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Current Treatment Options for Type 2 Diabetes Mellitus in Youth: Today's Realities and Lessons from the TODAY Study

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Abstract

The incidence of type 2 diabetes in children and adolescents has increased over the last 2 decades, paralleled by an increase in obesity over the same time period. Although the value of lifestyle modification in obese youth is unquestioned, scant evidence for optimal treatment of type 2 diabetes in this age group exists. Despite recent therapeutic drug trials, metformin and insulin are the only medicines currently approved by the US Food and Drug Administration for the treatment of type 2 diabetes in youth. Because of recently amended pharmaceutical regulations, however, it is likely that more anti-diabetic medications soon will be added to the armamentarium of therapeutic options for youth with type 2 diabetes. Additionally, the recently published TODAY study comparing safety and efficacy of 3 treatment regimens in maintaining glycemic control in youth with type 2 diabetes has shed new light on the problem.

Keywords

Type 2 Diabetes; Diabetes treatment in youth; Hyperglycemia; Insulin resistance; Insulin sensitivity; Metformin; Bariatric surgery; Diabetes Medications; TODAY trial

Introduction

Type 2 diabetes in children and adolescents is a new disease that has emerged over the last 2–3 decades [1–3]. Prior to this rise, almost all children and adolescents with diabetes were diagnosed with type 1 diabetes mellitus, with type 2 diabetes accounting for only a tiny fraction of all new cases of diabetes in this age group [4, 5]. Type 2 diabetes is a chronic, progressive state of beta cell dysfunction characterized by insulin resistance and hyperglycemia. Prediabetic states (Impaired Fasting Glucose – IFG /and Impaired Glucose tolerance - IGT) are typically present prior to the diagnosis of type 2 diabetes, and lead to frank diabetes in affected children [6, 7]. Although reliable data are scarce due to the recent appearance of this disease in youth, the risk of diabetes-related complications is expected to be high in the years and decades to come [8].

Epidemiology of Type 2 diabetes in Youth

As noted, the incidence and prevalence of type 2 diabetes in children and adolescents have increased, compared to just a few decades ago, especially in certain racial/ethnic populations [9, 10]. Estimates indicate that 8–45% of cases of recently diagnosed diabetes in children and adolescents are due to type 2 diabetes [4]. The SEARCH for Diabetes in Youth Study from the United States estimated the prevalence of type 2 diabetes as 0.22 cases per 1000 persons under the age of 20 years [9]. The same report indicated that type 2 diabetes was

rare even today in young children, but became much more prevalent after the age of 10 years, especially in children of certain racial/ethnic groups (e.g. Native American, Blacks, Hispanics, and Asian-Pacific Islanders). The highest prevalence in youth coincided with adolescence (0.42 cases per 1000 in children 10 to 19 years of age) [9]. The SEARCH for Diabetes in Youth Study observed physician-diagnosed type 2 diabetes in 6 centers and reported an incidence of 8.1 and 11.8 cases per 100,000 person years in children age 10–14 and 15–19 years, respectively [10]. The rates varied significantly based on the ethnic subgroup, with the lowest rate among non-Hispanic Caucasians and the highest among Native American youth [10].

Risk Factors for Type 2 Diabetes in Youth

Many of the risk factors for developing type 2 diabetes in childhood are similar to those for adults. Obesity is the most important modifiable risk factor for developing type 2 diabetes in children, and children with type 2 diabetes are virtually always overweight and usually profoundly obese [10]. A history of type 2 diabetes in a first or second degree family member is often present, with up to 90% of children and adolescents with type 2 diabetes having at least one affected relative [11, 12, 13]. As noted above, certain ethnic minority groups are known to be at high risk for developing type 2 diabetes [10], including Native Americans, African Americans, Asians, and Hispanics. This same variation in diabetes risk by ethnicity was reflected in the demographics of the TODAY cohort [13].

