



Diabetes: Overview, Diagnosis, and Management for Healthcare Professionals

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Purpose

The purpose of this course on diabetes is to educate healthcare professionals on the symptoms, course, and management of diabetes. The course contains useful information on vulnerable population groups and treatment options.

Learning Objectives

After successful completion of this course, you will be able to:

1. Identify two risk factors for pre-diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and diabetes
2. Describe the pathophysiology of type 1 and type 2 diabetes
3. Describe the pathophysiology of DKA and HHS
4. Identify two tools for monitoring treatment therapies
5. Describe current medications, use, side effects, and outcomes in the treatment of diabetes
6. Summarize current standards of care for patients with diabetes
7. List two lifestyle recommendations for patients at risk for diabetes

Introduction

Diabetes mellitus, commonly referred to as diabetes, is a chronic illness that requires lifelong and ongoing medical evaluation. It is a group of diseases resulting from defects in insulin production, insulin action, or both (Centers for Disease Control and Prevention [h], 2017). It is one of the oldest diseases known, described by the ancient Greeks as early as 100 AD. The word “diabetes” originates from the ancient Greek word for “flow-through,” and since two of the most common symptoms of diabetes are extreme thirst and a need to urinate frequently, the name seems very appropriate (Mandal, 2019).

Prevalence of Diabetes

The effects of diabetes exert a tremendous strain on individuals, families, and the economy.

According to recent statistics from the CDC (2018a & b):

- Diabetes affects 30.3 million people, equivalent to 9.4% of the U.S. population
- 7.2 million people were unaware that they had diabetes
- Among U.S. residents aged 65-74 years, 22.1% had diabetes and 21.2% had diabetes of those aged 74 years and older
- About 193,000 people younger than 20 years had diabetes (type 1 or type 2) in the United States in 2015
- About 1.4 million people aged 18 years or older were newly diagnosed with diabetes in the United States in 2015
- Over the past 35 years, from 1980 through 2015, the number of adults with diagnosed diabetes in the United States nearly quadrupled, from 5.5 million to 21.3 million.

What is Diabetes?

Diabetes is a metabolic disorder that can result in serious consequences no matter which type of diabetes has been diagnosed. It doesn't matter if diabetes developed during pregnancy (gestational diabetes), was acquired later in life (type 2), was diagnosed at birth, or discovered early on as a young child.

Regardless of when it started, the person with diabetes will have a metabolic system that is unable to process glucose effectively from the bloodstream into the cells.

Result	Fasting Plasma Glucose (FPG)
Normal	less than 100 mg/dL
Prediabetes	100 mg/dL to 125 mg/dL
Diabetes	126 mg/dL or higher

(American Diabetes Association [ADA], 2016a)

Classifications of Diabetes

There are four classifications of diabetes:

1. Type 1 diabetes, previously called insulin-dependent diabetes mellitus or juvenile-onset diabetes, accounts for approximately 5% of all patients with diabetes.
2. Type 2 diabetes, previously called non-insulin-dependent diabetes mellitus or adult-onset diabetes, accounts for approximately 95% of all patients with diabetes.
3. Gestational diabetes mellitus (GDM) is a form of glucose intolerance during pregnancy. The prevalence rate is estimated at 9.2% (ADA 2016b).
4. Other types of diabetes are caused by genetic conditions or defects, surgery, medications, infections, pancreatic disease, and other illnesses. These account for approximately 1-5% of all patients with diabetes (CDC, 2018).

Symptoms

Although large amounts of glucose may be present, the diabetes metabolism is unable to process the available sugar into energy. The three primary types of diabetes each have specific symptomology.

Type 1 Diabetes:

- Polyuria
- Polydipsia
- Extreme hunger
- Unexplained weight loss
- Extreme fatigue or irritability

Type 2 Diabetes:

- Any of the type 1 symptoms
- Frequent infections
- Blurred vision
- Cuts/bruises that are slow to heal
- Tingling/numbness in the hands/feet
- Recurring skin, gum, or bladder infections

Gestational Diabetes:

- Polyuria
- Polydipsia
- Extreme hunger
- Unexplained weight loss
- Extreme fatigue or irritability

(American Diabetes Association [ADA], 2016a)

Risk Factors for Diabetes

Age 45 and older
Overweight (BMI \geq 25)
Hypertension
Abnormal lipid levels
Family history of diabetes
Race/ethnicity
History of gestational diabetes
History of vascular disease
Signs of insulin resistance
Pre-diabetes
Inactive lifestyle

(ADA, 2019; CDC, 2017)

Diagnosing Diabetes

The American Diabetes Association (2016a; 2019) recommends that testing to detect pre-diabetes and type 2 diabetes be considered in adults without symptoms, who are overweight and have one or more additional risk factors for diabetes. In those without these risk factors,

testing should begin at age 45. People younger than 45 should consider testing if they are overweight, obese or extremely obese, and have any risk factors for diabetes. If results of testing are normal, testing should be repeated at least every three years.

Frequency of Testing

Doctors may recommend more frequent testing depending on initial results and risk status. People whose test results indicate they have pre-diabetes should have their blood glucose checked again in one to two years and take steps to prevent type 2 diabetes.

When a woman is pregnant, the physician will assess her risk for developing gestational diabetes at her first prenatal visit. If she is at risk for developing GD, a Glucose Tolerance Test (GTT) is usually ordered between 24 to 28 weeks gestation. Women who develop GD should also have follow-up testing 6 to 12 weeks after the baby is born. The American Diabetes Association suggests the following targets for women who develop gestational diabetes during pregnancy. More or less stringent glycemic goals may be appropriate for each individual.

