Diabetes
Biochemistry and Endocrinology

Rho Chi Review Series
Insulin Hormone

- Which metal ion associates with insulin to help form aggregates of crystals?
  - These aggregates of crystals are known as __________

- Preproinsulin is cleaved in the _______ from the N-terminus to form _______

- _______ (also known as C-peptide) is cleaved in the _______ to form insulin
  - Insulin is composed of ________ bridges

- Insulin release follows two-phase kinetics. Explain what happens in the first phase and what happens in the second phase (what causes secretion of insulin and which types are being secreted).

- Put the following steps of insulin release in the correct order:
  - A. Voltage gated Ca²⁺ channels open causing an influx of calcium into the cytosol
  - B. ATP is produced through glycolysis and ATP-dependent K⁺ channels close, causing depolarization of the cell
  - C. High glucose concentration causes uptake by GLUT2 receptor
  - D. DAG targets the calcium channel on the endoplasmic reticulum, causing further calcium release into the cytosol, which triggers the release of insulin through vesicle exocytosis
  - E. Calcium activates phospholipase C, which cleaves phosphatidylinositol-4,5-bisphosphate into IP3 and DAG
Insulin Hormone

- Which metal ion associates with insulin to help form aggregates of crystals? **Zinc**
  - These aggregates of crystals are known as **hexamers**
- Preproinsulin is cleaved in the **endoplasmic reticulum** from the N-terminus to form **proinsulin**
- Proinsulin (also known as C-peptide) is cleaved in the **golgi apparatus** to form insulin
  - Insulin is composed of **sulfur** bridges
- Insulin release follows two-phase kinetics. Explain what happens in the first phase and what happens in the second phase (what causes secretion of insulin and which types are being secreted). The initial first phase release of insulin is triggered by glucose uptake and the insulin that is being released is stored insulin. The second phase is due to continued stimulation with high glucose levels and this insulin is being newly synthesized (the stored insulin has been depleted)
- Put the following steps of insulin release in the correct order:
  - C. High glucose concentration causes uptake by **GLUT2 receptor**
  - B. ATP is produced through glycolysis and ATP-dependent K+ channels close, causing depolarization of the cell
  - A. Voltage gated Ca2+ channels open, causing an influx of calcium into the cytosol
  - E. Calcium activates phospholipase C, which cleaves phosphatidylinositol-4,5-bisphosphate into IP3 and DAG
  - D. **DAG targets the calcium channel on the endoplasmic reticulum, causing further calcium release into the cytosol, which triggers the release of insulin through vesicle exocytosis**
Please indicate if insulin causes the following to occur in the liver and/or muscle and/or fat:

- Stimulates glucose uptake -
- Stimulates cellular respiration -
- Stimulates glycogen synthesis -
- Inhibits glycogen breakdown -
- Stimulates amino acid uptake -
- Stimulates protein production -
- Inhibits protein and amino acid degradation -
- Stimulates fatty acid and triglyceride synthesis -
- Inhibits breakdown of triglycerides to free fatty acids -
- Stimulates lipoprotein uptake -
Results of Insulin Release

- Please indicate if insulin causes the following to occur in the liver and/or muscle and/or fat: (know this for exam)
  - Stimulates glucose uptake – muscle, fat
  - Stimulates cellular respiration – liver, muscle, fat
  - Stimulates glycogen synthesis – liver, muscle
  - Inhibits glycogen breakdown – liver, muscle
  - Stimulates amino acid uptake – muscle
  - Stimulates protein production – liver, muscle, fat
  - Inhibits protein and amino acid degradation – liver, muscle, fat
  - Stimulates fatty acid and triglyceride synthesis – liver, fat
  - Inhibits breakdown of triglycerides to free fatty acids – liver, fat
  - Stimulates lipoprotein uptake – fat
What type of receptor is the insulin receptor? How many subunits are there, what are they, and where are they located?

The insulin receptor is a heterodimer. What stabilizes the dimer?

When insulin binds to the receptor it causes closing of ____ subunits and activation of ____ subunits. This leads to autophosphorylation of ____ residues on beta chains.

Signaling cascade through the cell due to ______ (activation) of various signaling proteins.

List the correct order for which the following signaling proteins are phosphorylated (activated):
- IRS-1 (insulin receptor substrate 1), PKB (protein kinase B), PIP 3 kinase, Tyrosine residues on beta chain of insulin receptor
- PKB moves which receptor to the cell membrane to stimulate glucose uptake?
What type of receptor is the insulin receptor? How many subunits are there, what are they, and where are they located? Tyrosine kinase receptor. Four subunits – Two beta subunits and two alpha subunits. Alpha subunits located extracellularly and have hormone binding domain. Beta subunits span the membrane and have ATP binding and tyrosine kinase domains.

