In Brief

The metabolic syndrome and type 2 diabetes are occurring at alarming rates in children. Obesity plays an important role in the increased prevalence of its comorbid conditions including dyslipidemia, hypertension, and type 2 diabetes. Lifestyle modification is the mainstay of prevention and treatment for metabolic syndrome and type 2 diabetes; however, it can be costly and labor-intensive. Pharmacotherapy is considered a second line of therapy in adults, but its use in children is controversial. This article reviews current and potential future drugs for the treatment of obesity, dyslipidemia, hypertension, and type 2 diabetes in children. Surgical procedures for treating severely obese adolescents are also discussed.

Current and Future Treatment of Metabolic Syndrome and Type 2 Diabetes in Children and Adolescents

Johanna T. Mallare, MD, FAAP; Ana H. Karabell, MD; Pedro Velasquez-Mieyer, MD; Sarah R.S. Stender, MD, FAAP; and Michael L. Christensen, PharmD

Treatment of Obesity

Metabolic syndrome includes a cluster of risk factors for atherosclerotic cardiovascular disease (CVD) and type 2 diabetes, including insulin resistance, obesity, hypertension, and dyslipidemia.[1] Obesity in children and adolescents has reached epidemic proportions, with the prevalence tripling in the past 3 decades. Metabolic syndrome and type 2 diabetes have paralleled this obesity epidemic in children.[2] Cook et al.[3] estimated the prevalence of metabolic syndrome among adolescents to be 4% overall, but 30–50% in overweight children. This extrapolates to ~ 1 million adolescents having metabolic syndrome.[3] Because obesity plays a central role in metabolic syndrome, and the probability of childhood obesity persisting into adulthood is estimated to increase from ~ 20% at age 4 years to 80% by adolescence, the epidemic of pediatric obesity can translate into increased prevalence of hypertension, type 2 diabetes, and CVD in adulthood.[1]

Childhood obesity is defined using age- and sex-specific nomograms for BMI. BMI between the 85th and 95th percentiles is defined as at risk for overweight, and BMI

≥ the 95th percentile is defined as overweight.[4] However, the terms overweight and obese are often used interchangeably in the pediatric population.[2] In children, the ideal goal is to prevent children with a normal BMI (< the 85th percentile) from becoming overweight.[2]

Treatment of obesity should rarely be instituted in children < 2 years of age because this is a period of rapid growth and development, and there is little correlation with obesity in adulthood.[2] Weight control for all overweight children > 2 years of age is actually weight maintenance through modest changes in diet and physical activity.[5] For overweight children < 7 years of age and without comorbid conditions, prolonged weight maintenance will result to a gradual decrease in BMI as height increases. If comorbid conditions are present and a child's BMI is > the 95th percentile, gradual weight loss is recommended. For children > 7 years of age whose BMI is between the 85th and 95th percentile with no comorbidities, prolonged weight maintenance is recommended. However, if comorbidities are present and the BMI is between the 85th and 95th percentile, or if BMI is > 95%, gradual weight loss is recommended.[5]

Treatment of obesity includes two major approaches: lifestyle-based intervention (diet, exercise, and behavior therapy) and medical/surgical intervention (pharmacotherapy or bariatric surgery). Dietary modification should be age-specific, providing appropriate optimum nutrient intake for the maintenance of normal growth and development. It should also help the child sustain healthy eating habits.[2] Regular physical activity is important for the prevention of excessive weight gain or to maintain weight. The current recommendation is for 30–60 minutes of regular physical activity daily. Restricting sedentary activities to < 2 hours/day is also recommended.[2] Behavior modification programs have been shown to have both short- and long-term beneficial effects on BMI in some patients, but they are usually labor-intensive, are not easily applied in the primary care setting, and involve intensive parental involvement.[6]

In children, most interventions for obesity have focused on behavioral approaches; the use of pharmacological therapy remains controversial.[2] Weight-loss medications can have significant adverse effects, and only a few of these drugs are approved for use in children. However, it may be useful to consider medications found to be safe and effective for adults as treatments that may be on the horizon for pediatric patients.[7] Pharmacotherapy, if utilized, should always be an adjunct to continued lifestyle changes.

There are several mechanisms by which drugs may be amenable to the treatment of obesity. These include limiting the absorption of food, suppressing appetite and reducing food intake, and altering metabolism or increasing energy expenditure.[7]

Pharmacological therapy

Orlistat is a gastric and pancreatic lipase inhibitor that decreases free fatty acid and cholesterol absorption and is approved by the Food and Drug Administration for the treatment of obesity in adolescents >12 years of age. Orlistat, 120 mg three times daily with meals, in combination with diet, exercise, and behavior modification significantly improved weight management in adolescents compared to placebo.[8] It can reduce fat absorption by ~ 30% in individuals eating a 30% fat diet. Orlistat is associated with gastrointestinal side effects, such as steatorrhea, increased defecation, abdominal pain, and fecal urgency, and requires fat-soluble vitamin supplementation.[7]

Sibutramine is a serotonin and adrenaline reuptake inhibitor that decreases appetite and reduces food intake and is approved for use in adolescents > 16 years of age. Sibutramine's safety and efficacy was assessed in a study of obese 12- to 16-year-old adolescents (BMI 36 kg/m^2).[9] Subjects were randomized to sibutramine, 10 mg, or placebo with behavior therapy. The dose of sibutramine was increased to 15 mg if weight loss was inadequate after 6 months. The change in BMI at 12 months with sibutramine was significantly greater than with placebo. A decrease in initial BMI by 10% was found in 40% of adolescents treated with sibutramine, compared to 15% of adolescents treated with placebo. However, the weight loss response tended to plateau after 6 months of therapy. Side effects included increases in heart rate and blood pressure resulting in the dose being reduced or discontinued in 44% of the adolescents during the first 6 months. Additionally, there was no improvement in the comorbid conditions associated with obesity, such as insulin resistance and dyslipidemia.[9]

Metformin is a biguanide frequently used to treat type 2 diabetes in adolescents. The mechanism of action of metformin on body weight is unclear. Metformin is likely to prevent weight gain primarily through a direct anorectic effect or possibly indirectly by stimulating glucagon-like peptide 1 (GLP-1) secretion.[10]

There is limited well-controlled research information about the use of metformin to promote weight loss in adolescents. Freemark and Bursey[11] randomized 29 obese adolescents with hyperinsulinemia to metformin, 500 mg twice a day, or placebo without any dietary therapy and found a 1.3% decrease in BMI after 6 months of metformin use compared to a 2.3% increase in BMI for those taking placebo. Kay et al.[12] randomly assigned 24 hyperinsulinemic, normoglycemic adolescents to metformin, 850 mg twice daily, or placebo. The metformin group had greater weight loss and improved insulin sensitivity compared to the placebo group.