Additional clinical features are indicative of diabetes risk. Acanthosis nigricans and polycystic ovarian syndrome both are suggestive of insulin resistance in youth [14]. Intrauterine exposure to hyperglycemia predisposes the fetus to type 2 diabetes later in life, and in one study, 47.2% of children with type 2 diabetes had a prior exposure to maternal diabetes and obesity in utero [15]. In the SEARCH study, exposure to maternal diabetes in utero resulted in increased risk for type 2 diabetes with an odds ratio of 5.7 [16]. Puberty itself is yet another risk factor for type 2 diabetes because of the well-described increase in insulin resistance related to increased secretion of growth hormone and sex steroids [17]. This transient insulin resistance state is characterized by an approximately one third decline in insulin sensitivity in both sexes [18, 19]. The expected compensatory increase in insulin secretion of normal youth in response to the pubertal decrease in insulin sensitivity appears to be greater in Caucasians compared to African American adolescents, and may explain some of the ethnic differences in diabetes incidence [20].

Pathophysiology

Obese adolescents with glucose dysregulation, including IFG, IGT, or a combination, are likely to have more impairment in insulin secretion compared to reduced insulin sensitivity [21]. Secretion of insulin and C-peptide can be divided into 2 phases, first and second, using a 2 hour hyperglycemic clamp, and insulin stimulated glucose disposal can be calculated using a euglycemic clamp [22]. Recent data indicate that in children with IFG, insulin stimulated glucose disposal is not different from children with normal glucose tolerance. However first and second phase insulin secretion is approximately 50% and 30% that of normal children, respectively. In children with IGT, the first phase insulin secretion is approximately 40% lower compared with that of children with normal glucose tolerance and second phase insulin secretion is preserved. When IFG and IGT coexist, the impairment is a mixture of both - approximately 55% lower first phase insulin and 30% lower second phase insulin secretion. In full-blown diabetes, insulin stimulated glucose disposal is impaired by approximately 30%, first phase insulin is impaired by approximately 75%, and second phase insulin is impaired by approximately 65% compared with children with normal glucose tolerance [21]. This implies that children who have a combination of impaired fasting

glucose and impaired glucose tolerance have a higher risk of progression to type 2 diabetes, compared to those with either IFG or IGT in isolation. Beta cell dysfunction relative to reduced insulin sensitivity (glucose disposition index or GDI) also was lower in those with IFG, IGT, and IFG plus IGT (40, 47, 47% respectively); this decreased further to 80% in those with type 2 diabetes [21]. Youth on various treatments for type 2 diabetes did not differ with respect to peripheral glucose disposal, insulin secretion, or GDI [21].

Treatment options

There is a paucity of information available on effective treatment options for type 2 diabetes in children. Primary prevention still remains the ideal modality, and lifestyle modification is the safest and most commonly used intervention. Once type 2 diabetes in youth develops, lifestyle changes are exceedingly difficult to effect (32), emphasizing the urgency for the development of safe and effective anti-diabetic drugs in youth. Although insulin is almost uniformly effective in lowering blood sugars, the need for injections and the risk of hypoglycemia render it rarely the first modality to consider, unless metabolic decompensation is present at the time. Few oral medications have been tested in children with type 2 diabetes; only metformin has been approved by the US FDA for use in children (to the age of 10 years). Although many anti-diabetic drugs are available, the great majority has been studied for safety and efficacy only in adults. Although off label use of non-approved drugs in youth with type 2 diabetes is common, this practice requires taking a risk that such use may be associated with unexpected side effects, complications, or ineffectiveness related to physical or metabolic immaturity. Bariatric surgery has emerged as a new avenue for surgical treatment of Type 2 diabetes in the adult literature but there is limited experience with its use in pediatrics. Recent reports in youth [23] suggest the value of a multidisciplinary team including doctors, diabetic educators, nutritionists, mental health professionals, and social workers, all providing coordinated care for children treated with this modality.

