DIABETES MELLITUS:
Beyond Insulin Shock and Coma
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OBJECTIVES

Upon completion, the participant will

1. define diabetes mellitus.

2. discuss the functions of the islets of Langerhans, including the formation and function of insulin, glucagon, and somatostatin.

3. describe how the body normally metabolizes and controls blood glucose.

4. compare and contrast the classifications of diabetes including type 1, type 2, and gestational diabetes.

5. identify the classifications and actions of oral diabetes medications and the various types of insulin.

6. outline the epidemiology and causes of diabetics ketoacidosis (DKA).

7. sequence the development of dehydration and acidosis in DKA.

8. separate the signs and symptoms of DKA into those that reflect acidosis and those that reflect dehydration.

9. differentiate DKA and hyperglycemic, hyperosmolar, non-ketotic syndrome (HHNS).

10. list the precipitating factors for HHNS.

11. discuss the pathophysiology of hypoglycemia.

12. list the signs and symptoms of hypoglycemia.

13. describe the body's compensatory mechanisms to hypoglycemia.

14. anticipate the effects of elevated insulin levels in the body.

15. give examples of the long-term effects of hyperglycemia on the body systems, including the kidneys, heart and blood vessels, eyes, and nervous system.

16. discuss the management of hyper and hypoglycemia.

17. state the recommended concentrations and doses of dextrose to administer to infants, children, and adults.

18. describe the methods to obtain a glucose reading.

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 dietary habits have lead to a global epidemic of obesity and type 2 diabetes with a consequent rise in multiple interrelated cardio-metabolic risk factors (Mason, 2007). 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 (Zimmet, 2007).

      2. It is estimated that a total of 20.8 million Americans have diabetes (14.6 million are diagnosed and 6.2 million are undiagnosed), which translates to about 7% of the population (CDC, 2005).

      3. Perhaps 246 million people worldwide may be diabetic with projections estimating a rise up to 380 million by 2025. Many are hyperglycemic for up to six years before being diagnosed with diabetes. 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/ diabetic patient is $10,000 compared with $2,700 for non-diabetic persons (Robertson, 2001).

   C. **Morbidity:** DM is listed as the 4th leading cause of death by disease and a leading cause of adult blindness, end-stage renal disease, and nontraumatic lower extremity amputations (Robertson, 2001). 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 strict control of blood glucose and new treatment options.

   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.

   E. DM is defined as 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 and molecules needed for cell growth or repair (Bledsoe, 2006). One form will build complex molecules from simpler ones (**anabolism**) and 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 breakdown into its component glucose molecules

C.   Serum glucose concentrations fluctuate continuously based on the time of day, food or beverage ingestion, 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 generally range between **70 - 120 mg/dL**. The lowest levels are attained when food has not been eaten for a number of hours and is known as the **fasting state**. Highest levels are usually seen one to two hours after eating, especially meals with a high carbohydrate load. A blood glucose level lower than baseline (< 70-80 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 - 110 mg/dL	Normal range

F.   **Mechanisms that govern glucose metabolism**

1.   It was first discovered in 1889 that the **pancreas** is largely responsible for maintaining a specific blood glucose level. 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 (Bretzel et al, 1995) 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 the blood glucose levels. Glucose must enter a cell to produce energy, but the molecule is too large to readily diffuse across the cell membrane. In some cells, it needs a "facilitator" to help transport it through the membrane.

(2)   As glucose levels rise, the pancreas automatically produces the right amount of insulin to move glucose into the cells (high insulin/low glucagon state) and lower blood glucose levels.

(3)   Insulin binds with **insulin receptors** on the cell membrane, allows 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.

(4)   Insulin is needed by cardiac, skeletal, and fat tissues to actively transport glucose into cells where the mitochondria use it to produce ATP and store it as an energy reserve.

(5)   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.

(6)   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.

(7)   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.

(8)   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 (Nath, Ponte, & Byrd, 2000).

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 stored glycogen in the liver to be broken down into glucose (**glycogenolysis)** and 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** (Jones, 1994). 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** (Jones, 1994).