The most common side effects of metformin include nausea, flatulence, bloating, and diarrhea at initiation of therapy. Vitamin B_{12} deficiency also has been seen. The most serious complication of metformin is lactic acidosis, which occurs primarily in patients with renal insufficiency (serum creatinine ≥ 1.4 mg/dl in women or ≥ 1.5 mg/dl in men, congestive heart failure requiring medication, cardiac or pulmonary insufficiency with severe hypoxia and reduced peripheral perfusion, and liver disease, including alcohol-induced acute hepatic toxicity).

Noradrenergic drugs, such as phentermine, chlorphentermine, phenylpropanolamine, and amphepramone (diethylpropion), decrease appetite and food intake without specific effects on macronutrient selection. In a 12-week trial, Rauh and Lipp[13] compared weight change in 28 adolescent girls randomized to chlorphentermine, 65 mg per day, or placebo with diet and exercise. Subjects receiving chlorphentermine lost significantly more weight (−6.7 kg) than did those taking placebo (+0.55 kg).

No study has provided evidence of the long-term safety of noradrenergic drugs in children. The most common side effects of phentermine and diethylpropion include insomnia, restlessness, dry mouth, asthenia, eupho-

ria, palpitations, hypertension, cardiac arrhythmias, dizziness, blurred vision, and ocular irritation.[14]

Promising new drugs

Octreotide suppresses pancreatic insulin secretion. The rationale for the use of octreotide in the treatment of obesity is to decrease insulinemia and insulin hypersecretion.[15] Octreotide treatment caused weight loss, reduced insulin resistance, and reduced acanthosis nigricans.[15] In a more recent study of obese adults, monthly injection of long-acting–release octreotide promoted significant body weight and fat mass loss in 43% of subjects with concomitant modulation of caloric intake and macronutrient preference.[16] The side effects include pain at injection sites, gallstones, diarrhea, abdominal pain, nausea, vitamin B_{12} deficiency hypothyroidism, suppression of growth hormone secretion, diabetes, and abnormalities in cardiac function.

Topiramate is a novel broad-spectrum anticonvulsant drug used in children and adults.[17] Topiramate causes weight loss in normal-weight and obese patients.[17] The weight loss has been associated with decreased food intake, but the precise mechanism of action is unknown. There are only limited data on the use of topiramate specifically for weight loss. Retrospective and prospective studies in children and adults suggest that topiramate in doses of 0.5–22 mg $\cdot$ kg^{-1} $\cdot$ day^{-1} are associated with dose-dependent weight loss.[18,19] In children receiving topiramate as adjunctive therapy for seizure disorders, weight loss in a range of 10–40% has been observed.[18] In children, topiramate is well tolerated. Side effects may include somnolence, anorexia, fatigue, weight loss, nervousness, decreased concentration, difficulty with memory, and aggression. Despite the extensive worldwide use of topiramate in children, no effect on linear growth, hepatotoxicity, or hematologic, cutaneous, or idiosyncratic reactions have been reported.

Rimonabant is the first in the class of selective endocannabinoid type 1 receptor blockers. Blocking these receptors is thought to decrease feeding behavior. Overweight or obese adult patients with dyslipidemia were randomized to rimonabant, 5 mg/day or 20 mg/day, or placebo.[20] After 52 weeks of treatment, the higher-dose rimonabant group lost significantly more weight than the placebo group (−8.6 and −2.3 kg, respectively).[20] The most common side effects with rimonabant were nausea, dizziness, arthralgia, and diarrhea.

Bariatric surgery

Studies utilizing bariatric surgery as a treatment option for severely obese adolescents who failed to lose weight on diet and behavior modification programs have been undertaken by several centers.[2] Among the indications used are a BMI ≥ 40 kg/m^2 with severe comorbidities, such as obstructive sleep apnea, type 2 diabetes, or pseudotumor cerebri. BMI ≥ 50 kg/m^2 may be an indication for surgery if associated with less severe comorbidities, such as hypertension and dyslipidemia.[2]

Bariatric procedures for weight loss can be divided into malabsorptive and restrictive procedures. Malabsorptive procedures include jejunoilial bypass, biliopancreatic diversion, and duodenal switch.[21] Surgeons are reluctant to perform these procedures, although they are effective in inducing weight loss, because of the increased risk of metabolic complications, including protein malnutrition, metabolic bone disease, and deficiency of iron, calcium, and vitamins A, B_{12}, D, E, and K.[22]

Restrictive procedures include water-filled balloons, gastroplasty, gastric banding, and gastric bypass. Water-filled balloons have not been shown to decrease BMI in morbidly obese children.[23] Gastroplasty is a procedure that decreases the storage capacity of the stomach and consumption of solid food. The high incidence of stomach stenosis or staple line dehiscence and disappointing long-term weight maintenance have led surgeons to abandon gastroplasty as a primary antiobesity procedure.[24] Gastric banding is another restrictive procedure in which a prosthetic band encircles the proximal stomach to compartmentalize into a small pouch and a large remnant.[25] The theoretical advantage of this technique is decreased risk of staple line dehiscence.[21] The more recent introduction of a new laparoscopic approach and the use of an adjustable band have made this procedure more attractive.[26]

Limited data are available regarding these surgical procedures to induce weight loss in severely obese children and adolescents. There are several reports on bariatric surgery in adolescents supporting sustained weight loss and improvement or resolution in obesity-related morbidity.[27,28] Complications have included iron-deficiency anemia (50%), transient folate deficiency (30%), and events requiring surgical intervention (40%). The latter have included cholecystectomy in 20%, small bowel obstruction in 10%, and incisional hernia in 10%).[21] The perioperative mortality rate of the gastric banding procedure is ~ 1–1.5% and is largely attributable to sepsis and pulmonary embolus. The risk of early postoperative complication is ~ 10%.