Lifestyle modification

Lifestyle modification, also referred to as behavioral weight control, includes 3 essential components: diet, exercise, and behavioral therapy. The goal of lifestyle modification is gradual and sustained weight loss. Dietary recommendations include limiting consumption of foods with high levels of fat, sugar, and salt; absolute elimination of high calorie beverages from the diet; decreasing portion sizes; and a combination of these interventions. Increased consumption of healthy alternatives, particularly fruits and vegetables, is recommended. The American Diabetes Association recommends a balanced diet rich in fiber, whole grains, and legumes; contains less than 7% saturated fat and reduced trans fats; and is limited in calories and foods with a high glycemic index [24]. Studies in adults indicate that modest weight loss (even less than 10% from initial body weight) by a reduced calorie diet combined with increased physical activity has been shown to improve and sustain improvements in glycemia, with reductions in glycated hemoglobin (A1C), changes that may be maintained despite weight gain many years later [25]. A ketogenic, low calorie diet in children has been shown to be effective in a sample of 20 adolescents with type 2 diabetes. After about 2 months on average, the mean A1c decreased from 8.8% to 7.4% and all the patients came off their prior antidiabetic treatment with metformin or insulin [26]. Obese individuals can lose weight on a variety of diets varying widely in macronutrient composition, although caloric restriction is common to all effective diets [27]. A successful diet is defined as one in which 5–10% of the initial weight is lost over several months. Greater weight loss is linearly associated with greater improvements in many risk factors including A1C and cardiovascular risk [28].

Physical activity also plays an integral role in the treatment of type 2 diabetes in children. Improved insulin sensitivity, increased uptake at the level of the muscle and a decreased need for insulin therapy are all benefits seen with increased physical activity [29]. Screen time should be reduced to no more than 1–2 hours per day; which will lead to a decrease in sedentary activities [30]. Patient and family education with focus on diet and exercise with the psychological needs of the youth in mind should be done in a culturally sensitive and age appropriate manner [31]. Healthy behaviors need reinforcement in order to lead to a permanent change in lifestyle. While lifestyle change is the cornerstone of type 2 diabetes management in children, only about 10% of adolescents with type 2 diabetes achieve adequate metabolic control with lifestyle modification alone [1].

Oral Medications

In addition to lifestyle intervention, many pediatric patients require glucose lowering medication in order to achieve normalization of blood glucose and A1C levels. Although many oral glucose lowering medications have been approved for adults with type 2 diabetes, only metformin has been approved by the FDA for use in pediatric patients aged 10 years and older (Table 1). Metformin, an oral biguanide insulin sensitizer, binds to insulin receptors in liver, muscle, and fat tissue. Its mechanism of action is twofold: 1) the primary effect of metformin is to reduce hepatic glucose production. 2) metformin also increases glucose uptake of peripheral tissues (muscle and fat), with a net effect of improving insulin sensitivity and reducing both pre- and postprandial blood glucose levels. Metformin rarely if ever causes hypoglycemia in type 2 diabetes patients, a distinct advantage of metformin over most other oral medications. Appropriate counseling and gradual titration of dose is helpful in dealing with its most common adverse effects (GI intolerance - nausea, abdominal discomfort and diarrhea) - symptoms which tend to improve with continued use. Metformin is contraindicated in patients with impaired renal function, cirrhosis, hepatitis, alcoholism, cardiopulmonary insufficiency. These potential risk factors should be evaluated for each individual patient before initiating therapy. One of the most serious risks of metformin is lactic acidosis, although it only occurs in the context of renal failure and its incidence in youth is extremely low [32]. Patients taking metformin are advised to take daily multivitamins due to a possible poor absorption of vitamin B12 and/or folic acid [33]. Metformin also should be withheld before radiographic studies requiring the administration of iodinated contrast dye, because of the potential for renal deterioration in its immediate aftermath. Metformin should be initiated at 500 mg orally daily or twice daily with meals and slowly titrated up over 3–4 weeks to 1000mg orally twice daily with meals as tolerated. Some suggest that metformin should be temporarily discontinued during a gastrointestinal illness [34].

Studies with metformin

Metformin was found to be effective and safe in a 16 week randomized, placebo-controlled, multicenter trial involving 82 adolescents (10–16 years of age) with type 2 diabetes [35]. In that randomized study, metformin significantly improved fasting plasma glucose and A1c values compared to placebo (–42.9 versus +21.4 mg per day and 7.5% versus 8.6%, respectively) [35]. A modest amount of weight loss, with a reduction of 1.5 kg and a BMI decrease of –0.05 was observed in the same trial [35].

