DIABETES MELLITUS
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OBJECTIVES

Upon completion of the class and studying the post-test questions, each participant will independently do the following with a degree of accuracy that meets or exceeds the standards established for their scope of practice:

1.   Describe the pathophysiology of Type I diabetes mellitus.

2.   Describe the pathophysiology of Type II diabetes mellitus.

3.   Compare and contrast the management of diabetic emergencies.

4.   Interpret the pathophysiological principles & the assessment findings to formulate a field impression & implement a treatment plan for the patient with a diabetic emergency.

5.   Recognize the signs and symptoms of the patient with hypoglycemia.

6.   Sequence the compensatory mechanisms utilized by the body to promote homeostasis relative to hypoglycemia.

7.   Correlate abnormal findings in assessment with clinical significance in the patient with hypoglycemia.

8.   Correlate abnormal findings in assessment with clinical significance in the patient with hyperglycemia.

9.   Choose the appropriate management of the patient with hyperglycemia.

10.   Integrate the pathophysiological principles and the assessment findings to formulate a field impression and implement a treatment plan for the patient with hyperglycemia.

11.   Discuss the pathophysiology of nonketotic hyperosmolar coma.

12.   Recognize the signs and symptoms of the patient with nonketotic hyperosmolar coma.

13.   Correlate abnormal findings in assessment w/ clinical significance in the pt with nonketotic hyperosmolar coma.

14.   Integrate the pathophysiological principles and the assessment findings to formulate a field impression & implement a treatment plan for the patient with nonketotic hyperosmolar coma.

15.   Discuss the pathophysiology of diabetic ketoacidosis.

16.   Recognize the signs and symptoms of the patient with diabetic ketoacidosis.

17.   Correlate abnormal findings in assessment with clinical significance in the patient with diabetic ketoacidosis.

18.   Integrate the pathophysiological principles and the assessment findings to formulate a field impression and implement a treatment plan for the patient with diabetic ketoacidosis.

19.   Interpret assessment findings of an unconscious pt to conclude a diagnosis of diabetic ketoacidosis to treat according to SOP.

20.   Appreciate the added long term effects of diabetes and how the disease impacts other conditions.

I.   **Introduction**

    A.   **Incidence:** *Diabesity* (the combination of diabetes and obesity) is the largest epidemic the world has faced (Zimmet, 2007).

        1.   Modern lifestyles and poor dietary habits have led to a global epidemic of obesity and type 2 diabetes with a consequent rise in multiple interrelated cardio-metabolic risk factors. On December 21, 2006, the UN General Assembly unanimously passed a resolution declaring diabetes an International public health issue, only the 2nd disease after HIV/AIDS to attain that status.

        2.   The Centers for Disease Control and Prevention (CDC) estimates that a total of 26 million Americans have diabetes and 79 million more have prediabetes (2013). This translates to 8.3% of Americans of all ages and 11.3% of adults aged 20 and older with a confirmed diagnosis and 27% or 7 million people that do not know they have the disease. Up to 35% have prediabetes. Half of Americans 65 and older have prediabetes and 27% have the disease.

        3.   Perhaps 246 million people worldwide may be diabetic with projections estimating a rise up to 380 million by 2025. It's estimated by the CDC that in 2050, 1 in 3 Americans will have type 2 diabetes. Many are hyperglycemic for up to 6 yrs. before being diagnosed. For additional statistics; see the *National Diabetes Statistics* fact sheet online at www.diabetes.niddk.nih.gov/dm/pubs/statistics.

    B.   **Cost:** Diabetes costs are projected at $138 billion annually. Average medical costs for a diabetic patient are $10,000 compared with $2,700 for non-diabetic persons.

    C.   **Morbidity:** DM is listed as the 7th leading cause of death and a leading cause of heart attacks, strokes, high blood pressure, blindness, kidney failure, and nontraumatic lower extremity amputations. New research has demonstrated that 65% of type 2 diabetics will die from CV complications. The good news is that the morbidity can be reduced with increasing physical activity and losing weight.

    D.   **Definition: Diabetes mellitus** (DM) The Egyptians described DM 4000 years ago. A Greek physician named it 2000 years ago when he observed that afflicted persons produced large amounts of urine that attracted bees and other insects. *Diabetes* means "to siphon" or "to pass through" and *mellitus* means "honey sweet" due to the sugar in the urine.

        A group of chronic metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, metabolism, function, or all of the above. This results in **abnormal carbohydrate, fat and protein metabolism** arising from the deficient action of insulin on target tissues producing an impairment of the normal ability to use glucose.

II.   **Glucose metabolism**

    A.   **Metabolism** is the sum of the processes that produce the energy & molecules needed for cell growth or repair (Bledsoe, 2006). One form will build complex molecules from simpler ones (**anabolism**) & the other will break down complex molecules into simpler ones (**catabolism**).

    B.   Normally, the body fuels metabolic processes from three food sources: **carbohydrates**, used in the form of glucose; **fats**, which convert to fatty acids; and **proteins**, in the form of amino acids. Glucose is the main source of fuel for the body.

        1.   **Sources of glucose**

            a.   Ingestion of complex or simple carbohydrates (sugars)

                (1)   Simple sugars: Glucose, galactose, fructose

                (2)   Complex sugars must be broken down into simple sugars for use

            b.   If you have not recently eaten, the body has two additional methods of keeping glucose levels constant:

                (1)   **Gluconeogenesis** (*gluco* = glucose; *neo* = new; *genesis* = origin):

New glucose molecules are produced from non-sugar sources in the liver.

(2) **Glycogenolysis** (*glyco* = sugar; *gen* = origin; *lysis* = to loosen or unbind): Hepatic glycogen break down into its component glucose molecules.

C. Glucose levels fluctuate continuously based on time of day, food or beverage ingested, stress, exercise, and hormone activity. Glucose homeostasis is achieved through the interactions of circulating levels of insulin, glucagon, cortisol, catecholamines, growth hormones, and other counter-regulatory hormones and their subsequent effects on hepatic, fat, and muscle cells.

D. Normal glucose levels range between **70 - 120 mg/dL**. Lowest levels are attained when food has not been eaten for a number of hours (**fasting state)**. Highest levels are usually seen one to two hours after eating, especially following a high carbohydrate load. A glucose level lower than baseline (< 70 mg/dL) is called **hypoglycemia** and one higher than 140 mg/dL reflects **hyperglycemia.**

E. Individual targets for blood glucose ranges are based upon medications, age, general health, activity patterns, and the types of complications for which a person is at greatest risk. The goal is to keep blood glucose levels within appropriate ranges to minimize the risk of complications based on an individualized profile.

Elevated blood glucose ranges	Risk of complications
Above 800 mg/dL	Life threatening acute risk
400 mg/dL - 800 mg/dL	Very high risk
250 mg/dL - 400 mg/dL	High risk
180 mg/dL - 250 mg/dL	Moderate risk
110 mg/dL - 180 mg/dL	Low risk
70 mg/dL - 120 mg/dL	Normal range

F. **Mechanisms that govern glucose metabolism**

1. It was discovered in 1889 that the **pancreas** is largely responsible for maintaining blood glucose. The liver and kidneys are also essential for glucose regulation.

2. The pancreas is located in the upper retroperitoneum, behind the stomach and between the duodenum and spleen. It regulates glucose metabolism through the release of three hormones from endocrine tissue known as the **islets of Langerhans**. A healthy pancreas contains about one to two million islet cells weighing about one gram or about 2% of the total pancreas mass. There must be a balance between insulin and glucagon to maintain normal blood glucose levels.

Islet cell type	% of islet tissue	Hormone secreted
Alpha cells	25%	**Glucagon** in response to ↓ blood glucose levels
Beta cells	60%	**Insulin** (antagonist of glucagon) in response to ↑ blood glucose levels
Delta cells	10%	Somatostatin

3. **Insulin**

a. **Primary actions**

(1) Immediately after eating, carbohydrates are converted to simple glucides or sugars that increase blood glucose levels. The glucose needs to move out of the blood into cells to be burned as fuel.

(2)   Glucose molecules are too large to readily diffuse across all cell membranes. Cardiac, skeletal and fat cells needs a "facilitator" to help transport it through the membrane into the cell.

(3)   So, as glucose levels rise, a healthy pancreas automatically produces the right amount of insulin to facilitate glucose uptake into insulin-dependent cells (high insulin/low glucagon state).

(4)   How? Insulin binds with **insulin receptors** on cell membranes. These activated receptors allow glucose to attach to the receptor site and then to be released into the cell (**facilitated diffusion)**. Glucose moves into these cells 10 X faster with insulin present.

(5)   Once in the cells, the mitochondria use glucose to produce ATP and store it as an energy reserve.

(6)   The **brain** uses more glucose than any other organ system. Its glucose uptake **is not insulin dependent**. When insufficient glucose is available, brain function immediately decreases and lethargy, confusion or loss of consciousness may result in rapid succession. Intestinal, liver and kidney tubule cells are also not dependent on insulin.

(7)   Insulin prompts liver cells to stop producing glucose and to **convert excess glucose to glycogen** for storage in the liver and muscle cells. While liver cells do not need insulin to absorb glucose, it is needed to convert glucose to glycogen.

(8)   It is the only hormone that leads to **lipogenesis** (formation and storage of fat) by converting fatty acids and glycerol into **triglycerides** which are bound to very-low-density lipoproteins and transported to fat cells for storage.

(9)   Insulin stimulates the use of amino acids for **protein synthesis** and prevents tissues from catabolizing or breaking down. Thus, insulin is an **anabolic hormone** that builds you up.

    b.   **Factors that stimulate insulin release:** Insulin has a half-life of only minutes. A healthy liver removes circulating insulin within 10-15 minutes of being secreted (Bledsoe, 2006). A normal pancreas must continuously produce small amounts to control excess glucose output by the liver and keep glucose levels in the blood stream constant. During fasting states, the basal secretion rate is about 1 unit/hour.

    c.   In people with diabetes, the pancreas either produces little or no insulin or there is a problem with the insulin receptors, so the cells in the muscle, liver, and fat do not use insulin properly. As a result, glucose builds up in the blood while some cells are starved of energy.

Factors that stimulate insulin release	Factors that inhibit insulin release
- After eating, an increase in blood glucose causes a five to tenfold increase in insulin secretion to pull glucose out of the blood and into cells to prevent hyperglycemia. - Ketone bodies; free fatty acids - Glucagon release - Gastric secretions - Salicylates - Hyperkalemia	- Hypoglycemia (glucose < 80-85 mg/dL) - Hypokalemia - Hydrochlorothiazide - Beta and Ca channel blockers - Phenytoin (Dilantin) - Alcohol

4.   **GLUCAGON** (*gluco* = glucose; *agon* = to drive - drives an increase in blood glucose)

    a.   **Catabolic hormone** discovered in 1923, less than two years after the

discovery of insulin. When a person has not eaten, serum glucose levels begin to drop. This reduction suppresses insulin secretion and causes the release of glucagon.

b. Glucagon causes the opposite effect of insulin. It causes the liver and skeletal muscles to convert glycogen back into glucose. (Aehlert, 2010) stored glycogen in the liver to be broken down into glucose (**glycogenolysis)** and in addition, glucagon causes an increase in the breakdown of fats into fatty acids and body proteins into amino acids for conversion by the liver into glucose. (Aehlert, 2010) the conversion of free fatty acids to glucose (**gluconeogenesis**) to raise blood sugar levels. For example, at night, the liver releases glucose from glycogen stores at 2 mg/kg/min to maintain normal blood sugar levels. These pathways become the body's major sources of glucose but they only work if there are sufficient stores of glycogen available in the liver.

c. As insulin levels drop, protein synthesis by muscle cells ceases and **proteolysis** (protein breakdown) begins, leading to increased circulating amino acids.

d. Fat storage also declines. Without the suppressive effects of insulin, the enzyme **lipase** is activated in fat cells, resulting in **lipolysis** (breakdown) of stored triglycerides and **liberation of free fatty acids** into the circulation. That's how one looses weight when dieting!

e. Glucagon also serves as the **"on" switch** for the hepatic *ketogenic pathway* where fatty acids convert into acetoacetate and ß-hydroxy-butyrate (**ketoacids and ketone bodies**) that the liver oxidizes for energy.

f. The activation of lipolysis and the ketogenic pathways result in an increase in circulating levels of fatty and ketoacids, which serve as a **feedback loop stimulus for insulin secretion**. The initial fall in insulin levels is followed by increased glucagon release that stimulates additional insulin secretion and protects the body from ketoacidosis and hyperglycemia in non-diabetic persons.

g. **The link between carbohydrate and lipid metabolism is of great significance in uncontrolled diabetes**.

5. **Somatostatin** (growth-hormone inhibiting hormone): Inhibits insulin and glucagon secretion. It keeps secretion of the other two hormones in balance. It also retards nutrient absorption from the intestines (Bledsoe, 2006).

6. Recognition of the incretin system as a key pathway in glucose homeostasis has led to the development of glucagon-like peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. Approved as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM), the benefits of incretin-based therapy offer the ability to further individualize glucose-lowering therapy.

7. **Other counter-regulatory hormones** impair insulin secretion/antagonize its action

a. **Epinephrine** stimulates hepatic glucose production, stimulates secretion of glucagon, suppresses secretion of insulin, inhibits peripheral glucose use, and stimulates lipolysis.

b. **Cortisol** functions much like glucagon, but with less potency.

c. Growth hormone

Actions of insulin	Actions of counterregulatory hormones: Glucagon, epinephrine, cortisol, & growth hormone
Promotes: • Glycogen synthesis in muscle and liver • Peripheral uptake of glucose by muscle • Uptake of amino acids by muscle and liver • Protein synthesis • Synthesis of fatty acids from glucose • Change of fatty acids & glycerol into triglycerides • Storage of triglycerides in fat tissue • Movement of extracellular K, phosphate, and Mg into cells	**Promotes:** • Glycogen catabolism • Lipolysis of stored triglycerides • Mobilization of stored fatty acids • Ketone production • Resistance to insulin • **Accelerates:** • Hepatic glucose production (gluconeogenesis)
Inhibits: • Glucagon release • Lipolysis of triglycerides in adipose tissue • Mobilization of stored fatty acids • Proteolysis • Hepatic glucose production (gluconeogenesis) • Fatty acid oxidation	**Inhibits:** • Glycogen synthesis • Use of glucose by muscle • Change of fatty acids and glycerol into triglycerides

III. **Classifications of diabetes**

A. In 1997, an American Diabetes Association (ADA) expert committee recommended universal adoption of a simplified approach to classifying diabetes. They ceased basing the names of the two main types on treatment or age at onset because those descriptions did not define the nature of the diseases or the care. The committee was composed of clinicians and researchers from academia, the private sector, the National Institutes of Health (NIH), and the ADA in collaboration with the World Health Organization. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) agreed.

Former names	Names now
Type I Juvenile diabetes insulin-dependent diabetes mellitus (IDDM)	**type 1 diabetes** Characterized primarily by an absolute deficiency of insulin
Type II Adult-onset diabetes Noninsulin-dependent diabetes mellitus (NIDDM)	**type 2 diabetes** Characterized primarily by insulin resistance (insulin ineffective in target tissue) and an inadequate compensatory insulin secretion response

1. **Other specific types**" Cases where specific genetic defects, surgery, drugs, or other things, have caused hyperglycemia.

2. **Gestational diabetes** mellitus (GDM): Diabetes that develops during pregnancy.

3. **Impaired glucose tolerance** or IGT (2-hour post-meal glucose between 140 and 199 mg/dL and impaired fasting glucose (IFG) between 110 mg/dL and 125 mg/dL.