The insulin receptor is a heterodimer. What stabilizes the dimer? Sulfur bonds.

When insulin binds to the receptor it causes closing of alpha subunits and activation of beta subunits. This leads to autophosphorylation of tyrosine residues on beta chains.

Signaling cascade through the cell due to phosphorylation (activation) of various signaling proteins.

List the correct order for which the following signaling proteins are phosphorylated (activated):

1. Tyrosine residues on beta chain of insulin receptor
2. IRS-1 (insulin receptor substrate 1)
3. PIP 3 kinase
4. PKB (protein kinase B)

PKB moves which receptor to the cell membrane to stimulate glucose uptake? GLUT-4
Which cells in the pancreas stimulate release of glucagon? What is its overall effect on glucose levels in the blood? Proglucagon is cleaved to _____ in the pancreas and _____ in the intestinal cells.

Circle which processes are promoted by glucagon release:
- Glycogenesis or Glycogenolysis?
- Glycolysis or Gluconeogenesis?
- Lipogenesis or Lipolysis?
- Ketone formation or Ketone breakdown?
- Amino acid uptake or Amino acid release?

What type of receptor is the glucagon receptor? When glucagon binds, this leads to an increase in which secondary messenger? This subsequently activates which signaling protein?
- Which cells in the pancreas stimulate release of glucagon? Alpha cells. What is its overall effect on glucose levels in the blood? Increases glucose levels in blood. Proglucagon is cleaved to glucagon in the pancreas and GLP-1 in the intestinal cells.

- Circle which processes are promoted by glucagon release:
  - Glycogenesis or Glycogenolysis?
  - Glycolysis or Gluconeogenesis?
  - Lipogenesis or Lipolysis?
  - Ketone formation or Ketone breakdown?
  - Amino acid uptake or Amino acid release?

- What type of receptor is the glucagon receptor? G-protein coupled receptor. When glucagon binds, this leads to an increase in which secondary messenger? cAMP. This subsequently activates which signaling protein? PKA.
Which cells in the pancreas stimulate release of somatostatin?

Somatostatin has many different effects. What are the effects on insulin release, glucagon release, and its own release? The overall effect in the body is a/an stimulatory/inhibitory (CHOOSE) effect.

GLP-1 (glucagon-like protein 1) release is stimulated by ________ and stimulates/inhibits (CHOOSE) insulin release and stimulates/inhibits (CHOOSE) glucagon release.

IGF-1 stands for ___________. This hormone has how many receptor types?

Amylin is secreted with what other hormone? What is its effect?
- Which cells in the pancreas stimulate release of somatostatin? **Delta cells**

- Somatostatin has many different effects. What are the effects on insulin release, glucagon release, and it’s own release? **Inhibits insulin and glucagon release as well as its own release.** The overall effect in the body is an **inhibitory** effect.

- GLP-1 (glucagon-like protein 1) release is stimulated by **food intake** and **stimulates** insulin release and **inhibits** glucagon release.

- IGF-1 stands for insulin-like growth factor 1. This hormone has how many receptor types? **Two**

- Amylin is secreted with what other hormone? **Insulin.** What is its effect? **Slows digestion to control absorption of glucose.**
Insulin Preparations

- What is the half-life of endogenous insulin? Which two organs are mostly responsible for removing insulin?
- Insulin exists as a monomer/dimer (CHOOSE) at low concentrations and a monomer/dimer (CHOOSE) at high concentrations.
- Insulin is stored in which cells in the pancreas? The storage form of insulin is as a hexamer due to the presence of which metal ion?
- Which insulin form (monomer, dimer, hexamer) has the poorest absorption?
- Which basic protein can be added to insulin to further slow its absorption?
- What are the four principle types of injectable insulin?
What is the half-life of endogenous insulin? Which two organs are mostly responsible for removing insulin? 3-5 minutes. Liver and kidney

Insulin exists as a monomer at low concentrations and a dimer at high concentrations

Insulin is stored in which cells in the pancreas? The storage form of insulin is as a hexamer due to the presence of which metal ion? Beta cells. Zinc ion

Which insulin form (monomer, dimer, hexamer) has the poorest absorption? Hexamer

Which basic protein can be added to insulin to further slow its absorption? Protamine

What are the four principle types of injectable insulin? Rapid-acting, short-acting, intermediate-acting, long-acting
Diabetes Pharmacology and Medicinal Chemistry

Rho Chi Review Series
Insulin Analogsues

- Match the insulin type with its duration of action:
  - Insulin aspart
  - Insulin detemir
  - Insulin glargine
  - Insulin lispro
  - NPH (neutral protamine Hagedorn)
  - Insulin glulisine
  - Regular insulin

