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REVIEW ARTICLE

Type 2 Diabetes in Children: A Growing Epidemic

Erin L. St. Onge, PharmD, Carol A. Motycka, PharmD, and Renee L. Rose, PharmD

University of Florida College of Pharmacy, Gainesville, Florida

In the pediatric population, type 2 diabetes has become a growing concern. A correlation appears to exist among type 2 diabetes in children, obesity, and a sedentary lifestyle. If obesity and diabetes are left untreated, conditions such as cardiovascular disease, nephropathy, and retinopathy may result as well. These conditions indicate the incredible strain on the health care system caused by diabetes and obesity. This strain may be eased by logical treatments such as exercise and healthy eating habits for the child and family. However, these lifestyle changes are not always effective in controlling blood sugar. When lifestyle changes do not yield positive results, the clinician must decide which (if any) pharmacological treatments are safe to use in the pediatric population. Orlistat and sibutramine have been studied in children as treatments for obesity and appear to be safe and effective for this population. Metformin and insulin are among the medications approved to treat diabetes in children and adolescents. Healthcare practitioners must play a role in educating parents and their children about the effects of obesity on the development of diseases like diabetes, as well as various therapies used to manage diabetes. In addition, healthcare practitioners can assist patients and their parents in understanding the benefits and risks of medications used in the treatment of the disease, assistance that may result in them making informed decisions regarding their overall health.

KEYWORDS diabetes, obesity, pediatrics, type 2 diabetes

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INTRODUCTION

Type 2 diabetes is a chronic disease that may lead to serious complications if not properly managed. Historically, it has been considered an adult disease, and children diagnosed with diabetes were commonly labeled as type 1 diabetics. It is now recognized that children may also develop type 2 diabetes, which has become a major health problem especially among specific pediatric populations such as the Pima Indians of Arizona.[1] The growing rate of childhood obesity is the common link in most cases of type 2 diabetes.

If a child is not treated early for impaired glucose tolerance and develops diabetes, many complications may arise, including retinopathy, cardiovascular disease, skin and soft tissue infections, neuropathy, and nephropathy. In addition, young women diagnosed with diabetes before adulthood may also have evidence of polycystic ovary syndrome (PCOS). In fact, 31% of women with PCOS have impaired glucose tolerance with up to 16% developing type 2 diabetes.[2] Another devastating, and often

ABBREVIATIONS ADA, American Diabetes Association; BMI, body mass index; CDC, Centers for Disease Control; PCOS, polycystic ovary syndrome; TODAY; treatment options for type 2 diabetes in adolescents and youth; VLCD, very low calorie diet

Address correspondence to: Erin L. St. Onge, PharmD, 2725 S. Binion Rd, Apopka, FL 32703,
email: stonge@cop.ufl.edu

Table 1. Comparison of type 1 and type 2 diabetes

Variable	Type 1 Diabetes	Type 2 Diabetes
Other terminology	juvenile diabetes, insulin-dependent diabetes mellitus, childhood diabetes, and ketosis prone diabetes	formally known as adult-onset diabetes and non- insulin dependent diabetes mellitus
Incidence (Prevalence)	5%-10% of all diabetes in the US (0.5%)	90% to 95% of all diabetes in the US (5%-6%)
Age of onset	More common in children and young adults < 20 years of age	More common in adults > 35 years of age
Family history	Infrequent	Common
Gender	Same frequency	Occurs more frequently in males
Ethnicity	More common in Caucasians	More common in African American, American Indian, Asian American, Hispanic, and Pacific Islander
Genetic basis	Probably	Definitely
Primary cause	Pancreatic β-cell deficiency	Receptor unresponsive to insulin
Insulin defect	Impaired secretion	Insulin deficiency and resistance
Onset	Abrupt	Gradual
Clinical Presentation	polyuria, polydispia, polyphagia; weight loss; nausea, vomiting; blurred vision	May not be apparent; polyuria, polydispia

overlooked, complication of type 2 diabetes is psychological impairment; therefore, it is often important to include a psychologist or psychiatrist in the team of health care professionals treating a child with diabetes.[3] This article will review type 2 diabetes as a major public health concern in children, detailing the aforementioned complications and the role obesity plays as a risk factor of the disease. In addition, the article will review medications used to treat type 2 diabetes in pediatric patients.

