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Type 2 Diabetes: The Prevention and Treatment

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LEARNING OBJECTIVES

1. Review the pathophysiology of type 2 diabetes.
2. Discuss and compare the American Diabetes Association (ADA) and American Association of Clinical Endocrinologist (AACE) guidelines for glycemic control in type 2 diabetes.
3. Explain a pathophysiologic approach to optimizing glycemic control.
4. Discuss the following current therapies:
    a. Mechanisms of action
    b. Recommendations for indications and usage
    c. Adverse effects
5. Present new and upcoming treatments for type 2 diabetes.

ABSTRACT: With the rise in obesity and the emergence of type 2 diabetes, treatment of diabetes and its complications have become increasingly challenging. Clinical studies such as the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Complication and Control Trial (DCCT) have helped to shape today's standards in diabetes care. These landmark studies set guidelines for hemoglobin A_{1c} (Hb A_{1c}) as a primary gauge for treatment of diabetes. Type 2 diabetes is a disease that is a combination of insulin resistance and insulin deficiency. To combat complications and the progression of diabetes, there are a variety of pharmacotherapeutic agents available, with many new treatments continuously in research and development. Having diabetes also predisposes patients to cardiovascular disease, and is considered to be a cardiovascular disease risk equivalent. Lifestyle interventions, such as diet and exercise, are also important in preventing and treating diabetes. Pharmacotherapeutic options range from insulin sensitizers, secretagogues, α glucosidase inhibitors, to insulin. Traditionally, insulin therapy was used as a last-line agent for type 2 diabetes treatment, when all oral options were exhausted. Now, insulin therapy is being used earlier on in the treatment of type 2 diabetes, and is being shown to be a very effective agent in optimizing glycemic control.

The purpose of this continuing pharmacy education (CPE) article is to review the prevention and treatment options for type 2 diabetes. Pathophysiology, diagnosis, and therapeutic approaches in optimizing glycemic control are covered in this paper. This CPE article also gives a brief overview

of landmark trials in type 2 diabetes therapies, as well as new and upcoming agents for the treatment of type 2 diabetes.

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TYPE 2 DIABETES: THE PREVENTION AND TREATMENT

INTRODUCTION

Type 2 diabetes is a growing problem with today's growing epidemic of obesity and sedentary lifestyle. Approximately 18 million people in the United States have diabetes. Unfortunately, one-third (approximately 5.2 million people) of these people go undiagnosed.[1] The vast majority of these cases are of type 2 diabetes, which is associated with advancing age, obesity, and sedentary lifestyle. However, diabetes does not afflict only the aging population. There is an increasing amount of case reports and studies showing type 2 diabetes in these groups: Native American/American Indian, African American, Hispanic, and Latino children and adolescents.[1] Treatment of type 2 diabetes and prevention of its long-term complications, such as retinopathy, nephropathy, and neuropathy, are becoming increasingly challenging in the United States.

Diabetes is a chronic disorder characterized by impaired glucose metabolism that is, in turn, characterized by hyperglycemia. It is associated with a relative or absolute impairment of insulin secretion, insulin resistance, or both. Chronic hyperglycemia may cause long-term damage, dysfunction, and failure to various organs, such as the eyes, kidneys, heart, and blood vessels. There is a myriad of pathogenic processes that are involved with the development of diabetes, ranging from pancreatic β cell destruction, insulin deficiency, or abnormalities that result in resistance to the action of insulin.[2]

Symptoms of hyperglycemia include polyuria, polydipsia, weight loss, sometimes polyphagia, and blurred vision. Chronic hyperglycemia can increase susceptibility to certain infections and impair growth and development in children. Uncontrolled diabetes can lead to acute, life threatening consequences, such as ketoacidosis or nonketotic hyperosmolar syndrome.[2]

The main topic of this continuing pharmacy education (CPE) article will cover type 2 diabetes and its prevention and treatment. Type 2 diabetes accounts for approximately 90% to 95% of those patients with diabetes. These individuals usually have insulin resistance and varying degrees of insulin deficiency. These patients still retain significant capacity to produce insulin; however, the amount of insulin produced is ineffective in overcoming insulin resistance. These patients fail to respond to normal concentrations of insulin and have coexisting hyperinsulinemia. Type 2 diabetes usually occurs after the age of 40, and can be associated with obesity. Obesity in itself has some degree of insulin resistance, and may contribute to an increased risk of cardiovascular disease.

This form of diabetes often goes underdiagnosed.