A. Rapid acting
B. Short acting
C. Intermediate acting
D. Long acting
Insulin Analogues

- Match the insulin type with its duration of action:
  - Insulin aspart - A
  - Insulin detemir - D
  - Insulin glargine - D
  - Insulin lispro - A
  - NPH (neutral protamine Hagedorn) - C
  - Insulin glulisine - A
  - Regular insulin – B

A. Rapid acting
B. Short acting
C. Intermediate acting
D. Long acting
Insulin Analogues

Changes in amino acids on the ___ chain of insulin will vary its duration of action

Match the amino acid change with the insulin analogue it is associated with, state how this effects the duration of action of that insulin:

- B3 Asp substituted with a Lys and B29 Lys substituted with a Glu
  - A. Insulin aspart
- Two Arg groups attached to B30 and A21 Asp substituted with a Gly
  - B. Insulin lispro
- B28 Pro and B29 Lys swap places
  - C. Insulin glulisine
- B28 Pro substituted for an Asp
  - D. Insulin glargine
- B30 Thr is removed and myristic acid is added to B20 Lys
  - E. Insulin detemir
Insulin Analogues

Changes in amino acids on the B chain of insulin will vary its duration of action

Match the amino acid change with the insulin analogue it is associated with, State how this effects the duration of action of that insulin:

- B3 Asp substituted with a Lys and B29 Lys substituted with a Glu
  - C. Reduced ability to self-associate
- Two Arg groups attached to B30 and A21 Asp substituted with a Gly
  - D. Soluble in acid but precipitates slowly in body at neutral pH
- B28 Pro and B29 Lys swap places
  - B. Makes steric hinderance and reduced ability to self associate
- B28 Pro substituted for an Asp
  - A. Charge repulsion and steric hinderance
- B30 Thr is removed and myristic acid is added to B20 Lys
  - E. Increases self-aggregation

A. Insulin aspart
B. Insulin lispro
C. Insulin glulisine
D. Insulin glargin
E. Insulin detemir
Insulin Preparations

Regular insulin (short-acting insulin) is formulated in a crystalline zinc solution/suspension (CHOOSE)

- Onset is ______ minutes, peak is ______ hours, and duration of action is ______ hours

Ultralente (long-acting insulin) is formulated in a zinc solution/suspension (CHOOSE)

NPH insulin (intermediate-acting) is formulated in a crystalline zinc solution/suspension (CHOOSE) along with what basic molecule?

- Action of NPH is highly predictable/unpredictable (CHOOSE)
**Insulin Preparations**

Regular insulin (short-acting insulin) is formulated in a crystalline zinc **solution**

- Onset is 30 minutes, peak is 2-3 hours and duration of action is 5-6 hours

Ultralente (long-acting insulin) is formulated in a zinc **suspension**

NPH insulin (intermediate-acting) is formulated in a crystalline zinc **suspension** along with what basic molecule? **Protamine**

- Action of NPH is highly **unpredictable**
State if the following chemical changes of insulin inactivate it or not:

- Deamidation of B3 Asp
  - With which insulin formulation does this not occur? Why?
- Oxidation of S-S bridges
- Cyclization of C-terminal Asn and deamidation of resulting anhydride

Which enzyme in the bloodstream degrades insulin?

Chemical Degradation of Insulin
State if the following chemical changes of insulin inactivate it or not:

- Deamidation of B3 Asp – **still active**
  - With which insulin formulation does this not occur? Why? **Insulin glargine. The B3 Asp is replaced with a Gly**
- Oxidation of S-S bridges – **inactivates**
- Cyclization of C-terminal Asn and deamidation of resulting anhydride – **inactivates**

Which enzyme in the bloodstream degrades insulin? **Insulinase**

**Chemical Degradation of Insulin**
What is the mechanism of action of sulfonylureas?

Variations in the size and complexity of the R1/R2 (CHOOSE) group varies the potency of the drug

State if the following drug is a first or second generation sulfonylurea and if it is short-acting, intermediate-acting, or long-acting:
- Glipizide
- Glyburide
- Tolbutamide
- Chloropropamide
- Tolazamide
- Glimepiride

What is the major difference between first and second generation sulfonylureas?

What is the major adverse effect of these drugs?

Where are these drugs metabolized?
What is the mechanism of action of sulfonylureas?

