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# Type 2 Diabetes: Preventing Complications with Drug Therapy

**Goals: A review of the etiology, complications and current available treatments for Type 2 diabetes.**

## **Credits:**

## **Objectives:**

- Define the diagnostic criteria for diabetes.
- Describe the physiologic complications associated with diabetes.
- Describe and discuss the current drug therapies available for Type 2 diabetes.
- Discuss the guidelines for the treatment of Type 2 diabetes
- Discuss the management and prevention of complications associated with diabetes

## **Overview**

Diabetes is reaching epidemic proportions in the United States with seven percent of the population suffering from the disease. Direct and indirect costs are \$130 billion annually. Type 2 diabetes, which is caused by high blood glucose levels, accounts for 90 to 95 percent of all cases. The long term objective for treating Type 2 diabetes is to reduce complications of the disease by using a variety of drug therapies and encouraging lifestyle changes.

## **Prevalence and Diagnostic Criteria of Diabetes**

Diabetes is a disease characterized by high levels of glucose in the blood. This could be the result of impaired insulin production, inadequate response of the body to insulin secretion, or a combination of the two. High blood glucose levels and other metabolic disorders associated with diabetes may lead to many complications such as renal disease, retinopathy, neuropathy, cardiovascular disease and hypertension.

According to the Center for Disease Control (CDC), diabetes affects an estimated 20 million people in the United States. This represents 7 percent of the entire population.<sup>1</sup> Estimates indicate that only 14 million of that 20 million are diagnosed. Based on figures from the CDC, in 2002 the annual cost of treating diabetes was more than \$92 billion. Indirect costs associated with the disease such as disability and loss of productivity were another \$40 billion.<sup>1</sup>

Type 1 diabetes is a condition where the body produces little or no insulin. Insulin is produced and secreted by the beta cells of the pancreas. Insulin is the hormone that allows glucose to enter cells in the body. In Type 1 diabetes, the beta cells of the pancreas have been either destroyed or lost. Patients with Type 1 diabetes are incapable of producing adequate amounts of insulin, therefore, they are dependent on insulin therapy. Onset of Type 1 diabetes usually occurs in childhood or in young adults.

Type 2 diabetes, previously referred to as adult onset or non-insulin dependent diabetes, accounts for 90 to 95 percent of all diabetes cases and is associated with a gradual increase in insulin resistance over many years.<sup>1</sup> Cells in the body begin to improperly use insulin and the pancreas loses its ability to produce enough insulin to meet the metabolic demands of the body. Type 2 diabetes is associated with an older age of onset, obesity, physical inactivity, heredity and impaired glucose metabolism.

Before patients develop Type 2 diabetes they often have insulin resistance, which is characteristic of a condition referred to as metabolic syndrome. Many will progress to pre-diabetes. Diagnostic criteria for metabolic syndrome, pre-diabetes and diabetes are included in Table 1.<sup>2,3</sup>

## Screening for Type 2 Diabetes

According to the American Diabetes Association (ADA), testing for diabetes should be considered in all individuals age 45 years or older, particularly those who are overweight or have a body mass index (BMI) of 25 kg/m<sup>2</sup> or greater. If the initial results are normal, testing should be repeated at three-year intervals unless the patient has excessive weight gain or symptoms of diabetes are noted (e.g. polyuria, polydipsia, unexplained weight loss).<sup>2</sup> Younger people should be tested if they are overweight and have additional risk factors, such as physical inactivity, family history of diabetes, hypertension or vascular disease.

**Table 1. Diagnostic Criteria for the Metabolic Syndrome, Pre-diabetes and Diabetes**

### Metabolic Syndrome

- Waist circumference > 40 in men; > 35 in women
- Low HDL-C < 40 mg/dL men; < 50 mg/dL women
- High triglyceride level of > 150 mg/dL
- Impaired fasting blood glucose level of > 100 mg/dL
- Hypertension defined as > 130/85 mm Hg on two or more occasion.

### Pre-diabetes

- Impaired fasting glucose, defined as: fasting blood glucose of 100 mg/dL to 125 mg/dL
- Impaired glucose tolerance, defines as: 2 hour plasma glucose of 140 mg/dL to 199 mg/dL

### Diabetes

- Symptoms of diabetes (polyuria, polydipsia, unexplained weight loss) and a casual blood glucose of 200 mg/dL or higher
- Fasting blood glucose of 126 mg/dL or higher
- 2-hour blood glucose of 200 mg/dL or higher during oral glucose tolerance test (75gm glucose load)

## Insulin Resistance

While a complete understanding of the underlying mechanism and pathophysiology of insulin resistance is unknown, it involves defects or deficiencies in insulin-signaling pathways or the molecular communications that take place at the cellular level. These pathways are responsible for the movement or transport into the cell. Defects in insulin-signaling pathways within the cell are a major cause of insulin resistance.

Researchers are better understanding the role of obesity and excess fat accumulation in the development of the metabolic syndrome, insulin resistance and Type 2 diabetes. Patients who consume a high-fat diet combined with a sedentary life-style produce greater amounts of adipose tissue, which is used to store fat. Adipose tissue can produce various hormones and cytokines such as tumor necrosis factor-alpha and interleukin-6, which have the potential to produce detrimental metabolic and inflammatory effects.<sup>4</sup> Some of these cytokines promote vascular inflammation and cause the release of free-fatty acids, which in turn impairs the ability of insulin to assist the cell in moving and metabolizing glucose. Free fatty acids also have a detrimental effect on the anti-inflammatory actions of nitric oxide, which is important in maintaining normal vascular health and endothelial function.

