Prevention and Treatment of Type 2 Diabetes in Youth

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Abstract

Parallel to the increase in obesity worldwide, there has been a rise in the prevalence of type 2 diabetes mellitus (T2DM) in children and adolescents. The etiology of T2DM in youth, similar to adults, is multifactorial including genetic and environmental factors, among them obesity, sedentary lifestyle, family history of the disease, high-risk ethnicity and insulin resistance phenotype playing major roles. Treatment of T2DM should not have a glucocentric approach; it should rather target improving glycemia, dyslipidemia, hypertension, weight management and the prevention of short- and long-term complications. Prevention strategies, especially in high-risk groups, should focus on environmental change involving participation of families, schools, the food and entertainment industries and governmental agencies. Presently, limited pharmacotherapeutic options need to be expanded both for childhood T2DM and obesity. The coming decades will prove very challenging for healthcare providers battling socioeconomic waves conducive to obesity and

T2DM. Evidence-based research and clinical experience in pediatrics, possibly modeled after adult trials, need to be developed if this public health threat is to be contained.

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Introduction

Not long ago, type 2 diabetes mellitus (T2DM) was regarded as a disease of adulthood, with type 1 diabetes (T1DM) accounting for almost all cases seen in children and adolescents [1]. While it is true that T2DM is still more prevalent in adults, there is increasing evidence that onset in youth is frequently observed [2]. This relatively new phenomenon, strongly associated with the escalating prevalence of obesity, brings a serious new aspect to the diabetes epidemic, especially in certain ethnic groups (African-Americans, Native Americans and Hispanics) [3–7]. However, the problem of youth T2DM is not unique to North America because it has also been reported in children from Africa [8], Asia [9–12], Australia [13], and Europe [14–17]. For a comprehensive evaluation of prevention and treatment strategies of youth T2DM, this chapter will briefly review the pathophysiology, risk factors, diagnosis and screening of the disease.

Pathophysiology

The etiology of T2DM in youth, similar to adults, is multifactorial including genetic and environmental factors. It results from the combination of insulin resistance and impaired β -cell function. Insulin resistance is strongly associated with obesity, mainly visceral adiposity, and is believed to be an early abnormality in the development of T2DM preceding the impairment in insulin secretion [18, 19]. Early in the pathogenesis of glucose intolerance, insulin-producing β -cells are able to compensate for the insulin resistance by increasing insulin secretion. This compensatory hyperinsulinemia maintains glucose homeostasis in the face of insulin resistance. The failure of the pancreatic β -cell, resulting in insufficient insulin secretion, underlies the transition from insulin resistance to impaired glucose tolerance (IGT) and clinical diabetes [18, 20]. Limited cross-sectional studies in children show that T2DM and IGT are characterized by impaired insulin secretion in the backdrop of insulin resistance [21–26]. Our group was the first to demonstrate that in adolescents with T2DM, insulin sensitivity is around 50% lower, and first phase insulin is $\sim$ 75% lower compared with obesity-matched non-diabetic adolescents [24]. This degree of impairment in insulin secretion appears to be more severe than that observed in adults, especially considering the relatively short duration of diabetes in youth. There are no systematic longitudinal observations regarding the natural history of progression to T2DM in high-risk youth. In adults, the United Kingdom Prospective Diabetes Study (UKPDS) found that β -cell function was 50% of normal at the time of clinical diagnosis of T2DM [27]. In 5,396 adults from the Botnia Study, an absolute decompensation of β -cell function characterized the transition from IGT to T2DM [20]. Limited longitudinal case observations by our group are consistent with the adult findings [28, 29]. In a high-risk youth the transition from normal glucose tolerance to IGT or pre-diabetes was associated with rapid weight gain and decline in the insulinogenic index, and progression to T2DM was associated with further weight gain, decrease in insulin sensitivity and a dramatic decline in insulin secretion [28]. In an established T2DM youth followed over 6 years, the decline in β -cell function was approximately 15%/year with no substantial change in insulin sensitivity [29]. This is a more than twofold faster decline in β -cell function compared with adult UKPDS data (7%/year) [27]. Additional studies are needed to determine if this accelerated loss of β -cell function is generalizable to all youths with T2DM.

Risk Factors

Risk factors for youth T2DM include family history of the disease, high-risk ethnicity, obesity, sedentary lifestyle and insulin resistance phenotype.