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. **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 (Jones, 1994).
   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 the intracellular space	**Promotes:** ➢ Glycogen catabolism ➢ Lipolysis of stored triglycerides ➢ Mobilization of stored fatty acids ➢ Ketone production ➢ Resistance to insulin **Accelerates:** ➢ Hepatic glucose production (gluconeogenesis)

Inhibits:	Inhibits:
➢ Glucagon release ➢ Lipolysis of triglycerides in adipose tissue ➢ Mobilization of stored fatty acids ➢ Proteolysis ➢ Hepatic glucose production (gluconeogenesis) ➢ Fatty acid oxidation	➢ 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 moved away from basing the names of the two main types on treatment or age at onset [*Diabetes Care* (1997), 20(7), 1183-97]. 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 (WHO). The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) agreed.

B.   **Major recommendations for classification changes**

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

▪   Use a category called "**Other specific types**" in cases where specific genetic defects, surgery, drugs, or other things, have caused hyperglycemia.

▪   Retain the term **Gestational diabetes** mellitus (GDM) as a fourth category to describe diabetes that develops during pregnancy.

▪   Add **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 as risk categories for DM.

IV.   **Type 1 diabetes mellitus**

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

B.   **Onset:** Prior to age 40; usually pre-teens or early teens with a peak incidence at age 13 (hence the outdated term, "juvenile onset" diabetes). However, it can develop in those as young as one year or as old as 70 (Robertson, 2001). 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.

Nice to know...One possible cause of **immune system attack** on the islet cells is some kind of **viral infection**. Coxsackie virus, rubella virus, and cytomegalovirus have all been seen invading and destroying islet ß cells. The Coxsackie virus has a peptide very similar to that of the pancreatic ß cell enzyme glutamic acid decarboxylase (GAD). It is possible that human **GAD antibodies** created in response to a viral infection are confusing the body's ß cells with virus and attacking them (Kobayashi et al, 1996).

Reporting in the *J of Science* (1999), researchers at the University of Calgary found that GAD triggered an autoimmune disorder in mice. Blocking the action of this protein prevented a diabetes-like illness from occurring giving rise to speculation that Type 1 diabetes could be prevented by a vaccine-based approach.

One **genetic factor** is called *major histocompatibility complex* (MHC). This takes the form of molecules called **human leukocyte antigens** (HLA). There are many varieties of HLA (or a substance that provokes human antibodies), but over 95% of caucasian patients with type 1 DM have a strong association with an HLA-DQ subtype that causes a cascade of immunological responses. Defensive cells of the immune system, called CD8 T lymphocytes, may have a defect which can generate **islet cell antibodies** (ICA). This allows them to react to the antigens on the ß cells and attack the body's own tissues (**autoimmune process**), causing their destruction with consequent insulin deficiency and abnormalities that result in resistance to insulin. ICAs appear 3-4 yrs prior to the onset of disease (Bancroft, 1998).

Research by Drs. Denise Fausman and Takuma Hayashi (Mass General and Harvard Medical School) have identified a **genetic malfunction** that may be another key to type 1 DM. They found that a gene called Lmp2, which is needed to help the immune system to recognize "self" proteins, is inactivated. They also found that the inactivation of Lmp2 has a profound impact on another protein called nuclear factor kappa B (NF-kB), which controls several immune system activities. NF-kB was ↓ in diabetic mice with possible implications for research in humans.

Further, German and Austrian researchers found that cytotoxic **"killer" T cells** that destroy the Islet cells lack a specific cell receptor called CD30. CD30-deficient T cells are about 6,000 times more destructive than normal T cells. Introducing just 160 of them led to complete destruction of the ß cells and the rapid onset of diabetes. Now that the specific antigen has been identified by immunobiology researchers, they hope to find ways of using it to desensitize the body, similar to the way allergy shots work (Mediconsult, 1999).