TYPE 2 DIABETES IN CHILDREN

Incidence and Pathophysiology

Previously, type 2 diabetes accounted for 2%-3% of all diabetes mellitus in children.[4] Today, almost half of all newly diagnosed cases of diabetes in children are type 2, with the largest increase occurring in the Pima Indian adolescent population.[4,5] In the United States, type 2 diabetes is most commonly diagnosed in patients 12 to 16 years of age, and the disease affects females more than males.[6]

Control of glucose is dependent on three factors: 1) the release of insulin from pancreatic β-cells, 2) the glucose production of the liver, and 3) the adequate response to insulin at the tissue level. Most individuals with type 2 diabetes can produce insulin at the time of diagnosis; however, some have a total lack of insulin or relative deficiency. When glucose cannot be absorbed, hyperglycemia ensues, and pancreatic β-cells increase insulin production to cause hyperinsulinemia. Ultimately, insulin resistance occurs as the muscle, adipose, and hepatic cells develop a decreased sensitivity to insulin. Insulin resistance due to elevated plasma concentrations of both insulin and glucose leads to type 2 diabetes. Unlike type 1 diabetes, there is no autoimmune destruction of pancreatic β-cells in type 2 diabetes.

Clinical Presentation

The differences between type 1 and type 2 diabetes in children are often hard to distinguish (Table 1). Children with type 2 diabetes are often obese, 10 to 16 years of age, and have a family history of the disease. Findings range from asymptomatic glucosuria to ketonuria or ketoacidosis with dehydration.[5] If the patient presents with ketonuria or ketoacidosis, the initial diagnosis is more likely type 1 diabetes. Patients may also report weight loss, increased thirst, frequent urination, and recurrent vaginal yeast infections. Children may also have sleep apnea, hypertension, and acanthosis nigricans.[5]

Table 2. Criteria for the diagnosis of diabetes*

Random plasma glucose concentration ≥ 200 mg/dL plus symptoms (e.g., polyuria, polydipsia)
Fasting plasma glucose concentration ≥ 126 mg/dL following an 8-hour fast.
2-hour plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test†

** Repeat testing on a different day should occur in the absence of hyperglycemia*
† The glucose load should be equivalent to 75 grams of anhydrous glucose dissolved in water.

Seventy to ninety percent of those with type 2 diabetes may have acanthosis nigricans.[7] Acanthosis nigricans is a darkening of the skin surfaces in the neck, axillae, and waistline regions. Children often refer to this velvety plaque on the skin's surface as a dirty mark they cannot clean off. This condition occurs when hyperinsulinemia activates receptors in the skin to cause abnormal cell growth.

Laboratory tests may be necessary if there is still uncertainty about the classification of diabetes. In individuals with type 2 diabetes, fasting serum insulin concentrations and C-peptide are normal to elevated while individuals with type 1 diabetes have low to undetectable levels.[5] Along with the patient history and physical examination, use of the diagnostic criteria (Table 2), as stated by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, will assist in an initial diagnosis of diabetes mellitus.[8]

Testing and Diagnosis

Insulin resistance and fasting hyperpinsulinemia appear to be the greatest predictors of impaired glucose tolerance. The American Academy of Pediatrics and American Diabetes Association (ADA) recommend testing be initiated in children who are overweight and have at least two risk factors for developing type 2 diabetes (Table 3).[6] Screening should be initiated at 10 years of age and should be repeated every two years. The ADA recommends the fasting plasma glucose test because of its convenience and low cost.[6] A fasting serum insulin level above the upper limits of the reference range for the assay used (about 60 mg/dL) is considered evidence of insulin resistance. An oral glucose tolerance is another common method used to test for diabetes in obese children who may be at risk for diabetes.[9] In a recent study, Sinha et al., determined the prevalence of impaired glucose tolerance in 167 obese children and adolescents.[10] They reported impaired glucose tolerance in 25% of the obese children 4 to 10 years of age and in 21% of obese adolescents 11 to 18 years of age. They also noted that approximately 4% had silent type 2 diabetes. This study reinforces the importance of testing and treating obese and overweight children not only for diabetes, but for obesity.

Contributing Factors

Characteristics common to children with type 2 diabetes are multifactorial and include diagnosis at the time of puberty, family history of type 2 diabetes, and genetics. The onset of puberty produces many physical changes, including a temporary increase in insulin resistance caused by an increase in growth hormone. Children with normal pancreatic β-cell function compensate for this change by increasing insulin secretion. When puberty ends, there is a decrease in growth hormone secretion, and insulin resistance declines. During puberty, children with a genetic predisposition as well as risk factors (e.g., obesity, sedentary lifestyle, and high-calorie diet) can no longer compensate for the insulin resistance by increasing insulin secretion, and they continue to have hyperglycemia after puberty ends.[5]

