 2 diabetes in youth, but many gaps remain. Continued research on this relatively new pediatric disease is needed, and there is much more to be learned before we can make an impact in the lives of people with youth-onset type 2 diabetes.

ACKNOWLEDGMENTS

Efforts related to the content reviewed herein are supported by grants from the National Institutes of Health (R01 DK124395 and R01 DK121843-01 to M.J.R. and R01 DK119450 to A.S.S. and K.J.N.).

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