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 diabetes died within a few years after diagnosis. Insulin was first given to a diabetic patient 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 diabetes. The amount of insulin must be balanced with food intake and daily activities. The goal of diabetes 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 choose is based on an individual's lifestyle (usual type and amount of exercise), a physician's preference and experience, and the person's blood sugar levels. Many people take at least 2 types. 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

Onset, peak and duration of different insulins				
Insulin	**Onset**	**Peak**	**Therapeutic***	**Pharmaceutic****
Rapid acting **Insulin analogue** insulin lispro***(Humalog) insulin aspart (Novolog) insulin glulisine (Apidra)	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
Prompt insulin zinc (Semilente, slightly slower acting)	1 - 3 hrs	5 – 10 hrs	10-16 hrs	
Inhaled insulin (Exubera)	30-90 min	60 min	6-8 hrs	
Intermediate-acting Isophane insulin, neutral protamine Hagedorn (NPH) (Humulin N, Novolin N), Insulin zinc (Lente)	2-4 hrs	4 – 12 hrs	12-18 hrs	16-26 hrs
Long acting Extended insulin zinc Ultralente (U)	6-10 hrs	8-20 hrs	20-24 hrs	
Premixed 70/30, 50/50 **75/25 analog mix**	Combine the actions of R and NPH insulins. In 70/30 insulin (30% Regular and 70% NPH), the regular starts acting within 30-60 min and the NPH starts working in about 2-4 hrs. 50/50 has equal parts Regular and NPH insulins. 75% Humulin NPH and 25% Humalog (Lilly): Rapid onset, intermed. duration			
Very 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

*   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.

The short duration analogues are usually used in conjunction with longer-acting insulins 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.

Rapid-acting insulins must be given within 15 minutes before a meal, within 20 minutes of starting a meal, or immediately after a meal.

Insulin strength: All insulins 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 temperature. 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.

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 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

For additional information on the different types of insulin, use the following link: FDA Consumer magazine, Chart of Insulin Preparations (January-February 2002) http://www.fda.gov/fdac/features/2002/chrt_insulin.htmL

G. **Delivery routes for insulin: Currently available: Note: EMS personnel are never to give or assist a patient in giving themselves insulin**

1. **Insulin syringe** (3 sizes: U30, U50, and U100 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** (disposable or reusable): Humulin or Humalog Pen (Lilly); NovoPen 3 (Novo Nordisk): 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. **Novolin Innolet:** Prefilled disposable insulin dosing device available with Novolin N or Novolin 70/30. Can deliver a dose up to 50 units. Patient attaches a NovoFine PenFill needle and primes the device by dialing a 2-unit dose. Doses up to 50 units can be dialed on an easy-to-read dial that resembles a kitchen timer. The patient next inserts the needle and depresses a large button on top of the Innolet that delivers the desired dose. The needle is left in the skin for at least 6 seconds, then discarded.

5. **Innovo:** Reusable insulin doser that accepts Novolin PenFill 3-mL insulin cartridges. Patient dials the dose from 1 to 70 units in 1-unit increments. Insulin mixing and priming are similar to the Innolet.

6. **InDuo**: First combined glucose monitor and insulin doser. Identical to the Innovo, but cap is a glucose meter. Accepts OneTouch Ultra test strips.

7.   **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.

8.   **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.

9.   **Inhaled insulin** delivery system provides rapid-acting insulin as a dry powder that is inhaled through the mouth into the lungs. The insulin then passes into the bloodstream. The FDA approved inhaled insulin (Exubera) on January 27, 2006, for adults with type 1 or type 2 diabetes. For more information, see the FDA news release: FDA Approves First Ever Inhaled Insulin Combination Product for Treatment of Diabetes.

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 (NDIC, 1998).

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.

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)

H.   **Delivery methods under development**

1.   **Implantable insulin pumps:** Surgically implanted devices, usually on the left side of the abdomen. The pump is disk shaped, 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.