Genetics also plays a role in predisposing one to the development of type 2 diabetes. A child with a first-degree biological relative who has a history of type 2 diabetes has an increased likelihood to develop the disease. These individuals may already have a 20% decrease in insulin sensitivity, which causes further insulin release leading to pancreatic β-cell "burn out".[1] Specific genes have been identified in several ethnic groups including African-Americans, Hispanic-Americans, and Native North Americans.[11] Chromosome two in Hispanic-Americans and chromosome 4q in Pima Indians may be affected. Mutations in the β-adrenergic receptor may also lead to early onset of type 2 diabetes.[12-14]

Environmental factors such as obesity, sed-

Table 3. Risk factors

Family history of type 2 diabetes in a first- or second-degree relative
Race or ethnicity (e.g., American Indian)
Signs or conditions associated with insulin resistance (e.g., acanthosis nigricans)

Adapted from the ADA guidelines[6]

entary lifestyle, and diet also play a role in the development of type 2 diabetes.[6,11] There appears to be a correlation between type 2 diabetes and the increasing incidence of obesity and lack of physical activity.[15] The obesity epidemic continues to be problematic, not only in the United States, but across the globe. Members of society at large and those in the health care system are increasingly concerned about how widespread this epidemic has become in children. In the United States, the number of overweight children has increased two fold over the past 30 years, bringing the percentages of overweight and obese preschool children to 22% and 10%, respectively.[9] The largest increases have been among boys, particularly in non-Hispanic blacks and Hispanics.[16]

Not only has the percentage of children who are defined as overweight increased, but the severity of the condition has increased as well.[17] In adults, a person is considered obese if the body mass index (BMI) is calculated to be ≥ 30 kg/m^2. However, in children, the classification is based on growth charts developed by the Centers for Disease Control and Prevention (CDC). The growth charts are specific for gender and age and are used to guide a health care provider when caring for a child between the ages of 2 and 19 years. Children are considered overweight or obese if their BMI falls at or above the 95th percentile for children in their age and gender category. Children who fall between the 85th and 95th percentile are considered at risk for becoming overweight. As children continue to get heavier, our threshold for overweight and obesity continues to increase, making the severity of overweight and obesity in children an ever-increasing problem.[16]

A number of causes contribute to this epidemic, including genetics, endocrine and/or neurological disorders, medication intake such as high-dose glucocorticoids, environment, psychosocial factors, diet, and exercise. It is believed that poor diet and lack of exercise are the factors most likely to influence the rapid increase in this epidemic. In fact, the results of the CLASS survey indicated that children who attended physical education at school two or more times weekly were at lower risk for overweight and obesity than those who exercised less frequently.[18] In light of the prevalence of high fat and high calorie diets, the fight to halt this epidemic becomes a difficult one.[16]

The increased incidence of obesity is a co-morbid factor in a number of diseases and contributes to increasing health care costs.[19] An obese child is at risk for developing diabetes, metabolic syndrome, hyperandrogenism, cardiovascular disease, asthma, sleep apnea, liver and/or gallbladder disease, orthopedic abnormalities, dermatologic disorders, and neurological disorders. All of these conditions put a tremendous strain on health care resources. For these reasons, children with a BMI at or above the 85th percentile should be treated with increased physical activity and a healthy diet that includes mild caloric restriction. For children at or above the 95th percentile, a more aggressive approach may be entertained. As a last resort, bariatric surgery may be considered. Most clinicians would agree that attempting pharmacological therapy should be attempted before such a drastic surgical procedure.

MEDICAL MANAGEMENT

Non-pharmacological therapies

According to the ADA, the goals of treatment for type 2 diabetic children are weight loss, achievement of normal blood glucose and HgbA1c, and control of co-morbid conditions such as hypertension and hyperlipidemia.[6] Non-pharmacological therapy is an appropriate first step in the management of pediatric patients with type 2 diabetes. Such therapy includes basic information about diabetes as well as education on blood glucose monitoring, dietary modifications, and the importance of exercise. Dietary modifications should be taught by a dietician, and parents should be

Table 4. Insulin sensitizing oral hypoglycemic agent

	Tradename (formulation)	Dosage	Monitoring	Comments
Metformin	Glucophage (500, 850, 1000 mg) Glucophage XR (500, 750 mg) Riomet (100 mg/mL)	500 mg qd increasing by 500 mg each week up to 2,550 mg/day divided bid. If more than 2,000 mg, divide tid. XR formulation may be given qd	Periodic renal and hepatic tests. Contraindicated if SCr >1.4 mg/dL in women and >1.5 mg/dL in men	Take with meals; Pregnancy category B; Temporarily D/C for radiological studies involving iodinated contrast materials due to alteration of renal function
Pioglitazone	Actos (15, 30, 45 mg)	15-30 mg up to 45 mg qd	LFTs at baseline and periodically thereafter	Pregnancy category C
Rosiglitazone	Avandia (2, 4, 8 mg)	4 mg qd or divide bid; if response is inadequate after 8 to 12 wks increase, increase to 8 mg qd or divide bid	LFTs at baseline and periodically thereafter	May be taken with or without food; Pregnancy category C