Pharmacokinetics studies with metformin in pediatric patients have been reported; 500 mg oral tablet with food administered to children between 12–16 years of age showed similar parameters (area under the curve + maximum plasma concentration) compared with those of gender and weight matched-healthy adults [36]. Efficacy of metformin in children with type 2 diabetes has been demonstrated in numerous other clinical trials, and improvement in insulin sensitivity is well documented, as indicated by reductions in fasting insulin levels,

increases in glucose to insulin ratio, and reductions in insulin resistance by homeostasis model assessment in insulin resistant obese adolescents [37].

Other Medications not approved for use in children

Thiazolidinediones: The thiazolidinediones are insulin sensitizers that function as selective agonists, activating the peroxisome proliferator-activated receptor-gamma (PPAR gamma) expressed in adipose tissue, liver and skeletal muscle, all key sites of insulin action. Drugs in this family include rosiglitazone and pioglitazone. Both have been demonstrated to improve insulin sensitivity and glycemia [38] although the former is no longer available for regular prescription in the US or Europe, for children or adults. Numerous pharmacologic studies indicate their mechanism of action to be related to inhibition of hepatic gluconeogenesis and stimulating increased insulin sensitivity in peripheral tissues including liver, muscle, and adipose tissue. Like metformin, clinical hypoglycemia is rare. The molecular mechanism of action of the thiazolidinediones involves the regulation of transcription of several insulin-responsive genes involved in the control of glucose production, transport, and utilization in the regulation of fatty acid metabolism. Limited studies in children indicate pharmacokinetics similar to those reported for adults [39, 40]. A clinical trial conducted in obese children with type 2 diabetes who received either rosiglitazone or metformin for 24 weeks showed that both drugs lowered A1c from baseline (−0.49% vs. −0.14%, metformin and rosiglitazone, respectively)[39, 40]. Results indicated that efficacy was dependent on body weight, BMI, and whether the patient had received prior anti-diabetic drug therapy. Rosiglitazone was associated with significantly more weight gain (2.8 kg and 0.2 kg, rosiglitazone and metformin, respectively). Overall study results indicated superior glycemic effects of metformin, with less weight gain, compared to rosiglitazone. Thus this multicenter, randomized, active controlled clinical study failed to demonstrate noninferiority of rosiglitazone to metformin, precluding its petition to the FDA for a new indication for use in children (age 10–17 years of age) with type 2 diabetes [40].

Sulfonylureas: Glimepiride & Glyburide

Sulfonylureas are the major drugs in the family of insulin secretagogues. They exert their actions by stimulating insulin release from intact and functioning beta cells through an interaction with ATP-sensitive potassium channels on the beta cell membrane. In addition, these drugs increase insulin sensitivity in peripheral tissues indicating that extra pancreatic effects are also involved in the activity [41]. Pharmacokinetic studies of these drugs in pediatrics are limited. One study examined children 10–17 years of age with type 2 diabetes who were given single oral doses of 1 mg of glimepiride. These children demonstrated pharmacokinetics comparable to those described previously in adults [41]. In other studies, glimepiride therapy has been shown to reduce A1C, but less so than that associated with metformin use. Although efficacy as an anti-diabetic drug has been demonstrated, the glimepiride pediatric trial failed to demonstrate non-inferiority to metformin in reducing A1C; thus, it has not received FDA approval in this age group [42]. In addition, glimepiride stimulates weight gain more than that associated with metformin [42]. Another randomized controlled trial compared the efficacy of metformin alone and glyburide alone with a combination of metformin plus a sulfonylurea (Glucovance) in children 9–16 years of age [40]. In this trial, all 3 treatment groups were effective in lowering A1C and fasting glucose although the combination therapy was not superior to metformin or glyburide monotherapy, and approval for use in children was not granted [42].

Insulin Therapy

Insulin therapy is a key component in the treatment of youth with type 2 diabetes, in part because of a familiarity of pediatricians with the use of insulin from experiences in treating

children with type 1 diabetes, and in part because of the paucity of oral drugs studied in children, as noted above. Many care providers prefer insulin at the time of diagnosis for all patients with type 2 diabetes, and its use is essential for those with significant hyperglycemia or ketosis. For patients treated with oral medications, insulin is often the first step toward intensification of therapy, once oral medications and lifestyle interventions are insufficient for achieving optimal glycemic control.