B. **2010 Clinical Practice Recommendations** (Jan 2010 suppl of *Diabetes Care*)

1. The American Diabetes Association (ADA) revised clinical practice recommendations for diabetes diagnosis to promote hemoglobin A1c as a faster, easier diagnostic test that could help reduce the number of undiagnosed patients and better identify patients with prediabetes.

a. Glucose binds irreversibly with hemoglobin in the blood (**glycosylated hemoglobin**) causing an increased level of **HbA1c**.

          b.   It is believed that the use of A1c, because it doesn't require fasting, will encourage more people to get tested for type 2 diabetes and help further reduce the number of people who are undiagnosed but living with the disease. Type 2 DM can be prevented as long as lifestyle changes are made while glucose levels are still in the pre-diabetes range.

          c.   The A1c test, which measures average blood glucose levels for a period of up to 3 months, was previously used only to evaluate diabetic control with time. An A1c level of approximately 5% indicates the absence of diabetes, and according to the revised evidence-based guidelines, an A1c score of 5.7% to 6.4% indicates prediabetes, and an A1c level of 6.5% or higher indicates the presence of diabetes.

          d.   For optimal control, the recommended ADA target for most people with diabetes is an A1c level no greater than 7%. It is hoped that achieving this target would help prevent serious diabetes-related complications including nephropathy, neuropathy, retinopathy, and gum disease.

      2.   Categories of increased risk for diabetes: A1c range of 5.7% to 6.4%, impaired fasting glucose and impaired glucose tolerance levels.

IV. **Type 1 diabetes mellitus**

    A.   **Incidence**: Accounts for 5%-10% of all diagnosed diabetics in the United States.

    B.   **Onset:** While usually diagnosed prior to age 40, in pre-teens or early teens with a peak incidence at age 13 (hence the outdated term, "juvenile onset" diabetes), it can occur at any age. Symptoms of type 1 diabetes usually develop over a short period, although beta cell destruction can begin years earlier.

    C.   **Causes:** Autoimmune disease in which the body's immune system attacks and destroys the insulin-producing beta cells in the pancreas. The pancreas then produces little or no insulin. At present, scientists do not know exactly what causes the body's immune system to attack the beta cells, but they believe that autoimmune, genetic, environmental factors, and possibly viruses, are involved.

    D.   **Pathophysiology**

      1.   Type 1 DM is characterized by an absolute **lack of functioning insulin** or **insulin secretion deficiency** due to pancreatic ß cell depletion. When cells cannot use glucose, **blood glucose levels rise** and cells transition to burning fat for energy.

      2.   As a result of this exaggerated fasting state and physiologic stress, glucagon and other counter-regulatory hormones are produced and the glucagon/insulin ratios are disrupted.

    E.   **Signs and symptoms**

      1.   Post-prandial (after eating) hyperglycemia transitioning to fasting hyperglycemia
      2.   Weight loss (catabolic state)
      3.   Extreme fatigue, weakness, and lethargy (muscle cells are fuel deprived and less able to perform work; dehydration also causes fatigue)
      4.   **P**olyuria (frequent urination): Glucose exceeds renal threshold for reabsorption (170-200 mg/dL); is spilled into the urine and pulls extra water with it. This leads to losses of Na, K, Mg, and phosphate.
      5.   **P**olydipsia (excessive thirst) due to dehydration
      6.   **P**olyphagia: hunger and increased food intake
      7.   Abdominal pain with vomiting
      8.   Blurred vision: Rapidly rising blood sugar levels can cause fluid shifts in the lens
      9.   **Ketones** in the urine
      10.   Frequent/**persistent infections** of the gums, vagina, bladder, and skin. Germs thrive in the high sugar content of the blood and body fluids.

F. **Treatment**

1. Before the discovery of insulin in 1921, everyone with type 1 DM died within a few years after diagnosis. Insulin was first given in 1922. FDA approval began in 1939. The complete synthesis of the hormone was achieved in 1963.

2. Today, healthy eating, physical activity, and taking insulin are the basic therapies for type 1 DM. The dose of insulin must be balanced with food intake and activity. The goal of management is to keep levels of blood glucose, blood pressure, and cholesterol as close to normal ranges as safely possible. Blood glucose levels must be closely monitored through frequent checks.

Types of insulin

- There are more than 20 types of insulin products available, each with a different time of onset and duration of action. The decision as to which insulin to use is based on an individual's lifestyle (usual type and amount of exercise), a physician's preference, and the person's blood sugar levels. Many people take at least 2 types.

- **Rapid-Acting -** This insulin starts working within 15 minutes after injected. It is mostly metabolized after a few hours. It should be taken just before or just after the patient eats.

- **Short-Acting** - This insulin starts working within 30 minutes to 1 hour after injected. It is also mostly metabolized after a few hours. It should be taken 30-45 minutes before the patient eats.

- **Intermediate-Acting** - This insulin starts working within 2-4 hours after injection. It reaches its highest level in the blood in about 6-8 hours. It is often used to help control blood sugar between meals. Some people use this type of insulin in the morning, at bedtime, or both.

- **Long-Acting** - This insulin starts working within 2 to 4 hours after injection. It can last in the body for up to 24 hours. It is often used in the morning or at bedtime to help control blood sugar throughout the day.

- **Pre-Mixed** - This is a mix of two different types of insulin. It includes one type that helps to control blood sugar at meals and another type that helps between meals (FDA, 2013).

Onset, peak and duration of different insulin				
Insulin	**Onset**	**Peak**	**Therapeutic***	**Pharmaceutic****
Rapid acting **Insulin analogue** insulin lispro***(Humalog) insulin aspart (Novolog) insulin glulisine (Apidra; Apidra Solostar)	5-15 min 5-15 min 5-15 min	45-90 minutes 1-3 hrs Half-life 42 min	3.5-4.5 hrs	3-6 hrs
Short-acting Regular: (Humulin R, Novolin R)	30-60 min	2-3 hrs	3-6 hrs	5-16 hrs
Intermediate-acting Human Insulin Isophane suspension, neutral protamine Hagedorn (NPH) (Humulin N, Novolin N)	2-4 hrs	4 – 12 hrs	12-18 hrs	16-26 hrs
Long acting Insulin glargine (Lantus) Insulin detemir (Levemir)	Taken at bedtime to avoid nocturnal hypoglycemia 1-4 hr hour	None 6-8 hrs	24 hours Mimics natural basal insulin	Note: Cannot mix Lantus w/ any other insulin in same syringe due to acidic pH

Premixed Brand Name	Other Names	Type of Insulin
Humalog Mix 75/25 Humalog Mix 75/25 Pen	75% Insulin Lispro Protamine Suspension 25% Insulin Lispro Injection	Intermediate and Rapid Acting
Humalog Mix 50/50	50% Insulin Lispro Protamine Suspension	Intermediate and Rapid Acting

Humalog Mix 50/50 Pen	50% Insulin Lispro Injection	
Humulin 70/30 Humulin 70/30 Pen	70% NPH Human Insulin 30% Regular Human Insulin Injection	Intermediate and Short Acting
NovoLog Mix 70/30 NovoLog Mix 70/30 FlexPen	70% Insulin Aspart Protamine Suspension 30% Insulin Aspart Injection	Intermediate and Rapid Acting
Novolin 70/30	70% NPH Human Insulin 30% Regular Human Insulin Injection	Intermediate and Short Acting

*   Therapeutic or effective duration of action: The amount of insulin needed to keep blood glucose levels in normal limits.

**   Pharmaceutic (or pharmacokinetic): The action of insulin on "entrance" into and "exit" from the body.

***   Switch of lysine and proline at positions 28 & 29 on the beta chain leads to quicker absorption and onset of action, shorter duration of action, higher peak concentrations compared to regular insulin, and same glucose lowering capacity as regular insulin. Adverse effects include hypoglycemia. All rapid acting analogues should give within 15 min before a meal or immediately after a meal. It takes approximately 30 min for non-lispro insulins to saturate the receptor sites on peripheral tissues to enable glucose to enter the cells and prevent a postprandial (after eating) rise in blood sugar.

Among the criteria considered in choosing insulin are:

- **Onset:** Length of time before insulin reaches the bloodstream and begins lowering blood glucose. This can be affected by the place on the body where the injection is given.

- **Peak time:** Time during which insulin is at maximum strength in terms of lowering blood glucose.

- **Duration**: (How long it lasts in the body) The short duration analogues are usually used in conjunction with a longer-acting insulin or with insulin pump therapy. The only human insulin that can be mixed with Apidra is NPH human insulin. It must be injected immediately after the mixture is made.

Insulin strength: All insulin come dissolved or suspended in liquids. However, the solutions have different strengths. The most commonly used strength in the U.S. is U-100 (100 units of insulin per milliliter of fluid).

Insulin storage: Open insulin bottles that will be used within 30 days should be kept at room temp. If it will not be used within 30 days, it should be stored in the refrigerator. Insulin breaks down in very hot or very cold temperatures. Extra closed bottles of insulin should be stored in the refrigerator. Some pens are only good for 14 days.

Synthetic human insulin derived from genetically engineered bacteria first became available in the 1982, and now all insulin available in the U.S. is manufactured in a lab. While synthetic, it is exactly like human insulin, so no antibodies are formed. Examples: **Humulin** and **Novolin**.

Other resources for information about insulin
NIDDK: Medicines for People with Diabetes - What Do I Need to Know About Insulin?
http://www.niddk.nih.gov/health/diabetes/pubs/med/index.htm#6

G.   **Delivery routes for insulin:**

Note: *EMS personnel are never to give or assist a patient in giving themselves insulin*

1.   **Insulin syringe** (3 sizes: 3 units, 50 units, and 100 unit syringes) with 27-31 g needles that vary from ½ to 1/8-inch lengths. Subcutaneous injection allows insulin to be absorbed gradually, but absorption rates vary by site. The abdomen absorbs fastest, followed by the arms, thighs, and buttocks. Regular insulin may also be given IV to treat emergencies such as severe hyperglycemia.

2.   **Injection aids:** Devices that help users give injections with needles and syringes through the use of spring-loaded syringe holders or stabilizing guides. Many of these aids use push-button systems to administer the injection.

3.   **Insulin pens** (mostly disposable): Humulin or Humalog Pen (Lilly); Helpful if patient takes at least three doses of insulin a day. Looks like a pen with a cartridge that holds 150 to 300 units

of insulin. Some use replaceable and other use disposable cartridges. It has a fine, short needle (similar to the needle on an insulin syringe) on the tip of the pen. Users prime the pen then turn a dial to select the desired dose and press a plunger on the end to deliver the drug sub-q.

4. **Insulin jet injectors** (Medi-ject or Vita-Jet): Look like large pens. They send a fine spray of insulin through the skin via pressurized air instead of using a needle. This is a costly alternative.

5. **Subcutaneous infusion sets**, also called **insulin infusers**, provide an alternative to injections. A catheter (a flexible hollow tube) is inserted into the tissue just beneath the skin and remains in place for 3 to 6 days. Insulin is then injected into the infuser instead of through the skin. Very rarely used.

H. **External insulin pumps** (MiniMed™): People of all ages with type 1 diabetes use insulin pumps and people with type 2 diabetes have started to use them as well. An insulin pump is a small electronic device (worn externally) attached to the body through long (60-100 cm), narrow, flexible tubing with a needle or Teflon catheter inserted into the abdominal sub-q tissues. The pump is about the size of a deck of cards or pager and weighs approximately 4 to 6 ounces. A 3 mL refillable cartridge holds enough rapid- or short-acting insulin for two days. The needle and tubing are changed every two to three days. The pump is set to deliver a steady basal amount of insulin continuously over 24 hours, mimicking the normal pancreas to keep blood glucose levels in range between meals and overnight. Users can program different amounts of insulin at different times of the day and night. Users inject bolus doses at meals or at times when blood sugar is too high. Frequent glucose monitoring is necessary to determine insulin doses and to ensure that insulin has been injected.
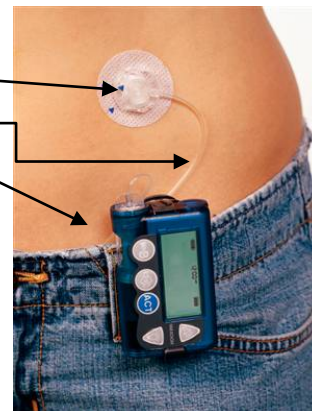
A pump can be attached to a waistband, pocket, bra, garter belt, sock, or underwear. Excess tubing can be tucked into the waistband of underwear or pants. When the patient is sleeping, the pump can be placed next to them on the bed. Some wear it on a waistband, armband, legband, or clip it to a blanket, sheet, pajamas, stuffed toy, or pillow with a belt clip.

Although insulin pumps are water resistant, they should not be set directly in water. All insulin pumps have a disconnect port for activities such as swimming, bathing, or showering. Some pumps can be placed on the side of the tub, in a shower caddy, or in a soap tray. There are also special cases that can be hung from the neck or from a shower curtain hook.

When the pump is disconnected, basal and bolus insulin delivery is stopped by the pump. If a patient is hyperglycemic and wearing a pump, check catheter placement for disconnects, look for kinks in the tubing or assess for pump malfunction. Patients with type 1 DM can go into DKA quickly.

Important tips to remember when disconnecting a pump

- If the pump is stopped while it is in the middle of delivering any bolus - it will **NOT** be resumed. The patient may need to program a new one.
- If blood glucose is under 150, the patient can wait an hour to bolus.
- The patient should not go longer than one to two hours without any insulin.

To search FDA's 510(k) database for insulin pumps, use the following link:
FDA 510(k) Database Search (Insulin Pumps)

I.   **Delivery methods in research phase**

    1.   **Implantable insulin pump:** Surgically implanted device, usually on the left side of the abdomen. Disk shaped, it weighs about 6-8 ounces, and delivers a basal dose of insulin throughout the day. Users deliver bolus doses with a handheld telemetry unit that instructs the pump to give a specified amount of insulin before meals or snacks. The insulin from the pump goes directly to the liver to prevent excess glucose production. The pump is refilled with insulin every 2 to 3 months.

    2.   **Insulin patch:** Placed on the skin and gives a continuous low dose of insulin. To adjust doses before meals, users can pull off a tab on the patch to release insulin. A disadvantage is that insulin is not well-absorbed through the skin. Delivery of insulin through the skin is aided with sound waves or an electrical current.

    3.   **Insulin pills** provide insulin in tablet form. Because insulin is a protein, the body would break it down and digest it before it could get into the blood. Researchers are working on ways to get the insulin into the bloodstream before it is changed by normal digestive processes.

    4.   **A buccal spray** delivers liquid insulin into the mouth. Insulin is then absorbed through the tongue, throat, and inside of the cheeks. **An intranasal spray** delivers insulin as a nose spray.
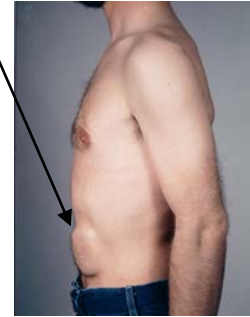
    5.   An artificial pancreas, a surgically implanted device, imitates the action of the pancreas by sensing blood glucose levels and secreting insulin in response. The user also can release insulin using a remote control.

V.   **Type 2 diabetes**

    A.   **Incidence:** Most common form (90% to 95% of all diagnosed cases), yet as many as 50% of all persons, or eight million people with type 2 diabetes are undiagnosed which makes it difficult to estimate the actual prevalence.