A multidisciplinary team with medical, surgical, nutritional, and psychological expertise should carefully select adolescents as candidates for bariatric surgery. Extensive counseling, education, and support are required both before and after gastric bypass. Adolescents undergoing the gastric banding procedure require lifelong medical and nutritional surveillance after surgery, especially during pregnancy.[29]

Treatment of Dyslipidemia

The dramatic rise in the prevalence of pediatric obesity and the metabolic syndrome leads to increased CVD rates in adulthood, and this association may be linked to dyslipidemia.[30] High total serum cholesterol levels and high LDL cholesterol levels have been associated with increased risk of coronary heart disease.[31] High triglyceride levels, usually associated with decreased HDL cholesterol levels, are also related, although to a lesser degree, to increased coronary heart disease risk.[31]

Several studies have shown that lipid levels, primarily LDL, track from childhood into adulthood.[32] The 1998 American Academy of Pediatrics recommendation states that children aged ≥ 2 years should be screened for high cholesterol if they have a family history of premature CVD (< 55 years of age) or hypercholesterolemia (≥ 240 mg/dl). For youths whose family history is not available and for those with other CVD risk factors, screening is recommended at the physician's discretion.[33] Borderline levels of total and LDL cholesterol are defined as 170–199 and 110–129 mg/dl, respectively. Elevated levels are ≥ 200 mg/dl for total cholesterol and ≥ 130 mg/dl for LDL.[33]

Lifestyle changes are the foundation of primary preventive treatment of dyslipidemia. These include

decreased intake of saturated fat and cholesterol, increased physical activity, and weight control to lower population cholesterol levels.[34] Recent recommendations suggest the use of the American Heart Association Step 2 diet (dietary cholesterol < 200 mg/day and saturated fat < 7% of total calories) on confirmation of hyperlipidemia.[35] Several studies have shown that dietary intervention in children results in improved lipid profiles without affecting growth.[36,37]

Pharmacological therapy

Pharmacotherapy has been recommended in children > 10 years of age if, after an adequate trial of dietary therapy, LDL levels remain > 190 mg/dl in those with no CVD risk factors or > 160 mg/dl in those with risk factors. The optimal LDL level is < 130 mg/dl for children in general and < 100 mg/dl in those with diabetes.[33]

Bile acid sequestrants (resins, such as cholestyramine and cholestipol) used to be the preferred drug in pediatric patients with familial hypercholesterolemia. However, because of their poor palatability and modest (10–15%) lipid-lowering effects,[38] other lipid-lowering medications emerged as first-line agents.

The preferred drugs for the treatment of hypercholesterolemia in adults are the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), some of which have been proven to be effective and safe in children > 8–10 years of age. The age of the youngest patients reported in clinical trials varied from 4 to 10 years. Statins inhibit cholesterol synthesis, resulting in increased LDL receptor activity with enhanced clearance of LDL particles and precursors.[39] Several trials have demonstrated the efficacy and short- and longer-term safety of statin therapy in children and adolescents with heterozygous familial hypercholesterolemia.[40–42]

Statin therapy results in an up to 30–40% reduction in LDL, a more modest reduction in triglycerides, and an elevation in HDL levels.[40–42] Simvastatin and pravastatin have been well tolerated in children in doses up to 40 mg/day, as have atorvastatin and lovastatin in doses up to 20 mg/day. There have been no adverse effects on growth, sexual maturation, or markers of liver or muscle tissue damage. Adverse events include myalgia, asymptomatic increase in creatine kinase concentration, and very rarely rhabdomyolysis, as well as elevation in liver enzyme concentration.[40]

Statins also improve surrogate markers of atherosclerosis.[43] Carotid intimal medial thickness (CIMT) measured by B-mode ultrasonography has been shown to be a strong predictor of atherosclerosis progression in adolescents and adults. Serial LDL levels from childhood to adulthood predicted CIMT in adulthood.[44] Reversal of endothelial dysfunction, as well as regression of CIMT after lipid reduction, reflect an improvement in the atherosclerosis process.[43] The lipid-lowering effects of statins have been accompanied by CIMT regression in children.[42]

Prepubertal children with familial hypercholesterolemia are shown to have endothelial dysfunction by the age of 5 years,[45] and CIMT already deviates from normal by the age of 12 years.[42] Treatment of children < 10 years of age should be investigated.[43] Initiation of lipid-lowering medication in childhood may inhibit progression or might even lead to regression of atherosclerosis.[42]

When statins are used, treatment should begin at the lowest available dose, and increases should be based on LDL levels and side effects. Liver function tests should be monitored, and medication should be discontinued if liver enzyme values are more than three times the upper limit of normal,[46] if there is increased creatine kinase activity more than five times the upper limit of normal, or if the patient develops myalgia or muscle weakness.[39]

Alternative drugs that primarily lower LDL levels by reducing cholesterol absorption in the intestine, such as ezetimibe, are now available.[39] Although ezetimibe is already approved for use in hypercholesterolemic children > 10 years of age, long-term efficacy and safety studies in children are needed.[47] Monotherapy with ezetimibe, 10 mg/day, reduced LDL by 15–20%, whereas beneficial effects on triglyceride and HDL were marginal.[46] The addition of ezetimibe to statin therapy achieves an additional reduction in LDL concentration of 25.8% compared to an additional 2.7% reduction with placebo plus statin therapy.[48] Ezetimibe is well tolerated, but long-term experience is limited, and its long-term effects on cardiovascular outcomes are unknown.[39]

Fibrates (gemfibrozil, fenofibrate) are primarily used to treat high triglyceride levels, usually with accompanying low HDL levels.[39] They stimulate peroxisome proliferator activated receptor-α (PPARα), a nuclear transcription factor that controls the expression of genes mediating triglyceride metabolism. This leads to decreased synthesis of fatty acids and triglyceride-rich lipoproteins and increased synthesis of apolipiprotein A1 and lipoprotein lipase, promoting HDL production and triglyceride catabolism.[39] Gemfibrozil, 600 mg twice daily, reduces triglyceride concentration by up to 50% and increases HDL by up to 20%, but changes in LDL are variable and usually small.[39] Fibrate therapy is usually well tolerated, but myalgia and increased liver enzymes may occasionally occur. Fibrates slightly increase the risk of cholelithiasis and do potentiate the action of warfarin.[39]