1.   Estimated to have 600,000 new cases/year with about 15 million people in the US currently affected.

2.   Incidence increases with age. Usually strikes adults over 40-45 years of age, but younger and younger patients are developing this type. 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. Pre-diabetes is also called impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), depending on the test used to diagnose it. Some people have both IFG and IGT (Campos, 2007).
   a.   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.)
   b.   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.

2.   Pre-diabetes is becoming more common in the United States according to new estimates provided by the U.S. Department of Health and Human Services. About 40 percent of U.S. adults ages 40 to 74—or 41 million people—had pre-diabetes in 2000. Later data suggested that at least 54 million U.S. adults had pre-diabetes in 2002. 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 (Robertson, 2001, Barclay, 2007). Prediabetes affects 41 million Americans aged 40-74 years (Mason, 2007).

2.   **Adolescents aged 10 to younger than 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 to these disorders. 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 (Robertson, 2001).

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 $\uparrow$ 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; muscle cramps
3.   Chest pain can occur due to a reduction in collateral coronary artery blood flow
4.   Non-healing infections of skin, vagina or bladder
5.   Fatigue to exhaustion; dry, itchy skin
6.   Impotence
7.   Night-time diarrhea (excess Sorbitol in the gut)
8.   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.   **Sulonylureas** (*SUL-fah-nil-YOO-ree-ahs*) stimulate the pancreas to make more insulin. Inexpensive but may also cause weight gain and hypoglycemia

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

d. **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.

e. **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 (Barclay & Vega, 2006).

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

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

h. **Combination oral medications** put together different types of pills. (NDIC, 2007)

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.

6. **New injectable drugs recently approved by the FDA for type 2 diabetics**

a. **Pramlintide** (brand name **Symlin**)

(1) 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.

(2) 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.

(3) 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.

b. **Exenatide** (**Byetta** [*bye-A-tuh*]) (Amylin Pharmaceuticals)

(1) Approved in April 2005, it is the first in a new class of drugs for the treatment of type 2 DM called incretin mimetics. Exenatide is a synthetic version of exendin-4, a naturally-occurring hormone that was first isolated from the saliva of the lizard known as a Gila monster.

(2) Exenatide has been 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. Byetta works to lower 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.

(3) Byetta comes in a prefilled pen (5 mcg or 10 mcg) that contains 60 doses to provide 30 days of twice-a-day injections. Like pramlintide, Byetta is injected any time within 60 minutes before the morning and evening meals about 6 hours or more apart. Dose: 5 or 10 mcg twice a day

(4) The primary SE are nausea, vomiting, diarrhea, dizziness, headache, feeling jittery, and acid stomach. Nausea is most common but tends to improve over time. Stored similar to insulin. Exenatide is expensive ($225/month) and has little clinical experience. Patients have generally experienced modest weight loss as well as improved glycemic control.

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). The problem is compounded by various secondary hormones produced by the placenta during pregnancy, i.e., cortisol, estrogen, and human placental lactogen (HPL) that make her insulin resistant, usually starting about the 24th 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.

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 (Mediconsult, Jan. 2000).

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 (Chansky, 1997). Hypokalemia ($\downarrow$ K) further decreases insulin release.

ECG changes with hyperkalemia	ECG findings with hypokalemia
▪ Peaked T wave (See below) ▪ Depressed S-T segments ▪ Disappearance of the P wave ▪ Widened QRS (sine waves) ▪ Cardiac arrest: asystole	▪ Low voltage of all EKG waves ▪ Flattened T wave ▪ Depression of S-T segment ▪ Presence of U wave ▪ Dysrhythmias; PACs → VF
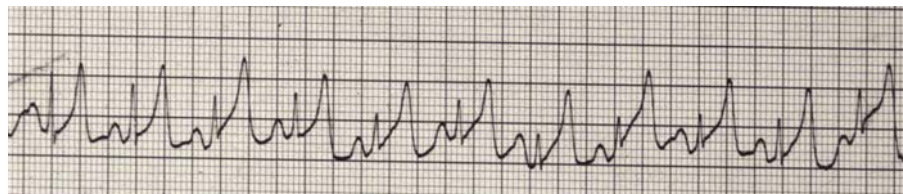
13.   **Mental status: U**p to this point, the brain has been using glucose as neural cells are not insulin-dependent and mental status has been relatively normal. However, the combination of **dehydration and acidosis** directly depress brain function leading to a **decrease in the patient's level of 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.
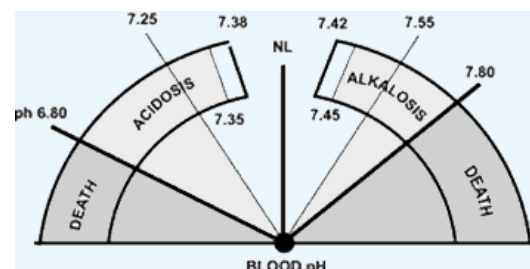
E.   **Essential aspects to assess**