Pathogenesis

The pathology of type 2 diabetes is complicated by several factors, such as insulin resistance, genetics, and environment. Insulin resistance is a good predictor of type 2 diabetes.[3] Genetic factors also appear to play a role in the development of type 2 diabetes. These factors, in combination with environmental components causing insulin resistance, may eventually lead to overt hyperglycemia.[4] Finally, decreased insulin secretion itself adds to the hyperglycemia.

Insulin Resistance

Insulin resistance is the marked impairment of insulin action on peripheral tissues and organs. The insulin dose response curve for glucose uptake into peripheral tissue is shifted to the right, meaning that it takes more insulin to get a response. Inhibition of hepatic glucose production and lipolysis also show reduced sensitivities to the action of insulin. The processes for insulin resistance are poorly understood, but it is proposed that genetic abnormalities affecting insulin receptor and postreceptor binding are involved.[5] Abdominal obesity is more likely to be associated with insulin resistance and diabetes versus peripheral obesity. Abdominal fat cells have an increased rate of lipolysis than peripheral fat cells. This contributes to the increased production of free fatty acids leading to "lipotoxicity," a syndrome resulting in increased gluconeogenesis, impaired muscle glucose metabolism, and impaired β cell function.[5] Hyperglycemia also impairs β cell response to glucose and promotes insulin resistance, which further exacerbates this vicious cycle.

Diagnosis

Under the American Diabetes Association (ADA) guidelines, there are three ways to diagnosis diabetes based on plasma glucose concentration and its temporal relationships. The first diagnostic is to have symptoms of diabetes and a casual plasma glucose concentration
≥ 200 mg/dl (11.1 mmol/l). Casual plasma glucose is taken at anytime without regard to meals. The classic symptoms of diabetes are polyuria, polydipsia, and unexplained weight loss. A fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l) is the second marker to diagnose diabetes. Fasting is defined as no caloric intake for at least 8 hours. And third, a 2-hour postprandial glucose ≥ 200 mg/dl during an oral glucose tolerance test is also diagnostic of diabetes. The oral glucose tolerance test is performed using an equivalent of 75 g of anhydrous glucose dissolved in water.[2] Two other categories of hyperglycemia are impaired fasting glucose (IFG) or impaired glucose tolerance (IGT); these categories have been recently termed as "prediabetes." IFG is a fasting plasma glucose ≥ 100 mg/dl and IGT is a 2-hour postprandial glucose ≥ 140 mg/dl.[6]

Complications

Poorly controlled diabetes can have long-term consequences potentially leading to renal failure; blindness; risk of foot ulcers and amputations; gastrointestinal (GI), genitourinary, and cardiovascular symptoms; and sexual dysfunction. Cardiovascular disease is the leading cause of diabetes death. The risk of death from cardiac disease and stroke is 2 to 4 times greater in patients with diabetes. Hypertension is a common comorbidity in patients with diabetes, about 20% to 60%, depending on ethnicity, obesity, age, and gender.[7] In addition, hypertension increases the risk of heart attacks, strokes, peripheral vascular disease, retinopathy, nephropathy,

and neuropathy. ADA guidelines recommend a blood pressure goal <130/80 mmHg for patients with diabetes.[6] Dyslipidemia is also common in patients with diabetes and further adds to cardiovascular risk. The type of dyslipidemia that is most commonly seen in patients with diabetes is low HDL and elevated triglycerides.[8] According to the National Cholesterol Education Program (NCEP) expert panel adult treatment plan III (ATP III), diabetes is considered to be a coronary heart disease risk equivalent, and thus incurs a risk of a coronary event >20% within 10 years.[9]

Several studies have compared long-term treatments for type 2 diabetes and their effects with long-term complications. The United Kingdom Prospective Diabetes Study (UKPDS) recruited over 5000 patients with newly diagnosed type 2 diabetes (mean starting hemoglobin A_{1c} [Hb A_{1c}] 9.1%) and followed them over an average of 10 years. The study showed that intensive glycemic control (goals: fasting plasma glucose <108 mg/dl and Hb A_{1c} <6%) versus standard glycemic control (goals: fasting blood glucose <270 mg/dl) had decreased in diabetes complications. A 1% decrease in Hb A_{1c} related to a 37% decrease in risk for microvascular complications and a 21% decrease in the risk of any end point or death related to diabetes.[10] Final Hb A_{1c} in the intensive group was 7%, while the conventional group was 7.9%. A similar Japanese study using intensive insulin therapy to prevent the progression of diabetic microvascular complications showed similar results.[11]

The Hb A_{1c} reflects glycemic control over the previous 2 to 3 months; therefore, it is recommended to check Hb A_{1c} levels approximately every 3 months. ADA recommends a Hb A_{1c} of less than 7% for glycemic control. It is, however, important to individualize goals. Newer recommendations are more stringent (i.e., normal Hb A_{1c} <6%) and can be considered in individual patients to further reduce cardiovascular risk. Postprandial blood glucose may be targeted if Hb A_{1c} goals are not met despite reaching preprandial glucose goals.[6] Table 1 lists a current comparison of the ADA and the American Association of Clinical Endocrinologist (AACE) recommendation for adults with diabetes.