LFTs, liver function test; SCr, serum creatinine

included in these educational sessions. Due to the beneficial effects of exercise on blood glucose, patients should be encouraged to exercise at least 30 minutes per day. Often patients find it helpful if the parents and/or entire family adopt the same exercise regimen.[20]

Attempts at managing weight via diet, exercise, behavioral modification, and pharmacological means may translate into control of plasma glucose.[21] Pharmacological treatment of obesity may become more prevalent as clinicians attempt to treat overweight and obese children who have diabetes as a means to prevent glucose intolerance. Typically a low-fat, low-calorie diet should be used as first-line therapy. However, recent data have shown that low carbohydrate diets may provide equal or greater weight loss and glucose tolerance in overweight or obese adults.[22] Another diet that may be considered is the ketogenic diet, which his a very low calorie diet (VLCD). Willi and colleagues conducted a chart review of 20 hospitalized children who were given a VLCD as primary or secondary treatment of type 2 diabetes. [23] The mean age of the subjects was 14.5 years, and all were considered obese (BMI 43.5 ± 1.8 kg/m^2). The VLCD was found to have profound effects on blood pressure, glycemic control, and weight loss. Five children, who were initially hypertensive, were no longer hypertensive by day three of the diet. In addition, the HgbA1c went from an average of 8.8% at baseline to 7.4% at completion of the diet. All subjects lost weight, with 11 losing more than 10 kg. The diet appeared to be well tolerated as no children experienced nausea, vomiting, dehydration, orthostatic dizziness, muscle cramps, fatigue, or halitosis.

Further studies in children and adolescents are needed to determine which approach may prove most beneficial in this population. Although direct treatment of obesity in children is now more commonly occurring, secondary conditions such as diabetes are often treated more immediately by a clinician. By treating these conditions through diet, exercise, and other means, weight loss often will follow.

Pharmacological therapies

Obesity

A variety of medications may be used to treat obesity and/or diabetes. Unfortunately, most pharmacological agents used to treat obesity have not been well studied in children. However, metformin, orlistat, and sibutramine have been used successfully in adolescents.[16] A recent multi-center, randomized, double-blind, placebo-controlled study compared 539 obese adolescents (aged 12-16 years). Orlistat (120 mg TID) or placebo was given for 54 weeks

Table 5. Insulin secretagogues oral hypoglycemic agent

	Tradename (formulation)	Dosage	Monitoring	Comments
Glimepiride	Amaryl (1, 2, 4 mg)	1-4 mg qd up to 8 mg qd	Weight	Take with meals; Pregnancy category C
Glipizide	Glucotrol (5, 10 mg) Glucotrol XL (2.5, 5, 10 mg)	10-20 mg qd or divided	Weight	Take 30 min before meals; Administer XL with breakfast; Pregnancy category C
Glyburide	Diabeta and Micronase (1.25, 2.5, 5 mg) Glynase (1.5, 3, 6 mg)	5-20 mg qd or divided	Weight	Take 30 min before meals; Pregnancy category C
Nateglinide	Starlix (60, 120 mg)	120 mg tid; If near goal HgbA1c initiated at 60 mg tid	Weight and serum lipids	Take 1-30 min before meals; Pregnancy category C
Repaglinide	Prandin (0.5, 1, 2 mg)	0.5-4 mg up to 16 mg qd	Weight	Take 15-30 min before meals; Pregnancy category C

to 357 and 182 patients, respectively.[21] Both groups were placed on a mildly hypocaloric diet (30% calories as fat), given exercise counseling, and provided specific behavioral modifications. No assessment was made to determine if the participants followed these guidelines. At the end of the study, a statistically significant difference in BMI (–0.55) was noted in the orlistat group while an increase in BMI (+0.31) occurred in the placebo group (P = .001). Although not statistically significant, the orlistat group showed a decrease in 2-hour insulin concentrations from baseline. The overall results of this study led to an expanded product labeling to include adolescents 12 years of age and older.

Another randomized, double-blind, placebo-controlled study compared sibutramine to placebo plus behavioral therapy in 82 obese adolescents whose ages ranged from 13 to 17 years.[24] During the first week of the trial, all participants received placebo. Patients received placebo or sibutramine 5 mg daily at the beginning of the second week and received either placebo or sibutramine 10 mg (titrated up to 15 mg) daily during weeks 3 to 15. After six months, all participants were given sibutramine for an additional six months. The sibutramine group exhibited an 8.5% reduction in BMI compared to 4% in those given placebo (P = 0.001).