The metabolic consequences, such as insulin resistance, induced by obesity are not the only harmful effects of excess weight gain. Inhibition of anti-inflammatory actions, as a result of increased free-fatty acids in the circulation, also causes endothelial dysfunction and an increased risk for thrombus formation.<sup>5</sup> Not only does obesity result in insulin resistance, but it also has direct links to pro-inflammatory processes that increases the risk of thrombotic events such as stroke or myocardial infarction. In addition, patients who are obese often accumulate and store fat in other tissues of the body such as the liver, heart and pancreas. This excess fat may cause organ dysfunction.

## **Complications of Diabetes**

The long term objective for treating diabetes is to reduce complications of the disease, which result from high blood glucose levels. There are both microvascular and macrovascular complications associated with the disease. Microvascular disease affects the small vessels of the eyes, kidneys and nerves. Macrovascular disease involves the large vessels of the body, such as the coronary arteries, carotid arteries, renal arteries, and the femoral and popliteal arteries.

### **■ Retinopathy**

As a result of the high circulating glucose concentrations, abnormal blood vessels can develop and leak blood into the center of the eye resulting in blurred vision. Known as proliferative retinopathy, it is the most advanced stage of the disease. Fluid can leak out of damaged blood vessels into the center of the macula, the part of the eye that controls sharp, straight-ahead vision. The fluid causes the macula to swell, leading to blurred vision. This condition, called macular edema, can occur at any stage of diabetic retinopathy.

Diabetic retinopathy is the leading cause of blindness in the United States for working-age adults.<sup>6</sup> Estimates suggest that by the time patients are diagnosed with Type 2 diabetes as many as 20 percent already have some type of retinopathy. Over a lifetime of living with diabetes as many as 70 percent of patients will develop retinopathy.<sup>6</sup>

### **■ Nephropathy**

Damage to the glomerulus of the kidney is a result of high blood glucose levels and uncontrolled hypertension. As kidney function declines, small amounts of albumin appear in the urine. This is known as microalbuminuria.<sup>7</sup> As diabetic nephropathy progresses, an increasing numbers of glomeruli are destroyed and kidney function is further reduced. Greater amounts of albumin will appear in the urine causing macroalbuminuria. Diabetic nephropathy is one of the most common causes of end-stage renal disease and the need subsequent need for dialysis.

### **■ Neuropathy**

Diabetic neuropathy is a result of damage to nerve cells by high circulating blood glucose levels. Symptoms commonly include tingling of the legs and feet. Continued uncontrolled diabetes can lead to worsening symptoms and loss of sensation. With the loss of sensation, infections often go undetected and untreated by patients. Wound healing also is impaired. Serious lower limb infections are common in patients with uncontrolled diabetes. The rate of amputation for people with diabetes is estimated to be ten times higher than for people without diabetes. The symptoms of diabetic neuropathy respond to improved glycemic control.

### **■ Cardiovascular Disease**

Hyperglycemia, combined with hypertension, dyslipidemia, and impaired vascular function, are all major contributors to thrombus formation resulting in cardiovascular disease or stroke. Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes. Based on the latest national guidelines and recommendations, diabetes is considered a risk equivalent for cardiovascular disease.<sup>3</sup> Patients with diabetes are at the same risk of cardiac events as those with a history of myocardial infarction or ischemia. Cardiac disease and stroke account for about 65 percent of deaths in patients with diabetes. The rate of heart disease deaths in patients with diabetes is about two to four times higher than those without diabetes.<sup>8</sup> Men are at greater risk for cardiovascular disease than women. However, women with diabetes have the same risk for cardiovascular disease as men with diabetes.

## Drug Therapy for Type 2 Diabetes

The primary strategy for reducing the long term complications of diabetes is effective glycemic control without placing the patient at risk for hypoglycemia. Since hemoglobin A1c is a better measure of long term glucose control rather than individual fasting blood glucose, the American Diabetes Association (ADA) uses hemoglobin A1c as the primary indicator of effective glycemic control.<sup>9,10</sup> The hemoglobin A1c goal established by the ADA is <7 percent.<sup>2</sup>

Lifestyle modifications are normally the first step in treating Type 2 diabetes. These include diet, weight management and exercise. Most patients also require oral antidiabetic agents. Currently, five types of oral agents are used to treat Type 2 diabetes. The types of oral agents, along with newer injectable agents, are listed in Table 3.

Hemoglobin A1c	< 7%*
Fasting blood glucose	90 to 130 mg/dL
Peak postprandial blood glucose	< 180 mg/dL
Blood pressure	< 130/80 mm Hg
LDL-Cholesterol	< 100 mg/dL**
Triglycerides	< 150 mg/dL
HDL-Cholesterol	> 40 mg/dL
*A1c goal for individual patients is an A1c level as close to normal (< 6%) without significant hypoglycemia. **patients with known cardiovascular disease should achieve an LDL goal of < 70 mg/dL.	