        Incidence increases with age. Usually strikes adults over 40-45 years of age; found in 18% of 64-75 year olds and in as many as 40% of those over age 80. This form of diabetes is most often associated with obesity, family history of diabetes, previous history of gestational diabetes, physical inactivity, and certain ethnicities. An alarming new trend is the rising incidence of type 2 DM in children who are obese, spend more than five hours per day in front of the TV or computer, rarely exercise, and eat poor diets (low in fiber)..the same risk factors that lead to diabetes in adults.

    B.   Onset: The symptoms of type 2 diabetes develop gradually. The onset is not as sudden as in type 1 diabetes. Some people have no symptoms.

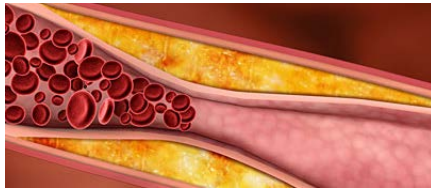   C.   **Pre-diabetes**

        1.   People with pre-diabetes have blood glucose levels that are higher than normal but not high enough for a diagnosis of diabetes. This condition raises the risk of developing type 2 diabetes, heart disease, and stroke. They have a high incidence of cardiac disease and do not know they are at risk.

        2.   Early warning signal: **Hemoglobin A1c** measures average glucose levels for up

to 3 months. It is a fast, easy test that could reduce the number of undiagnosed patients and better identify those with prediabetes. It does not require the patient to fast before the test so encourages more testing.

   a. Early detection makes a difference. Type 2 DM can be prevented as long as changes are made while glucose levels remain while in the pre-diabetes range

   b. A1c levels
      (1) < 5% - no diabetes
      (2) 5.7% to 6.4% - prediabetes
      (3) ≥ 6.5% - presence of diabetes
      (4) For optimal control in diabetics, recommended target is ≤ 7%

   c. Achieving this target should prevent serious diabetes-related complications.

3. Impaired fasting glucose: IFG is a condition in which the blood glucose level is high (100 to 125 mg/dL) after an overnight fast, but is not high enough to be classified as diabetes. (The former definition of IFG was 110 mg/dL to 125 mg/dL.)

4. Impaired glucose tolerance levels: IGT is a condition in which the blood glucose level is high (140 to 199 mg/dL) after a 2-hour oral glucose tolerance test, but is not high enough to be classified as diabetes.

5. Many people with pre-diabetes go on to develop type 2 diabetes within 10 years.

D. **Metabolic syndrome – risk factors for type 2 diabetes**

1. **Adults and adolescents 16 and older:** A cluster of risk factors for cardiovascular disease and type 2 DM that include abdominal obesity, dyslipidemia (high triglycerides, low levels of HDL (*healthy*) cholesterol, and a change in the size and density of LDL (*lethal*) cholesterol), glucose intolerance, hypertension and hyperinsulinemia (Barclay, 2007). Prediabetes affects 41 million Americans aged 40-74 years (Mason, 2007).

2. **Adolescents aged 10 to 16 years**: metabolic syndrome is diagnosed by abdominal obesity (waist circumference ≥ 90th percentile or adult cutoff if lower), and the presence of 2 or more other clinical features (triglycerides ≥ 1.7 mmol/L; high-density lipoprotein cholesterol < 1.03 mmol/L; SBP ≥ 130 mmHg or DBP ≥ 85 mmHg; glucose ≥ 5.6 mmol/L [oral glucose tolerance test recommended]; or known type 2 diabetes mellitus.

3. **In children aged 6 to younger than 10 years**, the at-risk group for later development of metabolic syndrome consists of obesity (waist circumference ≥ 90th percentile). Care providers should strongly encourage weight reduction in these children. Further measurements should be made if there is a family history of metabolic syndrome, type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, hypertension or obesity (Barclay, 2007).

4. Unhealthy diet and sedentary life-styles are the major contributors. In a study published in the July 23, 2007 Circulation, Dhingra & Vasan reported that persons who drink more than one soft-drink daily had a 44% higher risk of developing new onset metabolic syndrome. Drinking at least 1 soft-drink per day significantly increased the risks for obesity, increased waist circumference, impaired fasting glucose, caused

hypertriglyceridemia, and reduced HDL cholesterol levels.

E. **Pathophysiology:** People with type 2 DM either produce too little insulin, produce it too late to match the rise in blood glucose, or do not respond correctly to the insulin that is produced. It usually begins with **insulin resistance**, a condition in which muscle, liver, and fat cells do not use insulin properly. In time, however, the beta cells fail and the pancreas loses the ability to secrete enough insulin in response to glucose loads. The result is the same as for type 1 diabetes—glucose persistently builds up in the blood and the body cannot make efficient use of its main source of fuel.

1. **Major causes of insulin resistance**

   a. **Obesity**: There is a strong link between obesity, particularly abdominal obesity, and cardiometabolic risk factors including diabetes (Mason, 2007). More than 90% of type 2 diabetics are significantly over weight. The risk of insulin resistance syndrome has been shown to increase by 20% for each 5% gain in weight from age 20 to age 53. Excess fat decreases the number of insulin receptors and increases the resistance of those receptors to the function of insulin.

   b. **Hyperglycemia:** Blood sugar levels > 300 trigger insulin resistance.

   c. **Stress:** Physical, emotional, or traumatic that increases insulin-neutralizing hormones such as cortisol, adrenalin, and glucagon.

2. **Hyperinsulinemia:** At first, the pancreas keeps up with the increased blood sugar levels by producing more insulin but that insulin can't achieve normal glucose metabolism due to the insulin resistance. This produces a state of impaired glucose uptake and hyperglycemia even though **blood levels of insulin may be high**. This extra insulin promotes fat storage, suppresses protein breakdown, and helps protein synthesis.

   a. **Damaging effects of hyperinsulinemia:** Insulin acts as an oxidant. Blood vessels increase production of substances that prevent the breakdown of clots and leads to microthrombi and endothelial inflammation (Robertson, 2001). This initiates the process of plaque formation and **atherosclerosis**. Hyperinsulinemia is associated with an ↑ in triglycerides and in both total and LDL (lethal) cholesterol and a decrease in HDL (healthy) cholesterol.

   b. High insulin levels increase plasma Ca levels that increase vascular tone and produce **hypertension**. Vascular changes place the patient at risk for early ACS, HF, and stroke. Insulin is also an important **salt-retaining hormone**, secondary only to aldosterone. Hyperinsulinemia can produce rapid weight gain from fluid retention alone.

3. Later in the disease, beta cells fail and patients experience insulin deficiency due to pancreatic cell dysfunction. This results in persistent hyperglycemia and insulin may be needed in combination with oral antihyperglycemic agents.

F. **Signs and symptoms**: All these symptoms occur because body tissues are not receiving adequate glucose for energy and normal function.

1. 3 Ps like type 1 DM but may be more subtle
2. Blurred vision
3. Muscle cramps
4. Chest pain can occur due to a reduction in collateral coronary artery blood flow
5. Non-healing infections of skin, vagina or bladder
6. Fatigue to exhaustion
7. Dry, itchy skin
8. Impotence
9. Night-time diarrhea (excess Sorbitol in the gut)
10. Long-term effects begin to develop at least 6 years before the clinical dx

G. **Treatment**

1. In August 2006, The ADA and European Association for the Study of Diabetes (EASD) published a consensus statement on the management of hyperglycemia of type 2 diabetes (Barclay & Vega, 2006). Treatment focuses on maintaining glycemic levels as close to the nondiabetic range as possible, but also addresses dyslipidemia, hypertension, hypercoagulability, obesity, and insulin resistance.

2. **Step 1**

    a. **Lifestyle changes** to decrease weight and increase activity, including meal planning for blood glucose (sugar) control and exercising. Even a 4 kg weight loss may lead to better blood glucose control.

    b. If the patient is not meeting glycemic goals after a maximum of 3 months, the next step is to add an oral medication that lowers blood glucose (metformin) to its maximally effective dose for 1 to 2 months.

    c. **Oral antihyperglycemic agents are prescribed if**

       (1) random glucose levels < 300 mg/dL;
       (2) fasting glucose levels < 250 mg/dL; or
       (3) inadequate control after dietary changes and exercise.

3. **Step 2: Additional therapy**

    a. Some of the pills work by stimulating the pancreas to secrete more insulin. Others decrease insulin resistance, helping the body more effectively use the insulin it makes. Some stop the liver from releasing too much glucose. Still others partially block the digestion of some carbohydrates. The pills may lose their effectiveness over time.

    b. The American Association of Clinical Endocrinologists/American College of Endocrinology recommend either insulin alone or with other agents, or metformin in combination with a GLP-1R agonist, DPP-4 inhibitor, or thiazolidinedione as initial therapy for individuals with an A1C >9.0%. Among the glucose-lowering agents, the relative risk of hypoglycemia is greatest with insulin, sulfonylureas, and meglitinides. The risk of hypoglycemia with the GLP-1R agonists and DPP-4 inhibitors is low, which is likely related to their glucose-dependent manner of stimulating insulin release and inhibiting glucagon secretion (Shahady, 2012).

    c. **Glucagon-like peptide-1 receptor (GLP-1R) agonists** (exenatide twice daily, exenatide once weekly, liraglutide) and **dipeptidyl peptidase-4 (DPP-4) inhibitors** (linagliptin, saxagliptin, sitagliptin).

    d. **Sulonylureas** (*SUL-fah-nil-YOO-ree-ahs*) stimulate the pancreas to make more insulin. Inexpensive but may also cause weight gain and hypoglycemia

    e. **Biguanides** (*by-GWAN-ides*) decrease the amount of glucose made by the liver.

    f. **Alpha-glucosidase inhibitors** (*AL-fa gloo-KOS-ih-dayss in-HIB-it-ers)* slow the absorption starches. Weight neutral but have frequent GI adverse effects, require 3-times daily dosing and are expensive.

    g. **Thiazolidinediones** (*THIGH-ah-ZO-li-deen-DYE-owns*) increase sensitivity to insulin that is present by decreasing insulin resistance. They improve the lipid profile but are expensive and may cause fluid retention and weight gain.

    h. **Meglitinides** (*meh-GLIT-in-ides*) stimulate the pancreas to make more insulin.

    i. **D-phenylalanine** (*dee-fen-nel-AL-ah-neen) derivatives* help the pancreas make more insulin quickly.

    j. **Combination with other medications:** Lowering BP to 130/80 mm Hg

in individuals with diabetes may reduce the risk of cardiovascular and kidney disease. Combination therapy with 2 or more drugs is recommended with options including a diuretic, beta-blocker, calcium channel blocker, angiotensin converting enzyme inhibitor (ACE-I), or angiotensin receptor blocker (ARB). Among these, a cornerstone of antihypertensive therapy in people with diabetes is either an ACE-I or ARB. A low-dose diuretic (eg, hydrochlorothiazide 12.5-25 mg/d) is also recommended as part of combination therapy (Shahady, 2012).

4. **Notes on oral diabetes medications: See chart at end of handout**

   a. These pills work best when used with meal planning and exercise. Diabetes pills don't work for everyone. Pills are often ineffective if the patient has had diabetes for more than 10 years or already takes more than 20 units of insulin each day. On the other hand, they work well if the disease was recently diagnosed or the patient needs little or no insulin to keep blood glucose levels near normal.

   b. Diabetes pills sometimes stop working after a few months or years. The cause is often unknown. When this happens, oral combination therapy can help. Even if pills do bring the blood glucose levels near the normal range, patients may still need to take insulin if they have a severe infection or need surgery. Pills may not be able to control blood glucose levels during these stressful times when blood glucose levels shoot up.

   c. There is no "best" pill or treatment for type 2 diabetes. Patients may need to try more than one type of pill, combination of pills, or pills plus insulin.

5. **Insulin in type 2 diabetics**: Uncontrolled hyperglycemia damages pancreatic ß cells which further decreases insulin production and secretion. Adding insulin assists in achieving normal glucose levels that allows pancreatic islets and ß cells to rest, reduces the production of islet antibodies and may prevent further ß cell destruction.

   a. **Insulin is prescribed in about 40% of type 2 diabetics based on several factors:**

      (1) How long the patient has had diabetes
      (2) How high their blood glucose level is
      (3) What other medicines they take
      (4) The patient's overall health

   b. Insulin may be appropriate early if glucose levels are higher than 250 mL/dL, glycated hemoglobin is about 10% or the patient has symptoms of hyperglycemia. Insulin improves the lipid profile. However, it may be associated with hypoglycemia and weight gain.

VI. **Gestational diabetes mellitus (GDM)**

A. **Incidence/those at risk:** GDM occurs in 3%-8% of all pregnancies but is more prevalent in those over 30, who have a family hx of DM, are of African American, Hispanic, and Native American descent; have given birth previously to a very large infant, a stillbirth, or a child with a birth defect; or have too much amniotic fluid (polyhydramnios).

B. **Pathophysiology:** The pancreas functions normally but the extra metabolic demands require more insulin than is normally produced (relative insulin deficiency). Problem is compounded by various secondary hormones produced by the placenta during pregnancy, i.e., cortisol, estrogen, and human placental lactogen (HPL) that make pt insulin resistant, starting about the 24th to 28th weeks of gestation. Ketosis occurs because of ↑ fat metabolism.

C. **Consequences to the fetus:** GDM is associated with increased fetal complications due to maternal hyperglycemia. The extra sugar goes to the baby who makes extra insulin in an effort to lower its blood glucose.

   1. The infant converts the extra glucose to fat, resulting in large baby (**fetal**

> **macrosomia** or "large body") that may experience a shoulder dystocia at delivery.

2. The infant is also at risk for **hypoglycemia** following delivery as fetal insulin was secreted in response to the mother's high blood glucose and that supply is cut off at birth. Fetal hypoglycemia is most likely if the mother's glucose level was high during the last few days before delivery.

3. **Jaundice:** The infant may have a build-up of bilirubin causing jaundice and may need to be placed under special lights at the hospital.

4. High levels of maternal **ketones** will pass across the placenta and are dangerous for the baby. High maternal blood sugars may also cause preterm deliveries and rarely, stillbirth.

D. **Maternal consequences:** GDM usually has no symptoms and needs to be diagnosed during prenatal care. Most women complete pregnancy and labor without problems. There is a slightly increased (5%) risk for preeclampsia. If the baby is too large, a C-section may be necessary. After delivery, most women return to normal metabolic function, but nearly 2% remain diabetic, 8% have blood sugars that are higher than normal, but not high enough to be called diabetic, and 20%-50% are at risk of developing diabetes within 5 to 10 years. Maintaining a reasonable body weight and being physically active may help prevent development of type 2 diabetes. Obese women have the highest risk of developing diabetes after having GDM.

1. Screening recommendations for gestational diabetes are to use risk factor analysis and an oral glucose tolerance test, if appropriate. Women diagnosed with gestational diabetes should be screened for diabetes 6 to 12 weeks postpartum and should have subsequent screening for the development of diabetes or prediabetes.

2. **Treatment** includes careful glucose control, moderate exercise, and 20%-50% may be taking insulin. The amount of insulin needed will increase as the pregnancy progresses as a normal result of the baby's growth. Maternal insulin does not cross the placenta, but mom's extra blood sugar will.

VII. **Other specific types of diabetes**: Other types are rare (1%-2% of all diagnosed cases), but represent eight different causes of altered glucose metabolism. These include genetic defects of beta cells, genetic defects in insulin action, diseases of the pancreas, several endocrine diseases, drug or chemical injury to the pancreas, infectious diseases which attack the pancreas, rare immune disorders, and other genetic syndromes sometimes associated with diabetes.