- Before a meal (pre-prandial): 95 mg/dL or less
- 1-hour after a meal (postprandial): 140 mg/dL or less
- 2-hours after a meal (postprandial): 120 mg/dL or less

(ADA, 2016b)

Pre-Diabetes

Pre-diabetes is higher than normal blood glucose, but not high enough to be classified as diabetes. There is an increased risk for type 2 diabetes and cardiovascular disease. Pre-diabetes is associated with obesity, dyslipidemia, and hypertension.

Pre-diabetes is identified when a patient's blood glucose level is higher than normal but not significantly high enough to be type 2 diabetes. People with pre-diabetes are more likely to develop type 2 diabetes within ten years, and may have some symptomology from diabetes already.

Pre-Diabetes Screening Tests

Pre-diabetes screening tests include:

Fasting Plasma Glucose Test (FPG)

This test checks fasting blood glucose levels where patients cannot have anything to eat or drink (except water) for at least eight hours before the test. This test is usually done first thing in the morning, before breakfast.

- Diabetes is diagnosed as fasting blood glucose of greater than or equal to 126 mg/dL

Result	Fasting Plasma Glucose (FPG)
Normal	less than 100 mg/dL
Prediabetes	100 mg/dL to 125 mg/dL
Diabetes	126 mg/dL or higher

Oral Glucose Tolerance Test (OGTT)

- The OGTT is a two-hour test that checks blood glucose levels before and two hours after a person drinks a special sweet solution.
- Diabetes is diagnosed at a two hour blood glucose of greater than or equal to 200 mg/dL

Result	Oral Glucose Tolerance Test (OGTT)
Normal	less than 140 mg/dL
Prediabetes	140 mg/dL to 199 mg/dL
Diabetes	200 mg/dL or higher

A1C

The A1C test measures the average blood glucose for the past two to three months. The advantages of being diagnosed this way are that the patient doesn't have to fast or drink anything.

- Diabetes is diagnosed at an A1C of greater than or equal to 6.5%

Result	A1C
Normal	less than 5.7%
Prediabetes	5.7% to 6.4%
Diabetes	6.5% or higher

Overview of Type 1 Diabetes

Type 1 diabetes is an auto-immune disease in which the body's immune system attacks and destroys the insulin-producing beta cells in the pancreas. These beta cells are the only cells that make the insulin hormone to regulate blood glucose. A diagnosis of type 1 diabetes means that these diabetics will require daily insulin to survive. This form of diabetes usually strikes children and young adults, although disease onset can occur at any age. Risk factors for type 1 diabetes may be autoimmune, genetic, or environmental. There is no known way to prevent type 1 diabetes at this time (ADA, 2016a).

Pathophysiology of Type 1 Diabetes

In type 1 diabetes the body's immune system strikes the insulin-producing beta cells in the pancreas, leaving little or no insulin in the body. Without the proper amount of insulin, the body cannot metabolize glucose and it accumulates in the blood stream, causing hyperglycemia. Hyperglycemia causes a hyperosmolarity of the blood, resulting in polyuria, and polydipsia. Marked polyuria leads to dehydration, electrolyte disturbances, and pH imbalance. If type 1 diabetes goes untreated or undiagnosed, diabetic ketoacidosis (DKA) may occur causing the person to lapse into a diabetic coma (ADA, 2016a).

Diabetic Ketoacidosis (DKA)

Diabetic ketoacidosis results from the buildup of by-products of fat breakdown, called ketones. Ketones cause the blood to become more acidic than body tissues.

When glucose is absent or is present but not available as a fuel source for the body, fat is used instead. Glucose can't be metabolized without insulin. Without insulin, blood glucose levels rise (usually greater than 250mg/dL). The liver tries to combat the problem by producing more glucose, resulting in even higher glucose levels.

It is not unusual that a first time episode of DKA may lead to an initial diagnosis of type 1 diabetes. In addition, a known type 1 diabetic can also develop DKA if they are not receiving enough insulin. It is unusual for type 2 diabetics to develop DKA, but under extreme stress it has occurred (ADA, 2015a).

Causes & Symptoms of DKA

The most common causes of DKA are:

- Infection
- Stress
- Missed insulin dose
- New onset diabetes
- Cardiovascular disease (e.g. acute myocardial infarction)

Symptoms of DKA include:

- Polyuria
- Polydipsia
- Polyphagia
- Weakness
- Rapid deep respirations (Kussmaul breathing)
- Coma
- Nausea and vomiting
- Fruity odor of breath

(ADA, 2015a)

Diagnostic Criteria for DKA

The diagnostic criteria for DKA are as follows:

Plasma glucose (mg/dL)

- >250 in diabetic ketoacidosis (DKA)

Arterial pH

- 7.25 to 7.3 in mild DKA
- 7.00 to <7.24 in moderate DKA
- <7.00 in severe DKA

Serum bicarbonate (mEq/L)

- 15 to 18 in mild DKA
- 10 to 15 in moderate DKA
- <10 in severe DKA

Urine and serum ketones

- + in DKA

Effective serum osmolality (mOsm/kg)

- variable in DKA

Anion gap (mEq/L)

- >10 in mild DKA
- >12 in moderate and severe DKA

Mental status

- alert in mild DKA
- alert/drowsy in moderate DKA
- stupor/coma in severe DKA and HHS

(ADA, 2019; Gosmanov, Gosmanova, & Kitabchi, 2018)

Management of DKA

Care of a patient with DKA involves:

- intravenous (IV) re-hydration to correct for cellular dehydration
- IV insulin to lower blood glucose
- Blood glucose monitoring every one to two hours
- Correction of acidosis- bicarbonate may be indicated in severe DKA
- Frequent laboratory monitoring of blood urea nitrogen, creatinine, sodium, potassium, and bicarbonate levels
- Potassium supplementation if hypokalemia occurs
- Telemetry monitoring as electrolytes will fluctuate as the ketosis is reversed
- Vital signs
- Intake and output

(Gosmanov, Gosmanova, & Kitabchi, 2018)

Type 2 Diabetes

Type 2 diabetes usually begins as insulin resistance, as opposed to a lack of insulin production in type 1 diabetes. As the need for insulin rises, the pancreas generally loses its ability to produce it. Type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity. African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans, Native Hawaiians or other Pacific Islanders are at particularly high risk for type 2 diabetes and its complications.

Characteristics of Type 2 Diabetes

Characteristics of type 2 diabetes include:

- Diagnosis usually after the age of 30 (although more children are being diagnosed)
- Patient is often overweight or obese
- A predisposition to infections or infections that do not resolve easily
- Metabolic syndrome
- Insulin resistance
- Impaired insulin secretion
- Increased hepatic glucose production

(ADA, 2016a)

Pathophysiology of Type 2 Diabetes

In type 2 diabetes, insulin resistance and abnormalities of pancreatic insulin secretion are initially manifested. The pancreas tries to compensate by secreting more insulin to maintain the pre-diabetic state. In time the pancreas fails to maintain equilibrium resulting in hyperglycemia.

Many patients with type 2 diabetes can control their blood glucose levels by lifestyle modification including exercise, diet changes, and oral hypoglycemic medications. Exogenous insulin is usually not required to control hyperglycemia initially. However, insulin dependence may occur as the disease progresses (ADA, 2016a).

Hyperosmolar Hyperglycemic State (HHS)

Hyperosmolar hyperglycemic state (HHS) is when blood glucose rises to dangerously high levels without ketones in the urine. HHS is usually seen in older patients, with type 2 diabetes.

Excessive urine output due to the extremely high glucose level leads to dehydration and hypotension. Neurological symptoms associated with HHS range from dizziness to hallucinations. HHS can lead to irreversible coma and death.

Signs & Symptoms of HHS

The following are signs and symptoms of HHS:

- Dry, parched mouth
- Extreme thirst
- Warm, dry skin, without sweat
- High fever
- Sleepiness or confusion
- Loss of vision
- Hallucinations
- Weakness on one side of the body

(ADA, 2019)

Treatment of HHS

Treatment of HHS is similar to DKA and includes:

- Rapid IV re-hydration
- IV insulin administration
- Glucose monitoring every one to two hours
- Monitoring and correcting electrolyte levels
- Telemetry monitoring as electrolytes will fluctuate as the ketosis is reversed
- Vital signs
- Intake and output

(Gosmanov, Gosmanova, & Kitabchi, 2018)

Fetal Complications of GDM

Pregnant women who have never had diabetes before but who have high blood sugar (glucose) levels during pregnancy are said to have gestational diabetes (GDM). Gestational diabetes affects 2-10% of all pregnant women.

Gestational diabetes increases the risk of fetal complications, therefore it is recommended that pregnant women are screened for gestational diabetes between the 24th and 28th week of their pregnancy.

Fetal complications of gestational diabetes include:

- Large birth size with extra fat; this is associated with trauma during delivery
- Hypoglycemia after birth
- Jaundice
- Breathing problems

(ADA, 2016b)

Management of GDM

The mother may be able to control her blood glucose by exercise only, or she may need insulin to maintain normal blood sugar levels. After pregnancy, most patients' blood glucose returns to normal – unless they had an underlying type 2 or pre-diabetes that was undiagnosed.

Note!

- Women who have had gestational diabetes have a 35 to 60% chance of developing diabetes in the next 10 to 20 years.

GDM Characteristics

Characteristics of patients with gestational diabetes include:

- Abnormal blood sugar levels during pregnancy with no history of diabetes
- Symptoms of diabetes
- Family history of diabetes

- Overweight
- 25 years or older
- Previous birth of a baby weighing more than nine pounds

(ADA, 2016b)

Testing for Diabetes

The A1C Assay

The A1C test, also known as the HbA1c or glycated hemoglobin test, measures average blood glucose control over the past two to three months. This test measures the concentration of hemoglobin molecules in red blood cells that have glucose attached to them. The result indicates the percentage of glycated hemoglobin, or HbA1c, in the blood. This test also can predict the chance for future complications, such as nerve, eye and kidney damage.

The A1C assay is becoming the new standard test for diabetes, replacing the standard fasting plasma glucose test (FPG) or the less common oral glucose tolerance test. Unlike the others, the A1C measures average blood glucose over the preceding two to three months, rather than just at one point in time. Since the A1C assay measures long term or chronic glycemic levels, it is believed to be a more accurate diagnostic tool than other tests. There is no fasting required and is thus more convenient for the patient. An A1C assay $\geq 6.5\%$ is indicative of diabetes (ADA, 2016a).

Fasting Blood Glucose (FBG) Test

This is a convenient and low cost option, but it will miss some diabetes or pre-diabetes that can be found with an oral glucose tolerance test (OGTT). The FBG test is most reliable when done in the morning, after an eight hour fast. People with a fasting glucose level of 100 to 125 milligrams per deciliter (mg/dL) have a form of pre-diabetes called impaired fasting glucose (IFG). Having IFG means a person has an increased risk of developing type 2 diabetes but does not have it yet. A level of 126 mg/dL or above, confirmed by repeating the test on another day, means a person has diabetes (ADA, 2016a).