Family History of T2DM

Although few susceptibility genes have been identified so far, a very recent finding points towards a gene locus that dramatically increases the risk of T2DM in Icelanders, Danes and a US cohort, specifically a variant of transcription factor 7-like 2 (TCF7L2) gene [30]. The genetic component of T2DM is evidenced by the strong heritability of the disease [31]. A strong family history of T2DM is present in most pediatric patients regardless of ethnic background [32]. Our studies demonstrate that family history of T2DM is associated with approximately 25% lower insulin sensitivity in prepubertal healthy African-American children compared with their peers without a family history of T2DM [33]. White children who do not have diabetes, but have a positive family history of the disease, have lower insulin sensitivity with an inadequate compensation in insulin secretion compared with youngsters without a family history of diabetes [34].

Ethnicity

The highest incidence of T2DM in youth in the USA is evident in African-Americans, Native Americans, especially Pima Indians, and Hispanics [3–6]. Studies have shown that Black children and Hispanic youth are hyperinsulinemic and insulin-resistant compared with their white peers [35, 36]. These racial differences could be attributable to genetic differences [37] or to environmental/cultural differences [35]. Our studies have shown that for the same obese BMI, Black adolescents have around 30% lower visceral fat compared with their white obese peers but they are at higher diabetes risk because of inadequate compensation of insulin secretion for the degree of insulin resistance [38]. Moreover, differences in adiponectin levels, lower in Blacks, may be a biological marker which predisposes them to a greater risk of insulin resistance [39, 40]. In the presence of such racial differences in risk of T2DM, it remains to be determined if the natural history and the tempo of progression to T2DM differ between different racial groups.

Obesity and Sedentary Lifestyle

Obesity, an outcome of positive energy balance and the result of higher caloric intake and sedentary lifestyle, may be the most important environmental factor in the

Table 1. Criteria for the diagnosis of impaired glucose tolerance and diabetes

Plasma glucose (PG)	Normal	IFG	IGT	Diabetes
Fasting PG	<100 mg/dl (5.6 mmol/l)	100–125 mg/dl (5.6–6.9 mmol/l)	N/A	≥ 126 mg/dl (7.0 mmol/l)
OGTT 2-hour PG	<140 mg/dl (7.8 mmol/l)	N/A	140–199 mg/dl (7.8–11.1 mmol/l)	≥ 200 mg/dl (11.1 mmol/l)
Random PG				≥ 200 mg/dl (11.1 mmol/l) + symptoms

IFG = Impaired fasting glucose; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test; 2-hour PG = plasma glucose at 2 h after ingestion of glucose; N/A = not applicable.

Data from American Diabetes Association Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003; 26:316.

development of insulin resistance and T2DM [41]. Insulin resistance and hyperinsulinemia are metabolic features of overweight youth [42, 43]. As in adults [44], within a given ethnic group, it is visceral fat, rather than total body fat, that correlates with basal and stimulated insulin levels and inversely with insulin sensitivity [39, 42, 45–47]. With increasing rates of obesity in children [48] and enlarging abdominal girth [49], prevention and treatment of T2DM should target prevention and management of obesity.

Insulin Resistance Phenotype

Puberty [50], polycystic ovary syndrome [51, 52], acanthosis nigricans [53] and exposure to gestational diabetes [54, 55] or intrauterine growth retardation [56, 57] have insulin resistance as a metabolic feature and are associated with an increased risk of T2DM [58].

Diagnosis

The criteria for the diagnosis of diabetes in children, based on standard values of fasting blood glucose, random blood glucose and the oral glucose tolerance test (OGTT), are the same as in adults [59] (table 1). However, while the American Diabetes Association (ADA) defines impaired fasting glucose (IFG) as a fasting plasma glucose ≥100 mg/dl (≥5.6 mmol/l) but <126 mg/dl (<7.0 mmol/l), the International Diabetes Federation (IDF) [60] and the World Health Organization (WHO)