Rapid acting Insulin Analogues

The faster absorption of rapid acting insulin analogues results in higher and sharper peaks and shorter duration of action compared to regular insulin. This helps to control early postmeal hyperglycemia and to reduce late postprandial hypoglycemia [43]. Aspart (Novolog), lispro (Humalog), or glulisine (Apidra) are the three types of rapid acting insulin analogues available on the market currently. All are commonly used in children before meals, and no major differences in pharmacokinetics compared with those of adults have been noted, although a reduced biologic action because of the insulin resistance of puberty have been described in children with Type 1 diabetes [44]. All three insulins can be used in insulin pumps and all have been shown to be safe and effective in children with type 1 diabetes. Mixing with any of the long acting insulins is not recommended. All can be given intravenously, although none has been found to be superior to regular insulin [45].

Intermediate-acting Insulin Analogues

NPH is the only available intermediate acting insulin on the market currently. With its delayed peak of action it provides the means to cover lunchtime glucose excursions, and some insulin coverage throughout a full 24 hour period on a twice daily injection regimen. However, its duration of action typically is too short to provide adequate overnight basal insulin replacement without causing hypoglycemia [46]. With the advent of long-acting insulin analogues, NPH has largely been replaced in multiple-daily insulin regimens by the long-acting insulin analogs in all children with all types of childhood diabetes.

Long Acting Insulin Analogues

At the current time, two commercially available long-acting insulin analogs are available: glargine (Lantus) and detemir (Levemir). Both address basal insulin requirements for coverage of hepatic glucose production. Although few head-to-head comparisons in children have been reported, a more consistent pharmacodynamic profile with detemir compared with glargine has been reported in children with type 1 diabetes. On the other hand, detemir may have a shorter duration of action compared to glargine, suggesting that twice daily dosing with detemir may be necessary for some patients [47]. In children with type 2 diabetes needing intensification of therapy, one common starting place is the addition of a long-acting insulin injection at bedtime. When this regimen is not effective, other approaches may be employed, including the addition of rapid acting insulin injections at mealtime plus basal insulin coverage with a long-acting insulin at bedtime, or the use of combination insulins (such as 75/25 or 70/30 insulins in a twice-daily regimen). Intensive lifestyle changes and oral medications remain a key part of the treatment regimen and the goal should be to keep the patient on the regimen (including the one with the best chance for adherence for each individual patient) most likely to achieve glycemic target.

Changes in the regulatory laws

Numerous drugs available for treatment of type 2 diabetes in adults have never been fully tested in children, although several such studies are ongoing currently. These include clinical trials for some of the new oral hypoglycemic agents including DPP4 inhibitors

(sitagliptin, saxagliptin, and linagliptin), and several of the new injectable agents, including GLP-1 agonists (such as exenatide and liraglutide). As noted above a majority of the medications that have been tested in pediatrics have shown efficacy and pharmacokinetics similar to those in adults, but many of the clinical trials have not shown non-inferiority or superiority when compared to metformin, the gold standard of pediatric diabetes type 2 management. The FDA Amendments Act of 2007 requires a pediatric plan at the time of a new drug application (NDA) submission to the agency. This Act requires the applicant for pediatrics studies to provide a plan for obtaining pharmacokinetic/pharmacodynamics data, as well as for demonstrating both safety and efficacy in children.