A more recent and larger trial also studied the effects of sibutramine treatment in adolescents.[25] This study compared 10 mg of sibutramine plus behavioral therapy to behavioral therapy alone. At six months, 50% of participants in the sibutramine group had their dosage increased to 15 mg daily due to less than a 10% decrease in BMI. The primary outcome of this study assessed change in BMI from baseline to 12 months. A statistically significant decrease of BMI in the sibutramine group (–2.9 kg/m^2) over the placebo group was observed. Although the presence of type 1 or 2 diabetes was an exclusion to study enrollment, an interesting secondary endpoint found a statistically significant decrease in both insulin levels and insulin sensitivity in the sibutramine group. However, a statistically significant decrease in serum glucose concentration was not observed.

Kay and colleagues conducted an 8-week, double-blind, placebo-controlled trial of 24 hyperinsulinemic non-diabetic obese adolescents with a BMI of >30 kg/m^2.[26] They found that 8 weeks of metformin (850 mg BID) produced significant weight loss and decreased body fat with no serious side effects. Freemark and Bursey also studied metformin in obese adolescents.[27] This randomized, double-blind, placebo-controlled trial examined 32 patients between 12 to 19 years of age who had a BMI >30 kg/m^2. The authors concluded that based on metformin's effects on fasting blood glucose, insulin levels, and weight, metformin (500 mg

Table 6. Combination oral hypoglycemic agent

	Tradename (formulation)	Dosage	Monitoring	Comments
Pioglitazone and Metformin	Actoplus Met (15/500 mg, 15/850 mg)	15/500 mg or 15/850 mg qd or bid up to 45 mg of pioglitazone and 2550 mg of metformin	CBC, LFTs, SCr, BUN	Take with meals; Pregnancy C
Rosiglitazone and Metformin	Avandamet (1/500 mg, 2/500 mg, 4/500 mg, 2/1000 mg, 4/1000 mg)	2/500 mg to 2/1000 mg bid up to 8 mg/2000 mg.	CBC, LFTs, SCr, BUN	Take with meals; Pregnancy C
Glyburide and Metformin	Glucovance (1.25/250, 2.5/500, 5/500 mg)	1.25/250 mg qd or bid up to 10/2000 mg	CBC, SCr, BUN	Take with meals; Pregnancy B
Glipizide and Metformin	Metaglip (2.5/250, 2.5/500mg, 5/500 mg)	2.5/250 mg up to 10/2000 mg	CBC, SCr, BUN	Take with meals; Pregnancy C

BUN, blood urea nitrogen; CBC, complete blood count; LFTs, liver function test; SCr, serum creatinine

BID) along with diet and exercise may reduce the risk of type 2 diabetes in obese hyperinsulinemic children with a family history of type 2 diabetes.

Metformin has also been examined as a potential treatment for weight loss in pediatric patients receiving psychotropic medications that are known to cause weight gain.[28] This study included 19 patients between the ages of 10 to 18 years old who were chronically receiving olanzapine, risperidone, quetiapine, or valproate. During a 12-week, open-label study, 15 of the 19 patients who received 500 mg of metformin TID had lost weight with an average BMI decrease of 2.22kg/m^2. No safety issues were noted during this 12-week trial, and all laboratory tests remained within normal ranges. The authors concluded that metformin may be a viable alternative for the treatment of psychotropic-associated weight gain in adolescents.

Diabetes

If glycemic goals cannot be achieved with diet and exercise within three months, the patient should start pharmacological therapy.[20] In making this decision, the clinician should examine the risks versus benefits of such treatments. Once the decision to use drug therapy has been made, one should consider the medications' mechanisms of action, available dosage formulations and strengths, dosing requirements, and potential for adverse effects (Tables 4-7). The medications' pharmacokinetics and likelihood of drug interactions must also be examined (Table 8). Treatment should be aimed at decreasing insulin resistance, enhancing insulin secretion, and slowing absorption of glucose after meals.[20] Although few studies have been conducted in children, the medications reviewed below have been used by clinicians in an effort to achieve these goals.

