REVIEW ARTICLE

Type 2 Diabetes Mellitus in Children and Adolescents: The New Challenge

Michael L. Christensen, PharmD,[1,2,4] Sahar M. Rashed, PharmD, PhD,[1] Julie Sinclair, PharmD,[1] Patricia A. Cowan, PhD,[3] Pedro Velasquez-Mieyer, MD,[2,4] and George A. Burghen, MD[2,4]

[1]Department of Pharmacy, Pediatric Pharmacology Research Unit, Center for Pediatric Pharmacokinetics and Therapeutic, [2]Department of Pediatrics, [3]College of Nursing, University of Tennessee Health Science Center, [4]Children's Foundation Research Center, LeBonheur Children's Medical Center, Memphis, Tennessee

The epidemic increase in the incidence of type 2 diabetes mellitus (T2DM) in children and adolescents is presenting enormous challenges to the medical profession. The combination of factors such as obesity, ethnicity, puberty, and genetic predisposition has contributed to the development of T2DM in younger ages. These factors affect the regulatory mechanism of insulin secretion, insulin action, and hepatic gluconeogenesis. In contrast to adults, children appear to have a shorter latency to disease, a more rapid development of symptoms, and an increased ketoacidosis. There are limited therapeutic options to prevent or manage T2DM in children. Although the role of diet and exercise (lifestyle intervention) has not been adequately evaluated in children, they will remain important adjuncts in the prevention and treatment of T2DM. Insulin and metformin are currently the only approved medications for the treatment of T2DM in children. Clinical trials involving other oral agents used in adults are currently being conducted to evaluate their safety and efficacy in children.

KEYWORDS: drug therapy, obesity, pediatrics, type 2 diabetes mellitus

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ABBREVIATIONS: DM, diabetes mellitus; GDM, gestational diabetes mellitus; GIP, glucose insulinotropic peptide; GLP-1, glucagon-like-peptide 1; NEFA, non-esterified fatty acids; PAI-1, plasminogen activator inhibitor-1; T1DM, type 1 diabetes; T2DM, type 2 diabetes mellitus; VLDL, very low-density lipoproteins; ADA, American Diabetes Association; DKA, diabetes ketoacidosis; FDA, Food and Drug Administration; LDL, low-density lipoprotein; HDL, high-density lipoprotein

INTRODUCTION

Diabetes mellitus (DM) is a group of complex metabolic disorders characterized by hyperglycemia due to inadequate insulin secretion, peripheral insulin resistance, and increased hepatic gluconeogenesis. Depending upon which underlying impairment(s) are present, classifications of diabetes have emerged. Type 1 diabetes (T1DM), the most common type of DM in children, is usually mediated by an autoimmune destruction of pancreatic b-cells, resulting in little to no insulin production. Type 2 diabetes mellitus (T2DM), traditionally viewed as an adult disease, is the result of a failure of pancreatic β-cells to secrete adequate amounts of insulin to compensate for the marked insulin resistance and increased hepatic gluconeogenesis.[1] The prevalence of T2DM is now increasing in children and adolescents, particularly in those genetically predisposed, and is paralleling the rise of obesity that is being fueled by sedentary lifestyle and dietary indiscretions.[1-6]

The increasing prevalence of T2DM in this younger population will significantly impact the medical, financial, and health of humans worldwide. A multidisciplinary team of physicians, nurses, nutritionists, pharmacists, and educators must be thoroughly trained to meet the challenges. The improved awareness of health care providers of the growing problem of T2DM in

Address reprint request to: Michael L. Christensen, PharmD, LeBonheur Children's Medical Center, 50 North Dunlap, Room 306, Memphis, TN 38103, email: mchristensen@utmem.edu

children will enhance the identification of at-risk children, improve diagnostic criteria, and improve management. The earlier development of T2DM poses an enormous financial burden to the health care system, leads to a reduction in productivity associated with a chronic disease, and reduces life expectancy. The human element is self-evident in the lives of the children affected and their families, whose daily lives are fraught with profound psychosocial and physical comorbidities.

The goal of this paper is to review of epidemiology, pathophysiology, and complications of T2DM in children and adolescents and to focus on options for prevention and treatment.