Oral Glucose Tolerance Test (OGTT)

The oral glucose tolerance test (OGTT) is rarely used in hospitalized patients to diagnose diabetes because many factors such as stress and infection can alter the results. Typically a fasting blood glucose is obtained and then the patient is given 75g of glucose water to drink. Blood glucose levels are checked at one hour and two hours following the ingestion of the glucose water. Blood glucose of 200mg/dL or higher two hours after ingestion of the glucose water is diagnostic of diabetes (ADA, 2016a).

Testing for Diabetes

Random Glucose Level

A random, casual, or non-fasting glucose of greater than 200mg/dL is also diagnostic of diabetes in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis. Blood glucose levels fluctuate throughout the day, but typically rise after a stressful event or food ingestion. A random blood glucose should not be used alone in diagnosis (ADA, 2016a).

Additional Lab Tests

Other lab tests may be helpful in diagnosing diabetes. These are briefly mentioned here:

- Post load glucose: A post load glucose level is also known as a post prandial (after meal) level.
- Glycosylated albumin: Not only does glucose attach to red blood cells, it attaches to proteins such as albumin.
- Connecting peptide (C-peptide): In the pancreatic beta cells, pro-insulin is broken down and forms insulin and connecting peptide, also known as C-peptide. Insulin and C-peptide are formed in equal amounts during the breakdown of pro-insulin. By measuring C-peptide levels, you can indirectly measure endogenous insulin production.
- Ketonuria: Ketones can be present in diabetics when the body is using an abnormally large amount of fat for energy.

(ADA, 2016a)

Can Diabetes Be Prevented?

Most of the efforts related to diabetes prevention are aimed at type 2 diabetes since this affects 90% of patients with diabetes. Pre-diabetes and type 2 diabetes is related to lifestyle more than type 1 or gestational diabetes.

The Diabetes Prevention Program (DPP) was a major clinical trial (1996-2001) sponsored by the National Institutes of Health to determine whether diet and exercise or the oral diabetes drug metformin could prevent or delay the onset of type 2 diabetes.

The Diabetes Prevention Program Outcomes Study – or the DPPOS – is the follow-up study to the Diabetes Prevention Program (DPP) that was started in 2002. The study's aim was to assess the long-term effects of the original DPP interventions on the development of type 2 diabetes and the complications of diabetes.

Most of the DPP participants (over 80%) continued to participate in the DPPOS to examine the longer-term impact of the original treatment interventions (Diabetes Prevention Program Research Group, 2009; 2016).

DPP Research Results

After an average of ten years of follow up, intensive lifestyle changes aimed at modest weight loss had the following effects:

- Reduced the rate of developing type 2 diabetes by 34% compared with placebo.
- Reduced the rate of developing type 2 diabetes by 49% in those age 60 and older compared with placebo.
- Delayed type 2 diabetes by about four years compared with placebo.
- Reduced cardiovascular risk factors.
- Reduced hemoglobin A1C (A1C) and fasting glucose compared with placebo. The A1C test gives information about average blood glucose levels for the past two to three months.

(Diabetes Prevention Program Research Group, 2009; 2016)

Lifestyle Changes

Preventative measures involve the following lifestyle changes:

- **Losing weight:** Losing even a few pounds can help prevent type 2 diabetes. Being overweight or obese places a patient at greater risk for developing diabetes.
- **Making healthy food choices:** Following simple daily guidelines can decrease a patient's risk of diabetes. A healthy diet, eating a variety of foods including fresh fruits and vegetables, limiting fat intake to 30% or less of daily calories, and watching portion size, can all decrease the risk of type 2 diabetes. Healthy eating habits can go a long way in preventing not only diabetes, but also other health problems.
- **Exercising:** Regular exercise allows the body to use glucose without extra insulin. This helps combat insulin resistance, and is one of the keys to why regular exercise is helpful to people with diabetes. Patients should never start an exercise program without checking with their doctor first (Diabetes Prevention Program Research Group, 2009; 2016).

Diet

Newly diagnosed patients as well as those with uncontrolled diabetes can benefit from seeing a dietitian to develop a daily meal plan. Diet information can provide a basis for patients to begin controlling their disease. Generally a follow-up session is necessary to reinforce diet concepts. Most importantly, carbohydrate counting and portion control should be emphasized. The ADA (2016a) states that the average patient with diabetes should consume 45-60 g of carbohydrates at each meal.

In addition to carbohydrate counting and portion control the ADA (2016a) recommends that a diabetes patient:

- Limit sweets
- Eat frequent meals
- Eat whole-grain foods, fruits, and vegetables
- Eat less fat
- Limit consumption of alcohol

Medications

A patient should understand their medication(s). He or she should know the name of the medication, how it works, the proper dose, when to take the medication, and any side effects. Generally, this information should be provided with initiation of the medication but it is important to assess the patient's knowledge. In either case (initiation or follow-up), be certain to document the education given per your facility's standards. Patient comprehension is a key part of education for the diabetic patient.

DPP Study: Metformin

After an average of ten years of follow up, treatment with metformin has:

- Reduced the rate of developing diabetes by 18% compared with placebo.
- Delayed diabetes by two years compared with placebo.
- Reduced A1C and fasting glucose compared with placebo.

(Diabetes Prevention Program Research Group, 2009; 2016)

All patients with IGT, IFG, or A1C 5.7-6.4% may be considered for treatment with metformin if at particularly high risk for development of diabetes (IFG and IGT plus and additional risk factor) (ADA, 2015b).