- Increase insulin secretion, increase insulin receptor sensitivity, reduce glycogenolysis
- Increase insulin secretion by blocking potassium channel on pancreatic beta cells which causes depolarization and calcium channels to open → insulin secretion

- Variations in the size and complexity of the $R_2$ group varies the potency of the drug

- State if the following drug is a first or second generation sulfonylurea and if it is short-acting, intermediate-acting, or long-acting:
  - Glipizide – second gen; intermediate-acting
  - Glyburide – second gen; intermediate-acting
  - Tolbutamide – first gen; short-acting
  - Chloropropamide – first gen; long-acting
  - Tolazamide – first gen; intermediate-acting
  - Glimepiride – second gen; long-acting

- What is the major difference between first and second generation sulfonylureas? Fewer adverse effects and drug interactions

- What is the major adverse effect of these drugs? Hypoglycemia

- Where are these drugs metabolized? Liver
Meglitinides

- What is the mechanism of action of the meglitinides?
- What is the main difference between these drugs and sulfonylureas?
- When should these drugs be taken?
- Which drug has more drug interactions? What enzyme is it metabolized by?
Meglitinides

▪ What is the mechanism of action of the meglitinides? Increase pancreatic insulin release similarly to sulfonylureas (one common binding site and one unique binding site)

▪ What is the main difference between these drugs and sulfonylureas? Less hypoglycemic

▪ When should these drugs be taken? Immediately before meals

▪ Which drug has more drug interactions? Repaglinide more than nateglinide. It is metabolized by CYP3A4
Biguanides

- The structure of metformin is based off what chemical group?
- What is the probable mechanism of action of metformin? Does it require the presence of insulin to be effective?
- What is one rare but serious side-effect of metformin?
- How is metformin metabolized?
- What is one common OTC drug that can interact with metformin?
- Is there a high or low risk of hypoglycemia with metformin?
The structure of metformin is based off what chemical group? **Biguanidine**

What is the probable mechanism of action of metformin? Does it require the presence of insulin to be effective? **Possibly works by stimulation of AMPK due to inhibition of respiratory complex I and reduction of ATP levels. AMPK reduces hepatic glucose production and hyperlipidemia. This does require insulin to be present**

What is one rare but serious side-effect of metformin? **Lactic acidosis**

How is metformin metabolized? **It is not. It is excreted mostly unchanged in the urine**

What is one common OTC drug that can interact with metformin? **Cimetidine**

Is there a high or low risk of hypoglycemia with metformin? **Low risk**
Thiazolidinediones (TZDs)

- What is the mechanism of action of the TZDs? Do they require the presence of insulin to be effective?
- Chronic use of these drugs is associated with what toxicity? Why?
- Pioglitazone/rosiglitazone (CHOOSE) use is severely restricted due to increases in cardiac events
- Which TZD can decrease levels of oral contraceptives?
- Is there a high or low risk of hypoglycemia with TZDs?
Thiazolidinediones (TZDs)

- What is the mechanism of action of the TZDs? Do they require the presence of insulin to be effective? Increase sensitivity to insulin (in hepatocytes, skeletal muscle, and adipocytes) by acting on PPAR-gamma receptor, which activates insulin-responsive genes. Does require presence of insulin to be effective.

- Chronic use of these drugs is associated with what toxicity? Why? Hepatotoxicity because they are extensively metabolized by the liver.

- Rosiglitazone use is severely restricted due to increases in cardiac events.

- Which TZD can decrease levels of oral contraceptives? Pioglitazone.

- Is there a high or low risk of hypoglycemia with TZDs? Low risk.
Alpha-Glucosidase Inhibitors

▪ What is the mechanism of action of the alpha-glucosidase inhibitors?
  What are the three alpha-glucosidase inhibitor drugs mentioned in lecture?
  ▪ Which ones are poorly absorbed and which one is excreted unchanged in urine?
▪ What are the main adverse effects of these drugs?
▪ Is there a high or low risk of hypoglycemia with these drugs?
Alpha-Glucosidase Inhibitors

- What is the mechanism of action of the alpha-glucosidase inhibitors? **Inhibit the enzyme alpha-glucosidase, which acts to break down polysaccharides for absorption in the GI tract. By inhibiting this, there is a delayed/prolonged absorption of carbohydrates, so post-prandial blood glucose levels don’t jump so high so quickly.**

- What are the three alpha-glucosidase inhibitor drugs mentioned in lecture? **Acarbose, miglitol, voglibose.**
  - Which ones are poorly absorbed and which one is excreted unchanged in urine? **Acarbose and voglibose are poorly absorbed; miglitol is excreted unchanged in urine.**

- What are the main adverse effects of these drugs? **GI problems (flatulence, diarrhea, stomach pain).**

- Is there a high or low risk of hypoglycemia with these drugs? **Low risk.**
Glucagon-like Peptide-1 (GLP-1) Analogs

- What is GLP-1? What does it do in response to meals?
- How is GLP-1 degraded?
- What are the GLP-1 analogs mentioned in lecture? How are these drugs administered?
- Which GLP-1 analog has once a day dosing? Why is it long-acting?
- What rare but serious adverse events have been reported with these drugs?
Glucagon-like Peptide-1 (GLP-1) Analogs

- What is GLP-1? What does it do in response to meals? A peptide secreted from L-cells in the pancreas after a meal. Stimulates first phase release on insulin from pancreas in response to high glucose levels. Reduces glucagon concentrations, decreases appetite, and slows gastric emptying.