EPIDEMIOLOGY

Childhood T2DM is becoming a worldwide epidemic with increasing incidence reported in the United States (U.S.),[3-9] Canada,[10,11] Japan,[2,12,13] and Libya.[14] The rise in the incidence of T2DM has paralleled the increasing rate of childhood obesity.[20] In the U.S., T2DM in children was first reported in a Pima Indian population[15] and now predominates in certain ethnic groups including Asians,[2,12,13] Hispanics,[16,17] American-Indians,[7,15] and African-Americans.[5,18]

Pinhas-Hamiel reported a 4-fold increase in T2DM in the Greater-Cincinnati area, from 2–4% of new DM cases in 1982 to 16% in 1995.[3] The incidence was even higher (33%) for children between 10 and 19 years of age.[3] Among Mexican-American children, Neufeld reported that T2DM among Mexican-American children accounted for 31% of diabetes cases diagnosed between 1990 and 1994.[17] In the Mid-South portion of the US, mainly in African-American children, Scott reported an increased incidence of T2DM from 4% of new cases in 1988 to 34% in 1995.[4,5] Burghen reported a five-fold increase in T2DM in the Greater-Memphis, Tennessee area between 1990 and 2000.[18] The American Diabetes Association has stated that 8- 45% of children newly diagnosed with DM have T2DM.[19]

PATHOPHYSIOLOGY

The pathogenesis of T2DM in children and adolescents is poorly understood. The pathogenic mechanisms involve derangements in blood glucose regulation, impaired insulin secretion, insulin resistance, and increased hepatic gluconeogenesis. Risk factors for the development of T2DM include ethnicity, genetics, obesity, unhealthy lifestyle, gender, and puberty. Studies in minority children demonstrate more risk factors for the development of T2DM than those reported for their Caucasian counterparts. Differences in risk factors among African-American and Caucasian children include an increased β-cell activity, higher insulin secretion, reduced insulin clearance, and lower insulin sensitivity among African-American children.[20-23] African-American children with T2DM are more obese and have a more sedentary lifestyle, have a greater percentage of their caloric intake as fat, have lower resting energy expenditure, and lower rates of lipolysis. It is not clear if these factors associated with hyperinsulinemia are due to race-related intrinsic differences, lifestyle, or other biological factors, but these factors could easily explain the higher prevalence and incidence of children with T2DM in minorities.

T2DM is likely a polygenetic disease resulting from the interaction of multiple genes with environmental factors. The higher prevalence of T2DM in children of minority racial background, a history of macrosomia or underweight at birth, and a family history of DM suggest that genetic factors play an important role in the development of the disease.[2-4,16-18,24] However, many years are required for gene mutations to occur; therefore, the recent dramatic rise in the incidence of T2DM in children cannot be explained by a change in the genetic pool. Lifestyle changes in children with genetic risk predisposition are the most likely cause for the increased incidence of T2DM. The role of increased adiposity in the pathogenesis of T2DM has been demonstrated in the parallelism of both obesity and the T2DM epidemic and in the higher prevalence of T2DM among overweight and obese adolescents.[19,25,26] The severity and the duration of obesity, as well as the distribution of fat, have an important role in the genesis of T2DM.[27-32] Central obesity appears to have a greater influence on insulin sensitivity than peripheral obesity.[28] The relationship of excessive adipose tissue and the development of insulin resistance is not completely understood. Increased levels of non-esterified fatty acids associated with obesity may directly affect β-cell function, insulin secretion, and insulin resistance leading to glucose intolerance.[33-35] High plasma

non-esterified fatty acids concentrations may also impair the release of incretins. Incretins are major regulators of pancreatic insulin secretion that are released by intestinal cells in response to nutrient intake.[36] Two incretins, glucagon-like-peptide 1 (GLP-1) and glucose insulinotropic peptide and glucose-dependent insulinotropic peptide (GIP), are responsible for 80% and 20%, respectively, of the intestinal incretin effect on pancreatic insulin secretion.[37] Decreased GLP-1 and GIP responsiveness in obese subjects may be an important factor in the development of impaired glucose tolerance.[38]