Table 1.

Glycemic Control	ADA Guidelines[6]	AACE Guidelines[12]
Hb A_{1c}	<7%	<6.5%
Preprandial Plasma Glucose	90-130 mg/dl	<110 mg/dl
Postprandial Plasma Glucose	<180 mg/dl	<140 mg/dl

Prevention

Diet and exercise are essential components in the prevention and treatment of type 2 diabetes. Recently, there have been a number of studies investigating strategies to prevent or delay type 2 diabetes. Two large studies demonstrated that intense nutritional and exercise counseling had a significant impact on reducing the progression of glucose intolerance in patients with diabetes. In the Finnish study[13] (n = 522), IGT subjects were randomized to receive brief diet and exercise counseling or intensive diet and exercise counseling. The Diabetes Prevention Program[14]
(n = 3234) had similar characteristics as the Finnish Study, where patients were randomized to standard diet and exercise, metformin, or intensive diet and exercise. In the Diabetes Prevention Program, the crude

incidence for each group was 11.0, 7.8, and 4.8 cases per 100 person-years. The estimated number of persons needed to be treated in 3 years to prevent one case of diabetes is 5.4 (95%, confidence interval 5.4-9.5), for lifestyle intervention versus 13.9 (95%, confidence interval 8.7-33.9) versus with metformin. This shows that lifestyle modification is more effective for preventing diabetes than metformin. Both studies concluded that intensive diet and exercise had a 58% relative risk reduction in the progression to diabetes.[13,14]

To prevent or delay diabetes, the ADA recommends the screening of overweight men and women ≥ 45 years of age for prediabetes using the oral glucose tolerance test or a fasting plasma glucose. Patients with IGT should be given counseling on weight loss and instructions for increasing physical activity. Monitoring of these patients with prediabetes should be performed every 1 to 2 years. Attention should also be focused on the appropriate treatment for other cardiovascular disease risk factors such as hypertension, dyslipidemia, and tobacco use.[15] Based on the previously cited studies, the following plan is recommended:[16]

- Weight loss goals of 5% to 7% of initial body weight
- Physical activity of at least 150 to 200 min/wk (moderate aerobic activity)
- Low-fat diet (<30% of calories from fat and <10% from saturated fat)
- High-fiber diet
- Increased consumption of vegetables

Pharmacologic Therapy

Pharmacotherapy of type 2 diabetes is indicated when a patient fails to reach and maintain glycemic control goals with diet and exercise. Since the 1990s, medical therapy for type 2 diabetes has expanded beyond insulin and first-generation sulfonylureas. These include drugs of several other classes, such as the insulin sensitizers (metformin, Glucophage®) and thiazolidinediones (TZDs) (rosiglitazone, Avandia® and pioglitazone, Actos®), the α glucosidase inhibitors (acarbose, Precose® and miglitol, Glyset®), the third-generation sulfonylurea (glimepiride, Amaryl®), and, lastly, the meglitinides (repaglinide, Prandin® and nateglinide, Starlix®).

Current diabetes treatment goals vary according to the ADA and AACE to prevent and delay the progression of microvascular and macrovascular complications. The ADA recommends Hb A_{1c} <7 and the AACE recommends Hb A_{1c} <6.5.[6,12] In the past several years, new developments in oral agents as well as insulin preparations and analogs have expanded therapeutic choices and have made it possible to ensure effective glycemic control.

There are currently 4 therapeutic options for type 2 diabetes:

1. Increase insulin secretion by using a sulfonylurea and/or a meglitinide.
2. Increase insulin sensitivity with a biguanide and/or a thiazolidinedione.
3. Modify intestinal absorption of carbohydrates with an α-glucosidase inhibitor.
4. Treat with the currently available exogenous insulin.

ORAL AGENTS

Secretagogues

Sulfonylureas and meglitinides are medications known as secretagogues.

Mechanism of Action

Sulfonylureas exhibit their therapeutic effect by stimulating insulin secretion in the

pancreas. ATP-dependent potassium channels in the plasma membrane of pancreatic β cells stimulate insulin secretion. The potassium channels consist of two subunits, one with a sulfonylurea receptor and the other containing the channel itself. In type 2 diabetes, sulfonylureas bind to the sulfonylurea receptor and close the ATP-dependent potassium channel. As potassium accumulates inside the β cells' membrane, the β cell depolarizes, leading to an influx of calcium. This influx of calcium causes insulin granules to rise to the surface of the membrane, resulting in exocytosis and the release of insulin.[17] The timing of this process varies greatly among secretagogues. Patients with type 2 diabetes usually have defects in both insulin secretion and insulin action; therefore, regardless of how sulfonylureas work, they can be effective in controlling hyperglycemia in these patients.