Metformin

Metformin exerts its affects by decreasing hepatic glucose production and stimulating glucose uptake into peripheral tissues (Table 4).[29] When used appropriately, metformin not only lowers HgbA1c by up to 2%, but aids in weight loss.[32] Its most common side effects are gastrointestinal and include abdominal pain and diarrhea.[30] Although rare, lactic acidosis may occur and is evident by symptoms that include weakness, increasing sleepiness, bradycardia, cold feeling, muscle pain, shortness of breath, feeling light-headed, and/or fainting. Lactic acidosis appears to be a problem in patients with renal and/or hepatic impairment or cardiac/respiratory insufficiency. It may also be a problem when the drug is not stopped before a procedure involving contrast dye.[31]

Metformin is currently the only FDA-labeled oral medication for the treatment of type 2 diabetes in children (Tables 4, 7, and 8). A randomized, placebo-controlled study of 82 children and adolescents 10 to 16 years of age was conducted to determine the safety and efficacy of metformin in the treatment of type 2 diabetes.[33] Patients were randomized to receive metformin or placebo. The metformin dose was slowly titrated to the largest tolerable dose, not to exceed 2,000 mg daily. The metformin-treated group had a significantly lower HgbA1c (7.5%) compared to the placebo group (8.6%)

Table 7. Glucose absorption inhibitors

	Tradename (formulation)	Dosage	Monitoring	Comments
Acarbose	Precose (25, 50, 100 mg)	25 mg tid; adjusted q 4-8 weeks up to 50-100 mg tid	LFTs q 3 mo for 1 yr then periodically	Take with first bite of each meal; Pregnancy B
Miglitol	Glyset (25, 50, 100 mg)	25-100 mg tid	None recommended	Take with meals; Pregnancy B

LFTs, liver function test

($P < 0.001$). Although adverse events (e.g., abdominal pain, diarrhea, nausea/vomiting, and headache) occurred more frequently in the metformin group, no patient discontinued treatment due to an adverse effect. The authors concluded that metformin, in doses ≤ 2,000 mg/day, is safe and effective for the treatment of type 2 diabetes in pediatric patients.

Sulfonylureas

Because sulfonylureas, such as glyburide and glipizide, work by stimulating pancreatic β-cells to secrete insulin (Tables 5, 6, and 8), their usefulness is dependent on functioning β-cells. Adverse effects such as weight gain and hypoglycemic reactions also limit the use of sulfonylureas.[20] Although not labeled for use in pediatrics, sulfonylureas have been used safely in this population. Fajans and Brown prospectively evaluated 12 patients for up to 33 years (9 to 29 years of age with mean 16.4) for the effect of sulfonylureas (mainly chlorpropamide) on glucose-induced insulin secretion in patients with maturity-onset diabetes of the young (MODY).[34] The authors found that long-term administration of sulfonylureas significantly enhances glucose-induced insulin concentrations by about 68%. Culler and colleagues investigated the effect of glipizide treatment in 6 patients (12-25 years of age) with cystic fibrosis who had developed impaired glucose tolerance.[35] The authors concluded that 2.5 mg of glipizide twice daily improved glucose tolerance. Mild, symptomatic hypoglycemia was the only adverse effect that was noted with treatment.

Thiazolidinediones

The thiazolidinediones work to decrease blood glucose by increasing insulin sensitivity in liver, muscle, and adipose tissue and by decreasing hepatic glucose synthesis output (Table 6). Adverse effects associated with thiazolidinediones include edema, weight gain, anemia, and the potential for elevation of liver enzymes. Typically, long-term use of thiazolidinediones will decrease HgbA1c an average of 1%.[36]

Thiazolidinediones have not been well studied in children. However, they have been included in a study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) called the TODAY (treatment options for type 2 diabetes in adolescents and youth) trial, which is currently recruiting patients in 10 states throughout the US.[37] 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. The three treatments being investigated are: 1) metformin alone; 2) metformin plus a thiazolidinediones (rosiglitazone); and 3) metformin plus an intensive lifestyle intervention called the TODAY lifestyle program. The study will be a randomized, placebo-controlled, safety and efficacy study that will enroll patients over 3 years. Eligible patients will be 10 to 17 years old and will be followed for 2 years. This study is currently recruiting patients.

α-Glucosidase Inhibitors

Acarbose and miglitol affect serum glucose by slowing the absorption of carbohydrates in the lower small intestine (Tables 7 and 8). This, in turn, decreases post-prandial serum gluose results.[38] The decrease in HgbA1c achieved with acarbose and miglitol is approximately 0.5%-1%.[20] Common side effects such as flatulence, diarrhea, and abdominal cramps may make this class of medication less than ideal for use in children and adolescents.[39]

The use of acarbose in children has not been well studied. Kentrup and colleagues conducted a double-blind, randomized, crossover trial to determine the efficacy of acarbose in patients with cystic fibrosis who had impaired glucose

Table 8. Pharmacokinetics of various agents used in the treatment of type 2 diabetes