Sedentary lifestyle is an independent risk factor in the pathogenesis of T2DM.[39,40] Lower prevalence of T2DM has been found in subjects with increased levels of physical activity independent of the adiposity (i.e., Sumo wrestlers). Insulin sensitivity positively correlated with the maximum aerobic capacity in adult Pima Indian and Caucasian men with normal glucose tolerance.[24] Hyperinsulinemia has been associated with lower levels of physical activity in children.[41] Increases in physical activity improve insulin action, indices of insulin resistance, and glucose metabolism in both lean and obese subjects with or without T2DM.[42]

Gender is another factor associated with the development of T2DM in children. The male-to-female ratio in adolescents with T2DM has ranged from 1:1.6 to 1:2.8.[3,4,43] These data suggest that females are at greater risk than males for developing T2DM. The underlying cause for the greater prevalence of T2DM in adolescent females is unknown. However, girls gain more weight, have increased fat mass, decreased physical activity, and are more insulin resistant than boys during adolescence.[44]

Puberty is a peak time for the development of T2DM in children. Hormonal changes during puberty and increased secretion of growth hormone and sex hormones, antagonize insulin action, promoting insulin resistance and hyperinsulinism.[45-49] Glucose disposal rates are lower during puberty compared with pre-puberty and post-puberty rates.[46] Caucasian children compensate for the insulin resistance during puberty by secreting more insulin whereas compensation in African-American children may be reduced. These factors in conjunction with an increase in body fat (predominately in females) and a decrease in physical activity may explain the higher incidence of T2DM in African-American females.[43]

Progression from normal glucose tolerance through impaired glucose tolerance to T2DM is affected by a number of complex factors, the degree and order of which has yet to be elucidated. It is imperative that well-designed studies be implemented to improve the understanding of the pathogenesis and natural course of this challenging problem.

CLINICAL PRESENTATION

Children with T2DM are usually obese, from a minority group, and have a family history of diabetes. They may also have dyslipidemias, menstrual irregularities, hypertension, acanthosis nigricans, and microvascular changes.[50] Newly diagnosed children may present with mild to severe clinical symptoms. Approximately one third of these children present with glucosuria and hyperglycemia that may be detected during routine medical exam.[23,27,42,44] About 20–25% of children with T2DM may present with severe symptoms of polydipsia, weight loss, ketonuria, and ketoacidosis.[13,45] Hyperglycemia, ketonuria, and metabolic acidosis are usually milder in children with T2DM than in T1DM patients. Plasma insulin and c-peptide concentrations are usually higher in T2DM than in T1DM, reflecting insulin resistance; however, levels may also be normal or low at the time of diagnosis.[17] Children do not appear to have the long latency period seen in adults; rather, they develop symptomatic polyuria and nocturia early in the disease process.

The American Diabetes Association criteria for the diagnosis of diabetes is a fasting blood glucose ≥126 mg/dL (7 mmol/L), 2-hour blood glucose ≥200 mg/dL (11.1 mmol/L) following oral glucose tolerance test, or symptoms of DM and a random blood glucose ≥200 mg/dL (11.1 mmol/L). In the absence of symptoms, elevated fasting or random blood glucose should be confirmed on a separate day. Using the later parameters, screening for T2DM should be directed toward children at risk. Risk factors include severe obesity, minority ethnic background (Native Americans, Japanese/Pacific Islanders, Mexican-American, and African-American), acanthosis nigricans, hypertension, family history of T2DM, and children born to mothers with gestational DM (GDM). A high prevalence (>20%) of im-

paired glucose tolerance has been observed in a multiethnic group of obese children and adolescents, with obese African-American children having a 50% higher incidence of impaired glucose tolerance than obese Caucasian children.[51] Children of mothers with GDM have a higher incidence of T2DM compared to non-GDM, 19.3% versus 2.5%, respectively.[52-54] High-risk children and adolescents should undergo formal testing to rule out diabetes every two years starting at age 10 years old, or at the onset of puberty, or as symptoms develop.