**Table 3. Oral and Injectable Agents Used in the Treatment of Type 2 Diabetes**

<b>Class</b>	<b>Mechanism</b>
<b>Oral Agents</b>	
<b>Sulfonylureas</b> glipizide (Glucotrol <sup>®</sup> ), glyburide (Micronase <sup>®</sup> , Glynase <sup>®</sup> , and Diabeta <sup>®</sup> ), and glimepiride (Amaryl <sup>®</sup> )	Increases insulin secretion from the pancreas.
<b>Meglitinides</b> repaglinide (Prandin <sup>®</sup> ) and nateglinide (Starlix <sup>®</sup> )	Increases insulin secretion from the pancreas.
<b>Biguanides</b> metformin (Glucophage <sup>®</sup> )	Decreases hepatic glucose production, intestinal absorption of glucose, improves insulin sensitivity and increases skeletal muscle uptake of glucose.
<b>Thiazolidinediones</b> pioglitazone (Actos <sup>®</sup> ) and rosiglitazone (Avandia <sup>®</sup> )	Increases insulin sensitivity, thereby reducing insulin resistance. <ul style="list-style-type: none"> <li>• glucose uptake in insulin sensitive tissue</li> <li>• hepatic glucose production</li> </ul>
<b>α-Glucosidase inhibitors</b> acarbose (Precose <sup>®</sup> ) and miglitol (Glyset <sup>®</sup> )	Slows carbohydrate absorption from the intestine.
Dipeptidyl Peptidase (DPP-4) Inhibitors	By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagons levels in the circulation in a glucose-dependent manner
<b>Injectable Agents</b>	
Exenatide (Byetta <sup>®</sup> )	Enhances glucose dependent insulin secretions, suppresses elevated glucagon secretions and slows gastric emptying (the rate at which food is released from the stomach to the small intestine).
Pramlintide (Symlin <sup>®</sup> )	A synthetic analogue of the hormone amylin which slows gastric emptying, suppresses glucagons secretion and modulates appetite.

## Oral Antidiabetic Agents

### ■ Sulfonylureas

Sulfonylureas were the mainstay in the treatment of diabetes. Prior to the introduction of metformin, sulfonylureas were the only oral treatments available for Type 2 diabetes. This class of oral antidiabetic agents causes an increase in insulin secretion in the beta cells of the pancreas. Therefore, some functioning beta cells in the pancreas must be present for these agents to be effective. Sulfonylureas are long acting and as a result, the risk of hypoglycemia is a concern. These drugs will continue to be widely used for treating diabetes, but newer agents with more targeted mechanisms of action will play an increasingly important role in diabetes management.

### ■ Meglitinides

Repaglinide (Prandin®) and nateglinide (Starlix®) are structurally unrelated to the sulfonylureas, although they all have similar clinical effects of increasing insulin secretion from the pancreas. As with the sulfonylureas, functioning beta cells must be present. However, these drugs are shorter acting. The extent of insulin secretion produced by these agents is glucose dependent and will decrease as glucose levels decrease. Meglitinides should be taken with meals. The overall risk of hypoglycemia while taking the meglitinides may be lower than that seen with the sulfonylureas.

### ■ Biguanides

Metformin (Glucophage®) is a biguanide that lowers blood glucose levels by reducing hepatic glucose production and enhancing insulin-mediated glucose uptake by skeletal muscle. Metformin is not associated with hypoglycemia but can be associated with bloating, nausea, intestinal cramping and diarrhea. The likelihood of patients experiencing gastrointestinal effects can be reduced by taking the medication with food; starting with a low dose; using a slow up-titration schedule; and using the sustained release form of the drug. A rare but serious effect of metformin is lactic acidosis. Most cases of metformin-associated lactic acidosis are related to underlying renal impairment.<sup>11</sup>

Metformin is associated with beneficial effects on triglycerides and LDL-Cholesterol.<sup>11</sup> Significant reductions in myocardial infarctions, cardiovascular deaths and overall mortality in obese Type 2 diabetic patients have also been demonstrated in patients treated with metformin as compared to other treatments.<sup>12</sup>

### ■ Alpha-Glucosidase Inhibitors

Alpha-glucosidase is an enzyme found in the small intestine. Along with other enzymes, it is responsible for the hydrolysis and digestion of carbohydrates. Acarbose (Precose®) and Miglitol (Glyset®) inhibit the enzyme, and thus reduce the rate of complex carbohydrate digestion and absorption of glucose. This has the effect of lowering postprandial glucose levels in patients with diabetes.<sup>13</sup> If meals are missed, the drugs should not be taken at that time. Similar to metformin, these drugs may cause flatulence, diarrhea and abdominal discomfort.

### ■ Thiazolidinediones

Thiazolidinediones (TZD), Pioglitazone (Actos®) and Rosiglitazone (Avandia®) are insulin sensitizers that lower blood glucose by enhancing the action of insulin and reducing insulin resistance. Acting on muscle tissue, they increase insulin-stimulated glucose utilization. They also affect the liver, by decreasing excessive hepatic glucose production. These drugs lower blood glucose levels, reduce blood pressure and microalbuminuria, and increase HDL-C concentrations. Pioglitazone has been shown to reduce the risk of all-cause death, stroke and myocardial infarction in diabetic patients with pre-existing cardiac events.<sup>14,15</sup>

Liver function testing is recommended for patients receiving taking thiazolidinediones followed by periodic evaluations. Other adverse effects associated with thiazolidinediones may include edema and weight gain, which may worsen underlying heart disease. These drugs are not indicated for patients with New York Heart Association Class III or IV congestive heart failure.