	Bioavailability (Protein Binding)	Half-Life (hr)	Elimination	Substrate	Effects on CYP System
Acarbose	2%; metabolized in GI tract by gut bacteria	2	2% in urine; 51% excreted in feces	none	Inducer of CYP2E1
Glimepiride	100% (99.5%)	5-9	60% in urine; 40% in feces	CYP2C8 CYP2C9	none
Glipizide	Delayed with food (92%-98%)	2-4	60-80% in urine	CYP2C8 CYP2C9	
Glyburide	Well absorbed (>99%)	5-16	50% in urine as metabolite	none	Mild inhibitor of CYP3A4
Metformin	50%-60% if fasting* (0%)	6	90% unchanged in the urine; no hepatic metabolism or biliary excretion	none	none
Miglitol	100% (<4%)	2	>95% in urine	none	none
Nateglinide	73% (98%)	1.5	83% in urine; 10% in feces	CYP2C9 CYP3A4	none
Pioglitazone	50% in animals (99.8%)	3-7†	15-30% in urine	CYP2C8 CYP2C9 CYP3A4	Significant inhibitor of CYP2C8 and CYP2C9, moderate inhibitor of CYP2D6; mild inhibitor of CYP2C19; mild inducer of CYP3A4
Repaglinide	56% (98%)	1	8% in urine; 92% in feces	CYP3A4	none
Rosiglitazone	99% (99.8%)	3-4‡	64% in urine; N-demethylation, hydroxylation, conjugation with sulfate and glucuronic acid	CYP2C8 CYP2C9	Moderate Inhibitor of CYP2C8 and CYP2C9; mild inhibitor of CYP2C19 and CYP2D6

** lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination*
† parent
‡ dose-independent

tolerance.[40] They found that 50 mg of acarbose 3 times daily caused a significant decrease in serum glucose concentrations when compared to placebo and concluded that acarbose may be used safely in this population for at least 2 weeks with no serious side effects.

Insulin

Insulin is a hormone that is endogenously produced by pancreatic β-cells. Exogenous insulin helps regulate serum glucose by increasing its uptake into muscle and adipose tissue as well as decreasing hepatic glucose production.[41] Because side effects such as weight gain, hypoglycemia, and peripheral hyperinsulinemia are common with insulin, many practitioners prefer to delay the use of insulin in children with type 2 diabetes.[42] In fact, the ADA recommends that insulin be reserved for patients with very elevated blood glucose values or for those who are extremely symptomatic.[6] Once the serum glucose levels are within the target range, oral medication (e.g., metformin) should be started, and the dose of insulin should be gradually decreased and subsequently discontinued.[6]

SUMMARY

It is essential that all healthcare providers understand the importance of early screening for type 2 diabetes in children and the need for successful medical management. Research has shown that, with the proper supervision, type 2 diabetes can be well controlled in children and that these individuals can live healthy, happy lives while preventing or postponing the complications secondary to type 2 diabetes.[43]

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REFERENCES

1. Nesmith JD. Type 2 diabetes mellitus in children and adolescents. Pediatr Rev 2001;22:147-152.
2. Legro RS, Kunselman AR, Dodson WC, et al. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Meta 1999;84:165-169.
3. Wysocki T. Psychological complications of childhood diabetes: case examples. Diabetes Spectrum 1997;10:275-277.
4. Pinhas-Hamiel O, Dolan L, Daniels S, et al. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. J Pediatr 1996;128:608-615.
5. Rowell H, Evans B, Quarry-Horn J, et al. Type 2 diabetes mellitus in adolescents. Adolesc Med 2002;13:1-12.
6. American Diabetes Association. Type 2 diabetes in children and adolescents. Diabetes Care 2000;23:381-389.
7. Stuart CA, Gilkison CR, Smith MM, et al. Acanthosis nigricans as a risk factor for non-insulin dependent diabetes mellitus. Clin Pediatr 1998;37:73-79.
8. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2003; 26(Suppl 1): S5-11.
9. Rocchini AP. Childhood obesity and a diabetes epidemic. N Engl J Med 2002; 346:854-855.
10. Sinha R, Fisch G, Teague B, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. N Engl J Med 2002;346:802-810.
11. Libman I, Arslanian SA. Type II diabetes mellitus: no longer just adults. Pediatr Ann 1999;28:589-593.
12. Hanis CL, Boerwinkle E, Chakraborty R, et al. A genome-wide search for human non-insulin dependent (type 2) diabetes genes reveals a major susceptibility locus on chromosome 2. Nat Genet 1996;13:161-166.
13. Humphreys P, McCarthy M, Tuomilehto J, et al. Chromosome 4q locus associated with insulin resistance in Pima Indians. Diabetes 1994;43:800-804.
14. Waltson J, Silber K, Bogardus C, et al. Time of onset of non-insulin dependent diabetes mellitus and genetic variation in the β adrenergic receptor. N Engl J Med 1995;333:343-346.
15. Fagot-Campagna A. Emergence of type 2 diabetes mellitus in children: epidemiological evidence. J Pediatr Endocrinol Metab 2000;12 Suppl 6:1395-1402.
16. Speiser PW, Rudolf MCJ, Ahalt H, et al. Consensus statement: childhood obesity. J Clin Endocrinol Metab 2005;90:1871-1887.
17. Strauss RS, Pollack HA. Epidemic increase in childhood overweight. JAMA 2001;286:2845-2848.
18. Veugelers PJ, Fitzgerald AL. Prevalence of and risk factors for childhood overweight and obesity. CMAJ 2005;173:607-613.
19. Wang G, Dietz WH. Economic burden of obesity in youths aged 6 to 17 years:1979-1999. Pediatrics 2002;109:1-6.
20. Rosenbloom A. Increasing incidence of type 2 diabetes in children and adolescents: Treatment considerations. Pediatr Drugs 2002;4:209-221.
21. Chanoine JP, Hampl S, Jensen C, et al. Effect of orlistat on weight and body composition in obese adolescents. JAMA 2005;293:2873-2883.