VIII. **Hyperglycemia without DKA**

A. Just because a patient's glucose level is high, does NOT mean that they have DKA or HHNS. A number of things can cause hyperglycemia. A type 1 diabetic may not have given themselves enough insulin. A type 2 diabetic may have enough insulin, but it is not as effective as it should be. The patient may have eaten more than planned or exercised less than planned. The stress of an illness, such as a cold or flu, AMI, or other condition can also cause hyperglycemia as can other stresses such as family conflicts or school or dating problems.

B. **Hyperglycemia without dehydration and other S/S of DKA or hyperosmolar syndrome IS NOT treated with consecutive fluid challenges.** Assess the patient carefully to discover possible causes of the hyperglycemia and treat those.

Two extreme complications of uncontrolled diabetes are DKA and HHNS: Severe results of uncontrolled hyperglycemia and metabolic disruptions need immediate attention. Patient presentations are not always clear-cut as they may exhibit S&S of both.

IX. **Diabetic ketoacidosis** (DKA)

A. **Epidemiology**: Occurs in type 1 DM due to a total lack of insulin resulting in **uncontrolled hyperglycemia, dehydration and acidosis**.

B. **Causes**

1. Imbalance between food intake and insulin availability
2. Improper use of insulin
3. Puberty
4. Exercise
5. Stress
6. Illness/infection (look for occult focus)
7. Pregnancy
8. Myocardial infarction; stroke

C. **Pathophysiology of DKA**

1. To understand the complex pathophysiology of diabetic ketoacidosis, one must keep in mind that diabetes affects much more than glucose metabolism. Insulin deficiency severely distorts the metabolism of all three macronutrients -proteins, fats, and carbohydrates. Without insulin, glucose is not taken up by the cells.

2. Even though blood glucose may be high, as tissues starve for lack of usable sugar and a glucose deficiency is sensed **within the cells** and glucagon and other counterregulatory hormones are released.

3. As tissues starve due to lack of usable sugar, the body tries to compensate in three ways:

   a. **Hunger increases:** The patient consumes more food (**polyphagia**) but the carbohydrates cannot be used, raising blood sugar levels even higher.

   b. The liver converts amino acids taken from muscle tissue into glucose (**proteolysis**).

   c. Fat deposits are broken down, releasing fatty acids to be oxidized as fuel (**lipolysis**).

4. Sensing a glucose deficiency within the muscle cells, the liver begins releasing additional glucose into the bloodstream via **gluconeogenesis** and **glycogenolysis**.

   These processes worsen the hyperglycemia because there is no functioning insulin available to transport the glucose into the cells. Unusable glucose accumulates in the blood faster than the kidneys can get rid of it.

5. As hyperglycemia worsens, the **plasma becomes hypertonic**, pulling fluid from the cellular and interstitial spaces into the bloodstream to dilute the plasma. This causes **cellular dehydration**.

6. Osmo receptors in the brain sense the dehydration and activate the thirst center resulting in **polydipsia**. **ADH (vasopressin)** is released from the posterior pituitary to promote water retention.

7. When blood glucose levels rise above 180 mg/dL), sugar is spilled into the urine (**glycosuria**). You can't urinate "sugar cubes", so the spilled sugar pulls extra water with it producing an **osmotic diuresis** (**polyuria)** which may result in a total body water loss of 6 L or 10% of the body weight in adults and 50 - 100 mL/kg in children.

8. Uncorrected diuresis will result in a state of hypovolemia, **dehydration**, and decreased renal perfusion leading to a reduction in glomerular filtration rate (GFR), decreased renal function, and decreased urine output.

9. **Hepatic ketogenesis**: When the body breaks down fats, waste products called **ketones** are produced. The body cannot tolerate large amounts of ketones. In normal metabolism, muscles break down ketone bodies and small amounts pose no danger. But in a diabetic, they accumulate rapidly, overwhelming the liver's ability to metabolize them. This build up of ketone bodies is called *ketosis*.

10. In DKA, ketoacids overpower the buffer system and propel the patient into **ketoacidosis**. This process of ketogenesis occurs in only 10% of diabetics explaining why some develop ketoacidosis while others develop Hyperglycemic Hyperosmolar Non-Ketotic Syndrome (HHNS).

11.　Acetoacetate is spontaneously converted to **acetone**, which does not contribute to the acidosis (Jones, 1994). Acetone is excreted by the lungs, producing a **fruity or alcohol odor on the patient's breath**.

12.　Acidosis also causes life-threatening electrolyte imbalances.

Potassium imbalance is the single most common cause of death in DKA. In an acidosis, K shifts out of cells to the intravascular compartment causing hyperkalemia. The osmotic diuresis causes eventual loss of potassium, calcium, phosphorous and magnesium. Initial serum potassium may be high, normal, or low. The most dangerous situation is that in which serum K levels remain normal in the face of severe total potassium depletion. This phenomenon can occur when polyuria and vomiting cause large electrolyte losses while potassium shifts from the cells to the bloodstream, deceptively boosting serum levels temporarily. Normal and low levels represent severe K deficits. Hypokalemia ($\downarrow$ K) further decreases insulin release.

| ECG changes with hyperkalemia	ECG findings with hypokalemia
▪ Peaked T wave (See below)	▪ Low voltage of all EKG waves
▪ Depressed S-T segments	▪ Flattened T wave
▪ Disappearance of the P wave	▪ Depression of S-T segment
▪ Widened QRS (sine waves)	▪ Presence of U wave
▪ Cardiac arrest: asystole	▪ Dysrhythmias; PACs → VF
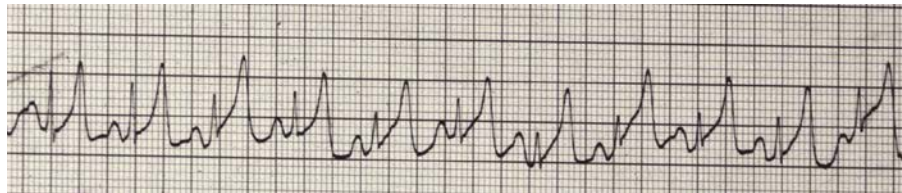
13.　**Mental status:** Up to this point, the brain has been using glucose as neural cells are not insulin-dependent and mental status has been relatively normal. However, the combination of **dehydration and acidosis** directly depress brain function leading to a **decrease in the patient's level of consciousness over days**. Without treatment, the patient gradually drifts from drowsiness to stupor to coma as the dehydration depresses CNS function.

D.　**Compensatory mechanism**: At a pH of 7.2, respiratory centers sense the acidosis and increase the rate and depth of ventilations (**Kussmaul pattern**) to rid the body of CO_2 to compensate for the acidosis. This is often the symptom that causes a patient to seek help.

E.　**Essential aspects to assess**

1.　Blood glucose level
2.　Volume/hydration status
3.　Degree of neurological impairment
4.　Severity of metabolic acidosis
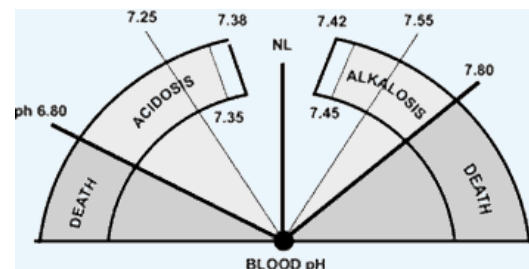
F.　**Clinical presentation of DKA based on the two limbs of pathology**

Dehydration (due to ↑ serum osmolality and osmotic diuresis)	Acidosis (due to ketone formation)
▪ Dry mouth, tongue and mucous membranes ▪ Poor skin turgor ▪ Soft, sunken eyes	▪ Sensation of shortness of breath ▪ Kussmaul respirations (pH < 7.2; may be depressed when pH < 6.9)

▪ Tachycardia ▪ (Orthostatic) hypotension ▪ Malaise, weakness ▪ Anorexia, nausea/vomiting ▪ Polydipsia (thirst) ▪ Polyuria (plus high levels of sugar in the urine) ▪ Electrolyte depletion; pseudohyponatremia; ↓ K, ↓ Mg, ↓ Ca ▪ ↓ muscle tone (especially if ↓ serum K^+ is present) ▪ CNS depression (H/A, drowsiness, confusion to coma)	▪ Dysrhythmias from potassium imbalance ▪ Seizures ▪ Nausea/vomiting ▪ Crampy musculoskeletal/diffuse abdominal pain ▪ Ketonuria

G. **The patient is said to be decompensated when they exhibit**

1. warm, flushed, dry skin from dilated peripheral vascular beds;
2. hypothermia due to vasodilation;
3. decreased level of consciousness; and
4. anuria.

H. **Treatment if patient is diabetic, has elevated glucose; is dehydrated and has S&S of acidosis (Kussmaul ventilations; + urine dipstick for ketones):**

1. Determine time & amount of last dose of diabetic medication/insulin & last oral intake
2. Vomiting & seizure precautions prepare suction
3. Obtain & record glucose level
4. Assess for medic-alert jewelry
5. Secure and maintain airway; especially if AMS
6. O_2 12-15 L/NRM: **DO NOT** attempt to stop Kussmaul ventilations!
7. Monitor ECG for dysrhythmias and changes to the T wave
8. IV NS wide open up to 1 liter **if not contraindicated** followed by consecutive 200 mL fluid challenges.
   a. The patient may have a 5-6 L fluid deficit. One liter can be safely given WO in severe dehydration if there is no cardiac history, dyspnea, or crackles suggesting possible HF or pulmonary edema. Continually monitor breath sounds and respiratory effort after each 200 mL in elderly of those with a history of CV disease to check for fluid overload. Fluid resuscitation alone can reduce hyperglycemia and acidosis. Blood sugar will drop 18% after 1.5 liters of NS without giving any insulin. Increased perfusion will improve tissue oxygenation, ↓ formation of lactate and reduce the severity of acidosis. Attempt to maintain SBP > 100.
   b. In children, replace fluid at a rate of 20 mL/kg in 15-20 minute boluses. Children may not need massive fluid replacement. Cerebral edema is more prevalent in children from fluid resuscitation and changes in level of consciousness need to be observed to alert you to edema formation.

X. **Hyperglycemic hyperosmolar nonketotic syndrome (HHNS)**

A. **Incidence**

1. Occurs approximately 1/6th as often as DKA
2. Patients are generally elderly (mean age near 60)
3. Those with a hx of DM have mild type 2 disease
4. Up to 2/3 of patients have no history of DM, and HHNS is the presenting sign

B. **Morbidity/mortality:** High potential for significant morbidity and mortality (24%) related to precipitating conditions, coexisting diseases requiring numerous medications, and the older age of the patients. Cardiovascular and renal diseases are common histories. There has been no correlation between the degree of hyperglycemia or hyperosmolarity and mortality.

C. **Precipitating factors**

1. Infection (vial and pneumonia; sepsis, particularly gram-negative)
2. Renal insufficiency or urinary tract infection
3. GI hemorrhage
4. Stroke; MI
5. Pancreatitis
6. Drugs: thiazide diuretics, Lasix, phenytoin (Dilantin), glucocorticoids, cimetidine, chlorpromazine, ß blockers (lol's), chlorthalidone, and ethacrynic acid
7. Trauma; burns
8. Surgery; dialysis; hyperalimentation

D. **Pathophysiology**

1. The patient experiences a combination of pancreatic and renal insufficiency precipitated by the above causes.

2. Normally, patients with hyperglycemia respond with an increase in insulin secretion. Older patients are more likely to have pancreatic ß-cell insufficiency, so the response may be inadequate.

3. The combination of **impaired insulin secretion** plus the catecholamine-induced **depression of insulin function** leads to **profound hyperglycemia** (often above 800-1000 mg/dL), which is higher than the levels seen in DKA.

4. Glucose excretion is impaired due to compromised renal function from pre-existing renal disease and/or dehydration further aggravating hyperglycemia.

5. The mechanisms leading to an osmotic diuresis are the same as DKA

   a. Cellular dehydration results from massive water shifts to the vascular space and the impaired ability to reabsorb water and electrolytes.

   b. Preservation of circulating volume means that hypotension is a late sign even in the presence of massive total body water losses due to diuresis. **Total fluid losses often range from 8-12 L.**

   c. Osmotic water loss causes concurrent losses of Na and K. Patients frequently need 400-1000 mEq of potassium at the hospital to restore losses.

6. Unlike DKA, **ketosis is absent** or minimal because there appears to be enough insulin secretion to block release of counter-regulatory hormones and lipolysis, thereby suppressing ketoacid formation but not hyperglycemia.

7. Patients with HHNS have at most a mild ketosis (perhaps from starvation as well as hyperglycemia) and mild acidosis (perhaps from lactic acidosis) but a **profound state of dehydration** and **hyperosmolality** that is greater than in DKA.

8. Rarely, patients will have both DKA and HHNS

E. **History of chief complaint**

1. Lack of history of DM or may have known type 2 DM
2. History of underlying disease that can precipitate HHNS: pneumonia etc.
3. More prolonged symptom onset than DKA - stay at home longer due to absence of acidosis (S&S that usually brings them in earlier)

F. **Clinical presentation of HHNS:** Dehydration; **no ketosis**

1. **No ketosis so no Kussmaul ventilations**; no acetone odor to breath; no abdominal pain, anorexia or vomiting
2. **Severe dehydration**: Mucous membrane/skin turgor exams may be unreliable in elderly. Fluid deficit of 24% is common in this condition.
3. **Major depression in mental status:** Confusion to delirium to coma.
4. **Fever** due to infection; may be due to central hyperpyrexia ($\uparrow$ core body temp)
5. **Polydipsia**; Diminished thirst response of some elderly contributes to high osmolality. Their usual state of health/disability may prevent access to fluids.

6. **Polyuria** - Sustained osmotic diuresis that may transition to anuria

7. **Glucose monitor reads HHH or high** (600 mg/dL plus common)

8. Excessive loss of electrolytes; severe potassium deficits

9. **Shock**, especially in those with infections

10. **Seizures**; partial or generalized

11. Myoclonus (twitching of muscles)

12. Hemianopsia (blindness in one-half of field of vision in one or both eyes)

13. Nystagmus; blurred vision; visual hallucinations

G. **Prehospital treatment is the same as for DKA**

1. Reliable venous access with fluid challenges of NS. Hospitals should replace ½ of estimated total water losses in first 12 hours. Do not correct too quickly.

2. Treat generalized tonic clonic seizures with midazolam.

Clinical Features	DKA Hyperglycemia w/ ketosis	HHNS Hyperglycemia w/o ketosis
Median age	38	61
Anorexia, nausea, vomiting	+	-
Crampy, musculoskeletal pain	+	-
Neurological abnormalities	Uncommon	Common
Dehydration	Common	Common
Kussmaul respiration	+	-
Hypotension	15%	30%
Ketonuria	Mark	Moderate to none
Acidosis	Common	Uncommon
Mortality rate	5-20%	40-70%

XI. **Hypoglycemia**

A. **Definition**: Acute hypoglycemia is defined as a very rapid drop in the blood glucose to < 70 mg/dL. While low level targets vary between individuals based on age, medical condition, and ability to sense hypoglycemic symptoms, levels below 45 mg/dL are almost always associated with a serious abnormality. Patients who have been diabetic for a long time may show S&S of hypoglycemia when blood levels are above 60 mg/dL.