- How is GLP-1 degraded? By dipeptidyl peptidase 4 (DPP-IV) enzyme

- What are the GLP-1 analogs mentioned in lecture? How are these drugs administered? Exenatide (Byetta), liraglutide (Victoza), dulaglutide (Trulicity), and albiglutide (Tanzeum). Administered SQ

- Which GLP-1 analog has once a day dosing? Why is it long-acting? Liraglutide, because of addition of fatty acid chain which promotes binding to albumin and protects the drug from DPP-IV degradation

- What rare but serious adverse events have been reported with these drugs? Pancreatitis and thyroid cancer

- Is there a high or low risk of hypoglycemia with these drugs? Low risk
DPP-IV Inhibitors

- What is DPP-IV? What is the mechanism of action of the 2-cyanopyrrolidine DPP-IV inhibitors?
  - What are the names of the two DPP-IV inhibitors that work this way?

- What is the mechanism of action of the non-substrate like DPP-IV inhibitor?
  - What is the name of the DPP-IV inhibitor that works this way?

- How are these drugs administered?
- Is there a high or low risk of hypoglycemia with these drugs?
What is the mechanism of action of the 2-cyanopyrrolidine DPP-IV inhibitors? Normally, the enzyme DPP-IV cleaves GLP-1 after a proline residue. These 2-cyanopyrrolidine DPP-IV inhibitors look similar to proline and so DPP-IV will target this residue. The nitrile group in these drugs form a reversible covalent bond with a serine in the active site of DPP-IV, thereby temporarily trapping the enzyme and keeping it from degrading GLP-1.

What are the names of the two DPP-IV inhibitors that work this way? Saxagliptan and vildagliptan.

What is the mechanism of action of the non-substrate like DPP-IV inhibitor? Interacts with DPP-IV with various amino acid residues (temporarily inactivates DPP-IV enzyme similarly to the other DPP-IV inhibitors but without having a proline-type residue): the trifluorophenyl group occupies S1 pocket of DPP-IV, amino group forms salt bridge with tyrosine and glutamate residues, triazolopiperazine group interacts with phenyl residue.

What is the name of the DPP-IV inhibitor that works this way? Sitagliptan.

How are these drugs administered? Orally.

Is there a high or low risk of hypoglycemia with these drugs? Low risk.
WHAT IS THE MECHANISM OF ACTION FOR THE AMYLIN AGONISTS?

WHAT IS THE NAME OF THE AMYLIN AGONIST MENTIONED IN CLASS?

IS THERE A HIGH OR LOW RISK OF HYPOGLYCEMIA WITH THESE DRUGS?
What is the mechanism of action for the amylin agonists? Mimic amylin, an enzyme that is secreted from the pancreas with insulin in response to meals. This enzyme slows gastric emptying and decreases glucagon levels.

What is the name of the amylin agonist mentioned in class? Pramlintide.

Is there a high or low risk of hypoglycemia with these drugs? Moderate-high.
What is the mechanism of action of these drugs?

What are the three drugs of this class mentioned in lecture?

Is there a high or low risk of hypoglycemia with these drugs?

Sodium Glucose Cotransport Inhibitors (SGLT-2 inhibitors)
- What is the mechanism of action of these drugs? Inhibit the sodium glucose cotransporter 2 in the kidney. This blocks reabsorption of glucose and allows it to be passed into the urine.

- What are the three drugs of this class mentioned in lecture? Canagliflozin, empagliflozin, canagliflozin.

- Is there a high or low risk of hypoglycemia with these drugs? Low.
Patients with type 1 diabetes have a genetic predisposition and will eventually have a positive ______ antibody.

Won’t show symptoms until ______% of beta cells in the pancreas have been destroyed.

There is a progressive impairment of insulin release which leads to a partial remission phase. Is this phase permanent or temporary?
Patients with type 1 diabetes have a genetic predisposition and will eventually have a positive islet cell antibody (ICA).

Won’t show symptoms until 70-80% of beta cells in the pancreas have been destroyed.

There is a progressive impairment of insulin release which leads to a partial remission phase. Is this phase permanent or temporary? Usually temporary. Will eventually require higher doses of insulin.
In pre-diabetes, beta cell function begins to deteriorate and there is an initial increase/decrease (CHOOSE) in insulin release.

Eventually, ____________ occurs, cells stop responding to insulin, and blood glucose begins to rise.

How long can it take from the onset of prediabetes to the diagnosis of diabetes?

Microvascular complications are associated with pre-diabetes/diabetes/both (CHOOSE).