Oral Hypoglycemics

Oral hypoglycemic agents are key to the management of type 2 diabetes. These medications will be briefly reviewed:

- Sulfonylureas
- Biguanides
- Thiazolidinediones
- Alpha Glucosidase Inhibitors
- Dopamine Receptor Agonist
- Bile Acid Sequestrant
- DPP-4 Inhibitors
- GLP-1 Agonists
- Combination agents

Sulfonylureas

The American Diabetes Association (ADA) recommends the use of oral sulfonylureas as part of a stepwise approach to treating type 2 diabetes mellitus. Second-generation sulfonylureas are a popular choice as they are mostly inexpensive and readily available as generics. Two of the most commonly used sulfonylureas are DiaBeta® (glyburide) and Glucotrol® (glipizide). Sulfonylureas produce an antihyperglycemic effect by stimulating insulin secretion from the pancreas.

Possible side effects:

- Hypoglycemia (glyburide is associated with a higher incidence of hypoglycemia than most other sulfonylureas)

- Upset stomach
- Skin rash
- Weight gain

Caution! Glipizide and glyburide should be avoided if the patient is allergic to sulfa drugs.

Glyburide is not recommended for patients with renal impairment or severe hepatic impairment because of the risk of hypoglycemia. It should be used with caution in elderly patients because they are also at increased risk for hypoglycemia (Lexicomp Online, 2019) .

Glyburide has been suggested as a therapeutic option for women with gestational diabetes mellitus. Glyburide is recommended for women with gestational diabetes mellitus who may not necessarily require insulin but who are unable to reach their blood glucose goals with medical nutrition therapy (ADA, 2015b).

Biguanides

- Glucophage® (metformin)

Decreases hepatic glucose production, and may enhance glucose transport into adipose and skeletal muscle. Metformin has been shown to decrease A1C by 1-2%.

Dosing:

- 500 mg to 2500 mg daily in divided doses

Side effects:

- Are usually mild and self-limiting, other than lactic acidosis which may be of concern in some patients

Other side effects may include:

- Gastrointestinal effects (metallic taste, nausea, bloating, diarrhea, and lactic acidosis)
- Decreased vitamin B12 levels

Advantages of drug therapy:

- Maintenance of normal glucose levels and neutral weight
- Is relatively inexpensive
- Has a positive effect on lipids
- May work better in a patient that is overweight, has dyslipidemia and high fasting plasma glucose levels

Note! Metformin should be administered with food.
(Lexicomp Online, 2019)

Thiazolidinediones

- Actos® (pioglitazone)
- Avandia® (rosiglitazone)

Acts by increasing the action of insulin at the receptor and post receptor level in peripheral tissues, and fights insulin resistance. Has been found to decrease A1C by 0.6 –1.9%.

Avandia has been linked to an increased risk of heart attack since 2007, but in November 2011, the FDA limited access to this drug to very few patients. Only a very limited number of patients are now able to receive this drug, if they are enrolled in a special program, and Avandia is only available via mail-order from specially-certified pharmacies.

Dosing:

- Once or twice daily

Side effects may include:

- Edema, weight gain, and liver failure
- Main risk being edema

Precautions:

- Not to be used during pregnancy, breastfeeding, in children, for patients with impaired hepatic function

(Lexicomp Online, 2019)

Alpha Glucosidase Inhibitors

- Glyset® (miglitol)
- Precose® (acarbose)

Acts by inhibiting alpha glucosidase in the small intestine, causing a decrease in absorption of starches and glucose absorption. Has been found to decrease A1C by 0.5-1%, and is effective in patients with high postprandial blood glucose, obesity, or high risk of hypoglycemia.

Dosing:

- TID before meals
- Increase dose slowly
- Note that this drug should be given with the first bite of a meal (at least 300 calories). If patients do not eat, the medication should not be administered.

Side effects:

- Are mainly gastrointestinal (GI) in nature, with possible elevated transaminase levels

Note! Acarbose does not cause hypoglycemia when given as monotherapy.

Precautions:

- Not to be used during pregnancy, breastfeeding, for children, for patients with intestinal, liver disorders, or inflammatory bowel disorders (Lexicomp Online, 2019)

Dopamine Receptor Agonist

- Cycloset® (bromocriptine)

This is the first drug for patients with diabetes that targets the body's dopamine activity. The mechanism of action is generally unknown, but pre-clinical studies have shown brain dopamine activity to be low in metabolic disease states and that this factor contributes to multiple metabolic dysfunctions such as insulin resistance.

The indication for use is as an adjunct to diet/exercise for type 2 diabetes, and this drug has the potential for use in combination therapy. Bromocriptine does not increase plasma insulin concentrations.

Dosing:

- 0.8 mg po within 2 hours of waking with food

Side effects:

- Nausea
- Dizziness
- Somnolence

Precautions:

- Hypotension
- Exacerbations of psychotic disorders
- Somnolence may occur
- Contraindicated in patients with syncopal migraines, pregnant and nursing women
- Should not be used together with other dopamine receptor agonists
- Should not be used in pediatric patients

(Lexicomp Online, 2019)

Bile Acid Sequestrant

- Colesevelam HCL (Welchol®)

Colesevelam binds with bile acids in the intestine thereby impeding their reabsorption. This drug has been shown to decrease A1C by 0.5%.