## ■ Dipeptidyl Peptidase (DPP-4) Inhibitors

DPP-4 exists as both a membrane-associated and circulating enzyme. This enzyme is widely distributed in numerous tissues in the membrane-associated form. DPP-4 inactivates several forms of the incretin hormones. By halting the inactivation of the incretin hormones, drugs in this class work to extend the hypoglycemic effect via stimulation of insulin secretion from the islet beta cells<sup>16,17</sup> Therefore, these agents should only be used in Type 2 diabetes.

Currently, sitagliptin (Januvia™), is the only DPP-4 inhibitor available. It has been approved for use in Type 2 diabetic monotherapy or in combination with metformin or a thiazolidinedione. Sitagliptin may be taken with or without food. Dosage adjustment is required for patients with renal insufficiency. Before initiating therapy, patients should have a renal assessment. The most common reported adverse reactions were nasopharyngitis, upper respiratory tract infection, and headache. Other side effects include abdominal pain, nausea and diarrhea. In early studies some patients also experienced a small increase in neutrophil count.<sup>18</sup>

## Injectable Antidiabetic Agents: Non-insulin

In addition to oral therapy, there are currently two injectable medications available to patients with Type 2 diabetes. These agents are not a form of insulin, but rather work with insulin and oral antidiabetic medications to lower and control elevated blood glucose levels.

### ■ Exenatide

Exenatide (Byetta®) a relatively new injectable agent that helps control hyperglycemia in several ways. This drug is a synthetic peptide whose structure closely resembles the naturally occurring human enteric incretin hormone, a glucagon-like-peptide-1 (GLP-1). Exenatide enhances glucose dependent insulin secretions, while suppressing elevated glucagon secretions. By slowing gastric emptying, the drug causes carbohydrate metabolism to be extended over time. This, in turn, reduces the large spikes of glucose resulting after ingestion of a meal. This agent is currently indicated for use in Type 2 diabetic patients who are not currently controlled with sulfonylureas or metformin. There is an increased risk of hypoglycemia when exenatide is combined with sulfonylureas. The drug is given twice daily as a subcutaneous injection. It should not be used in patients with renal failure or severe gastroparesis.<sup>19</sup>

### ■ Pramlintide

Pramlintide (Symlin®) is a synthetic analogue of the hormone amylin, which slows gastric emptying, suppresses glucagons secretion and modulates appetite. Pramlintide is currently indicated for use in Type 2 diabetes as an adjunct treatment in patients who use mealtime insulin therapy and have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin. The drug is also indicated for Type 1 diabetes as an adjunct treatment in patients who use mealtime insulin therapy and have failed to achieve desired glucose control despite optimal insulin therapy.

Mealtime insulin doses must be reduced by 50 percent when starting pramlintide. The drug should not be used in patients with severe gastroparesis. Pramlintide is given as a subcutaneous injection prior to each meal.<sup>20</sup>

## Subcutaneous Insulin Products

Despite the many oral treatments and new injectable agents available, many patients with Type 2 diabetes require insulin therapy to effectively control their hyperglycemia.

Currently, there are various insulin products available for subcutaneous injection, see Table 4. These products are either of human [rDNA] or animal (porcine) origin. Insulin is available in a wide variety of types based on their action. Insulin lispro, insulin aspart, and insulin glulisine are rapid-acting human insulin analogs made from recombinant [rDNA] technology. Regular human insulin is also made using [rDNA] technology, however, it is a short-acting insulin. NPH human insulin and lente human insulin are intermediate-acting insulins. The long-acting insulins glargine, detemir and ultralente are all of human origin as well. Insulin is also available in premixed formulations combining an intermediate-acting insulin with either a rapid- or short-acting insulin. Regular human insulin, NPH human insulin, lente human insulin, ultralente human insulin, and premixed products combining NPH and regular insulin are available to patients over the counter.

In addition to the various types of subcutaneous insulin, there is also an assortment of dosage forms, including vials, pens and cartridges. Rapid-acting insulin, short-acting insulin, insulin glargine and insulin detemir are clear solutions, whereas the NPH, lente, ultralente and premixed combination products are suspensions. It is possible that certain types

of insulin can be mixed in a single syringe as an added convenience for patients who are taking more than one type of insulin. However, this is not the case for all insulin types due to physiochemical changes that may occur as a result of mixing. Clinicians and patients should be advised that due to a delay in onset of action of the short-acting insulin, it is not recommended that short-acting insulin and lente/ultralente insulins be mixed. Lente/Ultralente insulins also should not be mixed with NPH due to the possible precipitation of zinc phosphate and the conversion of the longer-acting insulin to a shorter-acting insulin. Insulin glargine should not be mixed with any other insulin. Regular insulin is compatible with NPH insulin and can be mixed in the same syringe. Rapid-acting insulins like lispro, aspart and glulisine, can be mixed with NPH, lente, or ultralente insulin, but once combined, the mixture must be injected within 15 minutes before a meal.