Bariatric Surgery

There is strong evidence in adults indicating that bariatric surgery is capable of producing sustainable long-term weight loss in obese individuals [48]. Overweight and obese children [6], like adults, are at risk for progressing from insulin resistance (associated with obesity *per se*) to impaired glucose tolerance, and eventually to type 2 diabetes. Bariatric surgery consists of two main types of surgical interventions, resulting in weight loss caused by either physically restricting deposition of food into the stomach or creating a malabsorptive state or both [49]. Restrictive bariatric procedures include gastric banding and sleeve gastrectomy. Malabsorptive procedures include gastric bypass and biliopancreatic diversion. Malabsorptive procedures have been shown to be superior in producing dramatic weight loss along with a rapid resolution or improvement in type 2 diabetes, even prior to any significant weight loss, indicating that hormonal mechanisms are likely involved [50]. Whether adolescents and young adults with type 2 diabetes should undergo such drastic procedures remains controversial but current expert recommendations for guidelines and criteria needed to deliver safe and effective bariatric surgical care to adolescents have been published [51]. Limited reports suggest that bariatric surgery can reverse type 2 diabetes in certain severely obese children [49, 52]. In view of the dramatic results demonstrated in adults (and particularly in view of the disappointing effects of lifestyle interventions in youth), we believe that bariatric surgery for carefully selected youth with morbid obesity and type 2 diabetes should be investigated, but only in the context of a highly structured research environment and involving a multi-disciplinary approach (surgeons, endocrinologists, psychologist, etc.).

Lessons from the TODAY study

The TODAY study is a large multicenter clinical trial comparing treatment options in a large cohort of youth with recently diagnosed type 2 diabetes [53]. The cohort consisted of 699 carefully characterized randomly assigned participants between the ages of 10–17 years of age, whose mean duration of diagnosis of type 2 diabetes was 7.8 months [32, 13]. Participants were divided into 3 groups: one receiving metformin alone, another receiving metformin combined with rosiglitazone (4 mg twice a day), and yet another combining metformin with a lifestyle intervention program focusing on weight loss through dietary, physical activity, and behavior change. The TODAY lifestyle program was a standardized and exceptionally intense program delivered by a trained interventionist assigned to each participant in the lifestyle arm of the trial. The program consisted of weekly in person contact for the first 6 months, biweekly in person visits alternating with phone contact for the next 6 months, and one monthly in-person contact and one monthly phone contact for the remainder of the trial. The primary endpoint of the trial was loss of glycemic control defined as an A1C level of at least 8% for 6 months or an inability to wean from insulin after metabolic decompensation [53]. The results of the study indicated that metformin plus rosiglitazone was superior to metformin alone ($P = 0.006$); metformin plus lifestyle

intervention was intermediate but not significantly different from metformin alone [32]. The main overall lessons learned from the trial include the following:

1. ***Single drug monotherapy with metformin was ineffective in maintaining glycemic control for ~50% of the cohort within approximately one year of treatment.*** Failure rates of the three treatment arms were 51.7, 46.6, and 38.6% (metformin alone, metformin plus lifestyle, and metformin plus rosiglitazone, respectively), with metformin plus rosiglitazone significantly superior to metformin alone ($p=0.006$). Metformin was particularly ineffective in sustaining glycemic control in Black participants, with almost 70% of Blacks having failed within 3 years of treatment. On the other hand approximately 50% of the cohort remained in glycemic control over a long period of time, some for as long as 6 years, suggesting that future studies are needed to better characterize that subgroup of participants who maintain good control over a long duration.
2. ***Lifestyle changes are exceedingly difficult to effect in youth of this socio-economic demographic.*** The TODAY cohort was comprised of youth with significant barriers to good health: 41.5% had a household annual income of less than \$25,000, 26.3% had a highest education level of parent/guardian less than a high school degree, 38.8% were living with both biological parents, 41.1% were Hispanic, and 31.5% were black [13]. Despite the extraordinary resources and efforts devoted to lifestyle change, as noted above, weight loss was only modest and short-lived, even in the metformin plus lifestyle group. Even though the metformin plus lifestyle group experienced the greatest improvements in BMI and indices of adiposity relative to the other two treatment groups [54], these changes were not translated into effects on sustained glycemic control.
3. ***High rates of complications already are present in the first months after diagnosis.*** At the time of randomization into the TODAY trial, 26.3% had a blood pressure at the 90th percentile or greater; 13.6% had a blood pressure at the 95th percentile or greater; 13.0% had microalbuminuria; 79.8% had a low high-density lipoprotein level; and 10.2% had high triglycerides [13]. Furthermore, the rates of progression of these co-morbidities increased progressively throughout the duration of the trial (mean duration just less than 4 years), which emphasizes the importance of close surveillance and early and aggressive treatment [55].
4. ***Certain indicators at baseline and early in the course of treatment appear to predict success in maintaining durable glycemic control.*** Finally, characteristics of participants who maintained long-term durable glycemic control (for at least 4 years) were compared to those whose treatment failed before 4 years. Several variables predicted failure, including a higher BMI ($p<0.0001$), depression ($p=0.02$), race (Blacks compared to Whites; $p=0.03$), a higher A1C ($p<0.0001$), and a lower ability to secrete insulin, although when analyzed in a multivariate model, only A1C ($p<0.0001$) and insulin secretion ($p=0.0498$) remained significant predictors. When analyzed as change over time in the study, a rapidly increasing A1C predicted failure ($p<0.0001$) [56].