22. Arora SK, McFarlane SI. The case for low carbohydrate diets in diabetes management. Nutr Metab 2005;2:16.
23. Willi SM, Datko FM, Martin K, et al. Treatment of type 2 diabetes in childhood using a very-low-calorie diet. Diabetes Care 2004;27:348-353.
24. Berkowitz RI, Wadden TA, Tershakovec AM, et al. Behavior therapy and sibutramine for the treatment of adolescent obesity. JAMA 2003;289:1805-1812.
25. Berkowitz RI, Jujioka K, Daniels SR, et al. Effects of Sibutramine Treatment in Obese Adolescents. Ann Intern Med 2006;145:81-90.
26. Kay JP, Alemzadeh R, Langley G, et al. Beneficial effects of metformin in normoglycemic morbidly obese adolescents. Metabolism 2001;50:1457-1461.
27. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Pediatrics 2001;107:1-7.
28. Morrison JA, Cottingham EM, Barton BA. Metformin for weight loss in pediatric patients taking psychotropic drugs. Am J Psychiatry 2002;159:655-657.
29. DeFronzo RA, Barzilai N, Simonson DC. Mechanism of metformin action in obese and lean noninsulin-dependent diabetic subjects. J Clin Endocrinol Metab 1991;73:1294-1301.
30. DeFronzo RA, Goodman AM, and the Multicenter Metformin Study Group. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. N Eng L Med 1995;333:541-549.
31. Stang MR, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. Diabetes Care 1999;22:925-927.
32. Garber AJ, Duncan TG, Goodman AM, et al. Efficacy of metformin in type II diabetes: results of a double blind, placebo-controlled, dose-response trial. Am J Med 1997;103:491-497.
33. Jones KL, Park JS, Arslanian S, et al. Effect of metformin in pediatric patient with type 2 diabetes. Diabetes Care 2002;25:89-94.
34. Fajans SS, Brown MB. Administration of sulfonylureas can increase glucose-induced insulin secretion for decades in patient with maturity-onset diabetes of the young. Diabetes Care 1993;16:1254-1261.
35. Culler FL, McKean LP, Buchanan CN, et al. Glipizide treatment of patients with cystic fibrosis and impaired glucose tolerance. J Pediatr Gastroenterol Nutr 1994;18:375-378.
36. Aronoff S, Rosenblatt S, Braithwaite S, et al. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes. Diabetes Care 2000;23:1605-1611.
37. Clinical Trials.gov. Treatment options for type 2 diabetes in Adolescents and Youth (TODAY). Available at: http://clinicaltrials.gov/ct/show/NCT00081328?order=1 Accessed August 2006.
38. Coniff RF, Shapiro JA, Robbins D, et al. Reduction of glycosylated hemoglobin and postprandial hyperglycemia by acarbose in patient with NIDDM. Diabetes Care 1995;18:817-824.
39. Chiasson JL, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. Ann Intern Med 1994;121:928-935.
40. Kentrup H, Bongers H, Spengler M, et al. Efficacy and safety of acarbose in patients with cystic fibrosis and impaired glucose tolerance. Eur J Pediatr 1999;158:455-459.
41. Gold Standard, Inc. Clinical Pharmacology, Insulin Drug Monograph. Available at: URL:http://cp.gsm.com Accessed August 2006.
42. Henry RR, Gumbiner B, Ditzler T, et al. Intensive conventional insulin therapy for type II diabetes. Diabetes Care 1993;16:21-31.
43. Ludvigsson J. Prevention of adverse events in juvenile diabetes. Minerva Pediatr 2004;56:277-290.