Dosing:

- 3 tablets twice daily or 6 tablets once daily

- Or, oral suspension (3.75 g packet) once daily

Side effects:

- Main risk is hypertriglyceridemia
- GI side effects

Contraindications:

- GI obstruction
- Hypertriglyceridemia
- Pancreatitis

(Lexicomp Online, 2019)

DPP-4 Inhibitors

- Januvia® (sitagliptin)
- Onglyza® (saxagliptin)
- Tradgenta® (linagliptin)
- Nesina® (alogliptin)

Blocks the breakdown of GLP-1 in small intestine, thereby increasing concentration in the bloodstream. Has been found to decrease A1C by 0.5-0.8%.

Dosing:

- Sitagliptin 50 or 100 mg daily
- Saxagliptin 2.5 or 5 mg daily
- Linagliptin 5 mg daily
- Alogliptin 25 mg daily

Side effects:

- May include possible hypoglycemia when used with insulin or insulin secretagogues

Note! This drug can be added to metformin for maximum effect.

(Lexicomp Online, 2019)

GLP-1 Agonists

- Byetta® or Bydureon® (exenatide)
- Victoza® (liraglutide)

Mimics the actions of the Incretin hormone, glucagon-like peptide-1, secreted in the small intestine; increases first-phase insulin release from the pancreas, decreases glucose release from the liver, and slows gastric emptying and increases satiety. It has been found to decrease A1C by 0.9-2.1%.

Dosing:

- Exenatide 5 mcg or 10 mcg BID
- Liraglutide 0.6 mg, 1.2 mg, 1.8 mg once daily

Side effects:

- May include nausea and abdominal bloating

Advantages of drug therapy:

- Improve glucose levels with a low risk of hypoglycemia
- May improve cardiovascular markers
- Decrease appetite
- Reduce weight

(Lexicomp Online, 2019)

Oral Anti-Diabetic Medications: Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

- Invokana® (canagliflozin)
- Farxiga® (dapagliflozin)
- Jardiance® (empagliflozin)

Blocks reabsorption of glucose in the kidney. Also increases glucose excretion in the urine.

Dosing:

- Canagliflozin 100 mg daily
- Dapagliflozin 5 mg daily
- Empagliflozin 10 mg daily

Side effects:

- Genital yeast infections
- Urinary tract infections
- Dehydration
- Increase in LDL cholesterol
- Increased hematocrit
- Slight increase risk for hypoglycemia

Advantages of drug therapy:

- Reduces risk of cardiovascular mortality in adults with type 2 diabetes

(Lexicomp Online, 2019)

Combination Agent: Jentadueto®

Combination Product of Trajenta (linagliptin) with Metformin

Can be used alone or in combination with a sulfonylurea. Has been found to decrease A1C up to 1.7%.

Dosing:

- Is taken twice a day in dosages of:
 - 2.5 mg of linagliptin with 500 mg metformin
 - 2.5 mg of linagliptin with 850 mg metformin
 - 2.5 mg of linagliptin with 1000 mg metformin

Possible contraindications may include:

- Renal impairment
- Metabolic acidosis
- Hypersensitivity to linagliptin or metformin

Combination Agent: Janumet XR®

JANUMET XR® (sitagliptin and metformin hydrochloride (HCl) extended-release) tablets, a newer treatment for type 2 diabetes that combines sitagliptin, which is the active component of JANUVIA® (sitagliptin), with extended-release metformin. JANUMET XR® provides a convenient once-daily treatment.

Side Effects:

Metabolic Side Effects: Metabolic side effects include possible hypoglycemia and lactic acidosis, which is a potentially fatal metabolic complication. The risk of lactic acidosis is higher in patients with underlying renal insufficiency. Signs and symptoms of severe acidosis may include vomiting, abdominal pain, nausea, dyspnea, hypothermia, hypotension, and bradycardia.

Gastrointestinal Side Effects: Gastrointestinal side effects have included nausea, vomiting, indigestion, abdominal discomfort, diarrhea, dyspepsia, flatulence, and abdominal pain.

Nervous System Side Effects: Nervous system side effects have included asthenia and headache.

Respiratory System Side Effects: Respiratory side effects have included nasopharyngitis.

Hematologic System Side Effects: Hematologic side effects have included malabsorption of vitamin B12, due to intrinsic factor deficiency and possibly other mechanisms. Megaloblastic anemia can occur. Discontinuation of the drug or supplementation with vitamin B12 may be necessary.

Hypersensitivity Reactions: Hypersensitivity side effects may include serious allergic and hypersensitivity reactions in patients treated with sitagliptin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome.

Hepatic Side Effects: Hepatic side effects may include hepatic enzyme elevations.

Renal Side Effects: Renal side effects may include worsening renal function, including acute renal failure.

Insulin

Insulin is a key part to management of the patient with diabetes, particularly for the patient with type 1 diabetes, the type 2 patient who needs insulin as an adjunct to oral agents, or patients with gestational diabetes. Insulin has been available since 1925, when it was initially extracted from beef and pork pancreases. In the early 1980's, technology became available to produce human insulin synthetically, which has replaced beef and pork insulin in the US. And now, insulin analogs are replacing human insulin (University of California San Francisco, 2019).