[61] define the lower end of IFG as a fasting plasma glucose level ≥110 mg/dl (≥6.1 mmol/l). Moreover, there are some differences in terminology, with pre-diabetes used in Europe in favor of IGT by the USA. In adults, recent data from men in the Israeli Defense Forces 26–45 years of age, revealed a progressively increased risk of T2DM with fasting plasma glucose levels of 87 mg/dl (4.83 mmol/l) or more, as compared with those whose levels were in the bottom quintile <81 mg/dl (4.5 mmol/l) (*p* for trend <0.001). Higher fasting plasma glucose levels within the normoglycemic range, the authors concluded, constituted an independent risk factor for T2DM among young men, and such levels could help, along with body mass index (BMI) and triglyceride levels, to identify apparently healthy men at increased risk for diabetes [62]. In our research experience, the reproducibility of the fasting glucose in children is quite varied. Among 150 youth with normal glucose tolerance, ages 8–18 years old admitted twice within a 1- to 3-week period to the General Clinical Research Center at Children's Hospital of Pittsburgh, the correlation between the fasting plasma glucose performed during the two admissions is only 0.598. The variation was higher in the upper normal ranges of glucose [unpubl. data]. Moreover, data are lacking regarding the longitudinal outcome of different fasting cut-offs in children. Therefore, additional studies are needed to compare diagnostic categories in the pediatric population according to the ADA versus the WHO diagnostic criteria before arriving at valid conclusions. Once the diagnosis of diabetes is established, it is important to

Table 2. Screening guidelines for T2DM in children and adolescents

Major criteria: Obesity as defined by
BMI >85th percentile for age and gender or
Body weight for height >85th percentile or
Body weight >120% of ideal for height
Plus any two of the following risk factors:
Family history of T2DM in first- or second-degree relatives
Race/ethnicity (American-Indian, African-American,
Hispanic, Asian/Pacific Islander)
Signs/symptoms of insulin resistance (acanthosis nigricans,
hypertension, dyslipidemia, polycystic ovary syndrome)

Data from American Diabetes Association. Type 2 diabetes in children and adolescents. *Diabetes Care* 2000;23:381–389.

distinguish between T1DM and T2DM to optimize therapy. Given the heterogeneity of clinical presentation of T2DM in children, classification into type 1 or type 2 may not be made reliably on the basis of clinical presentation. Clinical signs helpful in distinguishing T2DM from T1DM are obesity, signs of insulin resistance and elevated C-peptide levels [58]. However, with the prevalence of obesity increasing not only in the general population but also in children with T1DM [63], it is becoming increasingly difficult to distinguish between the two types of diabetes. Markers of the cellular-mediated immune destruction of the β -cell such as islet cell antibodies, glutamic acid decarboxylase antibodies, tyrosine phosphatase-like protein autoantibodies, and insulin antibodies, can be useful, as they are usually identifiable in those individuals with or at risk of autoimmune T1DM. Currently, absence of diabetes autoimmune markers is a prerequisite for the diagnosis of T2DM in children and adolescents [32]. Some contradictory data exist in the literature, however. Studies from the First Nation Youth of Manitoba [64], the USA [65–67] and Germany [68] have shown the presence of pancreatic autoantibodies in children with clinically diagnosed T2DM. Preliminary unpublished data from our group suggest that the metabolic profile of insulin resistance and secretion is very different between those with vs. without pancreatic autoantibodies [69]. The clinical translation of the presence of β -cell autoantibodies in youth with clinically diagnosed T2DM is uncertain. Longer prospective studies are needed for definite answers.

Screening

In a clinical setting and in order to make a timely diagnosis of T2DM in children, the ADA recommends screening of high-risk children. The major criteria for screening are obesity with two additional risk factors (table 2). Screening should start at 10 years of age or at onset of puberty, if it occurs at an earlier age, and should be performed every 2 years. The ADA recommends fasting plasma glucose as a screening tool because of its greater convenience. This is in disagreement to the WHO recommendation of an OGTT. Adult data show that approximately 30% of all persons with undiagnosed diabetes have a non-diabetic fasting glucose [70]. A study in obese children with IGT showed that the prevalence of IFG (based on the former threshold of 111–125 mg/dl) was low (<0.08%) [71]. Another study, evaluating 710 Italian obese children, showed that 30 had IGT (4.2%) and 3 had IFG (0.4%), 2 of whom also had IGT [72]. Adult data suggest that screening with only a fasting glucose will miss around 30% of abnormal 2-hour glucose levels during an OGTT [73]. In a study of 102 high-risk obese children, using the ADA screening criteria would have missed 68% of IGT and 66% of T2DM diagnosed with an OGTT [74]. Unpublished preliminary data from our group shows that only 27% of children who had IGT, also had IFG (based on the current ADA threshold of 100–125 mg/dl), suggesting that an OGTT may be needed to identify those at high risk of developing diabetes. In our experience, we favor performing an OGTT if there is a high risk of developing diabetes. We would also check an HbA1c, not as a screening tool, but to monitor treatment if somebody is diagnosed with T2DM.