Alternative treatment for high triglyceride concentration is fish oil or omega-3 fatty acids. They contain highly polyunsaturated long-chain n-3 fatty acids. A daily intake of 2–5 g of omega-3 fatty acids (6–15 g of fish oil) decreases triglyceride concentration by up to 50% in adults. Changes in LDL and HDL levels are variable and small. Fish oils are safe and usually well tolerated.[39]

Adolescents with a significant family history of premature atherosclerosis who have mixed lipid patterns (familial combined hyperlipidemia, obesity, metabolic syndrome), despite weight loss and lifestyle changes, can be treated with extended-release niacin and/or fibric acid derivatives, such as fenofibrate or gemfibrozil. Statins may be combined with extended-release niacin for synergistic effects but should not be combined with fibrates because of the increased risk of myolysis.[46]

The most potent currently available HDL-raising therapy is nicotinic acid, which also has effects on the levels of LDL, triglyceride, lipid oxidation, and endothelial function.[49] Combination therapy with a statin can increase HDL levels by ~ 30%.[49]

A new trend is enrichment of food products with plant sterols and stanols. The use of a spread containing plant sterols decreased LDL by 14% compared to placebo in young children with familial hypercholesterolemia.[45] However, in contrast to statin therapy, plant sterol consumption did not

improve endothelial dysfunction in these children.

Cholesterol absorption inhibitors, or plant sterols and stanols coadministered with a statin, offer new options in the treatment of adult patients with familial hypercholesterolemia. This combination therapy may also be beneficial for children because *1*) low doses of statins coadministered with cholesterol absorption inhibitors may result in increased efficacy; *2*) high doses of statins may be avoided, thereby minimizing the chance of side effects; and *3*) although treatment with food products containing plant sterols or stanols does not improve endothelial dysfunction, it does reduce LDL by 10–15%, and there is an additive effect when combined with statins.

Promising new drugs

Low HDL may be a risk factor comparable in importance to high LDL, and the two risk factors are independent.[49] Colesteryl ester transfer protein inhibitors (JTT-705 and torcetrapib) could accelerate cholesterol transport to the liver by HDL and augment reverse cholesterol transport. Clinical trials using these drugs are underway.[49]

The PPARα/γ dual agonist drug has efficacious glucose- and lipid-lowering activities. Thus, this drug is ideal for treatment of type 2 diabetes and dyslipidemia. (See section on type 2 diabetes below.)

Colesevelam is the newest bile resin with fewer side effects and drug interactions. It has been found to be safe alone or in combination with statin therapy in lowering LDL levels. It has a dose-sparing effect on statin therapy.[50]

Treatment of Hypertension

Hypertension has also paralleled the rise in childhood obesity. The typical patient has evolved into an otherwise healthy adolescent with obesity and some combination of cardiovascular risk factors, including a family history of hypertension and an ethnic predisposition to hypertensive disease. The early clinical course of obesity hypertension appears to be characterized by a preponderance of isolated systolic hypertension (i.e., without diastolic hypertension). Because isolated systolic hypertension has been shown to be a major risk factor for cardiovascular morbidity and mortality in adults,[51] further investigation of causes and interventions for this pattern in children is clearly needed.

The benefits of weight loss on blood pressure reduction in children have been investigated in both observational and interventional studies. Although these studies suggest that blood pressure reduction is induced by weight loss in obese children, more studies are needed. Weight reduction through diet and exercise is the primary therapy for obesity-related hypertension. In one study,[52] the changes in systolic blood pressure in the diet-plus-exercise, diet-alone, and control groups were −16, −10, and +4 mmHg, respectively. The long-term benefits of weight loss on blood pressure remain to be defined because it is unknown whether the decline of blood pressure observed during acute weight loss is maintained.

Pharmacological therapy

Pharmacotherapy of obesity-related hypertension in childhood is indicated if there is persistent hypertension despite nonpharmacological measures, type 1 or type 2 diabetes, hypertensive target-organ damage, or multiple cardiovascular risk factors. When pharmacological therapy is indicated, it should be initiated with a single drug and started at the lowest recommended dose. Acceptable drug classes for use in children include ACE inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, and diuretics.[53]

Specific classes of antihypertensive drugs should be used preferentially in hypertensive children with specific underlying or concurrent medical conditions. Examples include the use of ACE inhibitors or angiotensin receptor blockers in children with diabetes and microalbuminuria or proteinuric renal diseases and the use of β-adrenergic blockers or calcium channel blockers in hypertensive children with migraine headaches.[53] For children with uncomplicated primary hypertension and no target-organ damage, the goal blood pressure should be < the 95th percentile for sex, age, and height, whereas for children with chronic renal disease, diabetes, or hypertensive target-organ damage, the goal blood pressure should be < the 90th percentile for sex, age, and height.

Promising new drugs

A number of novel drug classes are under active investigation in adults for the treatment of hypertension. These include endothelin receptor antagonists, renin inhibitors, and vasopeptidase inhibitors.[54]

Darusentan is a selective endothelin receptor A antagonist under development for treating cardiovascular disorders. Endothelin is a small peptide hormone important in the control of blood flow and cell growth. There are two known classes of endothelin receptors, A (ETA) and B (ETB). Endothelin binding to ETA on the smooth muscle cells causes vasoconstriction, whereas binding to ETB on the vascular endothelium causes vasodilatation through the production of nitric oxide.

Darusentan has been studied in adult hypertensive patients at doses of 10–100 mg administered once daily. A dose-dependent reduction in both diastolic and systolic blood pressure was observed.[55] Adverse effects included headache, flushing, and peripheral edema.

Aliskiren is a renin inhibitor that prevents the formation of both angiotensin I and II. Aliskiren in doses of either 150 or 300 mg once daily lowered blood pressure in a dose-dependent manner; 600 mg was no more effective than 300 mg.[56] The most common adverse effects have been headache, dizziness, and diarrhea.