Indications and Usage

Sulfonylureas are adjunct therapy for patients whose diabetes is uncontrolled by exercise and nutritional therapy alone. They are ideal for patients who have a significant amount of insulin deficiency but have residual β cell function that responds to stimulation. Extrapancreatic effects may also play a role in the activity of sulfonylureas.[18]

When choosing a sulfonylurea, consider intrinsic potency, onset of action, duration of action, pattern of metabolism, and side effects. Table 2 lists the current sulfonylureas with their duration of action. Intrinsic potency is defined as the binding affinity of the sulfonylurea to its receptor.[18] Glyburide (Diabeta®, Glynase®, Micronase®) and Glimepiride (Amaryl®) are the most potent sulfonylureas. Glimepiride does not affect the potassium channels in cardiac tissue as seen in other first- and second-generation sulfonylureas, which could cause problems in ischemic heart disesase.[19]

Sulfonylureas can be used as initial treatment in type 2 diabetes. They have been shown to decrease Hb A_{1c} by 1% to 2%, and may reduce fasting plasma glucose by 60-70 mg/dl.[18] The improvement in glycemic control that occurs with sulfonylureas, compared with other antidiabetic agents, is greater in patients who initially have less than optimal glycemic control. However, with progression of diabetes, the response to sulfonylurea treatment may diminish and changes to treatment strategy may be warranted.

Table 2. Secretagogues[20]

First Generation	Equivalent Therapeutic dose (mg)	Starting Dose (mg)	Duration (h)	Maximum Dose Per Day	Half-life (h)
Chlorpropamide (Diabinese®)	250	250	24-72	500 mg	35+
Tolazamide (Tolinase®)	250	100-250	12-24	750-1000 mg	7
Second Generation					
Glipizide (Glucotrol®,	5-10	5	10-24	40 mg, 20 mg	3

Glucotrol XL®)					
Glyburide (Diaβeta®, Micronase®)	5	2.5	18-24	20 mg	3
Glyburide, Micronized (Glynase®)	3	1.5-3	18-24	12 mg	3
Third Generation					
Glimepiride (Amaryl®)	2	1-2	18-28	8 mg	4-6
Meglitinides					
Repaglinide (Prandin®)	NA	0.5-1	4	16 mg/d or 4 mg per meal	1
Nateglinide (Starlix®)	NA	120 mg tid	4	120 mg tid w/ meals	1

Warnings and Precautions

Sulfonylureas have a special warning on increased risk in cardiovascular mortality. The warning is based on a study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial.[21] Tolbutamide was the only sulfonylurea used in this study, but it still may apply to other drugs of this class.

Hypoglycemia is the most serious adverse event of sulfonylurea therapy. All sulfonylureas are capable of producing hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking β-blockers or sympatholytic agents. Combination with insulin or other antidiabetic agents may increase the potential for hypoglycemia.[21]

Meglitinides

There are currently 2 drugs in this class: repaglinide (Prandin®) and nateglinide (Starlix®). Meglitinide agents are structurally and pharmacologically unrelated to sulfonylureas. They stimulate glucose-mediated insulin secretion differently from sulfonylureas. Meglitinides are rapidly absorbed when ingested, and have a rapid onset of action similar to the physiologic first-phase insulin release. These agents should be taken only when the patient eats, thus allowing the patient more freedom in the timing of meals. Meglitinides also have a very short half-life, and may reduce the risk of hypoglycemia.[22]

Mechanism of Action

These secretagogues act similarly to sulfonylureas by binding to the sulfonylurea receptor. This substrate receptor binding causes increased calcium in the cell, thus inducing insulin secretion.

Indications and Usage

Repaglinide and nateglinide are both indicated as monotherapy to lower blood glucose in patients with type 2 diabetes. Their hyperglycemia is not adequately controlled by diet and exercise, and they have not been chronically treated with other antidiabetic agents.[23,24] The meglitinides also are indicated for combination therapy

with metformin or thiazolidinediones when monotherapy combined with nutritional and exercise effects fail to lower blood glucose levels. In patients previously treated with diet and exercise, repaglinide and nateglinide had similar postprandial glycemic effects. Repaglinide monotherapy and combination therapy with metformin appear to be more effective than nateglinide in reducing Hb A_{1c}.[25,26] Meglitinides should be given 15 to 30 minutes before meals and titrated up by using the postprandial blood glucose. Initial starting doses for these medications are listed in Table 2.