B. **Causes**

   1. Too much insulin or oral hypoglycemic medications: Sulfonylureas, meglitinides, D-phenylalanine derivatives, combination oral meds
   2. Getting more exercise than usual; increased glucose metabolism
   3. Missed or delayed meals; eating less food than usual; starvation
   4. Alcohol use: Suppresses gluconeogenesis (liver is prevented from manufacturing glucose); alcohol also increases potency of drugs that reduce glucose levels such as insulin and ß-blockers. Young people, especially when they drink and have hypoglycemia and pass out are often viewed by friends as just being drunk. They could be dead from hypoglycemia. If you drink…EAT.
   5. Early pregnancy
   6. Aspirin, beta blocker ingestion
   7. Rapid gastric emptying
   8. Insulin producing tumors (insulinomas), some breast & adrenal cancers
   9. Thyroid insufficiency
   10. Chronic renal failure; renal insufficiency
   11. Hepatic failure
   12. Sepsis
   13. Any acute illness in a child

C. **Signs and symptoms**

   1. **Early S&S:** Evidence of sympathetic NS stimulation; Late: CNS depression

▪ Restlessness, shakiness, dizziness ▪ Confusion or sudden moodiness or bizarre behavior such as crying for no reason ▪ Irritability - can be violent ▪ Clumsiness or hyperactivity ▪ Inability to concentrate ▪ Pale skin color; tachycardia ▪ Tingling sensations around the mouth	▪ Headache; trembling ▪ Diaphoresis, cool skin ▪ Hunger; lack of energy ▪ Hypothermia ▪ Chest pain; cardiac ischemia; dysrhythmias (heart needs glucose to function) ▪ Seizures ▪ Fainting → coma

   2. **Hypoglycemic unawareness**: The longer a patient is diabetic, the less obvious are S&S of hypoglycemia and this becomes a very dangerous situation. Mechanisms

that raise blood sugar become less effective, so hypoglycemia can occur quickly without recognizable symptoms (hypoglycemia unawareness). Patients who have been diabetic > 10 years may not present with the classic symptoms. They may lose consciousness without ever knowing their blood glucose levels were dropping. They may present with numbness and/or tingling (around the mouth especially), yawning, and/or heaviness in the legs before rapidly losing consciousness.

    a. Hypoglycemia unawareness does not happen to everyone. It is more likely in those who have neuropathy, are on tight glucose control, and those who take certain heart or high blood pressure meds.

    b. As the years go by, many people continue to have symptoms of hypoglycemia, but the symptoms change. In this case, someone may not recognize a reaction because it feels different. They are not usually controlled as tightly as the "norm". Blood sugar levels for them are considered good at 150-200. **Treat low or dropping sugar levels even if the patient feels fine.** Patients should tell their physician if their blood sugar drops to less than 50 w/o any signs or symptoms.

D. **Obtaining blood for glucose monitoring**

1. **Assess glucose** on all patients with alcohol intoxication and/or altered mental status. Both are at risk for hypoglycemia.

2. Access capillary blood using lancets, a test strip and a glucose meter. At least 25 different meters are commercially available. They differ in several ways including

    a. Technology used to read the sample
    b. Allowable testing sites and amount of blood needed for each test
    c. Testing speed
    d. Overall size
    e. Ability to store test results in memory: Several models can record and store a number of test results
    f. Cost of the meter
    g. Cost of the test strips used

3. Point of care blood glucose meters vary in the **technology** used to read the sample and provide a glucose reading. Most use plastic or paper strips comprising electrochemical cells which contain the enzymes glucose oxidase, glucose dehydrogenase (GDH)-pyrroloquinoline quinone (PQQ), GDH-flavin adenine dinucleotide (GDH-FAD), or GDH-nicotinamide adenine dinucleotide (GDH-NAD) and a redox mediator.

"Blood placed on the test strip undergoes a complex biochemical reaction. The plasma separates from the whole blood and diffuses through an internal layer of the test strip containing the enzymes and electrodes. The enzymes catalyze the conversion of glucose to gluconic acid and the electrons resulting from this reaction generate a current calibrated to measure the concentration of glucose in the sample" (Hirsch et al, 2010).

Glucose oxidase method: Cobas® B221 [Roche Diagnostics], OneTouch® Ultra [LifeScan]

GDH-FAD method: Contour® TS {Bayer])

GDH-PQQ method: Accu-Chek® Inform [Roche], FreeStyle® Mini [Abbott]

4. **Allowable testing sites – sample size – meter operation:** Some meters allow blood to be sampled from the forearm, abdomen, or thigh instead of a finger. Some pull minute amounts of blood into the test strip like a straw rather than needing a full drop of blood to be placed on the end and interpret the results in 5 seconds instead of 30. Some models have automatic timing, error codes and signals, or barcode readers to help with calibration. Patients with arthritis need a monitor with easy to use buttons and those with vision impairments need a screen with large numbers or a voice-activator.

5. **Measurement range**. Interpret very high or low values carefully. Glucose readings are not linear over their entire range. If you get an extremely high or low reading, first confirm it with another reading. Also consider checking the meter's calibration.

   a. Low means < 20
   b. High means > 500

6. **Whole blood glucose vs. plasma glucose readings:** Glucose levels in plasma are generally 10-15% higher than glucose measurements in whole blood (and even more after eating). This is important because blood glucose meters measure the glucose in *whole blood* obtained in a fingerstick while most lab tests measure the glucose in *plasma* obtained from a blood sample.

   Depending on the type of meter, the mean glucose value for a particular test sample varied by >30% at glucose levels higher than 150 mg/dL and by 60% at levels in the hypoglycemic range (Dungan et al, 2007). This variability may stem from analytical differences or operator error.

   Fingerstick blood glucose testing may give inaccurate results when peripheral blood flow is decreased as in shock, severe hypotension, cardiac arrest, hyperosmolar hyperglycemia and severe dehydration. A venous sample may be preferable in these pts. See procedure on obtaining venous sample from IV catheter.

7. **Factors that affect the accuracy of glucose meter readings**

   Check the meter to determine the potential for substance interferences in the blood that may affect the reliability of results. These interferences may result in false high or low readings depending on the enzymatic reaction of the test strip being used.

   a. **Dehydration** can falsely lower results in some units.

   b. **Oxygenation**: High oxygen tension (pO_2 > 100 mm Hg) can falsely decrease glucose readings on some glucose oxidase-based blood glucose meters, especially when patients are receiving oxygen therapy. Conversely, glucose levels obtained at higher altitudes may be overestimated by as much as 15% with glucose-oxidase meters. In general, lower oxygen levels (40 mm Hg) have a negligible effect on glucose readings. Strips that use GDH as the enzyme are less affected by oxygen (Hirsch et al, 2010).

   c. **Hypotension.** Hypotension may reduce perfusion and increase glucose utilization, potentially masking true blood glucose levels. Peripheral hypoperfusion may cause glucose strip readings to vary from lab values by more than 20% (too high and too low). Fingerstick results may result in undetected hypoglycemia when a lower limit of 80 mg/dL is targeted in patients with hypoperfusion. Carefully confirm a clinical correlation to meter readings in these patients (Hirsch et al, 2010).

   d. **Maltose containing drugs:** Maltose is used in certain biological products as a stabilizing agent and osmolality regulator. Since maltose is a disaccharide derived from two units of glucose, its presence in the circulation may result in the overestimation of blood glucose levels with GDH-PQQ-based systems. When taking a medication history, it is important to clearly identify at-risk patients, particularly those with diabetes who are immunocompromised or on peritoneal dialysis. A drug-device interaction can occur up to a week or more after maltose-containing medications are administered. EMS personnel should note that their GDH-PQQ meters may be inaccurate when assessing these patients (Hirsch et al, 2010).

Product	Approved indication
Icodextrin products	
Extraneal	Long-dwell during CAPD and APD in patients with ESRD
Adept® Adhesion Reduction Solution (4% icodextrin)	Reduce post-surgical laparoscopic adhesions in gynecological surgery
Immunologic agents	
Orencia® (abatacept)	Rheumatoid arthritis
Octagam®	Primary immunodeficiency
WhinRho® SDF Liquid	Immune thrombocytopenic purpura and suppression of Rh isoimmunization
HepaGam B®	Prevention of hepatitis B recurrence following liver transplant and post-exposure prophylaxis
Bexxar®	Non-Hodgkins lymphoma

(Hirsch et al, 2010)

e.   **Peritoneal Dialysis.** Diabetes is the most common cause of dialysis-dependent renal failure in the Western World. The high prevalence of patients with end-stage renal disease (ESRD) has created an increasing demand for peritoneal dialysis. Dialysis solution typically contains dextrose as an osmotic agent to allow water to pass across the peritoneum, but this osmotic effect may quickly diminish. Alternative dialysis solutions containing icodextrin, a glucose polymer, were developed to prolong ultrafiltration in patients on continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis. Icodextrin is hydrolyzed to oligosaccharides, such as *maltose*, which are ultimately cleared by dialysis into the peritoneal cavity. Because absorption of icodextrin from the peritoneal cavity is relatively slow compared with that of dextrose, it is ideal for ultrafiltration over long dwell times. Multiple studies have shown that meter-read glucose levels are overestimated (too high) by an average of 60 mg/dL in these patients when using GDH-PQQ technology. Given the increasing understanding of risks associated with such discrepancies, alternatives to GDH-PQQ point-of-care monitoring should be actively pursued when treating peritoneal dialysis patients in any clinical setting (obtain venous samples to run in the lab if possible). Because renal failure and dialysis have a destabilizing effect on insulin and glucose metabolism, closely monitor these patients for a clinical correlation to their meter readings (Hirsch et al, 2010)

f.   **Drugs:** Acetaminophen, ibuprofen (Motrin, Advil), salicylates, tetracycline, mannitol, dopamine, L-dopa, tolazamide. Acetaminophen is associated with accidental and intentional poisoning and, at certain concentration levels, can affect some blood glucose meter readings. Although the interference of acetaminophen administered at therapeutic doses is negligible, all patients metabolize drugs differently so the concentration level at which an analytical interference may occur varies from patient to patient. Glucose concentration must be verified by laboratory techniques whenever an overdose is suspected.

g.   **Ascorbic acid** interfered with the measurements on all meters.

h.   **Hematocrit**. Patients with higher hematocrit values will usually test lower for blood glucose than patients with normal Hematocrit levels. Patients with lower hematocrit values will test higher. RBCs in a whole-blood sample can alter the ratio of blood glucose to plasma glucose, as well as the flow of plasma and delivery of oxygen into the test strip (Hirsch et al, 2008). The presence of an increased number of red

blood cells in the capillary blood could "mechanically" impede diffusion of the plasma through the layers of the strips, decreasing the volume of plasma available to the enzymatic reaction. So, for example, hypoglycemia could be masked in patients with anemia (hemorrhage) or glucose underestimated in patients with Polycythemia.

Hematocrit may also be affected by microclots in the blood samples or on the test strips, protein deposition, fibrin aggregation, and hemolysis. It is particularly important to consider hematocrit when treating patients with diabetes who smoke, live at high altitude, or present with anemia, sickle-cell disease, dehydration, polycythemia, or end-stage renal failure (Hirsch et al, 2010).

i. **Altitude, temperature and humidity**. Altitude, temperature, and humidity can cause unpredictable effects on glucose results. Low temperatures decrease circulation to the skin and may produce either positive or negative errors regardless of the enzyme method. Active warming could reduce the potential for erroneous results; the significance of fever is not known. Clinicians should remain aware that test strips exposed to extremes of temperature, humidity, or high altitude may produce falsely elevated readings (Hirsch et al, 2008). Check the meter and test strip package insert for information on these issues.

j. **Meter and strip maintenance** is important to yield accurate results. Make sure the meter and strips are stored and handled according to manufacturer's recommendations, are not outdated, and that the unit is appropriately calibrated for each set of strips.

k. **Third-party test strips**. Third-party or "generic glucose reagent strips" are developed as a less expensive option than the strips that the manufacturer intended to be used with the meter. These are not approved for use in the NWC EMSS. Test strips must be compatible with the glucose meter. Manufacturer changes to their meters or test strips are not always communicated to the third-party strip manufacturers. This can make third-party strips incompatible with your meter without your knowledge. Differences can involve the amount, type or concentration of the chemicals ("reagents") on the test strip, or the actual size and shape of the strip itself. Meters are sensitive to these features of test strips and may not work well or consistently if they are not correct for a meter.

Variables that Alter Blood Glucose Measurement*

Variable	Effect on reading
Hematocrit	
Anemia	Increases (GO & GDH)
Polycythemia	Decreases (GO & GDH)
Oxygen concentration	
Hypoxia (high altitude)	Increases (GO)
Oxygen therapy	Decreases (GO)
pH (6.8-7.55)	
Low pH	May decrease (GO)
High pH	May increase (GO)

Hypothermia	Increases (GO & GDH) or decreases (GDH)
Hypotension	Increases (GO & GDH) or decreases (GDH)
Uric acid	Decreases (GO)
Drugs	
Ascorbic acid	Increases (some GDH) and decreases (GO)
Acetaminophen	Variable (GO and GDH)
Dopamine	Variable (GO and GDH)
Icodextrin	Increases (GDH-PQQ only)
Galactos	Increases (GDH-PQQ only)
Xylose	Increases (GDH-PQQ only)
Tolazamide	Variable (GO)
Mannitol	Increases (GO)

Consult product package inserts for updated information regarding meter accuracy and interfering substances. GO = glucose oxidase (Hirsch et al, 2010).

E. **Obtaining a glucose reading using the Precision Xtra meter – See skill sheet**

1. Use a lancet to obtain a small drop of blood from the **side** of the finger. Do not use a lancing device as they pose a risk of transmitting blood-borne diseases between patients. Do not manipulate an IV catheter in any way including by milking it or blowing into it. The dates and times do not need to be set as the long term memory function is not used and we are not averaging readings over weeks. The NWC EMSS does not use ketone test strips at the present time.

2. Place a small sample of blood on a disposable "test strip" and place the strip in the meter. Meters measure glucose in different ways. Some measure the amount of electricity that can pass through the sample. Others measure how much light reflects from it. Refer to monitor manual to interpret error codes and troubleshoot the problem.

3. Carefully read all instructions for your meter and test strips. Calibrate the meter or test it to be sure it's calibrated before you use it.

4. Be sure that you're using test strips that are specified to work with your meter. Even if an incorrect test strip fits in your meter, it could give you the wrong results. Don't use test strips from a cracked or damaged bottle and don't use test strips that have passed their expiration date.

5. Once you're ready to test, wash your hands, because even a little bit of food or sugar can affect the results. Make sure the drop of blood is the right size. Let the blood flow freely; don't squeeze your finger, since that can affect the results. Always use a whole test strip and insert it into the meter until you feel it stop against the end of the meter guide.

6. Storage and maintenance are important, too. Be sure to keep your meter clean, and test it regularly with control solution. Have extra batteries charged and ready. Heat and humidity can damage test strips, so replace the bottle cap promptly after removing a strip. And store your meter and supplies according to manufacturer instructions.

7. What about glucose meters that allow you to use blood from places other than fingertips, such as the upper arm, forearm, base of the thumb, and thigh? This can give you more options. But blood from a finger stick shows changes in glucose levels more quickly than blood from other parts of the body. That means that glucose levels from these other places may not always be as accurate as

readings from the fingertips, particularly when glucose levels are changing rapidly, including after a meal, after taking insulin, during exercise, or when you're ill or under stress. During these times, you should use blood from a finger stick. You should also use fingertip blood if you think your blood glucose is low, if you don't usually have symptoms when your blood glucose is low, or if the result from the alternative site doesn't match how you feel.

8. **TEST ERROR 1**

   a. Indicates meter temperature is out of range
   b. Move normally heated/cooled area and wait 12 minutes

9. **TEST ERROR 2-4**

   a. Generally, repeat test with another strip
   b. If message still appears contact EMS Coordinator

F. **Treatment:** Focused on increasing the blood sugar after performing IMC and assessing blood glucose levels as being low.