Dosing of insulin is individualized and based on the patient's weight. The dose of insulin should also take into account the patient's dietary habits and physical activity. Once the initial dose is determined, the patient must be counseled on the proper way to administer an insulin injection. Prior to administering the insulin injection, the insulin product should be inspected for clumping, frosting, precipitation, or changes in color or clarity. Insulin should be gently rolled between the hands not only to warm the chilled product to room temperature, but also to ensure that those insulin products in suspension form are properly mixed. In addition to warming the insulin to room temperature, pain upon administration of an insulin injection also can be reduced by ensuring that alcohol used to clean the injection site has completely evaporated, penetrating the skin with the needle quickly, not changing the direction of the needle during its insertion or withdrawal, and not reusing needles. If two different types of insulin must be mixed, the short or rapid-acting insulin should always be drawn up into the syringe first to prevent contamination with the longer-acting insulin.

Once the insulin has been drawn into the syringe, it should be administered immediately. Rapid-acting insulin should be injected within 10-15 minutes of eating a meal. Short-acting insulin should be injected within 30 minutes of eating a meal. Insulin may be administered in a wide variety of sites on the body, including the upper arm, the anterior and lateral aspects of the thigh, buttocks, and abdomen. The abdomen has the fastest rate of absorption. To prevent lipodystrophy or lipohypertrophy, the injection site should be rotated.

Common side effects of insulin are hypoglycemia and weight gain. Patients should be advised to self-monitor their blood glucose levels at home and counseled on how to recognize and treat an episode of hypoglycemia. The American Diabetes Association recommends that all patients on insulin therapy wear a medical alert bracelet. Unopened vials of insulin should be refrigerated. Used insulin vials may be refrigerated or kept at room temperature.<sup>21</sup>

## Inhaled Insulin Products

The first inhaled powder form of insulin is now available. Exubera<sup>®</sup> is human insulin produced by recombinant [rDNA] technology. In Type 2 diabetes it may be used alone or in combination with oral antidiabetic agents or a long-acting insulin. However, in Type 1 diabetes, it always must be used in conjunction with a long-acting insulin. Exubera<sup>®</sup> has an onset of action similar to rapid-acting insulin (~10-15 minute) and a duration of action similar to short-acting insulin (~6 hours). Like subcutaneous insulin, the initial pre-meal dose of this product is primarily based on the patient's weight.

Exubera<sup>®</sup> is contraindicated in patients who smoke, patients who have discontinued smoking within the past 6 months, or patients with unstable or poorly controlled lung disease. If a patient begins or resumes smoking while taking Exubera<sup>®</sup>, this medication must be discontinued immediately. All patients should have their pulmonary function assessed prior to initiating therapy with Exubera<sup>®</sup>. Assessment of pulmonary function is also recommended after the first six months of therapy and annually thereafter. The most common non-respiratory adverse reactions are hypoglycemia, chest pain, and dry mouth. Cough, dyspnea, and reduced pulmonary function are the most common respiratory adverse reactions.

The inhaler should be replaced one year from the date of its first use. A powder release unit must be changed every two weeks.<sup>22, 23</sup>

## Combination Therapy

In many patients a combination therapy of oral or oral agents with insulin may be necessary to maintain optimal glucose levels. In general, oral agents with different mechanisms of action should be combined and not substituted for one another. The dose of oral agents may need to be decreased if insulin is added or oral agents may need to be discontinued altogether.

Fixed dose formulations of combination oral products are becoming more common on the market. These products may increase patient adherence if a fixed dose combination is appropriate. The risk of hypoglycemia increases, however, when oral agents are combined or used with insulin.

Table 4. Available Insulin Therapies	Brand Name	Availability	Onset (hrs)	Peak (hrs)	Duration *(hrs)	Additional Information
<b>Rapid-acting</b>						
Lispro	Humalog	RX	0.25	0.5 – 2.5	3.5 - 5	Should be injected within 15 minutes before a meal; Can be used in insulin pumps
Aspart	Novolog	RX	<0.25	1 - 3	3 - 5	Should be injected immediately before a meal; Can be used in insulin pumps
<b>Short-acting</b>						
Glulisine	Apidra	RX	<0.25	0.5 - 1.5	3 - 5	Can be used in insulin pumps
Regular	Humulin R, Novolin R	RX/OTC	0.5	1 - 3	6 - 8	Should be injected 30-60 minutes before a meal; Can be used in insulin pumps
<b>Intermediate-acting</b>						
NPH	Humulin N, Novolin N	OTC	2 - 4	4 - 12	18 - 26	
Lente	Humulin L, Novolin L	OTC	2 - 4	6 - 12	18 - 26	
<b>Long-acting</b>						
Detemir	Levemir	RX	1	No peak	24	Should not be mixed with other insulins; Should not be used in insulin pumps
Ultralente	Humulin U	RX	4 - 8	10 - 30	>36	
Glargine	Lantus	RX	1.1	No peak	>24	Should not be mixed with other insulins
<b>Combination</b>						
Lispro protamine w/ insulin lispro	Humalog Mix 75/25, 50/50	RX	<0.25	0.5-1	16-24	Should be dosed within 15 minutes of a meal; Longer duration than insulin lispro
Aspart protamine w/ insulin aspart	Novolog Mix 70/30	RX	<0.25	1 - 4	24	Should be dosed within 15 minutes of a meal; Longer duration than insulin aspart
Regular w/ NPH	Humulin 70/30, 50/50 Novolin 70/30, 50/50	OTC	0.5 - 1	2 - 12	14 - 18	A mixture of NPH human insulin & regular human insulin
<b>Inhaled</b>						
* All insulin products in this table are of human origin.	Exubera®	RX	0.25	2	6	Pulmonary function must be assessed prior to initiation of therapy
	[Insulin human (rDNA origin)]					

## Guidelines for the Treatment of Diabetes

Current published guidelines for the treatment of Type 2 diabetes are noted in Table 5. These guidelines suggest monotherapy with metformin as the first step in therapy along with lifestyle modifications. Secondary oral agents or insulin are then recommended. An algorithm for treatment based on A1C levels is reproduced in Table 6.