PREVENTION

The benefits of lifestyle modifications in preventing or delaying the progression to T2DM in adults with glucose intolerance have been reported in several studies.[55,56] The Diabetes Prevention Program trial has shown that a comprehensive individualized lifestyle modification program (i.e., improvement of diet, increase in physical exercise, and smoking cessation) lowered the risk for development of T2DM by 58% compared with placebo and was equally beneficial to all patients, regardless of ethnicity, body mass index, sex, or level of glycemia.[55] Treatment with metformin was also effective but to a lesser extent than lifestyle modifications, resulting in a 31% reduction in risk of T2DM compared with placebo.[55] Similarly, the Finnish Diabetes Prevention Study assessed the efficacy of an intensive diet and exercise program in preventing or delaying T2DM in overweight individuals with impaired glucose tolerance.[56] When individual dietary advice aimed at reducing weight, increasing dietary fiber, and decreasing intake of saturated fat was combined with individual guidance to increase level of physical activity, several positive indications resulted: significantly greater reductions in weight, 2-hour plasma glucose, fasting and 2-hour plasma insulin, systolic and diastolic blood pressure, and serum triglycerides than a control group who received general information regarding the benefits of weight reduction, physical activity, and healthy diet for the prevention of diabetes. These studies support the benefits of lifestyle modifications in preventing or delaying the onset of diabetes in high risk adults. Replication of the interventions with youth and their families are needed to determine whether the benefits achieved in adult populations are transferable to children.

Table 1. Injectable Insulin Products

GENERIC (Legend)	ONSET (hr)	PEAK (hr)	DURATION (hr)
Lispro (Humalog)	0.25–0.5	0.5–1.5	4–6
Aspart Insulin (Novolog)	0.25–0.5	1–3	3–5
Regular Insulin (Humulin R, Novolin)	0.5–1	2–3	8–12
Isophane insulin (NPH; Novolin N, Humulin N)	1–1.5	4–12	24
Insulin zinc (Humulin Lente)	1–2.5	8–12	18–24
Prompt zinc insulin (PZI)	4–8	14–24	36
Extended insulin zinc (Ultralente)	4–8	16–18	>36
Insulin glargine (Lantus)	1–2		24
Insulin combinations:			
Humulin 70/30	0.25–0.5	2–12	24
Humulin 50/50	0.25–0.5	2–12	18–24
Novolin 70/30	0.5	2–12	24
Humalog 75/25	0.25	1–6.5	18–26
Novolog 70/30	0.25–0.5	0.5–6	18–24

THERAPEUTIC MANAGEMENT METHODS

Diet, exercise, and weight loss are the cornerstone of any treatment regimen and must be reinforced throughout the entire course of the disease. Weight loss and exercise improve glycemic control in obese T2DM children by decreasing glucose production and increasing muscle sensitivity to insulin.[57-61] Unfortunately, as the sole method of treatment, diet and exercise have limited success in the long-term management of adults with T2DM and are likely to be no more effective in children and adolescents.[62,63] Nonetheless, investigations regarding the type and duration of exercise on the magnitude of glycemic control and insulin sensitivity are needed. Children appear to have a more overt disease course compared to the more insidious onset in adults. They have a shorter latency period and have more acute symptoms at presentation (20–25% with DKA or severe ketonuria), suggesting that children with T2DM have a more aggressive disease than that which occurs in adults. Therefore, pharmacological treatment is necessary in the majority of children diagnosed with T2DM. Effective pharmacological therapy may target insulin production, insulin action, hepatic gluconeogenesis, or a combination of these factors. Four classes of pharmacological agents are available for the treatment of T2DM (Tables 1 and 2). These agents include insulin, insulin-sensitizing agents, insulin-stimulating agents, and glucose absorption inhibitors. Each of these classes of agents possesses a different mechanism of action enabling the agents to be used either alone or in combination.[64-66]

Insulins. Insulin is approved for use in children with T2DM and, until recently, was the only