1. If GCS is 14 or 15 and patient is able to swallow, 10-15 grams of rapidly acting oral carbohydrates will increase blood glucose effectively. Examples:

   a. 3 or 4 glucose tablets to add up to 15 grams of carbohydrate
   b. 1 serving of glucose gel (Insta-Glucose, Glutose, Dextrasol, or gel frosting) = 15 gms of carbohydrate
   c. ½ cup (4 oz) fruit juice, 1 c (8 oz) milk, or ½ cup regular (not diet) soft drink
   d. 6-8 jelly beans; 5-7 pieces hard candy; 5 small sugar cubes
   e. 1 tablespoon of sugar or honey.

2. **Do not use chocolate or ice cream** to reverse hypoglycemia as the large fat content slows absorption of the sugar so blood glucose levels rise more slowly. This places the patient at risk of prolonged hypoglycemia. When the sugar is finally absorbed, the patient may become profoundly hyperglycemic due to excessive ingestion of sugar-containing substances and stimulation of counter-regulatory hormones (cortisol, epinephrine).

3. **If oral substances are contraindicated or the patient has AMS after IMC**

   a. **DEXTROSE should be administered IV/IO**.
      (1) **If borderline (60-70)**   Dextrose 10% 25 mL (12.5 Gm) IVPB
      (2) **If < 60 or low:**   Dextrose 10% 50 mL (25 Gm) IVPB
      (3) Peds patients (1-8):   Dextrose 25% at 2-4 mL/kg
      (4) Infants (0-12 mos):   Dextrose 10%-12.5% at 5-10 mL/kg

   b. **Notes on dextrose:** Start the IV in a large, more proximal (not hand) vein when dextrose administration seems likely. Confirm patency of vascular access line before infusing dextrose. Ex: Lower the IV bag and look for a flashback in the chamber. Dextrose can cause tissue necrosis if it infiltrates. Notify OLMC ASAP if the IV infiltrates while dextrose is being administered. If dextrose is given to a known alcoholic, alert the ED staff that you did not give thiamine. Dextrose may cause severe neuro S&S in alcoholics without thiamine. It may also cause intracranial hemorrhage and vein sclerosis in neonates if not diluted prior to administration.

   c. If no IV/IO: **GLUCAGON** 1 mg IM/IN

Profile: glucagon (Glucagen)	
Action	▪ Endogenous hormone synthesized by the alpha 2 cells of the islets of Langerhans. ▪ Action opposes insulin. Increases blood glucose by promoting the breakdown of glycogen stores in the liver to glucose (glycogenolysis). The degree to which glucagon ↑ blood glucose is dependent on liver glycogen reserves. ▪ Relaxes smooth muscle of the GI tract

Profile: glucagon (Glucagen)	
	▪ Positive inotropic and chronotropic effects on the heart by ↑ the production of adenylate cyclase which catalyzes the conversion of APT to cAMP. This initiates a series of enzymatic reactions that promote the breakdown of glycogen to glucose. The degree to which glucagon ↑ blood glucose is dependent on liver glycogen reserves and the presence of phosphorylases.
Onset of action	Max activity occurs w/in 30 min; glucose returns to normal or hypoglycemic levels w/in 1-2 hrs.
Indications	Treatment of severe hypoglycemia when vascular access is unsuccessful. Cardiac stimulant in ß blocker and Ca channel blocker overdose
Packaging	Packaged as a powder to be mixed with diluent.
Dose & Route	Adult: 1 mg IM/IN/IV/IO Peds: 0.03 mg/kg IM/IN/IV/IO
Side Effects	➢ Chest pain, palpitations ➢ Unusual weakness ➢ Dizziness or lightheadedness ➢ Muscle cramps ➢ Difficulty breathing ➢ Nausea/vomiting ➢ Rash; itching
Contraindications	Adrenal gland dysfunction, malnutrition, chronic hypoglycemia, pancreatic tumors, pheochromocytomas (adrenal gland tumors), liver disease.

Observe and record responses to treatment. Recheck glucose level in 5 minutes if IV/IO dextrose given. If still less than 70, repeat dextrose as necessary.

G. **Under what circumstances can a diabetic patient who has been unconscious with hypoglycemia refuse transport and what precautions must be taken?**

1. **Hypoglycemic patients are not considered decisional**. When hypoglycemia is corrected and confirmed by a repeat dextrose reading, they can be assessed for decisional capacity to refuse care.

2. **Decisional capacity** means the ability to understand and appreciate the nature and consequences of a decision regarding medical treatment or foregoing treatment and the ability to reach and communicate an informed decision in the matter as determined by the attending physician. 755 ILCS 40/10 (1996), as amended by P.A. 90-246.

3. The **test of decisional capacity** is whether or not a patient understands their condition, the nature of the medical advice given, and the consequences of refusing to consent. This can be determined by applying the following assessments:

    a. **Affect**: Is the patient's behavior consistent with the environmental stimuli?

    b. **Behavior**: Is the patient able to remain in control?

    c. **Cognition/judgment**: Does the patient understand the relevant information? Do they have the ability to manipulate the information? Can they draw reasonable conclusions based on facts? Can they communicate a choice?

    d. **Insight**: Can the patient pull all of these together to appreciate the implications of the situation and the consequences of their decision?

4. Inform the patient/guardian of the risks inherent in refusing care and/or transportation. Execute s refusal of service per policy.

5. Patients, in which BLS care was provided and are, now refusing transport, require OLMC documentation. (See Policy R-6, Refusal of Service stating, "BLS patients refusing care and/or transportation in whom a high risk potential exists are to be called in on the MERCI (VHF) radio. If no MERCI (VHF) radio is available, a standard phone line may be used.)

6. **Why does hypoglycemia due to oral diabetes pills place a patient at high**

risk and why should transport be strongly encouraged?

The patient may rebound back into hypoglycemia. Certain of the medications continue to stimulate the pancreas to secrete insulin and will have a longer duration of action than the glucose given to the patient by EMS.

7. **Why should patients be instructed to notify their physician of the hypoglycemic episode?**

To determine why they became hypoglycemic. Their medication may need to be adjusted to prevent recurrent episodes of low blood sugar.

8. **Why it is important to instruct patient to eat and what are the desirable types of food?**

If a patient still refuses transport after profound hypoglycemia is corrected, encourage them to eat a snack with starch and protein to prevent rebound hypoglycemia. Examples:

a. Crackers and peanut butter or cheese
b. Half of a ham or turkey sandwich
c. A cup of milk and crackers or cereal

9. **The EMS medical record must include the following**:

a. Patient demographic information
b. PMH as known
c. Vital signs and physical exam to the extent completed and appropriate for the complaint
d. Mental status exam that clearly documents decisional capacity to refuse treatment and/or transportation (must be alert and oriented with no significant impairment).
e. Note any interventions that were performed, the patient response, and a follow up glucose reading that is within the normal range. In the comments section note that the risks of refusing transportation were explained and understood by the patient and that a refusal form was signed.

XII. **Unique glucose abnormalities**

A. **Dawn phenomenon**: The biggest stress of our day is getting out of bed in the morning. To do this, the body releases hormones (cortisol, epinephrine, and growth hormone) that assist in the production of glucose to fuel needed energy requirements. This routine early morning stress response and glucose surge is referred to as a *daily biological rhythm* and is known as the Dawn phenomenon. This is much more common. A single dose of NPH insulin at bedtime blunts the 6-8 am elevation in blood glucose.

B. **Somogyi effect**: While less common, this also causes an early am rise in blood glucose, but is caused by a response to nocturnal hypoglycemia. If the blood sugar falls below 65 mg/dL during sleep, the body compensates by releasing stress hormones. This surge in epinephrine and cortisol occurs earlier than with the DAWN phenomenon and the blood sugar rises in response to the hypoglycemia. The patient may wake at 3 or 4 am with palpitations, fine tremors, sweating, and experience nightmares due to nocturnal hypoglycemia. This is often caused by a dinner dose of NPH insulin that peaks at 3 am. It is diagnosed by waking the patient between 2 and 3 am and checking the blood glucose level. Treatment consists of reducing or deleting the dinner dose of NPH.

XIII. **Complications of diabetes**

A. The ADA estimates that diabetes-related complications add up to nearly $100 billion annually. Encouraging new research finds that long-term intensive control of blood glucose levels has a positive effect on patients' chances of avoiding the devastating complications of DM. The downside is weight gain and an increase in hypoglycemic episodes that are almost inescapable side effects of intensive insulin treatment.

B. Not every diabetic develops each complication and researchers are looking at possible links

between them (concordance or discordance between complications).

C. **Heart disease and stroke**

1. Diabetes and CVD often appear as the two sides of a coin. Heart disease and stroke account for about 2/3 to ¾ of deaths in people with diabetes.

2. Adults with DM have heart disease death rates about 2 to 4 times higher than non-diabetics. Stroke risk is 2 to 4 times higher among people with diabetes.

3. Vascular disease results in impaired/poor perfusion to the lower extremities (cool or cold to touch) that may make extremity assessments difficult to interpret in cases of trauma.

4. **High blood pressure:** About 73% of adults with diabetes have blood pressures greater than or equal to 130/80 or use prescription medications for hypertension.

5. The NIH is studying the best strategies to prevent and treat CVD in people with diabetes in three major studies. These studies are all joint efforts of the NIDDK and the National Heart, Lung, and Blood Institute. A complete listing of clinical trials can be found at www.ClinicalTrials.gov.

6. Diabetics are more likely to experience accelerated vascular disease. Insulin resistance blunts the beneficial effect of insulin-produced nitric oxide, which is a local vasodilator. Nitric oxide normally inhibits vascular smooth muscle cell proliferation, platelet adhesiveness, vasoconstriction, and the development of hypertension. Thus, hyperinsulinemia, alone, may have crucial atherogenic or thrombogenic properties by aggravating dyslipidemia.

7. Risk of dying the first year after an ACS event for a diabetic with unstable anginal or a non-ST-elevation myocardial infarction is almost the same as that of a nondiabetic patient with an ST-segment elevation MI (STEMI). At 30 days after UA/NSTEMI, mortality was 2.1% in patient with diabetes vs. 1.1% in those without diabetes. At one year after UA/NSTEMI, patients with diabetes at presentation with ACS had significantly higher mortality vs. those without diabetes. For STEMI, 30-day mortality was 8.5% for patients with diabetes and 5.4% for those without diabetes. One year mortality for STEMI was 13.2% vs. 8.1% (Donahoe et al, 2007).

8. In a cohort of 117,599 patients in the Cooperative Cardiovascular Project, they found that diabetic patients had a higher prevalence of hypertension, prior AMI, prior CHF, and prior revascularization, especially those on insulin. They also found that these patients were less likely to be taking aspirin and beta-blockers and were less likely to have revascularization procedures. Dr. Schulman reports mortality rates with AMI to be highest for diabetics taking insulin, followed by diabetics taking oral hypoglycemic agents, followed by diet-controlled diabetics.

9. The American Diabetes Association recommends that in moderate- or low-risk patients, aspirin is of questionable benefit for primary prevention of cardiovascular disease. The 2010 recommendation is to consider aspirin treatment as a primary prevention strategy in patients with diabetes who are at increased cardiovascular risk, defined as a 10-year risk greater than 10%. Patients at increased cardiovascular risk include men older than 50 years or women older than 60 years with at least 1 additional major risk factor.

10. The Heart Outcomes Prevention Evaluation (HOPE) study found that diabetics taking Ramipril (ACE inhibitor) experienced 25% less CV events than those taking placebos. Diabetics can prevent CV and kidney disease by taking an ACEI in addition to lowering their BP and cholesterol, controlling blood sugar, ceasing smoking, and taking ASA.

D. **Nervous system disease**

1. About 60% to 70% of people with diabetes have mild to severe forms of nervous system damage. This results in impaired sensation or pain in the feet or hand, slowed digestion of food in the stomach, carpal tunnel syndrome, and other nerve

problems.

2. Almost 30% of people with diabetes aged 40 years or older have impaired sensation in the feet.

3. **Peripheral neuropathy:** High blood glucose levels cause chemical changes in nerves that impair their ability to transmit impulses. Hyperglycemia also damages vessels that bring O_2 and nutrients to the nerves.

   Nerve damage may present as tingling, burning, prickling, numbness or insensitivity to pain or temperature in the hands/feet in a "stocking/glove" distribution. Symptoms can progress to aching or pain, particularly at night, or as extreme sensitivity to even light touch. The longest nerves are affected first, thus the feet show early S&S. Patients lose light touch and vibration sense, balance, proprioception, and coordination. Nerve damage results in loss of reflexes and muscle weakness. The foot becomes wider and shorter, gait changes, and ulcers appear as pressure is put on less protected parts of the foot.

4. **Amputations**

   a. Severe forms of diabetic circulatory and nerve disease are a major contributing cause of lower-extremity amputations.
   b. More than 60% of nontraumatic amputations of the lower extremities occur in people with diabetes.
   c. This adds up to about 82,000 amputations per year.

5. **Autonomic (visceral) diffuse neuropathy**: Affects the nerves that innervate the heart and internal organs, producing changes in many systems.

   a. Tachycardia/bradycardia
   b. Many diabetics have a ↓ sensation of pain and therefore incur asymptomatic or "**silent" MI's.** Dysrhythmia, weakness, or fatigue may be the first sign of myocardial damage. Need high index of suspicion and early 12-lead ECGs.
   c. Postural hypotension (orthostatic) due to loss of autoregulation of vascular resistance

   Sweating: Can affect the sympathetic nerves that control sweating and interfere with the activity of the sweat glands. Body has difficulty regulating temperature. May see profuse sweating at night or while eating (gustatory sweating).

6. **Focal neuropathy:** May appear suddenly and affect specific nerves; most often in the torso, leg or head. Unpredictable and occur most often in older patients who have mild DM. They tend to improve spontaneously over a period of weeks or months without causing long-term damage.

   May present as

   a. pain in the front of a thigh,
   b. severe pain in the lower back or pelvis,
   c. pain in the chest, abdomen, or flank sometimes mistaken for ACS or appendicitis,
   d. aching behind an eye,
   e. inability to focus the eye, double vision,
   f. paralysis on one side of the face (Bell's palsy), or
   g. problems with hearing.

7. **Diffuse neuropathies:** Experienced by about 60%-75% of diabetic patients

8. **Compression neuropathies:** Carpal tunnel syndrome is common in diabetics. Most common symptoms are numbness and tingling of the hand.

9. **Treatments for neuropathies**

   a. Physicians may prescribe antidepressants (amitriptyline), anticonvulsants (gabapentin, carbamazepine, or phenytoin), antihypertensive agents

(clonidine - to relieve diarrhea and bowel problems); antidysrhythmics (Mexitil), NSAIDS, or Zostrix (capsaicin) ointment to treat symptoms.

b. Additional treatments may include transcutaneous electronic nerve stimulations (TENS). Electrodes are applied to the skin and small currents of electricity are passed to block pain impulses.

c. Alternative medicine approaches include hypnosis, relaxation, biofeedback, acupuncture, warm baths, and massage.

E. **Eye complications/blindness**

1. Diabetes is the leading cause of new cases of blindness among adults aged 20-74 years. One of the most common of all DM complications; 25 X greater risk of blindness.

   a. Diabetic proliferative retinopathy causes 12,000 to 24,000 new cases of blindness/yr in adults 20-74 years of age.

   b. Non-inflammatory disease of the retina which occurs due to capillary hemorrhage and microaneurysms which may lead to total blindness 10-15 years after the onset of DM.

   c. Found to be associated with poor control of high glucose levels over time and other long-term complications of diabetes such as proteinuria and hypertension.

   d. 60% reduction in severe visual loss in patients getting laser therapy.