Treatment

Ideally, the care of children with T2DM should be shared among a pediatric endocrinologist, diabetes nurse educator, nutritionist, physical-activity leader and behavioral specialist. It should be family-centered and, as obesity is at the core of this problem, include lifestyle modification with increase in physical activity, decrease in sedentary behavior and changes in nutritional habits. It is true that the effectiveness of lifestyle modification may be limited, but so are its risks [41, 58].

Treatment regimens should be individualized and glycemic goals clearly stated. Ideally, therapy should try to eliminate symptoms of hyperglycemia, promote achievement of a healthy body weight and growth and reach and

maintain near-normoglycemia (fasting blood glucose <126 mg/dl). Glycosylated hemoglobin (HbA1c) should be checked every 3 months. Based on the ADA recommendations, the goal should be $\leq 7\%$ [32]. The American College of Endocrinology [75] and the European Diabetes Policy Group of the International Diabetes Federation (European Region) [76] recommend a more stringent goal of $\leq 6.5\%$, for adults, based on evidence showing that there is no minimum increased level of HbA1c at which complications of diabetes and mortality do not occur [77]. Figure 1 provides a proposed algorithm for the management of children with T2DM based on our present knowledge and approved medications. The ultimate goal is to decrease the acute and chronic complications associated with diabetes mellitus and to reduce the risk of premature death. Atherosclerotic disease is the major cause of mortality and morbidity in adults with T2DM [78]. The origin of atherosclerosis is early in childhood with progression toward clinically significant lesions in adulthood [79, 80]. Carotid artery intima media thickness and aortic pulse wave velocity, a measure of arterial stiffness, are non-invasive measures of subclinical atherosclerosis that have been used as surrogate measures of cardiovascular events in adult studies [81, 82]. Our group has recently demonstrated significantly higher aortic pulse wave velocity measurements in adolescents with T2DM compared with obese and normal weight controls, with no differences in intima media thickness among the three groups [83]. The elevated aortic pulse wave velocity in the children with T2DM was comparable to values reported in 41- to 59-year-old obese adults [84] and in approximately 40-year-old men in the Baltimore Longitudinal Study of Aging [82]. Such an observation is consistent with a process of premature aging of the cardiovascular system in youth with T2DM and supports the need to achieve tight metabolic control in these children. In adults with T2DM, the UKPDS [85] and the Kumamoto Study [86] demonstrated that intensive treatment improved metabolic control and decreased the risk of complications. In the UKPDS, for each 1% reduction in mean HbA1c, there was an overall reduction of around 21% in risk of diabetes-related endpoints (i.e., 21% for deaths, 14% for myocardial infarction, and 37% for microvascular complications) [87]. Follow-up of a cohort of men in Norfolk participating in the European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk) showed that HbA1c concentration was a significant predictor of death from cardiovascular disease and all-cause mortality. An increase of 1% in HbA1c was associated with a 28% increase in risk of death independent of

Fig. 1. Proposed algorithm for the management of youth with T2DM. * 1,000 mg with dinner for 1–2 weeks, and if well tolerated without gastrointestinal discomfort increase the dose to 1,000 mg twice a day [adapted from 41].

age, blood pressure, serum cholesterol, BMI, and cigarette smoking habit [88]. Even though such information is not available in pediatrics, common sense would dictate that treatment of youth with T2DM should be comprehensive and not glucocentric (fig. 2). It should include screening and treatment of co-morbidities, particularly hypertension and dyslipidemia which are common conditions in this population.