Warnings and Precautions

Meglitinides have the ability to cause hypoglycemia alone or in combination with other glucose-lowering agents. Hypoglycemia is difficult to detect in the elderly, patients with autonomic neuropathy, and patients on β-blockers. Patients that skip their meals should be advised to skip their dose.[25,26]

Insulin Sensitizing Agents

Recently, many have debated using insulin sensitizing agents over secretagogues as initial therapy. Insulin sensitizers such as biguanide (metformin, Glucophage®) and the thiazolidinediones (pioglitazone, Actos® and rosiglitazone, Avandia®) effectively lower plasma glucose, while also lowering cardiovascular risk factors.[19]

Biguanides

Metformin has been used for over 40 years in Europe and has only been available in the U.S. since the 1990s. Metformin is considered an insulin sensitizer but its mechanism of action is unknown. It has a myriad of cellular effects, including carbohydrate, lipid, and lipoprotein metabolism. Metformin seems to decrease hepatic glucose production and appears to have an indirect effect on insulin mediated glucose uptake.[22] Metformin often leads to a modest weight reduction or weight stabilization. According to the UKPDS, metformin appears to decrease the risk of diabetes-related endpoints in overweight patients with type 2 diabetes over insulin and sulfonylureas.[27]

Indications and Usage

Metformin is indicated in obese and non-obese patients with type 2 diabetes that are not satisfactorily controlled by diet and exercise. It can be used as monotherapy or in combination with the following agents: sulfonylureas, thiazolidinediones, meglitinides, and insulin.[28] Metformin is contraindicated in patients with significant renal, cardiac, and hepatic disease where the potential for lactic acidosis is a concern. The usual starting dose of metformin is 500 mg with evening meal for 1 week or 850 mg once daily with meals, before increasing to avoid GI upset. A dosage increase should be made in increments of 500 mg weekly or 850 mg every 2 weeks, up to a total of 2000 mg daily, and should be given in divided doses, or 2550 mg daily, given in 3 divided doses with meals.[29] The maximum clinical effective dose of metformin is 2000 mg daily (no additional benefit with higher doses).

Warnings and Precautions

Metformin has a "black box" warning for lactic acidosis. This is very rare but is an extremely serious condition that can occur secondary to the accumulation of metformin. Lactic acidosis is fatal in ~ 50% of cases. The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.003 cases/1000 patient-years, with approximately 0.0015 fatal cases/1000 patient years). The majority of these cases has occurred in patients with significant renal insufficiency. The risk of lactic acidosis may be significantly reduced

by regularly monitoring renal function. Metformin is contraindicated in patients with renal disease or renal dysfunction, a serum creatinine ≥1.5 mg/dl in males and ≥ 1.4 mg/dl in females, congestive heart failure, known hypersensitivity, and acute or chronic metabolic acidosis. Metformin should also be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast media.[29] Metformin should be cautiously used in patients who are known to consume alcohol, since this may lead to acidosis.

GI symptoms, such as abdominal bloating, flatulence, anorexia, diarrhea, nausea, and vomiting are the most common side effects observed in patients treated with metformin. GI complaints are approximately 30% more in patients on metformin monotherapy than placebo, particularly in the initial stages of therapy.[29] Patients also have complaints of a metallic taste in their mouth.

Thiazolidinediones (TZDs)

Pioglitazone (Actos®) and Rosiglitazone (Avandia®) are the two currently marketed TZDs in the United States. A third, troglitazone (Rezulin®), was the first drug in this class to be marketed but was subsequently removed because it caused liver dysfunction and liver failure in some patients.

Mechanism of Action

The mechanism by which these agents increase insulin action is not well understood. These agents bind to and activate peroxisome proliferators–activated receptor gamma (PPARγ), a nuclear receptor that regulates the expression of several genes involved in metabolism and control of adipocyte differentiation, lipid storage, and insulin sensitization. With these agents, there is a decrease in insulin resistance and improvement in target cell response to insulin.[30] There are 3 different PPAR isoforms: alpha (α), delta (δ), and gamma (γ). Of these 3, PPARγ is probably the most important of the 3 isoforms. Thiazolidinediones also stimulate the expression of genes responsible for the production of glucose transporters (GLUT1 and GLUT4). PPARγ stimulation has also been shown to reduce tumor necrosis factor α (TNF-α). Thiazolidinediones may cause a reduction in the number of adipocytes and an increase in the number of small adipocytes leading to lower free fatty acid and triglyceride levels and improved insulin sensitivity.[31]

Indications and Usage

Pioglitazone and rosiglitazone are indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes . Both thiazolidinediones are approved for monotherapy of type 2 diabetes. They are also indicated for use with sulfonylureas, metformin, or insulin when diet and exercise plus the single agent do not result in adequate glycemic control.