Table 2. Oral Drugs for the Treatment of Type 2 Diabetes Mellitus

Drug	Usual Adult Dosage	Comments
Insulin Sensitizing Agents		
Metformin (Glucophage)	1500–2550 mg divided	Approved for use 10 to 16 yr, begin 500 mg twice daily, use lowest dose that controls blood glucose XR is not approve for use in children
Metformin XR	1000–2000 mg once or twice daily	
Pioglitazone (Actos)	15–45 mg once daily	Periodic Liver and kidney testing is required. Caution if creatinine >1.4 in women or >1.5 in men.
Rosiglitazone (Avandia)	4–8 mg once daily or divided	
Insulin Secretagogues		
Chlorpropamide (Diabinese)	250–375 mg once daily	Weight gain and hypoglycemia are side effects of all sulfonylureas, specifically glyburide due to its receptor high affinity. Take 30 min. before meals. Glipizide should be taken on empty stomach. Disulfiram-like syndrome. Syndrome of inappropriate secretion of antiduretic hormone (SIADH). Periodic liver function testing is required. Caution with drugs metabolized by CYP450. Caution heart failure patients.
Tolazamide (Tolinase)	250–500 mg once or twice daily	
Tobutamide	1000–2000 mg divided	
Glimepiride (Amaryl)	1–4 mg once daily	
Glipizide (Glucotrol)	10–20 mg once daily or divided	
Glyburide (DiaBeta, Micronase, Glynase)	5–50 mg once daily or divided	
Nateglinide (Starlix)	60–120 mg three times daily before meals	
Repaglinide (Prandin)	1–4 mg three times daily before meals	
Glucose Absorption Inhibitors		
Acarbose (Precose)	50–100 mg three times daily with meals	Increase dose slowly to decrease GI effects. Dose based on weight. Caution with liver or kidney problems.
Miglitol (Glyset)	50–100 mg three times daily with meals	
Combinations		
Metformin/glyburide (Glucovance)	250 mg/1.25 mg, 500 mg/2.5 mg, 500 mg/5 mg twice daily	See above comments for each drug Maximum dose is 2000 mg/20 mg divided twice daily
Metformin/glypizide (Metaglip)	250 mg/2.5 mg, 250 mg/5 mg, 500 mg/5 mg twice daily	
Metformin/rosiglitazone (Avandamet)	500 mg/1 mg, 500 mg/2 mg, 500mg/4 mg twice daily	Not for patients >80 years old.

agent approved for its treatment in children. The use of insulin has an important role in the early restoration of euglycemia in patients with new onset DM and who also have significant hyperglycemia. High glucose concentrations present a state of glucose toxicity to the pancreatic beta cells, resulting in decreased insulin production in the face of increasing insulin resistance and requirements. Short-term intensive insulin therapy to normalize blood glucose levels improves peripheral insulin sensitivity, restores pancreatic β-cell function, decreases hepatic gluconeogenesis, and can improve the subsequent response to oral antidiabetic therapy.[67-69]

Table 1 describes the rapid, short-acting, intermediate, and long-acting forms of insulin (including recombinant insulin analogs) with regard to the onset of action, peak, and duration of action. Commercial regular insulin exists as a hexamer (six molecule aggregates); after subcutaneous injection, the hexamer dissociates into dimers and monomers before significant absorption can occur. The short-acting insulins are derived from recombinant technology (Humolog, Novolog) or animal sources (Regular Ilente II) and is given 30 to 60 minutes before a meal to control the post-prandial glucose level.

The newer rapid acting insulins, lispro and aspart, differ from regular insulin by either transposing the amino acids at the 28 (proline) and 29 (lysine) positions on the insulin b chain (lispro) or by replacing proline at position 28 with aspartate (aspart). The modification in the β chain results in an insulin product that has fewer tendencies to self-associate into hexamers like regular insulin; therefore, the resulting insulin product is more rapidly absorbed into the bloodstream. The rapid-acting analogs just mentioned can be given within 15 minutes of a meal to control the post-prandial rise in blood glucose.

Intermediate-acting insulin is a suspension of zinc insulin crystals and protamine sulfate (isophane insulin, NPH and Lente). These insulins are usually given twice daily and are often given in combination with a rapid- or short-acting insulin. Long-acting insulins (extended insulin zinc suspension) are made by varying the concentration of zinc and protamine. The long-acting insulins are slowly absorbed with a peak at 16–18 hours and provide a basal level of insulin in the blood in an attempt to approximate the amount of insulin circulating in the body when not stimulated by glucose. A long-acting form of insulin has also been produced by modifying the α chain, replacing glycine with asparagine at position 21, and adding arginine at positions 31 and 32 of the β chain (glargine). This modification increases the stability of the hexamer structure, causing slower dissociation into dimers and monomers which results in slower absorption of insulin from the injection site. For ease of administration, some fixed combinations of NPH and regular or rapid-acting insulin are available as 70/30, 50/50, and 75/25 mixes. Insulin types are usually chosen according to their ability to achieve the best blood glucose control possible based on home glucose monitoring. The most common side effects are hypoglycemia, injection site reactions, and weight gain.[70] Patient education is needed regarding injection technique and timing, rotation of injection sites to avoid lipodystrophy, mixture and storage of insulin, home glucose monitoring, and treatment of hypoglycemia.