Omapatrilat is a vasopeptidase inhibitor that is furthest along in clinical development. Neutral endopeptidases are found in the brush border membrane of the renal tubules, and they metabolize natriuretic peptide. Vasopeptidase inhibitors block both neutral endopeptidase and ACE, resulting in greater availability of natriuretic peptides that have vasodilatory effects and reducing levels of angiotensin II. Omapatrilat in doses of 20–80 mg per day produces a dose-dependent reduction in blood pressure.[57] The effects on systolic blood pressure are greater than on diastolic blood pressure. Adverse effects include cough, hypotension, dizziness, flushing, hyperkalemia, and angioedema at a rate similar to that found with ACE inhibitors.

Treatment of Type 2 Diabetes

Successful treatment of type 2 diabetes is defined as cessation of excessive weight gain, normal linear growth, and attainment of fasting blood glucose levels < 126 mg/dl and hemoglobin A_{1c} < 7%. The U.K. Prospective Diabetes Study (UKPDS) demonstrated that intensive blood glucose con-

trol using oral hypoglycemic agents and insulin can substantially decrease the risk of the microvascular complications of retinopathy, nephropathy, and neuropathy in adults with type 2 diabetes. However, the UKPDS did not reveal any significant decrease in macrovascular complications through control of blood glucose alone. The UKPDS did find that the treatment of hypertension in individuals with type 2 diabetes significantly decreased the risk of CVD.

Dietary and exercise modification are the cornerstones of disease management. Unfortunately, lifestyle modification has limited success in the long-term management of adults with type 2 diabetes and will likely have similar limitations in children and adolescents.[6] Therefore, pharmacological treatment is necessary in children with type 2 diabetes.

Pharmacological therapy

Four classes of pharmacological agents are available for the treatment of type 2 diabetes: 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.[58]

There are four general types of insulin (rapid-acting, short-acting, intermediate-acting, and long-acting forms) classified based on onset, peak, and duration of action. The rapid-acting insulin analogs lispro and aspart can be given within 15 minutes of a meal to control the postprandial rise in blood glucose. The short-acting insulins (regular insulin) are given 30–60 minutes before a meal to control the postprandial glucose level. Intermediate-acting insulin is a suspension of zinc insulin crystals and protamine sulfate (isophane insulin, NPH, and lente). These insulins are usually given twice a day and are often given in combination with a rapid- or short-acting insulin. The long-acting insulins (glargine and ultralente) 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. 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 to achieve the best blood glucose control possible based on home blood glucose monitoring. The most common side effects are hypoglycemia, injection site reactions, and weight gain.[59]

There are two types of insulin secretogogues, the sulfonylureas (of which there are two generations) and the nonsulfonylureas. None of these drugs has been adequately tested in children. The first-generation sulfonylureas include tolbutamide, chlorpropamide, and tolazamide; second-generation sulfonylureas include glyburide, glipizide, and glimepiride.[60] The principle mechanism of action of the sulfonylureas is the stimulation of insulin secretion from the pancreatic β-cells in response to glucose.[61] Hypoglycemia is the most important adverse effect. These agents have no effect on plasma lipid levels.

Repaglinide and nateglinide are nonsulfonylurea agents that cause a prompt short-lived burst of insulin secretion.[62] These agents are taken within 30 minutes before each meal. The major side effect is hypoglycemia. They may also cause weight gain. These agents also have no effect on plasma lipids.

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. The mechanism of action by which metformin improves insulin sensitivity is not fully understood. Metformin decreases hepatic glucose production and likely inhibits hepatic glycogenolysis.[63] It suppresses the release of fatty acids and lipid oxidation (which also enhances glycemic control), leading to a reduction in triglycerides, very low-density lipoprotein (VLDL) cholesterol, and total cholesterol, as well as decreasing plasminogen activator inhibitor-1 levels. Metformin was associated with a significant reduction in macrovascular complications, myocardial infarction, and stroke in the UKPDS.[64] It is approved for use in children > 10 years of age.[65]

The thiazolidinediones include rosiglitazone and pioglitazone. (Troglitazone was removed from the market because of hepatotoxicity.) Thiazolidinediones improve tissue and liver sensitivity to insulin by binding to the nuclear receptor PPARγ, whose highest level of expression is in adipocytes and intestinal cells.[66] These agents decrease free fatty acid concentrations, and pioglitazone lowers plasma triglyceride concentration.[67] Thiazolidinediones increase fat cell numbers, which accounts for the weight gain reported with the use of these agents.[68] Liver disease is under close scrutiny for rosiglitazone and pioglitazone, but no studies have found the incidence of elevated liver enzymes to differ from that with placebo. Peripheral edema has also been reported in the use of thiazolinediones.

The glucose absorption inhibitors competitively inhibit α-glucosidase in the brush border of enterocytes of the gastrointestinal tract, preventing the breakdown of oligo- and disccharides into monosaccharides.[69] The available agents acarbose, miglitol, and voglibose retard the entry of glucose into the systemic circulation, allowing pancreatic β-cells more time to increase insulin secretion in response to the blunted rise in plasma glucose. No effect on weight has been observed. The most common adverse effects, reported in up to 80% of users, are gastrointestinal, including bloating, abdominal discomfort, diarrhea, and flatulence.[70] Starting with a low dose and slowly increasing the dose over several weeks can reduce gastrointestinal toxicity.

Diabetes is a progressive disease, and the majority of patients will eventually require the addition of a second drug to achieve acceptable glycemic control. Only ~ 25% of adult diabetic patients achieve adequate glycemic control on monotherapy. Additive glucose-lowering effects have been seen with a number of combination therapies, including metformin/sulfonylurea, thiazolidinedione/sulfonylurea, and α-glucosidase inhibitor/metformin or sulfonylurea. 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.[71] Continuous subcutaneous insulin infusion (through the use of an external insulin pump) may also be prescribed under these circumstances.

Promising new drugs

There are a number of promising new agents that control glucose levels, including amylin analogs, glucagon-like peptide 1 (GLP-1) agonists, dipeptidyl peptidase IV inhibitors, and glitazars (combined PPARα and -γ

agonists).[72] After these drugs have been studied and approved for use in adults, we can expect that they will also be studied for use in children.