Insulin Table

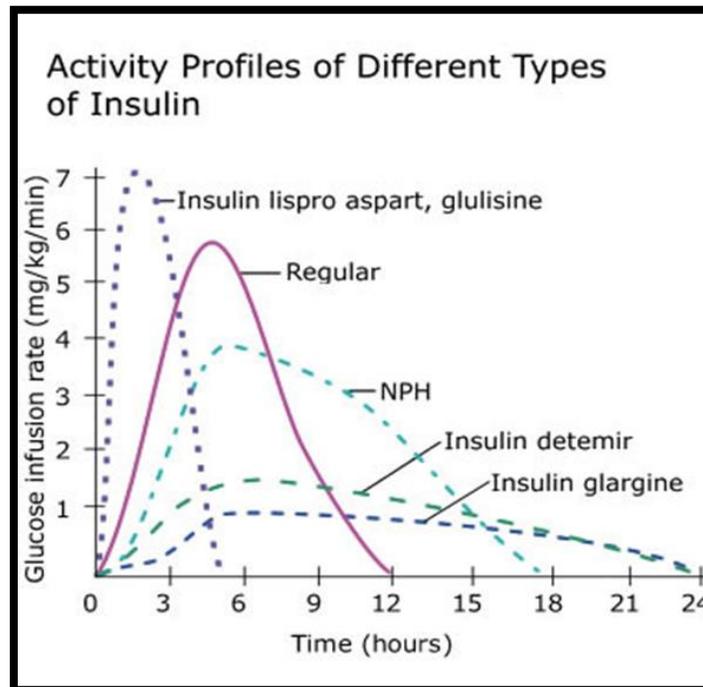
The following table reviews the key insulin agents, their onset of action, peak periods and duration of action:

Type	Onset	Peak	Duration
Rapid-acting bolus insulin <ul style="list-style-type: none"> ▪ Humalog® (lispro) ▪ Novolog® (aspart) ▪ Apidra® (glulisine) 	5-15 min	45-75 min	2-4 hours
Rapid-acting inhaled insulin <ul style="list-style-type: none"> ▪ Afrezza® (human insulin) 	3-7 min	12-15 min	2.5-3 hours
Short-acting bolus insulin <ul style="list-style-type: none"> ▪ Humulin R®, Novolin R® (regular insulin) 	<30 min	2-4 hours	5-8 hours
Intermediate-acting basal insulin <ul style="list-style-type: none"> ▪ Humulin N®, Novolin N® (NPH [neutral protamine Hagedorn]) 	2 hours	4-12 hours	18-28 hours
Long-acting basal insulin <ul style="list-style-type: none"> ▪ Lantus®, Basaglar® (glargine U-100) ▪ Levemir® (detemir) 	1-2 hours	Glargine relatively flat; detemir peaks within 3-9 hours	20-24 hours (glargine) 6-24 hours (detemir)

Ultra-long acting basal insulin <ul style="list-style-type: none"> ▪ Toujeo® (glargine U-300) ▪ Tresiba® (degludec U-100 and U-200) 	6 hours (glargine) 1 hour (degludec)	Both relatively flat without peak	36-42 hours
Pre-mix analog insulin <ul style="list-style-type: none"> ▪ Humalog Mix 75/25® (75% lispro protamine/25% lispro) ▪ Novolog 70/30® (70% aspart protamine/30% aspart) 	10-20 min	1-10 hours	10-16 hours
Pre-mix regular insulin <ul style="list-style-type: none"> ▪ Humulin 70/30® & Novolin 70/30® (70% NPH/30% regular) 	30-60 min	2-10 hours	10-16 hours
Pre-mix rapid and long acting insulin <ul style="list-style-type: none"> ▪ Ryzodeg 70/30® (70% degludec/30% aspart) 	<15 min	Variable	42 hours

(Lexicomp Online, 2019; University of California San Francisco, 2019)

Insulin Profiles



(University of California San Francisco, 2019)

Insulin Regimens

For patients with type 1 and type 2 diabetes on insulin, the combination of providing a basal coverage and bolus coverage for meals is recommended. This gives insulin replacement therapy that is similar to endogenous insulin secretion in the body. A basal insulin gives long-term coverage, by using either glargine or detemir. A rapid-acting insulin is added for a “bolus” prior to meals, based on calculated dose that incorporates carbohydrate intake.

Why Start Insulin in Type 2 Diabetes?

Timely initiation of insulin optimizes blood glucose and improves prognosis. A1C levels consistently > 7% indicate the patient may benefit from insulin. After oral antidiabetic drug failure, the combination insulin + oral hypoglycemic agent can improve glycemic control with less weight gain than insulin alone. Some patients may benefit from insulin therapy as soon as diet becomes inadequate. Insulin in type 2 diabetes also spares beta cells.

Hypoglycemia

Hypoglycemia (also called an insulin reaction or hyperinsulinism) occurs when blood glucose is too low. Hypoglycemia can be caused by a number of factors: too much insulin, not enough food, too much exercise, eating late, or not eating enough carbohydrates. In short, it happens

when there is too much insulin and not enough carbohydrates. Treatment of hypoglycemia in the awake patient includes, but is not limited to candy, fruit juice, or oral glucose (such as tablets). Patients at risk for hypoglycemia should be provided with a glucagon kit.

Signs & Symptoms of Hypoglycemia

A diabetic patient should understand the signs and symptoms of hypoglycemia include:

Hunger	Shakiness
Nervousness	Sweating
Dizziness or light-headedness	Sleepiness
Confusion	Difficulty speaking
Anxiety	Weakness

(ADA, 2016a)

Hyperglycemia

All patients with diabetes should also be educated on the short term and long term effects of hyperglycemia. Hyperglycemia occurs when blood glucose levels are too high. Increased glucose in the blood, which can lead to DKA, is caused by any of these factors or a combination of:

- Not enough insulin in the body
- Too much food
- Not enough activity
- Stress
- Illness

Signs & Symptoms of Hyperglycemia

The symptoms of hyperglycemia include:

Blurred vision	Fatigue, dry mouth
Polydipsia (thirsty)	Polyuria (frequent urination)
Polyphagia (hunger)	Dehydration
Vomiting	Abdominal pain

(ADA, 2016a)

Blood Glucose Testing

There is no absolute recommendation as to when and how often blood glucose should be tested. Testing times may depend on medication regimen, age, stability of blood glucose, personal preference, and finances. How often a person should test is defined by the individual and what information is required. Less than 60% of diabetic patients monitor on a regular basis. Finances may limit the frequency of testing, but people can be shown how to stagger

test times over a period of time to show results over the whole day. People should be taught to look for patterns or trends in their results, and what to do when one is found (ADA, 2016a).