Insulin Stimulating Agents. There are two types of insulin secretogogues, the sulfonylureas (of which there are two generations) and nonsulfonylureas, neither of which has been adequately tested in children. The first generation sulfonylureas include tolbutamide, chlorpropamide, and tolazamide; second generation sulfonylureas agents include glyburide, glipizide, and glimepiride.[71] The principle mechanism of action of the sulfonylureas is the stimulation of insulin secretion from the pancreatic β-cell in response to glucose.[72] These agents may also suppress hepatic gluconeogenesis by increasing portal insulin, which reduces fasting plasma glucose and improves peripheral tissue sensitivity to insulin.[73,74] An additional effect reported with glimepiride is the partial restoration of the first phase of insulin secretion, resulting in a more physiologic response.[75,76]

Most adverse events are mild and reversible upon drug withdrawal. Hypoglycemia is the most important adverse effect and occurs more commonly with the longer acting agents such as glyburide. Insulin stimulating agents also cause hyperinsulimemia, which is associated with microalbuminuria, arteriosclerosis, hypertension, and weight gain. These agents have no effect on plasma lipid levels.

Repaglinide and nateglinide are nonsulfonylurea agents that stimulate insulin secretion.

In contrast to sulfonylureas, they cause a prompt short-lived burst of insulin that raises plasma insulin for 1 to 2 hours.[77] These agents are taken within 30 minutes before each meal. The drug is usually started at the smallest dose with dosage titration occurring at weekly intervals until the desired glycemic control or the maximum recommended dose is achieved. The major side effect is hypoglycemia. Repaglinide and nateglinide may also cause weight gain, though usually less than that observed with sulfonylureas. Similar to the sulfonylureas, these agents have no effect on plasma lipids.

Insulin Sensitizing Agents. The two major classes of insulin-sensitizing agents are the biguanides and the thiazolidinediones. Metformin is the only biguanide available for clinical use and has no effect on pancreatic β-cell insulin secretion.[78] The mechanism of action by which metformin improves insulin sensitivity is not fully understood. Recent work suggests that metformin acts on the AMP protein kinase pathway to enhance GLUT4 translocation and glucose uptake in hepatic and peripheral tissue.[79] Metformin decreases hepatic glucose production and likely inhibits hepatic glycogenolysis.[80,81] Fasting and postprandial insulin levels decline as a normal pancreatic compensatory mechanism for improved tissue sensitivity to insulin.[80,81] Metformin reduces cardiovascular risk factors by suppressing the release of fatty acids and lipid oxidation (which also enhances glycemic control) leading to a reduction in triglycerides, very low-density lipoprotein (VLDL), and total cholesterol, as well as a decrease in plasminogen activator inhibitor-1 (PAI-1) levels. Metformin, but not sulfonylurea therapy, was associated with a significant reduction in macrovascular complications, myocardial infarction, and stroke in the United Kingdom Progressive Disease Study.[82] Metformin appears to be unique in promoting weight loss, whereas other oral glycemic agents and insulin promote weight gain. Metformin is the only oral agent in which there is appreciable experience in the treatment of children and adolescents with T2DM and is FDA approved for use in children greater than 10 years of age.[83] The usual starting dose of metformin is 500 mg twice a day, given with meals. Dosage increases should be made in increments of 500 mg weekly up to a maximum of 2000 mg per day, given in divided doses.

The most common side effects with metformin are gastrointestinal, including abdominal discomfort and diarrhea. These side effects tend to be transient and can be minimized by slow titration of the dose. Because metformin does not increase insulin secretion, hypoglycemia is a rare side effect. The most serious side effect is lactic acidosis, which occurs with a frequency of about 3 cases per 100,000 patient years. Avoiding metformin use in patients with other serious medical disorders including renal dysfunction, cardiogenic or septic shock, pulmonary insufficiency, and severe liver disease can reduce the risk for lactic acidosis.