Pioglitazone is available in 15-, 30-, and 45-mg tablets. Pioglitazone should be taken once daily without regard to meals. The dose can be increased to a maximum dose of 45 mg daily. Rosiglitazone is available in 2-, 4-, and 8-mg tablets. It can be given once daily or divided in the morning and evening and taken without regard to food. In clinical trials, rosiglitazone 4-mg, twice-daily regimen resulted in the greatest reduction in fasting plasma glucose and Hb A_{1c}. The onset of action of these drugs is slow, taking 2 to 3 months to see the full effect. Therefore, in clinical practice, it is recommended that patients be treated with thiazolidinediones for a period of time adequate enough to evaluate change in

Hb A_{1c} (3 months) unless glycemic control deteriorates.[32,33]

Warnings and Precautions

Use of thiazolidinediones may increase fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. Thiazolidinediones should be used with caution in patients at risk for congestive heart failure. These agents should be discontinued if deterioration in cardiac status occurs.

Hepatoxicity is another concern for thiazolidinediones use. In phase 3 clinical trials of troglitazone, 2.2% of patients treated with troglitazone had reversible elevation in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) greater than 3 times the upper limit of normal versus 0.6% of patients treated with placebo.[32,33] Troglitazone was associated with several cases of fulminant hepatic failure resulting in mortality or the need for liver transplant. No evidence of hepatoxicity has been observed with either rosiglitazone or pioglitazone. In phase 3 clinical trials, rosiglitazone and pioglitazone had similar elevations in AST and ALT greater than 3 times the upper limit of normal compared with placebo, which was approximately 0.2%.[32,33] Serum liver (hepatic) transaminase testing is recommended prior to starting therapy. The U.S. Food and Drug Administration (FDA) recently removed the mandate to monitor ongoing hepatic function in association with rosiglitazone and pioglitazone. Practitioners may use clinical judgment for routine monitoring of liver enzymes.

Thiazolidinediones may cause ovulation in premenopausal women with anovulation secondary to insulin resistance. Proper contraception is recommended in these women because they may be at risk for pregnancy.

Adverse Effects

Mild to moderate edema has been associated with rosiglitazone and pioglitazone. Reductions in hemoglobin and hematocrit have also been observed with the use of thiazolidinediones. These changes are possibly attributable to volume expansion, and have not been associated with significant hematologic effects.

Weight gain is a common side effect of thiazolinediones. Pioglitazone monotherapy has been associated with an average weight gain of 1.1 lbs to 6.2 lbs compared with placebo.[32] Rosiglitazone monotherapy has also been associated with a weight gain of 2.6 lbs to 7.7 lbs.[33]

α-Glucosidase Inhibitors

Currently, there are 2 products in the class of α-glucosidase inhibitors: acarbose (Precose®) and miglitol (Glyset®). Postprandial hyperglycemia is linked to overall glycemic control. This class of drug was designed to target postprandial blood glucose. These drugs act by delaying absorption of simple carbohydrates in the small intestine, thereby helping to decrease the postprandial peak seen after eating a meal. The medications are poorly absorbed, and do not cause the pancreas to secrete insulin; therefore, they do not cause hypoglycemia.

Mechanism of Action

α-glucosidase inhibitors competitively inhibit α-glucosidase enzymes in the epithelial brush border of the proximal small intestine. This inhibition delays hydrolyzation of polysaccharides and disaccharides into absorbable monosaccharides (e.g., glucose), thus inhibiting glucose absorption. By delaying

the absorption, the usual postprandial peak is blunted.[22]

Indications and Usage

The FDA has approved acarbose as monotherapy for type 2 diabetes patients who are not well controlled with nutrition therapy alone. It also has been approved for combination therapy with sulfonylureas, insulin, or metformin. Miglitol has been approved for a similar monotherapy indication as acarbose, but only has approval for combination with sulfonylureas. α-glucosidase inhibitors reduce Hb A_{1c} from 0.5% to 1.0%, but the benefit is related to carbohydrate content of the diet.[22]