2. Blurred vision; cataracts: 4-6 X greater risk

3. Glaucoma: 2 X greater risk

F. **Dermatological**/wound healing

1. Hyperglycemia (> 180 mg/dl) inhibits migration of WBCs (segs & macrophages essential for fighting infection and assisting in the repair and regeneration of tissue) resulting in poor skin healing

2. Skin ulcers - especially on feet caused by ↓ circulation; cause little pain
3. Urticaria; cellulitis
4. Fungal infections
5. Gangrene

G. **Kidney disease**

1. Diabetes is the leading cause of kidney failure accounting for 44% of new cases in 2002 (CDC, 2007).

2. Over 150,000 people with end-stage kidney disease due to diabetes live on chronic dialysis or with a kidney transplant.

3. The nephropathy that occurs in the diabetic kidney is due to poor glycemic control, HTN (systemic or glomerular), and a diet high in protein. Experienced by up to 30% of diabetics and is the leading cause of end-stage renal disease.

4. Renal disease is sequenced into five stages and is the major cause of death in type 1 DM. One-half of all pediatric diabetics die from renal disease. Pyelonephritis is a frequent cause of illness.

5. With uncontrolled hyperglycemia, there is an increase in glomerular capillary pressure due to prostaglandin-induced vasodilation of the arteriole leading to the glomerulus. This combines with a local increase in angiotensin-2 that constricts the arteriole distal to the glomerulus. Glomerular filtration rate is increased by up to 40% coupled with an increased resistance to outflow from the nephron. Increased transcapillary pressure eventually causes capillary wall damage. The first sign of renal disease may not be apparent until the onset of microalbuminuria or protein in the urine.

6. Prevention starts with better **glucose control** using insulin pumps or multiple insulin injections based on frequent glucose checks. Nephropathy with renal **hypertension** and persistent microalbuminuria should be treated with **ACE inhibitors** to decrease angiotensin 2 unless contraindicated. Patients should be encouraged to eat a **low protein diet**. Systemic HTN need not be present. Renal failure in the final stages signals the need for dialysis or a kidney transplant. New research is focused on the possibility of renal/pancreas, pancreas alone, or islet cell transplants.

H. **Digestion / gastrointestinal**

1. Gastric stasis (stomach empties too slowly); severe from (gastroparesis) produces persistent nausea, vomiting, bloating, belching and loss of appetite. For people with uncontrolled DM, gastric paresis can cause low blood sugar 2 hours after meals or very high sugars 4 hours after meals.
2. Nocturnal diarrhea caused by too much sorbitol
3. Poor peristalsis (constipation)
4. Malabsorption and weight loss
5. Gallbladder disease
6. Bacterial overgrowth

I. **Dental disease**

1. Periodontal (gum) disease is more common in people with diabetes. Among young adults, those with diabetes have about twice the risk.
2. Affects up to 30% of people aged 19 years or older with type 1 diabetes
3. Almost ⅓ of those with DM have severe periodontal disease with loss of gum attachment to the teeth measuring 5 mm or more. Can lead to tooth loss.

J. **Urination and sexual response**

1. Impotence
2. Impaired bladder emptying with hydroureter, hydronephrosis, and chronic bladder and kidney infections; incontinence

K. **Gynecological**

1. Pruritus (itching); often due to yeast infections
2. Fungal vaginal infections

L. **Complications of pregnancy**

1. Poorly controlled diabetes before conception and during the first trimester of pregnancy can cause major birth defects in 5% to 10% of pregnancies and miscarriages in 15% to 20% of pregnancies.
2. Poorly controlled diabetes during the 2nd and 3rd trimesters can result in excessively large infants posing a risk to both mother and child.

M. **Other complications**

1. Uncontrolled diabetes often leads to biochemical imbalances that can cause acute life-threatening events; such as DKA and HHNS.
2. Diabetics are more susceptible to many other illnesses and, once ill, often have a worse prognosis. Example: They are more likely to die of pneumonia or influenza than people who do not have diabetes. Need good aseptic technique when providing invasive interventions and wound management.
3. **Sepsis** - Especially when diabetes is uncontrolled

XIV. **Diabetes research**

A. Three focuses right now

1. Prevent diabetes
2. Cure diabetes
3. Take better care of those with diabetes to prevent complications

B. **Islet cell transplantation:** Islet cells are taken from a donor pancreas and transferred into a person with type 1 diabetes. Once implanted, the beta cells in these islets begin to make and release insulin. The goal of islet transplantation is to infuse enough islets to control the blood glucose level without insulin injections. For an average-sized person (154 pounds), a typical transplant requires about 1 million islets, extracted from two donor pancreases. Because good control of blood glucose can slow or prevent the progression of complications associated with DM, such as nerve or eye damage, a successful transplant may reduce the risk of these complications. However, transplanted islets lose their ability to function over time.

1. Researchers at the University of Alberta in Edmonton, Alberta, Canada, have continued to use a procedure called the Edmonton protocol to transplant pancreatic islets into people with type 1 diabetes. Before use of the Edmonton protocol, during the 1990s, <10% of islet cell transplant recipients were able to control blood glucose levels for more than 1 year without insulin injections.

2. The September 2005 CITR annual report noted that with use of the Edmonton protocol, after 1 year, 58% of those who had transplants no longer needed insulin. Of those who were still insulin-dependent 1 year after transplantation, (33% of those followed by the registry), requirements for insulin were decreased. The average reduction in insulin requirements was 69%. A total of 91% of those with transplants showed improvement following transplantation.

3. A transplant recipient needs to take immunosuppressive drugs to prevent rejection of the transplanted islets. These drugs have significant side effects, and their long-term effects are still unknown. Immediate side effects may include mouth sores and GI problems, such as stomach upset or diarrhea. Patients may also have increased blood cholesterol levels, decreased WBC counts, decreased kidney function, and increased susceptibility to bacterial and viral infections. Taking immunosuppressive drugs increases the risk of tumors and cancer as well. Researchers are trying to find safer or less toxic immunosuppressants or new approaches that will allow successful transplantation without the use of immunosuppressive drugs.

4. An obstacle to widespread use of islet transplantation is the severe shortage of islets. Only about 6,000 pancreases a year become available for transplantation or for harvesting of islets. Researchers are pursuing alternative sources, such as creating islets from other types of cells. New technologies could then be employed to grow islets in the laboratory.

C. **Preventing complications – Hope through research**

1. In recent years, advances in diabetes research have led to better ways of managing diabetes and treating its complications.

   Major advances:
   a. Development of quick-acting, long-acting, and inhaled insulins.
   b. Better ways to monitor blood glucose and for people with diabetes to check their own blood glucose levels.
   c. Development of external insulin pumps that deliver insulin, replacing daily injections.
   d. Laser treatment for diabetic eye disease, reducing the risk of blindness.
   e. Successful kidney and pancreas transplantation in people whose kidneys fail because of diabetes.
   f. Better ways of managing diabetes in pregnant women, improving their chances of a successful outcome.
   g. New drugs to treat type 1 and type 2 DM and better ways to manage diabetes through weight control.
   h. Evidence that intensive blood glucose control reduces and may prevent development of complications.
   i. Demonstration that ACE inhibitors and angiotensin receptor blockers, are

more effective than other antihypertensive drugs in reducing a decline in kidney function in people with diabetes.

     j.   Evidence that people at ↑ risk for type 2 diabetes can lower their chances of developing the disease through diet, weight loss, & physical activity.

XV.   **"Strategies for Improving Diabetes Care"** Successful strategies to improve diabetes care, (measurement of A1c levels, lipid levels, BP), and the following:

    A.   Delivery of diabetes self-management education

    B.   Adoption of practice guidelines developed with participation of healthcare professionals and having them readily accessible at the point of service

    C.   Use of checklists mirroring guidelines that help improve adherence to standards of care

    D.   Systems changes, including providing automated reminders to healthcare professionals and patients and audit and feedback of process and outcome data to providers

    E.   Quality improvement programs, in which continuous quality improvement or other cycles of analysis and intervention are combined with provider performance data

    F.   Practice changes, which may include access to point-of-care A1c testing, scheduling planned diabetes visits, and clustering dedicated diabetes visits into specific times

    G.   Tracking systems with either an electronic medical record or patient registry to improve adherence to standards of care

    H.   Availability of case or (preferably) care management services using nurses, pharmacists, & other non-physician healthcare professionals following detailed algorithms under MD supervision

ANTIDIABETES AGENTS – mostly oral				
CHEMICAL NAME	**TRADE NAME**	**DOSAGE**	**DURATION**	**SPECIAL PROPERTIES/ PRECAUTIONS/SE**
SULFONYLUREAS - FIRST GENERATION (Enhances insulin release from pancreas, increase glucose uptake in insulin target tissues by the binding of insulin to the receptor, and increase the number of insulin receptors). **VERY RARELY USED NOW**				
acetohexamide	Dymelor	No longer used due to prolonged duration of action and higher incidence of SE, i.e., Na depletion, prolonged hypoglycemia, interactions with other drugs including alcohol, acetazolamide (Diamox), MOA inhibitors, phenothiazines, rifampin, salicylates, sulfonamides, and some NSAIDs. Contraindicated in ACS, liver or renal impairment.		
tolazamide	Tolinase			
tolbutamide	Orinase			
chlorpropamide	**Diabinese**	100-250 mg starting; 500 mg max dose; q. d.	60-72 hours	Longest acting oral agent; SE include facial flush effect and lowering of Na levels.
SULFONYLUREAS - Second/Third Generation (Enhances insulin release from pancreas; severe hypoglycemia is a rare complication; causes wt gain of 2 kg)				
glipizide	**Glucotrol**	2.5-5.0 max starting; 40 mg max dose Taken 1-2 times/daily	16-24 hrs Take 30 min before meals	Generics may not be effective.
	Glucotrol XL	5 mg q.d. up to 10 mg 2 times daily	Time released; 24 hrs	Do not crush or break; excrete casing in stool
glyburide 2 X as potent as glipizide	**Diabeta, Micronase**	1.25 - 10 mg starting 20 mg max dose Taken 1-2 times daily	12-24 hrs	Generics may not be as effective.
	Glynase PresTab	0.75 mg - 1.5 staring; 12 mg max dose		
glimepiride	**Amaryl**	1-2 mg starting; 8 mg max dose Taken once/day	24 hrs Take with first meal	Daily dosing improves adherence; watch for ↓ Na levels; not for type 1
BIGUANIDES (Reduces hepatic glucose production, ↓ insulin resistance in peripheral tissues and modestly ↑ glucose uptake. Does not increase insulin release.)				
metformin	**Glucophage or Glucophage XR**	500 mg starting 500 - 850 mg TID max. 2550 mg/day	12-16 hrs Taken with meals	Contraindicated if known hypersensitivity to metformin, renal disease or dysfunction, metabolic acidosis, including DKA. Risk of acidosis increases with the degree of renal dysfunction and the pt's age, especially pts ≥80 yrs. Prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Avoid in pts >= 80 yrs old, those w/ impaired hepatic function, or in any condition assoc. w/ hypoxemia, dehydration, or sepsis. Caution pts against excessive alcohol intake. SE: Metallic taste in mouth, N/V, abdominal bloating, anorexia, or gas may occur, especially during initiation of therapy. Does not cause wt gain.
metformin hydrochloride oral solution	**Riomet**	Each 5-mL of Riomet is equivalent to the 500 mg tablet form of metformin Monotherapy: Use if 10 yrs & older. May be used together with a sulfonylurea or insulin in adults (17 and older).		
metformin hydrochloride extended release tablets	**Glumetza**™	May be used together with a sulfonylurea or insulin in adults 18 years of age and older with type 2 diabetes.		
ALPHA-GLUCOSIDASE INHIBITORS Blocks the breakdown of starches (read, potatoes, pasta) in the intestine. They also slow the breakdown of some sugars (sucrase), such as table sugar. Does not inhibit absorption of glucose, lactose, or dextrose. If hypoglycemic, must use **glucose**, not sucrose to reverse.				
miglitol	**Glyset**	50 mg TID Max dose 300 mg/day Take w/ first bite of meal.	6-8 hrs	↑ GI gas, diarrhea, abd. pain. Don't use w/ inflammatory or chronic bowel Dx. GI SE causes 25%-45% of pts to D/C pills.
acarbose Used infrequently	**Precose**	25 mg starting Max dose 100 mg TID	2 hrs Take with first bite of meals.	↓ post-prandial glucose. LOTS OF GAS! Don't use in DKA, cirrhosis
THIAZOLIDINEDIONES (Improves insulin receptor sensitivity in muscle and fat; ↓ hepatic glucose output)				
piglitazone	**Actos**	15 - 45 mg/day	24 hrs	Not for type 1 or DKA. Caution liver Dx,

ANTIDIABETES AGENTS – mostly oral				
CHEMICAL NAME	**TRADE NAME**	**DOSAGE**	**DURATION**	**SPECIAL PROPERTIES/ PRECAUTIONS/SE**
rosiglitazone	**Avandia***	4 mg/day X 1 or in 2 divided doses. Max dose 8 mg/day	12-24 hrs	HF, nrsg mothers SE: Infection, pain, HA, fluid retention leading to edema, wt. gain, HF. Avandia ↑ the risk of ischemic CV complications 31%. See black box warning below.
troglitazone	Rezulin	Removed from market d/t liver toxicity		
MEGLITINIDES (Enhances insulin release from pancreas after meals)				
repaglinide Similar to sulfonylureas	**Prandin, Actulin, NovoNorm**	0.5 - 4 mg up to 4 times/day	Approx. 6 hrs Taken 30 min - timed before meals	Cuts off at very low sugar levels. Complex dosing before meals.
nateglinide	**Starlix**		Taken TID before meals	Omit if meal is missed. Use w/ caution in liver failure.
D-phenylalanines: amino-acid derivative (Enhances insulin release from pancreas after meals)				
Combination oral meds: Enhances insulin release and decreases insulin resistance in one pill				
glyburide + metformin	**Glucovance**	1.25 mg/250 mg 2.5 mg/500 mg 5 mg/500 mg	24 hours	SE same as metformin and 2nd generation sulfonylureas
roziglitazone + glimepiride	**Avandaryl**			Rarely used d/t Avandia: Black box warning will advise health care providers to monitor pts carefully for S/S of heart failure.
rosiglitazone + metformin	**Avadnamet**			
pioglitazone + glimepiride	**Duetact**			
Dipeptidyl peptidase-4 (DPP-4) inhibitors that enhances the release of insulin and the regulation of digestive hormones that impact glucose metabolism plus the hepatic insulin sensitizer metformin				
linagliptin, saxagliptin, sitagliptin				
sitagliptin + metformin	**Januvia Janumet** sitagliptin/metformin	50/500 mg & 50/1,000 mg Max daily dose: 100 sitagliptin or 2,000 metformin	BID w/ meals Works v. well in newly diagnosed diabetics	SE: URI, headache, GI upset; reports of acute pancreatitis Contraindicated in renal failure, hepatic disease, metabolic acidosis, DKA. Stop when pts require diagnostic studies that require iodine contrast dye.
Glucagon-like peptide-1 receptor (GLP-1R) agonists: incretin mimetics -synthetic version of exendin-4, a naturally-occurring hormone that was first isolated from the saliva of the lizard known as a Gila monster.				
exenatide	(Byetta®) [*bye-A-tuh*]) (Amylin Pharmaceuticals)	Prefilled injection pen (5 mcg or 10 mcg) contains 60 doses. Given any time w/in 60 minutes before the morning & evening meals about 6 hrs or more apart. BID or once weekly		Nausea, vomiting, diarrhea, dizziness, headache, feeling jittery and acid stomach.
liraglutide	(Victoza®)		Once-daily	Rhinitis

Exenatide (**Byetta):** Approved for use by people with type 2 DM who have not achieved their target A1c levels using metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea. Lowers blood glucose levels primarily by increasing insulin secretion in response to fluctuations in blood sugar. When sugar levels return to normal, the drug stops acting. Because of this action, it does not tend to increase the risk of hypoglycemia on its own, although hypoglycemia can occur if taken in conjunction with a sulfonylurea. Expensive; patients have generally experienced modest weight loss as well as improved glycemic control.