Macrovascular complications are associated with pre-diabetes/diabetes/both (CHOOSE).
History of Type 2 Diabetes

- In pre-diabetes, beta cell function begins to deteriorate and there is an initial increase in insulin release.
- Eventually, insulin resistance occurs, cells stop responding to insulin, and blood glucose begins to rise.
- How long can it take from the onset of prediabetes to the diagnosis of diabetes? 5-10 years.
- Microvascular complications are associated with diabetes.
- Macrovascular complications are associated with both.
## Characteristics of Diabetes

- Fill in the following table:

<table>
<thead>
<tr>
<th></th>
<th>Type I Diabetes</th>
<th>Type II Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset (severe, acute?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin secretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin dependence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune etiology?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients diagnosed?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Characteristics of Diabetes

- Fill in the following table:

<table>
<thead>
<tr>
<th></th>
<th>Type I Diabetes</th>
<th>Type II Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of diagnosis</td>
<td>Mostly in childhood</td>
<td>Mostly in adulthood</td>
</tr>
<tr>
<td>Onset (severe, acute?)</td>
<td>Acute and severe</td>
<td>Severe but not usually acute (more insidious onset)</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td>Very low</td>
<td>Variable</td>
</tr>
<tr>
<td>Insulin dependence</td>
<td>Will be dependent permanently</td>
<td>Temporary or later in therapy</td>
</tr>
<tr>
<td>Obesity?</td>
<td>Usually not (sometimes later as disease progresses)</td>
<td>Common</td>
</tr>
<tr>
<td>Autoimmune etiology?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Number of patients diagnosed?</td>
<td>Small amount (5-10% diabetes cases)</td>
<td>Majority of patients (90% diabetes cases)</td>
</tr>
</tbody>
</table>
Egregious 11

- Insulin resistance is the start of it all!
- Please choose the correct answer for the following statements on the egregious 11:
  - 1.) Pancreas
    - Increase/decrease (CHOOSE) in beta cell function
    - Increase/decrease (CHOOSE) in beta cell mass
    - Increase/decrease (CHOOSE) in insulin secretion
  - 2.) Increase/decrease (CHOOSE) in incretin effect
  - 3.) Alpha cell defects
    - Increase/decrease (CHOOSE) in glucagon secretion
  - 4. Adipose
    - Increase/decrease (CHOOSE) in lipolysis
  - 5. Muscle
    - Increase/decrease (CHOOSE) in insulin uptake
  - 6. Liver
    - Increase/decrease (CHOOSE) in glucose production
Insulin resistance is the start of it all!

Please choose the correct answer for the following statements on the egregious 11:

1.) Pancreas
   - Decrease in beta cell function
   - Decrease in beta cell mass
   - Decrease in insulin secretion

2.) Decrease in incretin effect

3.) Alpha cell defects
   - Increase in glucagon secretion

4. Adipose
   - Increase in lipolysis

5. Muscle
   - Decrease in insulin uptake

6. Liver
   - Increase in glucose production
7. Brain
   ▪ Increase/decrease (CHOOSE) in appetite
   ▪ Increase/decrease (CHOOSE) in morning dopamine surge
   ▪ Increased/decreased (CHOOSE) sympathetic tone

8. Colon/biome
   ▪ Abnormal microbiota with increase/decrease (CHOOSE) in GLP-1 secretion

9. ______ dysregulation and inflammation

10. Stomach/small intestine
    ▪ Increase/decrease (CHOOSE) in amylin levels
    ▪ Increase/decrease (CHOOSE) in rate of glucose absorption
    ▪ Increase/decrease (CHOOSE) in gastric emptying time

11. Kidney
    ▪ Upregulation/downregulation (CHOOSE) in SGLT2 activity
    ▪ Increase/decrease (CHOOSE) in glucose reabsorption
7. Brain
   ▪ **Increase** in appetite
   ▪ **Decrease** in morning dopamine surge
   ▪ **Increased** sympathetic tone

8. Colon/biome
   ▪ Abnormal microbiota with **decrease** in GLP-1 secretion

9. **Immune system** dysregulation and inflammation

10. Stomach/small intestine
   ▪ **Decrease** in amylin levels
   ▪ **Increase** in rate of glucose absorption
   ▪ **Increase** in gastric emptying time

11. Kidney
   ▪ **Upregulation** in SGLT2 activity
   ▪ **Increase** in glucose reabsorption
Symptoms and Complications of Diabetes

▪ What are the “three Ps” (in regards to symptoms of diabetes)?