Pramilintide is a synthetic analog of amylin, a naturally occurring peptide that is cosecreted in equimolar amounts with insulin from the pancreatic β-cells in response to food intake. It was recently approved for use in both type 1 and type 2 diabetes. Pramilintide's mechanisms of action include *1*) slowing the rate of gastric emptying and thereby reducing the postprandial rise in plasma glucose, *2*) decreasing postprandial glucagon levels and reducing hepatic glucose production, and *3*) increasing satiety, possibly by inhibiting the appetite-stimulating stomach hormone ghrelin.[72]

The dose of pramlintide differs depending on whether the patient has type 1 or type 2 diabetes.[73] When starting pramlintide, the premeal insulin dose should be reduced by 50% in all patients to reduce the risk of hypoglycemia. Patients with type 2 diabetes should be initiated at a dose of 60 μg s.c. before major meals and increased to 120 μg when there has been no nausea for 3–7 days. Patients with type 1 diabetes should be initiated at a dose of 15 μg s.c. before major meals and titrated in 15-μg increments to a maintenance dose of 30 or 60 μg per dose as tolerated. The most common adverse events include nausea, vomiting, loss of appetite, and insulin-induced hypoglycemia.[73]

GLP-1, an incretin hormone, is secreted from intestinal cells in response to food intake and stimulates insulin secretion from pancreatic β-cells, inhibits glucagon secretion, delays gastric emptying, suppresses appetite, and may stimulate islet cell regeneration.[74] Endogenous GLP-1 is rapidly degraded by the ubiquitous endoprotease dipeptidyl peptidase IV (DPP-IV), thus limiting its clinical use and necessitating the development of analogs (liraglutide) and agonists (exenatide) that resist DPP-IV degradation and development of DPP-IV inhibitors that potentiate GLP-1 effects.[72,74]

Analogs of GLP-1 have been developed to mimic its insulinotropic effect.[71] Liraglutide is an acylated GLP-1 analog bound to albumin, resistant to DPP-IV, and with a half-life of 12–14 hours.[74] Exenatide is a synthetic analog of exendin-4, an incretin hormone originally isolated from the Gila monster that binds to the GLP-1 receptor but is resistant to degradation by the DPP-IV enzyme. Exenatide shares 53% homology to human GLP-1 and has an effect similar to that of human GLP-1. Clinical trials of liraglutide as a single daily injection and exenatide as a once- or twice-daily injection have resulted in improved glycemic control, reduced food intake, and weight loss. Nausea and vomiting are the most common side effects and are influenced by dose and titration schedule.

Vildagliptin (LAF237) is a DPP-IV inhibitor in phase III clinical trials.[72] The primary adverse effects have been nausea, diarrhea, diaphoresis, and pruritus. Vildagliptin does not appear to increase the risk for hypoglycemia.[72] The oral dosage form gives a distinct advantage over GLP-1 agonists, which must be given parenterally.

Glitazars represent a broad class of drugs that have combined PPARα and -γ agonist activity. Representative drugs under phase III investigation include muraglitazar and tesaglitazar. PPARγ agonists (thiazolidinediones) have a direct effect on peripheral insulin sensitivity. PPARα agonists (fibrates, such as gemfibrozil and clofibrate) modulate lipid metabolism, lowering triglycerides and raising HDL cholesterol.[75] Because dyslipidemia is a common problem with type 2 diabetes, the dual activity of PPARα and -γ agonists could lead to improved insulin sensitivity and lipid metabolism. PPARα and -γ agonists are associated with weight gain and edema, similar to the thiazolidinediones. Of concern also is the development of soft tissue tumors in rodents, which led to suspension of clinical trials for one compound.

Summary

In children, the first line of prevention and treatment of obesity, dyslipidemia, hypertension, and type 2 diabetes remains dietary modification, increased physical activity, and behavior modification. Certain medications used for treatment of dyslipidemia, hypertension, and type 2 diabetes in children have been well studied and approved for this use. However, more well-controlled studies are needed in children for medications approved for adults in the treatment of obesity. Bariatric surgery as a treatment option for severely obese adolescents remains investigational.

References

[1]Steinberger J: Diagnosis of the metabolic syndrome in children. *Curr Opin Lipidol* 14:555–559, 2003

[2]Daniels SR, Arnett DK, Eckel RH, Gidding SS, Hayman LL, Kumanyika S, Robinson TN, Scott BJ, Jeor SS, Williams CL: Overweight in children and adolescents: pathophysiology, consequences, prevention and treatment. *Circulation* 111:1999–2012, 2005

[3]Cook S, Weitzman M, Auinger P, Nguen M, Dietz WH: Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988 –1994. *Arch Pediatr Adolesc Med* 157:821–827, 2003

[4]Himes JH, Dietz WH: Guidelines for overweight in adolescent preventive services: recommendations from an expert committee. *Am J Clin Nut* 59:307–316, 1994

[5]American Academy of Pediatrics: prevention of pediatric overweight and obesity (Policy Statement). *Pediatrics* 112:424–430, 2003

[6]Yanovski JA, Yanovski SZ: Treatment of pediatric and adolescent obesity. *JAMA* 289:1851–1853, 2003

[7]Daniels S: Pharmacological treatment of obesity in pediatric patients. *Pediatr Drugs* 3:405–410, 2001

[8]Chanoine JP, Hampl S, Jensen C, Boldrin M, Hauptman J: Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. *JAMA* 293:2873–2883, 2005

[9]Berkowitz RI, Wadden TA, Tershakovec AM, Cronquist JL: Behavioral therapy and sibutramine for the treatment of adolescent obesity: a randomized controlled trial. *JAMA* 289:1805–1812, 2003

[10]Kreymann B, Ghatei MA, Burnet P,Williams G, Kanse S, Diani AR, Bloo SR: Characterization of glucagon-like peptide-1-(7-36)amide in the hypothalamus. *Brain Res* 502:325–331, 1989

[11]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* 107:E55, 2001

[12]Kay JP, Alemzadeh R, Langley G, D'Angelo L, Smith P, Holshouser S: Beneficial effects of metformin in normoglycemic morbidly obese adolescents. *Metabolism* 50:1457–1461, 2001

[13]Rauh JL, Lipp R: Chlorphentermine as an anorexigenic agent in adolescent obesity: report of its efficacy in a double-blind study of 30 teenagers. *Clin Pediatr* 7:138–140, 1968

[14]Bray G, Greenway F: Current and potential drugs for treatment of obesity. *Endocrine Rev* 20:805–875, 1999

[15]Lunetta M, Di Mauro M, Le Moli R, Burafato S: Long-term octreotide treatment reduced hyperinsulinemia, excess body weight and skin lesions in severe obesity with acanthosis nigricans. *J Endocrinol Invest* 19:699–703, 1996