Complications

Development of the same micro-and macro vascular complications seen in adults is assumed in youth with type 2 diabetes who have poor diabetic control over a long period of time. Recent evidence from the TODAY trial (bullet #3 above) indicates that complications are not only present in some youth shortly after diagnosis, but that the rate of development of complications after diagnosis appears to be similar to that observed in adults with type 2 diabetes [55]. The longer duration of disease burden in youth diagnosed with type 2 diabetes

can be expected to extract a substantial toll on both individuals and society, due to the chronic morbidity of these youth as they enter into adulthood.

Conclusions

The increasing prevalence of type 2 diabetes in youth over the past 20 years parallels and follows the worldwide epidemic of childhood obesity. Predisposing factors for the development of type 2 diabetes in the context of obesity in youth include obesity, family history, ethnicity, and an abnormal prenatal metabolic environment. Once diagnosed, type 2 diabetes in youth is exceedingly difficult to treat effectively; thus, primary prevention should be a major target of health care efforts and resources. Ideal management of youth with type 2 diabetes requires an expert diabetes team, experienced in delivering requisite diabetes education and aggressive care and monitoring. The only oral medication approved for use in youth with type 2 diabetes is metformin; thus metformin is the preferred first-line oral agent in stable patients. However, lessons learned recently from the TODAY trial indicate that rapid metabolic deterioration in youth treated with metformin alone is common, and that early and aggressive intensification of therapy is essential in many patients.

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Table 1

Type 2 diabetes medications currently approved for adults as antidiabetic agents

Class	Examples	Mechanism	Approved/Studies in Pediatric patients
Biguanide (insulin sensitizers)	Metformin, Metformin ER, Metformin Solution	Primarily decrease hepatic glucose production; increase muscle glucose uptake	Yes - regular Metformin is the only approved drug.
Thiazolidinedione (insulin sensitizers)	Rosiglitazone, Pioglitazone	Selective PPAR-gamma antagonists; increase glucose transport into adipose, muscle, and liver cells	No - failed noninferiority trial vs. Metformin
Sulfonylurea (insulin secretagogues)	Glimepiride, Glipizide, Glyburide	Enhance insulin secretion by their interaction with ATP sensitive K channel on the Beta Cell Membrane.	No – failed noninferiority trial vs. Metformin
Glucosidase inhibitors	Acarbose, Miglitol	Interferes with alpha glucosidase, thereby inhibiting the hydrolysis and absorption of carbohydrates in the GI tract.	No - None
Amylin analog	Pramlintide-Acetate	slows gastric emptying, promotes satiety, and suppresses the abnormal postprandial rise of glucagon	No - Recruiting
Meglitinide	Repaglinide, Nateglinide	blocks ATP-dependent potassium channels; stimulates insulin release from the pancreatic beta cells.	No - Completed
DPP-4 inhibitor	Saxagliptin, Linagliptin, Sitagliptin	prolonged active incretin levels; increasing insulin synthesis and release from pancreatic beta cells and decreasing glucagon secretion from pancreatic alpha cells.	No - Recruiting
GLP-1 Analog	Exenatide , Exenatide ER injection	dose dependent and glucose-dependent augmentation of insulin secretion. slows gastric emptying, suppresses inappropriately elevated glucagon levels, and leads to weight loss	No - Recruiting
Dopamine D2 Agonist	Bromocriptine-Mesylate	mechanism of action is unknown; may reset hypothalamic circadian activities which have been altered by obesity	No - None

Most type 2 diabetes medications are untested in children. Many combinations of the above medications also are approved for use in adults.