Pharmacologic Options

Pharmacologic management of youth with T2DM depends on the severity of presentation. Patients with mild hyperglycemia (126–200 mg/dl) and HbA1c <8.5% or an incidental diagnosis of T2DM can be treated initially with metformin, the only drug, except for insulin, approved in Europe and in the USA by the Food and Drug Administration for pediatric patients with T2DM. However, this must be combined with therapeutic lifestyle intervention with the objective of weight loss and maintenance. The antihyperglycemic action of metformin is due to the inhibition of endogenous (liver) glucose production, mainly gluconeogenesis, and improved insulin-stimulated glucose uptake in peripheral tissues [89]. In addition, it can cause modest weight loss in overweight

Fig. 2. Comprehensive care of T2DM in youth.

T2DM patients, improve lipid profile, increase fibrinolysis [90, 91] and decrease transaminases in patients with non-alcoholic steatohepatitis [92].

Metformin gained approval for its use in pediatrics based on a randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of the medication, at doses up to 1,000 mg twice daily in 82 children aged 10–16 years. The participants were treated up to 16 weeks. Metformin significantly improved glycemic control and HbA1c values with no cases of lactic acidosis and minimal side effects [93]. At the present, metformin is prescribed in non-ketotic patients starting at a low dose and escalating it over a 1- to 3-week period to the final therapeutic dose of 1,000 mg twice a day. We typically start patients on 1,000 mg with dinner for 1–2 weeks, and if well tolerated, without gastrointestinal discomfort, we increase the dose to 1,000 mg twice a day. On occasion we may start at a 500 mg/day dose based on the individual patient's need and increase slowly. A modest amount of weight loss is a desirable effect (the mechanism not clearly understood). This medication should not be given to a child who has renal impairment or hepatic or cardiopulmonary insufficiency, or is undergoing evaluation with radiographic contrast materials, because it may precipitate lactic acidosis. Patients and families should be instructed about the hazards of alcohol consumption while on metformin because of this risk. It should also not be prescribed to children with T2DM with ketosis. However, it can be started once the child recovers from ketosis after treatment by rehydration and insulin. The most frequently encountered side effect is mild gastrointestinal discomfort which rarely necessitates drug discontinuation.

There are no other oral hypoglycemic agents that have been approved for use in the pediatric population, though

rosiglitazone, a potent insulin sensitizer, was evaluated in juvenile-onset T2DM. The study included 195 obese T2DM children (age range 8–17 years), in a 24-week double-blind, randomized, metformin-controlled, parallel-group design. Participants were randomized to rosiglitazone, maximum dose of 4 mg twice a day, or metformin, maximum dose 1,000 mg twice a day. Median reductions in HbA1c from baseline (rosiglitazone group: -0.25% , $p = 0.027$; metformin group: -0.55% , $p < 0.0001$) and from screening (rosiglitazone group: -0.5% , $p = 0.011$; metformin group: -0.5% , $p = 0.0037$) to week 24 were statistically significant in both groups. Differences between groups were not statistically significant. The rosiglitazone group gained ~ 3 kg at 24 weeks, with the occurrence of peripheral edema in 1 child [94].

Sulfonylureas (e.g. glimepiride, glyburide, glipizide), which increase both basal and meal-stimulated insulin secretion, have been used in the treatment of T2DM in adults for more than half a century. A recent single-blind, 26-week study compared metformin and glimepiride in 263 obese youth with T2DM. Glimepiride was started at 1 mg once a day and increased to 8 mg once a day, with metformin escalated to a maximum of 1,000 mg twice a day. There was no significant difference in HbA1c reduction between the two groups (glimepiride: change from baseline $-0.85 \pm 0.30\%$, metformin: $-0.70 \pm 0.30\%$). However, there was a difference in weight gain (kg) (glimepiride: change from baseline $+2.2 \pm 0.6$ and metformin: $+0.7 \pm 0.64$) [95]. Recent therapeutic advances in adults with T2DM including GLP-1 analogs (exenatide) or amylin analogs (pramlintide) may prove to be beneficial in youth. GLP-1 is secreted upon the ingestion of food and has numerous functions including promoting satiety and reducing appetite, enhancing glucose-de-

pendent insulin secretion and decreasing postprandial glucagon secretion and helping to regulate gastric emptying [96–99]. In adults, amylin analogs have been shown to reduce food intake and weight. They also reduce glucose levels by suppressing postprandial glucagon secretion and delaying gastric emptying [100, 101]. These agents have not been tested in children to date.