The thiazolidinediones include rosiglitazone, pioglitazone, and troglitazone, the latter having been removed from the market because of hepatotoxicity. Most of our knowledge from this class of agents comes from the study of troglitazone. Thiazolidinediones improve tissue and liver sensitivity to insulin by binding to the peroxisome proliferator activated receptor (PPARg), a nuclear receptor whose highest level of expression is in adipocytes and intestinal cells and has very low levels of expression in other tissues, including muscle.[84-89] These agents decrease free fatty acid concentrations, and pioglitazone lowers plasma triglyceride concentration.[90] Thiazolidinediones increase fat cell numbers, accounting for the weight gain reported with the use of these agents, which is even greater when used in combination with insulin or a sulfonylurea.[91] About 2% of diabetic patients treated with troglitazone had an increase in serum liver enzyme levels. Liver disease is under close scrutiny for both rosiglitazone and pioglitazone, but no studies have found the development of increased levels of liver enzymes to be different from placebo. Edema has been reported in 2-4% of patients treated with thiazolidinedione monotherapy, 4-6% in patients on combination therapy with a sulfonylurea, and 10-15% in patients on combination therapy with insulin. This class of drugs should be avoided in patients with significant underlying heart disease.[92]

Glucose Absorption Inhibitors. The glucose absorption inhibitors are α-glucosidase competitive inhibitors of the brush border enzymes (maltase, isomaltase, sucrase, and glucoamylase) that break down oligo- and disaccharides into monosaccharides.[93,94] The available agents acarbose, miglitol, and vaglibose delay digestion

of complex carbohydrates within the gastrointestinal tract, leading to reduced glucose absorption and the postprandial rise in blood glucose levels.[93,94] These agents do not cause carbohydrate malabsorption. Rather, they retard the entry of glucose into the systemic circulation, allowing the pancreatic β-cell more time to increase insulin secretion in response to the blunted rise in plasma glucose. α-Glucosidase inhibitors appear to also improve insulin sensitivity by reducing the effect of glucose toxicity and cause a modest decline in plasma triglyceride levels without affecting LDL or HDL cholesterol.[95,96] No effect on weight has been observed. A limitation to the use of these agents is gastrointestinal side effects, including abdominal bloating, abdominal discomfort, diarrhea, and flatulence, which have been reported as high as 80%.[97] Starting with a small dose and slowly increasing the dose over several weeks can reduce gastrointestinal toxicity.

Combination Therapy. Only about 25% of adult diabetic patients achieve adequate glycemic control on monotherapy. In many patients, the use of two or more oral agents with differing mechanisms of action may result in additive effects. Furthermore, diabetes is a progressive disease, and the majority of patients will eventually require the addition of a second drug to achieve acceptable glycemic control. The additive glucose lowering effect has been seen with a number of combination therapies, including metformin/sulfonylurea, thiazolidinedione/sulfonylurea, and α-glucosidase inhibitor/metformin or sulfonylurea. Commercially available combination products are listed in Table 2. If the combination of two oral agents is not effective, a third agent, bedtime NPH or glargine insulin, or multiple daily injections of insulin can be used to improve glycemic control.[98] Continuous subcutaneous insulin infusion (through the use of an external insulin pump) may also be prescribed under these circumstances.

SUMMARY

T2DM constitutes an emerging epidemic in children, and it predominates in minority racial children. A number of intervening factors are contributing to the rise in the incidence of T2DM, including dietary and sedentary lifestyle habits that have lead to dramatic increase in the prevalence of obesity. There has been tremendous progress in the phamacologic management of adult T2DM with the introduction of a number of new classes of agents. Only recently have these newer agents undergone clinical testing in children. At the present time, only insulin and metformin are approved for use in children although many of the newer agents are currently undergoing clinical study in children. It will be important to understand which agent or combination of agents is optimal for children. The growing incidence of T2DM in children presents an enormous challenge to provide earlier diagnosis, methods of prevention, and effective treatment.

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