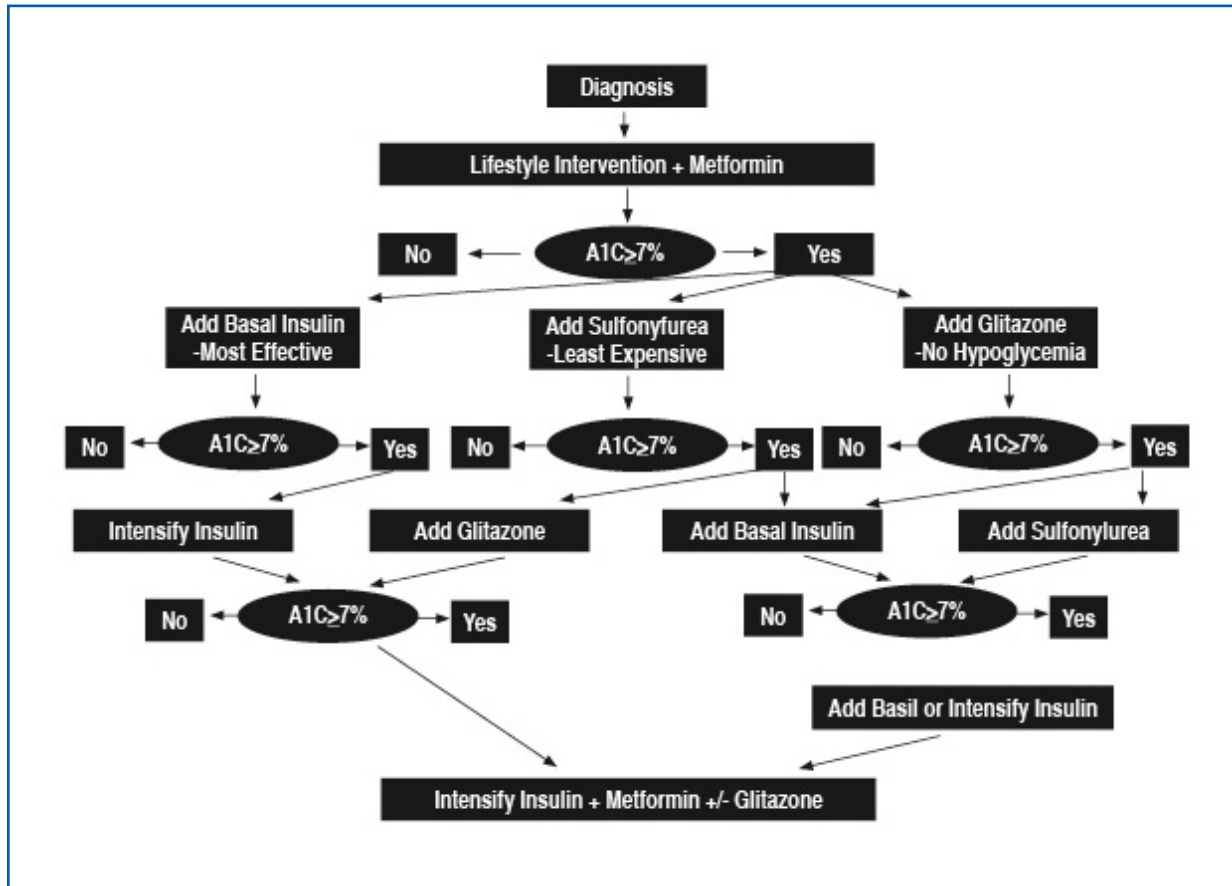
**Table 5: Management of hyperglycemia in Type 2 diabetes. Summary of antidiabetic interventions as monotherapy<sup>24</sup>**

<b>Interventions</b>	<b>Expected decrease in A1C (%)</b>	<b>Advantages</b>	<b>Disadvantages</b>
<b>Step 1: Initial Therapy</b>			
Lifestyle to decrease weight and increase activity	1–2	Low cost, many benefits	Fails for most in 1st year
Metformin	1.5	Weight neutral, inexpensive	GI side effects, rare lactic acidosis
<b>Step 2: Additional Therapy</b>			
Insulin	1.5–2.5	No dose limit, inexpensive, improved lipid profile	Injections, monitoring, hypoglycemia, weight gain
Sulfonylureas	1.5	Inexpensive	Weight gain, hypoglycemia*
TZDs	0.5–1.4	Improved lipid profile	Fluid retention, weight gain, expensive
<b>Other drugs</b>			
Glucosidase inhibitors	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Exenatide	0.5–1.0	Weight loss	Injections, frequent GI side effects, expensive, little experience
Meglitinides (Glinides)	1–1.5	Short duration	Three times/day dosing, expensive
Pramlintide	0.5–1.0	Weight loss	Injections, three times/day dosing, frequent GI side effects, expensive, little experience.