[16]Velasquez-Mieyer PA, Cowan PA, Arheart KL, Buffington CK, Spencer KA, Connelly BE, Cowan GW, Lustig RH: Suppression of insulin

secretion is associated with weight loss and altered macronutrient intake and preference in a subset of obese adults. *Int J Obesity Relat Metab Disord* 27:219–226, 2003

[17]Ormrod D, McClellan K: Topiramate: a review of its use in childhood epilepsy. *Pediatr Drug* 3:293–319, 2001

[18]Levisohn P: Safety and tolerability of topiramate in children. *J Child Neurol* 15:S22–S26, 2000

[19]Astrup A, Toubro S: Topiramate: a new potential pharmacological treatment for obesity. *Obes Res* 12 (Suppl.):167S–173S, 2000

[20]Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S, the RIO-Europe Study Group: Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* 365:1389–1397, 2005

[21]Mun EC, Blackburn GL, Matthews JB: Current status of medical and surgical therapy for obesity. *Gastroenterology* 120:669–681, 2001

[22]Murr MM, Balsiger BM, Kennedy FP, Mail JL, Sarr MG: Malabsortive procedures for severe obesity: comparison of pancreaticobiliary bypass and very long limb roux-en-y gastric bypass. *J Gastrointest Surg* 3:607–612, 1999

[23]Vandeplas Y, Bollen P, De Langhe K,Vandemaele K, De Schepper J: Intragastric balloons in adolescents with morbid obesity. *Eur J Gastroenterol Hepatol* 11:243–245, 1999

[24]Howard L, Malone M, Michalek A, Carter J, Alger S, Van Woert J: Gastric bypass and vertical banded gastroplasty: a prospective randomized comparison and 5-year follow-up. *Obesity Surg* 5:55–60, 1995

[25]Jones KB Jr: Experience with roux-en-y gastric bypass and commentary in current trends. *Obes Surg* 10:183–185, 2000

[26]Doldi SB, Micheletto G, Lattuada E, Zappa MA, Bona D, Sonvico U: Adjustable gastric banding; 5-year experience. *Obes Surg* 10:171–173, 2000

[27]Sugerman HJ, Sugerman EL, DeMaria EJ, Kellum JM, Kennedy C, Mowery Y, Wolfe LG: Bariatric surgery for severely obese adolescents. *J Gastroint Surg* 7:102–107, 2003

[28]Dolan K, Creighton L, Hopkins G, Fielding G: Laparoscopic gastric banding in morbidly obese adolescents. *Obesity Surg* 13:101–104, 2003

[29]Strauss R: Perspectives on childhood obesity. *Curr Gastroenterol Rep* 4:244–250, 2002

[30]Kohen-Avramoglu R, Theriault A, Adeli K: Emergence of the metabolic syndrome in childhood: an epidemiological overview and mechanistic link to dyslipidemia. *Clin Biochem* 36:413–420, 2003

[31]National Heart Foundation of Australia and the Cardiac Society of Austarlia and New Zealand: Lipid management guidelines—2001. *Med J Aust* 175 (Suppl. 5):S57–S88, 2001

[32]Katzmarzyk PT, Perusse L, Malina RM, Bergeron J, Despres JP, Bouchard C: Stability of indicators of the metabolic syndrome from childhood and adolescence to young adulthood: the Quebec Family Study. *J Clin Epidemiol* 54:190–195, 2001

[33]American Academy of Pediatrics, Committee on Nutrition: Cholesterol in childhood. *Pediatrics* 101:141–147, 1998

[34]Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive summary of the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III). *JAMA* 285:2486–2497, 2001

[35]Kavey REW, Daniels SR, Lauer RM, Atkins DL, Haymann LL, Tauebert K: American Heart Association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. *Circulation* 107:1562–1566, 2003

[36]Writing Group for the DISC Collaborative Research Group: Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol. *JAMA* 273:1429–1435, 1995

[37]Jacobson MS, Tomopoulos S, Williams CL, Arden MR, Deckelbaum RJ, Starc TJ: Normal growth in high-risk hyperlipidemic children and adolescents with dietary intervention. *Prev Med* 27:775–780, 1998

[38]Tonstad S, Knudtzon J, Sivertsen M, Refsum H, Ose L: Efficacy and safety of cholestyramine treatment in peripubertal and prepubertal children with familial hypercholesterolemia. *J Pediatr* 129:42–49, 1996

[39]Simons LA, Sullivan DR: Lipid modifying drugs. *Med J Aust* 182:286–289, 2005

[40]Hedman M, Matikainen T, Fohr A, Lappi M, Piippo S, Nuutinen M, Antikainen M: Efficacy and safety of pravastatin in children and adolescents with heterozygous familial hypercholesterolemia: a prospective clinical follow-up study. *J Clin Endocrinol Metab* 90:1942–1952, 2005

[41]Stein EA, Illingworth DR, Kwiterovich PO Jr, Liacouras CA, Siimes MA, Jacobson MS, Brewster TG, Hopkins P, Davidson M, Graham K, Arensman F, Knopp RH, DuJovne C, Williams CL, Isaacsohn JL, Jacobsen CA, Laskarzewski PM, Ames S, Gormley GJ: Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA* 281:137–144, 1999

[42]Wiegman A, Hutten BA, de Groot E, Rodenburg J, Bakker HD, Buller HR, Sijbrands EJ, Kastelein JJ: Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 292:331–337, 2004

[43]Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM, Berenson GS: Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA* 290:2271–2276, 2003

[44]Rodenburg J, Vissers MN, Wiegman A, Trip MD, Bakker HD, Kastelein JJP: Familial hypercholesterolemia in children. *Curr Opin Lipidol* 15:405–411, 2004

[45]de Jongh S, Lilien MR, op't Roodt J, Stroes ES, Bakker HD, Kastelein JJ: Early statin therapy restores endothelial function in children with familial hypercholesterolemia. *J Am Coll Cardiol* 40:2117–2121, 2002

[46]de Jongh S, Vissers MN, Rol P, Bakker HD, Kastelein JJ, Stroes ES: Plant sterols lower LDL cholesterol without improving endothelial function in prepubertal children with familial hypercholesterolaemia. *J Inherit Metab Dis* 26:343–351, 2003