When a child presents with severe hyperglycemia (>200 mg/dl, $\text{HbA}_{1c} > 8.5\%$ and/or ketosis), he/she should be treated initially with insulin to rapidly achieve metabolic control. Once the youth recovers from ketosis after hydration and treatment with insulin, and once the diagnosis of T2DM is made unequivocally (absent pancreatic autoantibodies), metformin with lifestyle intervention should be started and insulin may be weaned gradually if normoglycemia is maintained [58]. Accelerated deterioration in β -cell function may occur in some youth with T2DM needing the early introduction of insulin to achieve metabolic control [29].

Because evidence in adult patients suggests that the early introduction of insulin therapy facilitates glucose control in the long term, possibly reversing to some extent the damage induced by hyperglycemia on β cells and insulin-sensitive tissues, such an approach has been proposed by some in youth T2DM [102, 103]. New insulin analogs, such as glargine and detemir, may allow for more options in the treatment of patients with T2DM. Insulin glargine, a long-acting analog has a prolonged duration of action (~ 24 h) with a relatively smooth blood concentration profile without a pronounced peak, making it useful as a once-a-day basal insulin. Clinical trials in adults with T2DM have shown that bedtime insulin glargine is effective in promoting optimal glycemic control [104]. Similar studies in children with T2DM are needed.

Management of Complications

Acute Complications

Diabetic ketoacidosis and hyperosmolar non-ketotic coma can be life-threatening complications in youth with T2DM [32, 105, 106]. Diabetic ketoacidosis may not be present at diagnosis of T2DM but could present years later during acute intercurrent illness. Although hyperosmolar non-ketotic coma is much less frequent, its case fatality in youth is reported to be 14.3% [105]. Either of these acute complications requires tertiary care referral to specialized pediatric diabetes centers for inpatient management by a medical team with experience in the appropriate fluid hydration, insulin therapy, correction of electrolytes, neurologic/mental status evaluation and airway management [32, 106].

Dyslipidemia

Fasting lipid levels should be measured after establishing good metabolic control upon diagnosis and then annually. The management of dyslipidemia starts with dietary changes and increased physical activity. Target levels and treatment recommendations have been established by the ADA consensus for the treatment of diabetes in youth (fig. 2). Goals include an LDL cholesterol <100 mg/dl, HDL cholesterol >35 mg/dl and triglyceride levels <150 mg/dl. Treatment should include diet, maximizing glycemic control and weight reduction [107]. If lipid levels remain elevated after 6 months of lifestyle modification, medical therapy should be started. HMG-CoA inhibitors (statins) are the most commonly used lipid-lowering agents in pediatric patients and are currently indicated in boys >10 years and in postmenarchal girls with familial hypercholesterolemia.

Hypertension

Blood pressure should be measured in all children with T2DM at every clinic visit. Pre-hypertension is defined as either systolic or diastolic blood pressure between the 90th and 95th percentile for age, sex and height, and above the 95th percentile is considered hypertension (fig. 2). Every T2DM child's medical record should include the standardized blood pressure tables for an accurate evaluation of the patient's blood pressure percentile similar to BMI charts [108]. If and when hypertension is documented, treatment should be initiated including lifestyle modifications, with weight loss, dietary changes and increased physical activity. If it does not respond to these interventions, the first line of pharmacological treatment is angiotensin-converting enzyme inhibitors. If normotension is not achieved, combination therapy may be considered by adding angiotensin receptor blockers, calcium channel blockers, cardioselective β -blockers and/or low-dose diuretics [108]. To date, there are no pharmacotherapeutic outcome studies of hypertension or dyslipidemia in youth with T2DM.

Prevention

It is known that T2DM is a progressive disease that often begins years prior to clinical diagnosis, with an increase in insulin resistance, a period of compensatory hyperinsulinemia, and then a decline in pancreatic function with decrease in insulin secretion [23, 24, 40]. A proposed scheme of the natural history of T2DM progression in youth with several unknowns, represented as question

Fig. 3. Progression to T2DM in youth. IS = insulin sensitivity; IR-NGT = insulin resistance – normal glucose tolerance; IR-IGT = insulin resistance – impaired glucose tolerance [see 23, 24, 40].

marks, is depicted in figure 3. The natural course of T2DM provides the opportunity to intervene at different steps and prevent the development of T2DM. However, there are still many unanswered questions related to this progression in youth, i.e.: What is the induction time for obesity-related diabetes in youth? What is the population prevalence of T2DM and IGT? What is the magnitude of diabetes risk for every kilogram of weight gain and/or BMI increase in youth? And, as important, what are the methods that will prove to be feasible and effective to prevent this condition? These questions can only be answered with careful, systematic research in pediatrics, taking advantage of the accrued knowledge in adults.