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 ▪ 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)	▪ Sensation of shortness of breath ▪ Kussmaul respirations (pH < 7.2; may be depressed when pH < 6.9) ▪ 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 and 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 (Freas, 1997)
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 (↑ 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 or LR. Replace ½ of estimated total water losses in first 12 hours. Do not correct too quickly.

2. Treat generalized tonic clonic seizures with midazolam (Versed).

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: Suppresses gluconeogenesis (liver is prevented from manufacturing glucose); alcohol also increases potency of drugs that reduce glucose levels such as insulin and ß-blockers
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	▪ Headache; trembling
▪ Confusion or sudden moodiness or bizarre behavior such as crying for no reason	▪ Diaphoresis, cool skin
	▪ Hunger; lack of energy
▪ Irritability - can be violent	▪ Hypothermia
▪ Clumsiness or hyperactivity	▪ Chest pain; cardiac ischemia; dysrhythmias (heart needs glucose to function)
▪ Inability to concentrate	
▪ Pale skin color; tachycardia	▪ Seizures
▪ Tingling sensations around the mouth	▪ Fainting → coma

2. **Hypoglycemic unawareness**: The longer a patient is diabetic, the less obvious are S&S of hypoglycemia. 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 people who have neuropathy (nerve damage), people on tight glucose control, and people who take certain heart or high blood pressure medicines.

   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. **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. Amount of blood needed for each test
   b. Testing speed
   c. Overall size
   d. Ability to store test results in memory; several new models can record and store a number of test results
   e. Cost of the meter
   f. Cost of the test strips used

3. 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 new 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 (Passanza, 2001).

4. **Brand used by EMS personnel are System specific**. Check the unit to determine those factors that can affect the readings. Dehydration can falsely lower results in some units while anemia can cause a false high reading. Decreased blood oxygen due to hypoxia or hypotension can produce inaccurate results as can high doses of certain drugs such as acetaminophen, ibuprofen (Motrin, Advil), salicylates, and tetracycline (Passanza, 2001). Strip maintenance is important to yield accurate results. Make sure the strips are kept according to manufacturer's recommendations, are not outdated, and that the unit is appropriately calibrated for each set of strips.

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. You should also consider checking your 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..

    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 patients. See procedure on obtaining venous sample from IV catheter.

7. **Factors that affect glucose meter performance**

    a. **Hematocrit**. Patients with higher hematocrit values will usually test lower for blood glucose than patients with normal hematocrit. Patients with lower hematocrit values will test higher. Anemia and Sickle Cell Anemia are two conditions that affect hematocrit values.

    b. **Altitude, temperature and humidity**. Altitude, room temperature, and humidity can cause unpredictable effects on glucose results. Check the meter and test strip package insert for information on these issues. Store and handle the meter and test strips according to the instructions.

    c. **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. 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.

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 stylette in any way including by milking it or blowing into it. It is not vital that the dates and time are set as we will not be using the long term memory function and we will not be averaging the readings over weeks.

2. Place a small sample of blood on a disposable "test strip" and place the strip in the meter. The test strips are coated with chemicals (glucose oxidase, dehydrogenase, or hexokinase) that combine with glucose in blood. The meter measures how much glucose is present. Meters do this in different ways. Some measure the amount of electricity that can pass through the sample. Others measure how much light reflects from it. You will need the monitor manual to interpret any error codes and troubleshoot the problem.