▪ Name symptoms in terms of weight changes, vision changes, energy levels, wound healing/infections, extremity symptoms, urine changes

▪ Name the three microvascular complications

▪ Name the four macrovascular complications

▪ Name a few other disease states that diabetes increases the risk for
Symptoms and Complications of Diabetes

- What are the “three Ps” (in regards to symptoms of diabetes)? Polyphagia, polydipsia, polyuria

- Name symptoms in terms of weight changes, vision changes, energy levels, wound healing/infections, extremity symptoms, urine changes
  - Weight loss, blurry vision, fatigue, decreased wound healing, increase in number of infections, peripheral neuropathy, glucose in the urine (glucosuria)

- Name the three microvascular complications – Retinopathy, nephropathy, neuropathy

- Name the four macrovascular complications – cerebrovascular disease, coronary heart disease, peripheral vascular disease in lower extremities, ulceration and amputation for diabetic foot (can also be considered microvascular complication)

- Name a few other disease states that diabetes increases the risk for
  - Hypertension, kidney disease, heart disease, stroke, blindness/eye problems, nervous system disease, amputations, dental disease, pregnancy complications
What is the normal age we start screening for diabetes?

When should a repeat test be done if results are normal?

An exception to this normal age of screening is when a patient has a BMI greater than ______ along with 1 additional risk factor

Risk factors:

A1C > _______, impaired glucose fasting or impaired glucose tolerance test

____-degree relative with diabetes

High risk race (name a few)

History of CVD

BP > _______ (diagnosis of HTN)

HDL level < ______ and/or triglyceride level > ________

Physical inactivity

Women who were previously diagnosed with ________

Insulin resistance

Screening in children doesn’t start until ____ years old OR onset of ________

Must be overweight and have 2 risk factors present

What is A1C? What will it not tell you about blood glucose?
- What is the normal age we start screening for diabetes? 45 years old
  - When should a repeat test be done if results are normal? 3 years

- An exception to this normal age of screening is when a patient has a BMI greater than 25 along with 1 additional risk factor
  - Risk factors:
    - A1C > 5.7%, impaired glucose fasting or impaired glucose tolerance test
    - First-degree relative with diabetes
    - High risk race (name a few): African American, Hispanic, Asian
    - History of CVD
    - BP > 140/90 (diagnosis of HTN)
    - HDL level < 35 and/or triglyceride level > 250
    - Physical inactivity
    - Women who were previously diagnosed with gestational diabetes
    - Insulin resistance

- Screening in children doesn’t start until 10 years old OR onset of puberty
  - Must be overweight and have 2 risk factors present

- What is A1C? What will it not tell you about blood glucose?
  Percent hemoglobin that is coated with glucose. Gives average amount over past 2-3 months. Doesn’t tell you anything about how blood glucose fluctuates or what fasting BG looks like
Diagnosis of Diabetes and Pre-Diabetes

- Fill in the table with the correct values for diagnosing diabetes or pre-diabetes:

<table>
<thead>
<tr>
<th></th>
<th>Pre-diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb A1C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 hrs post oral glucose tolerance test (OGTT) with 75 g glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Can type II diabetes be diagnosed with only incidence of one of these lab values?
Diagnosis of Diabetes and Pre-Diabetes

- Fill in the table with the correct values for diagnosing diabetes or pre-diabetes:

<table>
<thead>
<tr>
<th></th>
<th>Pre-diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb A1C</td>
<td>5.7-6.4%</td>
<td>&gt;/= 6.5%</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>100-125 mg/dL</td>
<td>&gt;/= 126 mg/dL</td>
</tr>
<tr>
<td>2 hrs post oral glucose tolerance test (OGTT) with 75 g glucose</td>
<td>140-199 mg/dL</td>
<td>&gt;/= 200 mg/dL</td>
</tr>
<tr>
<td>Symptoms</td>
<td>No clear symptoms</td>
<td>Symptoms of hyperglycemia AND random fasting glucose of &gt;/= 200 mg/dL</td>
</tr>
</tbody>
</table>

- Can type II diabetes be diagnosed with only incidence of one of these lab values? No, must repeat test. Only exception is unequivocal hyperglycemia (like you know for sure there is no way this can just be some random high glucose from too many cupcakes, this has to be diabetes)
# Blood Glucose Goals

- Fill in the chart with the blood glucose goals for diabetes:

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>American Association of Clinical Endocrinologists</th>
<th>American Diabetes Association (ADA)</th>
<th>Pregnancy (from ADA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb A1C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postprandial glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Blood Glucose Goals

- Fill in the chart with the blood glucose goals for diabetes:

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>American Association of Clinical Endocrinologists</th>
<th>American Diabetes Association (ADA)</th>
<th>Pregnancy (from ADA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb A1C</td>
<td>&lt; 5.7%</td>
<td>&lt;= 6.5%</td>
<td>&lt;7% (varies based on pt factors)</td>
<td>&lt;6.5%</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>&lt;100 mg/dL</td>
<td>&lt;110 mg/dL</td>
<td>80-130 mg/dL</td>
<td>&lt;= 95 mg/dL</td>
</tr>
<tr>
<td>Postprandial glucose</td>
<td>&lt; 140 mg/dL</td>
<td>&lt;140 mg/dL (2 hrs post)</td>
<td>&lt;180 mg/dL</td>
<td>&lt;140 mg/dL (2 hrs post) and &lt;120 mg/dL (1 hr post)</td>
</tr>
</tbody>
</table>
The ADA has a goal A1C that is more or less stringent based on patient specific factors. What is the more stringent goal and what is the less stringent goal?