What Have We Learned from Adult Prevention Trials?

There is now convincing evidence from controlled clinical trials that, in adults, lifestyle modification can prevent or delay the development of T2DM in high-risk individuals. Two studies from the 1990s, the Malmo Feasibility Study [109] and the Da Qing Impaired Glucose Tolerance and Diabetes Study [110], reported that lifestyle changes in subjects with IGT led to a significant decrease in the incidence of diabetes. Two more recent randomized, controlled clinical trials have demonstrated the benefits of lifestyle intervention on the prevention or delay in the progression from IGT to T2DM. The Diabetes Prevention Program (DPP) demonstrated that among adults with IGT, over a 3-year period, a low-fat diet in combination with 150 min/week of exercise and around 5–7% body weight loss reduced the risk of converting to diabetes by 58% compared with no lifestyle intervention. Metformin also reduced the risk but not as dramatically as lifestyle changes (38%) [111]. A 58% reduction in progression from IGT to T2DM was also demonstrated in the Finnish Diabetes Prevention Study, comparing indi-

viduals with IGT who received aggressive lifestyle intervention with those who did not [112]. Other studies have focused on the use of different medications to prevent or delay the development of T2DM, among those the STOP-NIDDM randomized trial, which evaluated the effect of acarbose in subjects with IGT, showing that this medication was associated with a 32% decreased conversion to T2DM and an increased reversion of IGT to normal glucose tolerance [113], the TRIPOD Study which randomized Hispanic women with prior gestational diabetes mellitus to troglitazone versus placebo and found a reduction of 56% in diabetes risk in the group on the medication [114], and the XENDOS study which randomized subjects with a BMI >29 to lifestyle change plus either orlistat or placebo and found a 37% risk reduction in the incidence of diabetes in the former group [115]. Bariatric surgery-induced weight loss in adults with clinically severe obesity has also been found to prevent the progression from IGT to diabetes mellitus by >30-fold [116].

Regarding duration of the effects, information is quite limited. In the DPP, follow-up analysis showed that in patients who took metformin and were reassessed with a repeat OGTT 1–2 weeks after discontinuation of the medication, a sizable minority had developed diabetes, so the diabetes-preventing effect of metformin was reduced from 31 to 25% [117].

What Do We Know about Pediatric Prevention Trials?

Very limited studies in pediatrics have assessed the outcome of lifestyle intervention or pharmacotherapy on obesity and metabolic parameters but none in youth with IGT to evaluate progression to T2DM. One main reason for this is the fact that despite the escalating rates of childhood obesity, IGT and T2DM remain relatively uncommon compared with the rates in adults.

Family-based behavioral treatment has been associated with short- and long-term effects on weight control in obese children aged 6–12 years in a prospective randomized controlled study [118, 119]. Obese children and their parents were randomized to three groups that were provided similar diet, exercise, and behavior management training but differed in the reinforcement for weight loss and behavior change. The child and parent group reinforced parent and child behavior change and weight loss, the child group reinforced child behavior change and weight loss, and the non-specific control group reinforced families for attendance. Children in the child and parent group showed significantly greater decreases in percent overweight after 5 and 10 years (–11.2 and –7.5%, respectively) than children in the non-specific control group (+7.9 and +14.3%, respectively). Children in the child group showed increases in percent overweight after 5 and 10 years (+2.7 and +4.5%, respectively) that were midway between those for the child and parent and non-specific groups and not significantly different from either [119].