Blood Glucose Diaries

Diaries of blood glucose results allow the person with diabetes and the healthcare professional to review the day-to-day management. Sometimes people with diabetes will only record the results that they want the healthcare professional to see. Be sure to develop a trusting relationship with the people in your care so that they record all results. Tell them that it is just as important for you to see the results that are out of range as it is to see the ones that are in range.

Encourage patients with diabetes to add their comments to their diaries, such as food eaten or activity undertaken. This will help explain highs and lows. A good diary is one of the keys to self-management. Stress that the diary will help them manage their condition; it is not just for the healthcare professional (ADA, 2016a).

New Technology

Aside from multiple brands of glucometers, new technology also has continuous blood glucose monitoring and even apps available. Some devices have wireless capability, monitor blood glucose trends, or are part of an insulin delivery system. When evaluating new devices, patients should check to ensure that there is approval of the device from the Food and Drug Administration (FDA), and if their insurance will cover any of the costs.

Some examples of new technology include the BGluMon[®], a revolutionary iPad application that provides an advanced and easy-to-use tool to record and edit blood glucose information, export data, calculate dosages and run reports. Sanofi Aventis has also produced a standalone blood glucose monitor that can plug directly into an iPhone and iPod Touch. The device, known as the iBGStar[®], allows diabetics to test their blood sugar levels on the go, record notes, and send information to their healthcare providers via a free iPhone App.

Diabetes Complications

Diabetes is the leading cause of kidney failure, non-traumatic lower-limb amputations, and new cases of blindness among adults in the United States.

Diabetes is a major cause of heart disease and stroke.

Diabetes is the seventh leading cause of death in the United States.
(CDC, 2017)

Long Term Complications of Diabetes

Long-term complications of diabetes are generally due to macrovascular or microvascular disease.

Macrovascular complications are all related to the devastating effect that diabetes has on the circulatory system, including:

- Coronary artery disease
- Cerebrovascular accidents
- Peripheral vascular complications

Microvascular complications include:

- Neuropathy: Neuropathies most often occur in the lower extremities, causing numbness and tingling.
- Retinopathy: No symptoms are detected early in the stages of retinopathy. It is imperative for patients to have frequent ophthalmologic evaluations (yearly eye exams).
- Nephropathy: Structural and functional disease of the kidneys occurs in poorly controlled diabetes. Nephropathy can eventually lead to end stage renal disease. Laboratory values should be evaluated including Blood Urea Nitrogen, Creatinine, Microalbumin, and Creatinine Clearance
- Foot disorders: The ADA (2016a) recommends yearly foot exams. People with diabetes need to care for their feet and check them daily for cracks or sores. Foot sores are slow to heal and are at risk for infection; hence, a foot left untreated can lead to an amputation.

Prevention of Complications

The ADA (2016a) stress that the cornerstone of care for people with diabetes who want to achieve successful health-related outcomes and prevent long-term complications is diabetes self-management education (DSME). Healthcare professionals can assist in providing education to the patient about:

- Type of diabetes
- Blood glucose goals
- Hemoglobin A1C value
- Changes in treatment
- Presence of complications
- Other medical conditions
- Lifestyle

Continuing education should be provided or encouraged. A firm educational basis is the foundation that allows the individual and the family to be more independent.

Current Studies

Currently on ClinicalTrials.gov from the U.S. National Institute of Health, 14,114 studies concerning “diabetes” were found when searched on March 15, 2019.

Many of these trials are either recruiting, active, not recruiting, not yet recruiting, completed, or unknown (indicates status has not been verified in more than two years).

Trials are on devices, medications, education, and management of diabetes.

Conclusion

Diabetes can be a manageable disease. With the right tools, patients will reap the benefits of improved outcomes through diabetes education, access to education, and lifestyle changes.

Improvements in managing diabetes will increase the quality of life for those individuals that have been diagnosed with this disease. New advances in medications and technology, as well as continued research studies, assist in the treatment and management of this disease.

Healthcare professionals can contribute to the prevention of diabetes by becoming knowledgeable about the many faces of diabetes and how to provide the most appropriate care for and education of all patients that are at risk.

Resources

Agency for Healthcare Research and Quality: <https://www.ahrq.gov/topics/index.html>

American Association of Diabetes Educators: <http://www.diabeteseducator.org>

American Diabetes Association: <http://www.diabetes.org>

Centers for Disease Control and Prevention: <http://www.cdc.gov/diabetes>

Health Resources and Services Administration: <http://www.hrsa.gov>

Juvenile Diabetes Research Foundation International: <http://www.jdrf.org>

National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health: <http://www.niddk.nih.gov>

U.S. Food and Drug Administration: <http://www.fda.gov>

U.S. National Institutes of Health Clinical Trials: <http://clinicaltrials.gov>

Your Diabetes Info, a joint program of NIH and CDC: <http://www.yourdiabetesinfo.org>

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