Pramlintide (**Symlin**): Synthetic form of the hormone amylin, which is produced along with insulin by the beta cells in the pancreas. Amylin, insulin, and glucagon, work in an interrelated fashion to maintain normal blood glucose levels. Pramlintide injections taken with meals have been shown to modestly improve A1C levels without causing increased

hypoglycemia or wt gain and even promoting modest weight loss. The primary SE is nausea, which tends to improve over time.

Because of differences in chemistry, pramlintide cannot be combined in the same vial or syringe with insulin and must be injected separately. Pramlintide has been approved for people with type 1 diabetes who are not achieving their goal A1C levels and for people with type 2 diabetes who are using insulin and are not achieving their A1C goals.

Normal liver and kidney function is necessary for optimal use of all medications.

* **Comments about rosiglitazone (Avandia)**
Diabetes drugs with rosiglitazone will be available only through certified mail-order pharmacies after November 17, 2011. Doctors wishing to prescribe the drugs and patients planning to continue taking them should enroll in GlaxoSmithKline's Avandia Rosiglitazone Medicines Access Program by November 17 [1].

As of November 18, Avandia (rosiglitazone maleate), Avandamet (rosiglitazone maleate and **metformin** hydrochloride), and Avandaryl (rosiglitazone maleate and **glimepiride**) will no longer be available from retail pharmacies. The FDA is advising patients to ask their doctor whether they should continue taking any of these medications.

The **European Medicines Agency** suspended marketing of rosiglitazone drugs, and the FDA insisted that GlaxoSmithKline implement a stringent restricted-access program for the drugs after a meta-analysis of 52 studies showed that the drug is associated with a significantly increased risk of MI. The restricted-access program confines rosiglitazone prescriptions to patients who failed to control their blood glucose levels with other drugs and have decided, in consultation with their doctor, not to take pioglitazone (Actos, Takeda Pharmaceuticals).

In May, 2007, a meta-analysis study was published in the New England Journal of Medicine entitled "Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes". This has sparked huge debate in the medical community. They have launched a series of observational studies with questionable ability to determine risk. In the grand scheme of treating diabetes, it might not matter much whether the Food and Drug Administration halts sales of the drug Avandia. An FDA committee of outside experts in July 2010 to provide advice on whether any regulatory action — from stronger warnings to removal — is needed. The FDA has the final say on the committee's recommendations and could decide within weeks. *But doctors already have given their verdict. Avandia prescriptions have plummeted since a study in The New England Journal of Medicine in May 2007 raised concerns about whether the drug increased heart attack risk.* The drug will be used less and less as physicians switch to drugs with a better safety profile.

Avandia BLACK BOX WARNING: 11/07 FDA informed healthcare professionals of new information added to the existing boxed warning in Avandia's prescribing information about potential increased risk for heart attacks. The new information refers to a meta-analysis of 42 clinical studies, most of which compared Avandia to placebo, that showed Avandia to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. At this time, FDA has concluded that there isn't enough evidence to indicate that the risks of heart attacks or death are different between Avandia and some other oral type 2 diabetes treatments. People with type 2 diabetes who have underlying heart disease or who are at high risk of heart attack should talk to their healthcare professional about the revised warning as they evaluate treatment options. Healthcare professionals are advised to closely monitor patients who take Avandia for cardiovascular risks.

Oral combination therapy

Because the drugs listed above act in different ways to lower blood glucose levels, they may be used together. For example, a biguanide and a sulfonylurea may be used together. Many combinations can be used. Though taking more than one drug can be more costly and can increase the risk of side effects, combining oral medications can improve blood glucose control when taking only a single pill does not have the desired effects. Switching from one single pill to another is not as effective as adding another type of diabetes medicine.

Body Mass Index

	Normal						Overweight					Obese						
BMI	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Height (inches)	Body Weight (pounds)																	
58	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167	172
59	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173	178
60	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179	184
61	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185	190
62	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191	196
63	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	191	197	203
64	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204	209
65	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210	216
66	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216	223
67	121	127	134	140	146	153	159	166	172	178	185	191	198	204	211	217	223	230
68	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230	236
69	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236	243
70	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243	250
71	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250	257
72	140	147	154	162	169	177	184	191	199	206	213	221	228	235	242	250	258	265
73	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265	272
74	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272	280
75	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279	287
76	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287	295

	Obese			Extreme Obesity														
BMI	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
Height (inches)	Body Weight (pounds)																	
58	177	181	186	191	196	201	205	210	215	220	224	229	234	239	244	248	253	258
59	183	188	193	198	203	208	212	217	222	227	232	237	242	247	252	257	262	267
60	189	194	199	204	209	215	220	225	230	235	240	245	250	255	261	266	271	276
61	195	201	206	211	217	222	227	232	238	243	248	254	259	264	269	275	280	285
62	202	207	213	218	224	229	235	240	246	251	256	262	267	273	278	284	289	295
63	208	214	220	225	231	237	242	248	254	259	265	270	278	282	287	293	299	304
64	215	221	227	232	238	244	250	256	262	267	273	279	285	291	296	302	308	314
65	222	228	234	240	246	252	258	264	270	276	282	288	294	300	306	312	318	324
66	229	235	241	247	253	260	266	272	278	284	291	297	303	309	315	322	328	334
67	236	242	249	255	261	268	274	280	287	293	299	306	312	319	325	331	338	344
68	243	249	256	262	269	276	282	289	295	302	308	315	322	328	335	341	348	354
69	250	257	263	270	277	284	291	297	304	311	318	324	331	338	345	351	358	365
70	257	264	271	278	285	292	299	306	313	320	327	334	341	348	355	362	369	376
71	265	272	279	286	293	301	308	315	322	329	338	343	351	358	365	372	379	386
72	272	279	287	294	302	309	316	324	331	338	346	353	361	368	375	383	390	397
73	280	288	295	302	310	318	325	333	340	348	355	363	371	378	386	393	401	408
74	287	295	303	311	319	326	334	342	350	358	365	373	381	389	396	404	412	420
75	295	303	311	319	327	335	343	351	359	367	375	383	391	399	407	415	423	431
76	304	312	320	328	336	344	353	361	369	377	385	394	402	410	418	426	435	443

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Additional resources:

American Association of Diabetes Educators: http://www.aadenet.org
American Diabetes Association: http://www.diabetes.org
Centers for Disease Control and Prevention: http://www.cdc.gov/diabetes or cdc.gov/nchswww
Department of Veterans Affairs: http://www.va.gov/health/diabetes/
Juvenile Diabetes Foundation International: http://www.jdfcure.org
Health Resources and Services Administration: http://www.hrsa.dhhs.gov
National   Diabetes   Education   Program: A   joint   program   of   NIH   &   CDC: http://www.niddk.nih.gov/health/diabetes/ndep/facts.htm
National Eye Institute: http://www.nei.gov/publications/nehepov.htm
National Institute of Diabetes and Digestive and Kidney Diseases of the NIH: http://www.niddk.nih.gov

National Diabetes Information Clearinghouse (NDIC)
Service of the National Institute of Diabetes and Digestive and Kidney Diseases
        part of the National Institutes of Health under the U.S. Public Health Service
        1 Information Way; Bethesda, MD 20892-3560
        e-mail: ndic@info.nddk.nih.gov

Procedure: Obtaining Venous Blood from IV Catheter

Indications: Need for blood sample for glucose or CO level.

1. Identify appropriate site, vein, and catheter; prep and insert IV catheter per standard procedure.

2. When removing stylet from catheter, place one finger on hub of IV catheter (to stabilize), and another over the area where distal tip of catheter is located, to prevent blood return.

3. After removal of needle/stylet, place it directly in sharps container; do NOT manipulate IV needle to obtain blood sample.

4. Attach syringe to hub of IV catheter, briefly lift finger occluding the vein, and aspirate needed blood sample.

5. Before removing syringe from catheter, replace finger pressure over distal tip of IV catheter.

6. Remove syringe w/ blood sample from IV catheter, attach IV catheter, remove tourniquet, secure and begin infusion.
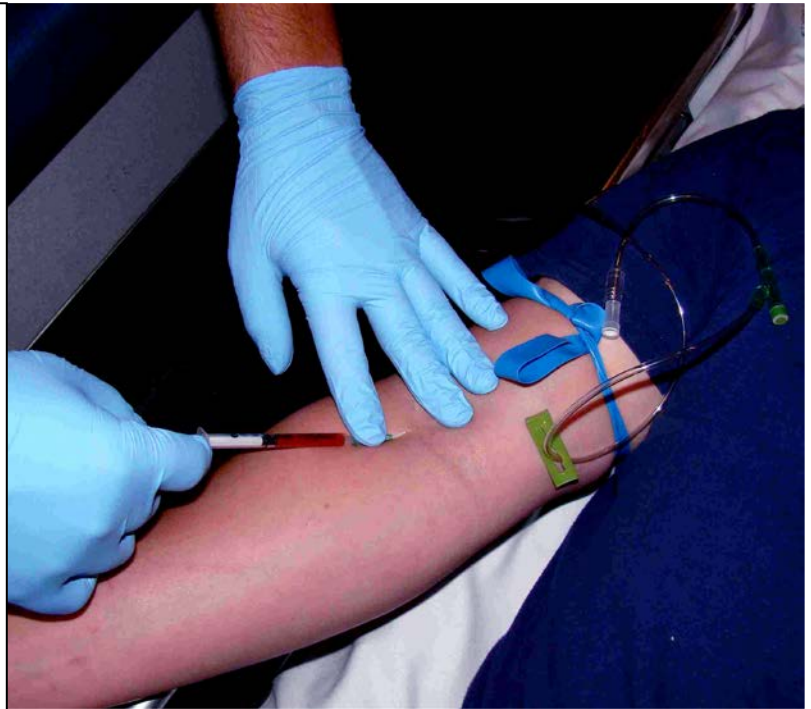
ADA's Clinical Practice Recommendations 2013 are published as a supplement to the January 2013 issue of *Diabetes Care*.

Blood pressure

The new ADA guidelines (2013) raise the target for systolic blood pressure from <130 mm Hg to <140 mm Hg based on evidence that there is not a great deal of additional value in aiming for the lower target, but there is an increase in risk in pushing systolic pressure lower than 140 mm Hg.

The primary data for that recommendation came from a meta-analysis that demonstrated that although the use of intensive vs standard blood-pressure targets in patients with type 2 diabetes was associated with a small reduction in the risk for stroke, there was no evidence for decreased mortality or MI, but an increased risk for hypotension and other adverse events.

The previous target of <130 mm Hg had not been derived from randomized, controlled trials, but from observational studies that seemed to suggest lower is better for blood pressure in those with diabetes.

However, the new ADA recommendations do say that a target <130 mm Hg might be appropriate for certain individuals, such as younger patients, as long as it can be achieved "without undue treatment burden."

Raising the systolic threshold should not be interpreted to mean that blood-pressure control is not important. "We really tried to communicate that it's crucially important that everyone with type 2 diabetes have a [systolic] blood pressure down to 140 [mm Hg]." "It's a very important threshold. Changing the recommendation is not meant to imply that excellent blood-pressure control is not as much of a priority as it was." However, **Dr Yehuda Handelsman** (Metabolic Institute of America, Tarzana, CA) said he is concerned about just that. "I believe the headline sends the wrong message. This will be interpreted that's it's less important to get to a more intensive goal."

There have been no new prospective data in the past year to merit the change, said Handelsman, immediate past president and chair of the **Diabetes Scientific Committee** of the **American Association of Clinical Endocrinologists** (AACE).

"There are no new studies, only meta-analyses, which are for generating hypotheses that need to be tested," said Handelsman.

Regarding adverse events, Handelsman pointed out that in the [Action to Control Cardiovascular Risk in Diabetes](#) [ACCORD] trial, the average blood pressure achieved in the standard group, which had a target of <140 mm Hg, was 133.5 mm Hg compared with 119.3 mm Hg in the intensive treatment group, which had a target blood pressure of <120 mm Hg.

In ACCORD, the annual stroke rates were 0.32% vs 0.53% in the intensive and standard BP-control groups, respectively (hazard ratio [HR] 0.59, 95% CI 0.39-0.89, p=0.01), whereas adverse events such as syncope and dizziness occurred in 1.3% vs 3.3% in the intensive and standard groups, respectively.

"Based on this trial, to say that a systolic blood pressure of 130 [mmHg] is dangerous is wrong," said Handelsman.

He added that he believes that what the ADA should have advised (and did, in fact, do so, but only secondarily) is that "if you can get to <130 [mm Hg] and do it safely, you should do it."

Handelsman noted that he was voicing his own views and not those of the AACE.

Blood glucose self-monitoring

The new ADA blood glucose self-monitoring recommendations do not prescribe how many tests should be done but rather focus on the individual situations in which testing should occur.

For patients with type 1 or type 2 diabetes who take multiple daily doses of insulin or are on pump therapy, the previous recommendation had been that these patients perform blood glucose self-monitoring "three or more times daily." Some payers had interpreted that to mean that three tests a day was sufficient for all patients, Grant noted.

The 2013 ADA advice for patients on intensive insulin therapy is for testing at least before meals, occasionally after eating, at bedtime, before exercise or critical tasks such as driving, when low blood glucose is suspected, and after treating low blood glucose to ensure normoglycemia has been reached.

"We're trying to say it's very situation-dependent both by the patient and the patient's context," he said.

In contrast, for patients with type 2 diabetes who take basal insulin or noninsulin diabetes treatments, blood glucose self-monitoring is still recommended as being potentially helpful to guide treatment decisions "when prescribed as part of a broader educational context," but only when patients are educated about how to use of the results.

In general, Grant said, for patients not taking insulin, blood glucose self-monitoring "is really not any use if it's not being acted on. If no one looks at the results, there's no sense testing."

With regard to the removal of the three-times-daily number, Handelsman expressed concern that insurers might actually interpret that as endorsing less frequent testing for patients who use insulin.

How messages are conveyed matters, he said. "It's about how you define the goals and where you put the emphasis."

However, Handelsman did endorse other revisions, including a new recommendation for hepatitis B vaccination in people with diabetes.

According to Grant, the new document was the ADA's best attempt to balance the evidence from the literature with the needs of the individual patient. "Evidence-based guidelines apply to populations of patients with diabetes, but we really need to tailor these population-level recommendations to the individual in front of us."

For diagnosis of diabetes

- Random glucose level greater than 200 mg/dL in patient with classic hyperglycemia symptoms or crisis

- Fasting glucose level (after 8 hours of fasting) greater than 126 mg/dL indicates diabetes; prediabetes is present if fasting blood glucose level is between 100 and 125 mg/dL.

- HbA1C value of greater than 6.5% (American Diabetes Association)

- Glucose level greater than or equal to 200 mg/dL during a 75-g oral glucose tolerance test (OGTT)

Other associated values

- Triglyceride levels greater than 250 mg/dL (goal is less than 150 mg/dL).

- HDL levels below 35 mg/dL (target levels for men should be greater than 45 mg/dL and for women, greater than 55 mg/dL); the target level for LDL cholesterol is less than 70 mg/dL.

High urine albumin (greater than 20 mcg/minute) can be a marker of early renal disease.