In a limited study of obese adolescents, a program of behavioral lifestyle intervention combined with sibutramine vs. placebo in a double-blind, placebo-controlled fashion demonstrated that, at month 6, participants in the behavioral therapy group with sibutramine lost around 7.8 ± 6.3 kg (SD), and had an $8.5 \pm 6.8\%$ reduction in BMI, which was significantly more than the 3.2 ± 6.1 kg weight loss, and the $4.0 \pm 5.4\%$ reduction in BMI in the behavioral therapy and placebo group. However, after unblinding and from months 7 to 12, adolescents initially treated with sibutramine gained weight despite continued use of the drug, whereas those who switched from placebo to sibutramine lost weight. The authors concluded that the addition of sibutramine to a comprehensive behavioral program induced significantly more weight loss than did behavioral therapy alone. However, they also cautioned that, until more extensive safety and efficacy data are available, medications for weight loss should be used only on an experimental basis in children [120]. Metformin use has been popularized for the treatment of pediatric obesity by practitioners despite no such labeling by the drug maker and despite the lack of convincing long-term, well-controlled, large-scale studies in pediatrics. Metformin treatment in morbidly obese adolescents, together with low calorie diet for only 8 weeks, when compared to placebo, resulted in greater weight loss (6.5 ± 0.8 vs. $3.8 \pm 0.4\%$), greater decrease in body fat, and greater attenuation of insulin area under the curve during an OGTT [121]. However, one has to interpret the results cautiously since the very low calorie diet may have

played a crucial role in the observed outcomes. In another double-blind, placebo-controlled study of metformin in only 29 obese adolescents (ages 12–19 years) with family history of T2DM, the metformin group had a modest decline of –1.3% from baseline in BMI compared with +2.3% in the control group after 6 months of treatment. There was a significant decline in fasting blood glucose and insulin levels; however, there were no significant improvements in insulin sensitivity, nor HbA1c or lipid levels [122]. It is clear that more studies are needed to clarify the potential benefits of behavioral lifestyle intervention and pharmacotherapy in obese children at high risk for T2DM. Until such studies become available, health-care providers should practice *primum non nocere*.

In general, weight loss and/or prevention of weight gain are considered the best approach to prevent T2DM and decrease the prevalence of risk factors among children who are at risk for the disease. This should be achieved by lifestyle modification including dietary change, increased physical activity and reduced sedentary behavior. Unfortunately, evidence for the long-term effectiveness of obesity treatment and prevention programs among children is scarce. The most promising approaches involve schools and families. Examples of programs include the Kahnawake Diabetes Prevention Project in Canada [123], the Ho-Chunk Youth Fitness Program in Native Americans in the USA [124], the Pathways Intervention [125], the Zuni Diabetes Prevention Program [126], also in Native Americans and the Bienestar school-based diabetes mellitus prevention program focusing on Mexican-American children [127], among others. These interventions have showed mixed results, with some of them improving knowledge of healthy lifestyles but most of them failing to have an impact on the prevention of obesity, glucose, insulin levels and other risk factors [128].

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) has sponsored a collaborative agreement entitled Studies to Treat or Prevent Pediatric Type 2 Diabetes (STOPP-T2D) to conduct a clinical treatment trial, Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY), and a school-based primary prevention trial of T2DM in children and youth, HEALTHY Trial. The primary objective of the TODAY trial is to compare the efficacy of three treatment arms on time to treatment failure based on glycemic control. Treatment failure is defined as: (1) HbA1c >8% over a 6-month period and (2) inability to wean from temporary insulin therapy due to metabolic decompensation.

The three treatment regimens are: (1) metformin alone; (2) metformin plus rosiglitazone, and (3) metformin plus an intensive lifestyle intervention [129]. The outcome of these studies will be instrumental in advancing the knowledge in pediatric T2DM.

The Future

With the unabated increasing prevalence of obesity, T2DM in youth is emerging as a serious new public health problem. Not only pediatricians' armamentarium in managing these children is very limited, but the future is unclear with respect to the chronic complications of the disease. Is it possible that we will witness these youngsters with T2DM succumb to CVD morbidity and mortality at the peak of their productive life? In the absence of evidence-based research and in the lack of information it is

only prudent to err on the safe side while learning from the experiences of our adult colleagues. Vigilance in managing glycemia, dyslipidemia, hypertension, smoking and weight control may prove essential in this patient population. Undoubtedly, focus should be directed towards strategies for disease prevention and treatment optimization. Prevention of obesity and its co-morbid conditions, T2DM being one of several, will require major environmental change. This necessitates the collaboration among all sectors of society, parents, schools, educators, healthcare providers, food and entertainment industries, economists, policy-makers, and governmental agencies. Safe and effective pharmacotherapeutic or surgical approaches may also be helpful in the treatment of obesity and T2DM. There is no question that the next decade will be a challenging one for all of us involved in the care of these young patients.

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