Both acarbose and miglitol are available in 25-, 50-, and 100-mg tablets. Treatment should be individualized for each patient to achieve glycemic goals with minimal adverse events. The initial starting dose of acarbose is 25 mg 3 times daily, but some patients may benefit with a starting dose of 25 mg daily to decrease GI side effects. One-hour postprandial blood sugars should be used to gauge the titration of therapy. The maximum dose is 100 mg three times daily. Miglitol starting dose is 25 mg 3 times daily for 4 to 8 weeks, then titrated up to 50 mg 3 times daily for 3 months when Hb A_{1c} can be assessed. Patients that are not at glycemic goal, and can tolerate the dose increase, may be titrated to 100 mg 3 times daily.[34,35]

α-glucosidase inhibitors are difficult medications to take. A larger amount of carbohydrate is delivered to the colon, where fermentation produces gas, so most patients experience flatulence; many have abdominal pain and diarrhea.[22] Acarbose and miglitol have similar efficacy; however, no comparative clinical trials have been conducted. Therefore, it is difficult to determine if there are any advantages of one product over the other.

Warnings and Precautions

α-glucosidase inhibitors are contraindicated in patients with inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, and other GI disorders. Acarbose is also contraindicated in patients with cirrhosis or patients with plasma serum creatinine > 2.0 mg/dl. Miglitol is not recommended in patients with renal insufficiency.[34,35]

Hypoglycemia is not associated with monotherapy of α-glucosidase inhibitors, but may occur in combination with other antidiabetic agents. If a patient experiences hypoglycemia, glucose tablets must be used instead of foods containing carbohydrates. If hypoglycemia is severe, a glucagon injection may be necessary.[34,35]

Side Effects

GI side effects are the most common side effects of the α-glucosidase inhibitors. Because of the delay in carbohydrate absorption, complex sugars are retained in the colon longer, thus leading to fermentation. Fermentation yields gas production causing flatulence, abdominal distention and pain, and diarrhea. These symptoms usually resolve within several weeks.[34,35]

In clinical trials, reversible elevated liver enzymes were observed at dosages above the recommended maximum dose of acarbose. The manufacturer recommends that liver transaminases be checked every 3 months for the first year of therapy and periodically afterwards.[34,35]

Insulin Therapy

Insulin therapy is inevitable as β cell function declines. Traditionally, insulin has

been used when patients fail oral agents. Insulin is often postponed until progression of diabetes is to the point where oral medications are unable to maintain glycemic goal. This postponement is, most likely, owing to the patient's concerns about acceptance of injections and the complex nature of medical management with insulin. In the near future, it may be more routine to use combination therapy with insulin in the early stages of type 2 diabetes for reaching intense treatment goals. Using insulin in conjunction with oral agents to maintain glycemic goals has a myriad of clinical benefits in the prevention of microvascular and macrovascular complications. Insulin may also preserve β cell function and prevent glucose toxicity.[10,11,36]

Available forms of insulin are long acting (glargine, ultralente, detemir), intermediate acting (neutral protamine hagedorn [NPH] and lente), short acting (regular insulin) and rapid acting (lispro, aspart, glulisine).

Table 3. Insulin and Insulin Analogs[37,38]

Insulin Formulation	Onset of Action	Peak Action	Duration of Action
Aspart (Novolog®)	5-10 min	1-3 h	3-5 h
Lispro (Humalog®)	<15 min	0.5-1.5 h	2-4 h
Glulisine (Apidra®)	<15 min	0.5-1.5 h	3-5h
Human Regular	30 min	2-3 h	3-6 h
Human NPH/Lente	2-4 h	4-12 h	10-18 h
Ultralente	6-10 h	-------	18-20 h
Glargine (Lantus®)	1.1 h	-------	24 h
Detemir* (Levemir®)	1 h	-------	24 h

*Only approved in Switzerland

Insulin Regimens

In type 1 diabetes, the primary defect is insulin deficiency; therefore, treatment is targeted at mimicking physiologic insulin secretion by the pancreas (i.e., continuous basal release with additional boluses with respect to meals).[28] Regimens such as these are not limited to patients with type 1 diabetes. They may also be used in patients with type 2 diabetes who are suboptimally controlled on combination therapy. To simplify insulin initiation, combination therapy supplemented with basal insulin is common practice.[39]

Basal Insulin

Initiation of insulin as a single bedtime injection is an easy and effective way to add insulin to oral therapy. Current intermediate acting products available are NPH and lente. Ultralente is a nonanalog form of long-acting insulin. NPH is most widely used for basal insulin supplementation, despite its duration of action of less than 24 hours. NPH also peaks 4 to 6 hours after administration, thus increasing the risk for nocturnal hypoglycemia. Insulin mixes 70/30 (70% NPH and 30% rapid-acting insulin) or 75/25 (75% NPH and 25% lispro) are other insulin products currently on the market. Two new long-acting insulin analogs are insulin glargine and insulin detemir (currently only available in Switzerland). These insulin analogs have flat peaks and last up to 24 hours, making them closer to physiologic basal pancreatic insulin secretion. Clinical experience is showing that glargine may have a slight peak effect (especially in the elderly), and

morning dosing rather than bedtime dosing may be considered.