3. Be prepared before you do the test. 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 50% 25 mL (12.5 Gm) IVP
(2)	**If < 60 or low:**	Dextrose 50% 50 mL (25 Gm) IVP/IO
(3)	Peds patients (1-8):	Dextrose 25% at 2 mL/kg
(4)	Infants (0-12 mos):	Dextrose 10%-12.5% at 5 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 will cause tissue necrosis if it infiltrates. Notify ED staff ASAP if the IV infiltrates while dextrose is being pushed. 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 - 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?

    e. Inform the patient/guardian of the risks inherent in refusing care and/or transportation.

4. **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.

5. **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.

6. **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

7. **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. A single dose of NPH insulin at bedtime blunts the 6-8 am elevation in blood glucose.

B. **Somogyi effect**: Also 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 diabetes have heart disease death rates about 2 to 4 times higher than non-diabetics.

3. The risk for stroke is 2 to 4 times higher among people with diabetes.

4. 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.

5. **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.

6. 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.

7. 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.

8. 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).

9. 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.

10. The American Diabetes Association recommends that, in the absence of specific contraindications, aspirin therapy be considered for adults with DM who have CVD or risk factors for cardiovascular disease (Reuters Health, 2001).

11. The Heart Outcomes Prevention Evaluation (HOPE) study found that diabetics taking Ramipril (ACE inhibitor) experienced 25% less CV events than those taking placebos. Their findings (The Lancet, Jan 2000) recommend that diabetics 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 (Mediconsult, 2000).

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 **tight 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 (Mediconsult, 2000).

H.   **Digestion / gastrointestinal**

1.   Gastric stasis (stomach empties too slowly); severe from (gastroparesis) produces persistent nausea, vomiting, bloating, belching and loss of appetite
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 1/3 of people with diabetes have severe periodontal disease with loss of attachment of the gums 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. **"Cure" options being studied**

1. **Islet cell transplantation:** In an experimental procedure, 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 diabetes, 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.

2. Since reporting their findings in the June 2000 issue of the New England Journal of Medicine, 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, less than 10 percent of islet cell transplant recipients were able to control blood glucose levels for more than 1 year without insulin injections.

3. 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.

4.   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.

5.   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. Glucose binds irreversibly with hemoglobin in the blood (**glycosylated hemoglobin**) causing an increased level of **HbA_{1c}**. The HbA_{1c} level reveals glucose control over the previous 8-12 weeks. Most physicians target a glycosylated hemoglobin level of less than 7% or 1.5% above the upper limits of normal for the assay used (Funnell & Barlage, 2000). Another long-term picture of glycemic control is fructosamine (Passanza, 2001).

   i.   Demonstration that two types of antihypertensive drugs, ACE (angiotensin-converting enzyme) inhibitors and ARBs (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 high risk for type 2 diabetes can lower their chances of developing the disease through diet, weight loss, and physical activity.

ORAL ANTIDIABETES AGENTS

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).				
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,

ORAL ANTIDIABETES AGENTS				
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**			Black box warming will advise health care providers to monitor pts carefully for S/S of heart failure.
rosiglitazone + metformin	**Avadnamet**			
pioglitazone + glimepiride	**Duetact**			
DPP-4 inhibitor that enhances the release of insulin and the regulation of digestive hormones that impact glucose metabolism plus the hepatic insulin sensitizer metformin				
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	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.

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

* **Comments about rosiglitazone (Avandia)**: 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. The drug will probably get 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

BMI	Normal						Overweight					Obese						
	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

BMI	Obese			Extreme Obesity														
	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
CDC contact: Faye L. Wong, MPH, RD, Associate Director for Diabetes Education e-mail: flw2@cdc.gov
NIH contact: Joanne Gallivan, M.S. RD, Director of Diabetes Outreach Program e-mail: gallivanj@hq.niddk.nih.gov
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