[47]Gagne C, Gaudet D, Bruckert E: Ezetimibe study group: efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. *Circulation* 105:2469–2475, 2002

[48]Pearson TA, Denke MA, Mc Bride PE, Battisti WP, Brady WE, Palmisano J: A community based, randomized trial of ezetimibe added-on to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the Ezetimibe Add-on to Statin For Effectiveness (EASE) Trial. *Mayo Clinic Proc* 80:587–595, 2005

[49]Forrester JS, Makkar R, Shah PK: Increasing HDL cholesterol in dyslipidemia by cholesteryl ester transfer protein inhibition: an update for clinicians. *Circulation* 111:1847–1854, 2005

[50]Steinmetz KL, Schonder KS: Colesevelam: potential uses for the newest bile resin. *Cardiovasc Drug Rev* 23:15–30, 2005

[51]Izzo JLJ, Levy D, Black HR: Importance of systolic blood pressure in older Americans. *Hypertension* 35:1021–1024, 2000

[52]Rocchini AP, Katch V, Anderson J, Hinderliter J, Becque D, Martin M, Marks C: Blood pressure in obese adolescents: effect of weight loss. *Pediatrics* 82:16–23, 1988

[53]National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents: The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 114:555–576, 2004

[54]Whitworth JA: Emerging drugs in the management of hypertension. *Expert Opin Emerg Drug* 8:377–388, 2003

[55]Nakov R, Pfarr E, Eberle S: Darusentan: an effective endothelinA receptor antagonist for treatment of hypertension. *Am J Hypertens* 15:583–589, 2002

[56]Gradman AH, Schmieder RE, Lins RL, Nussberger J, Chiang Y, Bedigian MP: Aliskiren, a novel orally effective renin inhibitor, provide dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation* 111:1012–1018, 2005

[57]Asmar R, Fredebohm W, Senftleber I, Chang PI, Gressin V, Saini RK: Omapatrilat compared with lisinopril in treatment of hypertension as assessed by ambulatory blood pressure monitoring. *Am J Hypertens* 13:143A, 2000

[58]Zuhir-Yafi MI, Brosnan PG, Hardin DS: Treatment of T2DM mellitus in children and adolescents. *J Pediatr Endocrinol Metab* 15 (Suppl. 1):541–546, 2002

[59]American Diabetes Association: Insulin administration (Position Statement). *Diabetes Care* 27:S106–S109, 2004

[60]Prendergast BD: Glyburide and glipizide, second-generation oral sulfonylurea hypoglycemic agents. *Clin Pharm* 3:473–485, 1984

[61]Skillman TG, Feldman JM: The pharmacology of sulfonylureas. *Am J Med* 70:361–372, 1981

[62]Fuhlendorff J, Rorsman P, Kofod H, Brand CL,

Rolin B, MacKay P Shymko R, Carr RD: Stimulation of insulin release by repaglinide and glibenclamide involves both common and distinct pathways. *Diabetes* 47:345–351, 1998

[63]Bailey CJ, Path MRC, Turner RC: Metformin. *N Engl J Med* 334:574–579, 1996

[64]U.K. Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in over-weight patient with T2DM (UKPDS 34). *Lancet* 352:854–865, 1998

[65]Jones KL, Arslanian S, Peterokova VA, Park JS, Tomlinson MJ: Effect of metformin in pediatric patients with T2DM: a randomized controlled trial. *Diabetes Care* 25:89–94, 2002

[66]O'Moore-Sullivan TM, Prins JB: Thiazolidinediones and T2DM: new drugs for and old disease. *Med J Aust* 176:381–386, 2002

[67]Egan J, Rubin C, Mathisen A, Pioglitazone 027 Study Group: Combination therapy with pioglitazone and metformin in patients with T2DM (Abstract). *Diabetes* 48:A117, 1999

[68]Egan J, Rubin C, Mathisen A, Pioglitazone 027 Study Group: Adding pioglitazone to metformin therapy improves the lipid profile in patients with T2DM. *Diabetes* 48:A106, 1999

[69]Salvatore T, Giugliano D: Pharmacokinetic-pharmacodynamic relationships of acarbose. *Clin Pharmacokinet* 30:94–106, 1996

[70]Clissold SP, Edwards C: Acarbose: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. *Drugs* 35:214–243, 1988

[71]Eldelman SV: Practice approach to combination therapy: daytime oral agent(s) and bedtime NPH insulin. *Clin Diabetes* 3:100–110, 1999

[72]Uwaifo GI, Ratner RE: Novel pharmacologic agents for type 2 diabetes. *Endocrinol Metab Clin N Am* 34:155–197, 2005

[73]Pramlintide (Symlin) for diabetes. *Med Letter* 47:43–44, 2005

[74]Nauck MA, Meier JJ: Glucagon-like peptide 1 and its derivatives in the treatment of diabetes. *Regul Pept* 128:135–148, 2005

[75]Guerre-Millo M, Gervois P, Raspe E, Madsen L, Poulain P, Derudas B, Herbert JM, Winegar DA, Wilson TM, Fruchart JC, Berge RK, Staels B: Peroxisome proliferators-activated receptor α activators improve insulin sensitivity and reduce adiposity. *J Biol Chem* 275:16638–16642, 2000

Johanna T. Mallare, MD, FAAP, is an assistant professor of pediatrics in the Department of Pediatrics, Division of Pediatric Endocrinology and Metabolism of the College of Medicine at the University of Tennessee Health Science Center, and Ana H. Karabell, MD, is a pediatric endocrinology fellow in the Department of Pediatrics, Division of Pediatric Endocrinology and Metabolism, of the College of Medicine at the University of Tennessee Health Science Center and LeBonheur Children's Medical Center in Memphis. Pedro Velasquez-Mieyer, MD, is a faculty member in the epidemiology program of the College of Graduate Health Sciences and an assistant professor in the College of Nursing and the Department of Pediatrics, Division of Endocrinology and Metabolism, of the same institution. Sarah R.S. Stender, MD, FAAP, is an assistant professor of pediatrics and adolescent medicine in the Division of General Pediatrics, and Michael L. Christensen, PharmD, is a professor of pharmacy and pediatrics in the Departments of Pediatrics and Pharmacy of the same institution.