The initial starting dose for NPH and insulin glargine is typically 10 units/day or 0.2 units/kg/day of actual body weight. The dose is usually titrated every 3 or 4 days based on fasting blood glucose values.[28] Prandial insulin can be added if glycemic goals are not met with basal insulin and combination therapy. Prandial insulin targets postprandial hyperglycemia.

Warnings and Precautions

Patients on insulin therapy should be properly educated and counseled to recognize adverse effects. Patients should be taught how to recognize and treat hypoglycemia. Common signs and symptoms of hypoglycemia are sweating, nervousness, irritability, anxiety, rapid pulse, and confusion. If possible, patients should first check their blood glucose levels. Hypoglycemia can be easily treated with 15 grams of carbohydrate in the form of glucose tablets, half glass of juice or soda, or 1 to 2 teaspoons of sugar or honey. Patients should retest their blood sugar in 15 minutes. At that point, if blood glucose is still below 70 mg/dl, another 15 grams of carbohydrate should be consumed. If blood sugar is not low, and the next meal is more than an hour away, a starchy or protein snack is recommended.

NEW PRODUCTS IN DEVELOPMENT

Glucagon-Like Peptide-1 (GLP-1)

Glucagon-like peptide is an incretin, a secretagogue hormone produced by enteroendocrine cells that enhance endocrine secretions from the pancreas. GLP-1 stimulates glucose-dependent insulin secretion by β cells. It may promote β cell neogenesis and differentiation while also enhancing satiety. The main disadvantages of GLP-1 are its injectable form and short half-life. Research is currently underway in the development of new formulations to prolong its half-life. Extendin-4, NN211, CJC-11131, and LY307161 are other agents in the pipeline.[40]

Dipeptidyl Peptidase IV Inhibitors

Dipeptidyl peptidase IV (DPP IV) is an enzyme located in endothelial tissues throughout the body. It facilitates the rapid breakdown of GLP-1. DPP IV inhibitors were designed to prolong the beneficial effects of GLP-1. LAF237 and NVPDPP728 are compounds currently in development.[41]

Amylin Analogs

Amylin is a hormone that is cosecreted with insulin from pancreatic β cells. Amylin inhibits gastric emptying time, delays nutrient absorption, and inhibits glucagon secretion after meals. Pramlintide is an amylin analog that is currently in development.[41]

Inhaled Insulin

Inhaled insulin is potentially another form of insulin therapy that may become available. Inhalation insulin is noninvasive and, potentially, a more practical form of insulin administration. Exubera®, a rapid-acting inhalation form of insulin, is currently in phase 3 clinical trials. AERx®, a regular-acting inhalation insulin, is in phase 2 clinical trials.[42] The current concerns of inhalation insulin are 1) the formation of insulin antibodies over time may potentially interfere with insulin absorption and 2) the possible long-term, late-developing effects of insulin on lung structure and function.

Oral Insulin

Research and development of orally active insulin is currently underway. Developmental strategies being studied are

1) the enteric coating of insulin molecules that would protect it from degradation, 2) the structural modifications, and 3) the use of protease inhibitors. Hexyl-insulin monoconjugate 2 (HIM2) was developed by covalently linking an amphilic oligomer to the insulin molecule. This results in enzymatic-resistant degradation, subsequently leading to improvement in absorption.[41] Calcium phosphate-PEG-insulin-casein (CAPIC) is an oral delivery system for insulin currently being developed. CAPIC formulation protects insulin degradation as it passes through the acidic environment of the GI tract.[43]

Diabetes is a complex disease with detrimental outcomes. Its complexity stems from the different degrees of insulin resistance and β cell dysfunction. Treatment goals and strategies are devised to prevent diabetic complications such as nephropathy, neuropathy, retinopathy, and cardiac disease. The myriad of medications on the market is very effective in controlling blood glucose and reducing Hb A_{1c}. Treatments range from different insulins, medications that promote insulin secretions and medications that influence insulin resistance, to medications that affect absorption of carbohydrates into the blood stream. Even with all these treatment modalities, there are currently no treatments focused at the source of the diabetes, the disease process itself, which is poorly understood.

In the past few years, there has been a focus on prevention of type 2 diabetes. Studies have shown that lifestyle modifications can greatly impact the prevention and the delay of onset of type 2 diabetes. There are many promising developments in the treatment of diabetes. Because of the many products in the early stages of development, the future of diabetes treatment is continuously and rapidly evolving.

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