\*Severe hypoglycemia is relatively infrequent with sulfonylurea therapy. The longer acting agents (e.g. chlorpropamide, glyburide, glibenclamide, and sustained-release glipizide) are more likely to cause hypoglycemia than glipizide, glimepiride and gliclazide.

*Reproduced from Management of Hyperglycemia in Type 2 diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy.<sup>24</sup>*

**Table 6 –Algorithm for Management of Type 2 diabetes based on A1C levels**



*Reproduced from Management of Hyperglycemia in Type 2 diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy.<sup>24</sup>*

## Management and Prevention of Complications Associated with Diabetes

### ■ Blood Pressure Control

Maintaining optimal blood glucose levels is not the only goal of managing diabetes. Controlling blood pressure and lipid levels is essential to the overall management of diabetes. It has been estimated that for every 10 mm Hg increase in systolic blood pressure, patients with diabetes may have as high as a 15 percent increased risk of a coronary events.<sup>25</sup>

Blood pressure control is the objective of treating hypertension in all patients but is critical for the diabetic patient. Controlling blood pressure provides protection from endothelial vascular damage and spares renal function. As a result of the protective effects on renal function and reduction in proteinuria demonstrated with Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs), these drugs have become the drug of choice in treating hypertension for patients with diabetes.<sup>24</sup> Many practitioners are treating patients who have diabetic proteinuria, with or without hypertension, with ACEIs or ARBs in an attempt to slow the progression of diabetic nephropathy.

Patients with diabetes often may require two or more antihypertensives to achieve target blood pressure goals.<sup>25</sup> Combination therapy may include diuretics with ACEIs or ARBs, or beta-blockers, and calcium channel blockers (CCBs) combined with ACEIs or ARBs.

### ■ Lipids

The presence of diabetes is considered equal to having a history of coronary heart disease (CHD) with respect to the risk of coronary events or stroke.<sup>3</sup> Patients with diabetes face the same risk of experiencing a primary event as patients with CHD face with developing a secondary event.

Patients with Type 2 diabetes usually have slightly elevated LDL-cholesterol levels, low HDL-cholesterol and high triglycerides. Current guidelines suggest that diabetic patients should be managed aggressively with target LDL-cholesterol levels under 100 mg/dL and as low as 70 mg/dL.<sup>3</sup>

## ■ Aspirin Therapy

The American Diabetes Association recommends aspirin therapy (75 to 162 mg/day) as a primary prevention for patients with Type 2 diabetes who are at increased risk for cardiovascular events and for those older than 40 with a family history of cardiovascular disease, hypertension, smoking or dyslipidemia.<sup>26</sup> Aspirin is recommended as a secondary prevention strategy for those with a history of coronary heart disease, peripheral vascular disease or claudication.<sup>27</sup>

## Conclusion

Type 2 diabetes can be treated successfully through aggressive control of blood glucose, hypertension, and lipid levels. While both microvascular and macrovascular complications are associated with Type 2 diabetes, the macrovascular or cardiovascular complications account for the majority of morbidity and mortality in those patients. Treating hypertension and dyslipidemia are as critical as treating hyperglycemia in patients with Type 2 diabetes. Specific drug therapies are available that promote insulin secretion and reduce insulin resistance. Many patients require insulin therapy for adequate control and many options for insulin therapy are now available. Multiple drug therapies along with lifestyle changes are often needed to manage Type 2 diabetes and reduce the risk of complications.

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## Post Test Questions

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Health Information Designs, Inc.  
213 West Main Street, Suite 204  
City Center Building  
Salisbury, Maryland 21801

*Circle your answer to each question below.*

- According to the Centers for Disease Control (CDC), diabetes affects what percent of the population?
  - 90 %
  - 20%
  - 7%
  - 14%
- In screening for Type 2 diabetes, a patient with a fasting glucose of 190 mg/dl and a 2-hour oral glucose tolerance test of 300 mg/dl would probably be diagnosed with which condition?
  - Hypertension
  - Pre-diabetes
  - Metabolic Syndrome
  - Diabetes
- Insulin resistance involves which of the following?
  - Defects in insulin-signaling pathways of the molecular communications that take place at the cellular level.
  - Defects in the inhibition of the enzyme that decreases cholesterol synthesis.
  - Defects in the body's natural ability to enhance the immune system's fight against infection and disease.
  - All of the above.
- Which complications are associated with Type 2 diabetes?
  - Retinopathy
  - Neuropathy
  - Cardiovascular disease
  - All of the above
- What is the primary strategy for reducing the incidence of long term complications associated with diabetes?
  - Effective glycemic control without placing the patient at risk of hypoglycemia
  - Maintaining all blood glucose levels at or below 70 mg/dl
  - Monitoring patient for complications associated with Type 2 diabetes
  - Meet recommended intakes within energy needs by adopting a balanced eating pattern.
- The ADA goals for Diabetes Therapy include all of the following EXCEPT?
  - Maintaining a hemoglobin A1c of less than or equal to 7 percent.
  - Maintaining a caloric intake of 2000-2600 calories per day.
  - Maintaining a fasting blood glucose of 90 to 130 mg/dl.
  - Maintaining blood pressure at 130/80 mm Hg.
- Which oral antidiabetic agents increase insulin secretion from the pancreas when functioning beta cells are present?
  - glyburide and exantatide
  - glipizide and repaglinide
  - acarbose and rosiglitazone
  - Pramlintide and Exenatide
- Side effects associated with Metformin therapy include which of the following?
  - Bloating
  - Lactic acidosis
  - Intestinal cramping and diarrhea
  - All of the above
- Which antidiabetic oral drug slows carbohydrate absorption from the tissues by inhibiting the activity of the enzyme responsible for carbohydrate hydrolysis and digestion.
  - miglitol
  - acarbose
  - Only A
  - Both A and B
- Which antidiabetic oral drug acts to enhance the action of insulin and reduces insulin resistance as well as reduces microalbuminuria.
  - Pioglitazone
  - Repaglinide
  - Glimepiride
  - Both A and C
- Exenatide helps to control hyperglycemia by which of the following actions?
  - Increases insulin secretion from the pancreas
  - Elevates glucagon secretions
  - Enhances glucose dependent insulin secretions and suppresses elevated glucagon secretion
  - Speeds up gastric emptying which leads to a shorter period of time for carbohydrate metabolism.
- Which patient specific parameter should be used to determine the dose of insulin
  - Weight of the patient

- B. Physical activity of the patient
- C. Dietary habits of the patient.
- D. All of the above.

13. Exubera®, the inhaled powder form of insulin, has an onset of action similar to \_\_\_\_\_ insulin; and a duration of action similar to short-acting insulin.
- A. Long-acting (around 1 to 8 hours)
  - B. Intermediate acting ( around 2 to 4 hours)
  - C. Rapid-acting (around 10 to 15 minutes)
  - D. Short-acting (around 30 minutes)

14. Current guidelines for the management of hyperglycemia in Type 2 diabetics recommend which course of action as initial therapy?
- A. Decrease weight
  - B. Metformin therapy
  - C. All of the above
  - D. A only

15. A patient who has failed to achieve a Hemoglobin A1c of < 7 after adequate trial of lifestyle interventions, metformin therapy and sulfonylurea, should receive which additional therapeutic approach?
- A. A basal insulin and pioglitazone or rosiglitazone
  - B. A second sulfonylurea
  - C. Discontinue metformin
  - D. All of the above

16. It has been estimated that for every \_\_\_ mm Hg increase in systolic blood pressure, the diabetic patient may have as high as a \_\_\_% increased risk of a coronary event.
- A. 30; 1

- B. 10; 15
- C. 50; 2
- D. 100; 1

17. Blood pressure control in the diabetic patient provides protection from which of the following?
- A. Endothelial vascular damage
  - B. Renal impairment
  - C. All of the above
  - D. None of the above

18. Patients with diabetes have the similar risk of experiencing a primary coronary event as patients with which medical condition?
- A. Coronary heart disease
  - B. Mitral valve prolapse
  - C. Peripheral neuropathy
  - D. Arteriovenous fistulas

19. Diabetic patients usually have which of the following lab findings?
- A. Slightly elevated HDL
  - B. Slightly low LDL
  - C. High HDL
  - D. Slightly elevated LDL

20. Maintaining optimal blood glucose control levels is not the only goal of managing diabetes, an optimized management plan will include which of the following?
- A. Blood pressure control
  - B. Lipid level control
  - C. Secondary prevention for cardiovascular events with aspirin
  - D. All of the above

## ANSWER FORM

- |                |                |                 |                 |                 |
|----------------|----------------|-----------------|-----------------|-----------------|
| 1. a. b. c. d. | 5. a. b. c. d. | 9. a. b. c. d.  | 13. a. b. c. d. | 17. a. b. c. d. |
| 2. a. b. c. d. | 6. a. b. c. d. | 10. a. b. c. d. | 14. a. b. c. d. | 18. a. b. c. d. |
| 3. a. b. c. d. | 7. a. b. c. d. | 11. a. b. c. d. | 15. a. b. c. d. | 19. a. b. c. d. |
| 4. a. b. c. d. | 8. a. b. c. d. | 12. a. b. c. d. | 16. a. b. c. d. | 20. a. b. c. d. |

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**Department of Health and Mental Hygiene**  
**Maryland Medicaid Pharmacy Program**  
Division of Clinical Pharmacy Services

**Continuing Education Evaluation Form**

Program Number MD-2007-20-003

1. Practice: years since graduation \_\_\_\_\_ employment \_\_\_\_\_ title \_\_\_\_\_

2. Please circle the number that best describes your response (one is poor or negative, five is excellent or positive), and make any comments if desired.

a. Overall evaluation of the seminar \_\_\_\_\_  
1   2   3   4   5 \_\_\_\_\_

b. Did the program meet the objectives? \_\_\_\_\_  
1   2   3   4   5 \_\_\_\_\_

c. Applicability and usefulness to your practice. \_\_\_\_\_  
1   2   3   4   5 \_\_\_\_\_

d. Usefulness of handout and other audio-visual materials \_\_\_\_\_  
1   2   3   4   5 \_\_\_\_\_

3. Was the internet access to the continuing education convenient for you?  
Yes \_\_\_\_\_ No \_\_\_\_\_

4. What did you like the most about this continuing education program? \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

5. What did you like the least? \_\_\_\_\_  
\_\_\_\_\_

6. Other topics and/or speakers you would like the Maryland Medicaid Pharmacy Program to provide  
\_\_\_\_\_  
\_\_\_\_\_

7. Final Comments: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_