More stringent goals are associated with:

- Higher/lower (CHOOSE) risk of hypoglycemia
- New/long-standing (CHOOSE) diagnosis
- Long/short (CHOOSE) life expectancy
- Many/few (CHOOSE) relative comorbidities
- Many/few (CHOOSE) vascular complications
- Poor/excellent (CHOOSE) patient attitude
- Readily available/limited (CHOOSE) resources and support
The ADA has a goal A1C that is more or less stringent based on patient specific factors. What is the more stringent goal and what is the less stringent goal? **More stringent is <6.5% and less stringent is <8%**

More stringent goals are associated with:

- Lower risk of hypoglycemia
- New diagnosis
- Long life expectancy
- Few relative comorbidities
- Few vascular complications
- Excellent patient attitude
- Readily available resources and support
Hemoglobin A1C

How often is Hgb A1C tested for patients:

• Who are at goal
• Who are not at goal
• Who have prediabetes

Higher A1C levels are more strongly associated with fasting/post-prandial (CHOOSE) glucose levels

• Therefore, it is important to correct the fasting/post-prandial (CHOOSE) blood glucose first and foremost
Hemoglobin A1C

How often is Hgb A1C tested for patients:

- Who are at goal – **every 6 months**
- Who are not at goal – **every 3 months**
- Who have prediabetes – **every year**

Higher A1C levels are more strongly associated with fasting glucose levels

- Therefore, it is important to correct the **fasting blood glucose** first and foremost
▪ What are some time-points at which patients should test their blood-glucose?
▪ Where does a continuous glucose monitor measure glucose from and for which type of patients may this device be good for?
▪ What is a goal weight loss and exercise frequency for patients with diabetes?
▪ What are the three main vaccines that diabetic patients should get?
▪ How often should diabetic patients get their teeth cleaned?
▪ How often should diabetic patients get an eye exam?
▪ How often should diabetic patients have an in-office foot exam? How often should they do at home foot exams?
▪ How often should diabetic patients have their albumin:creatinine ratio measured?
  ▪ What is considered microalbuminuria?
  ▪ What is considered macroalbuminuria?
  ▪ What are some medications that can be used to optimize BP and BG and help treat albuminuria?
Standards of Care

- What are some time-points at which patients should test their blood-glucose? Before meals, fasting, post-prandial (1-2 hrs after meals), bedtime, overnight, before exercise.

- Where does a continuous glucose monitor measure glucose from and for which type of patients may this device be good for? Measures interstitial glucose. Good for patients who are frequently hypoglycemic or who have poor awareness.

- What is a goal weight loss and exercise frequency for patients with diabetes? Wt. loss 7% and 150 min exercise a week.

- What are the three main vaccines that diabetic patients should get? Influenza, pneumococcal (PPSV 23), and hepatitis B.

- How often should diabetic patients get their teeth cleaned? Every 6 months.

- How often should diabetic patients get an eye exam? Annually.

- How often should diabetic patients have an in-office foot exam? How often should they do at home foot exams? Annually in office exam and daily self-inspection.

- How often should diabetic patients have their albumin:creatinine ratio measured? Annually.
  - What is considered microalbuminuria? albumin:creatinine ratio 30-299 mg/g.
  - What is considered macroalbuminuria? >= 300 mg/g.

- What are some medications that can be used to optimize BP and BG and help treat albuminuria? ACE inhibitors and ARBs.
Standards of Care: Hypertension and Hyperlipidemia

- What is the goal blood pressure for diabetic patients with hypertension?
- What are the first line therapies for initial treatment of hypertension (there are 4 different classes)?
- When should patients be initiated on 2 agents instead of just 1 (at what BP is this necessary)?
- What medication can be used for patients with a >10% risk of ASCVD as a form of primary prevention?
- What are some medications used for coronary heart disease?
Standards of Care: Hypertension and Hyperlipidemia

- What is the goal blood pressure for diabetic patients with hypertension? **<140/90 mm Hg**
- What are the first line therapies for initial treatment of hypertension (there are 4 different classes)? **ACE inhibitor or ARB or calcium channel blocker (CCB) or thiazide**
- When should patients be initiated on 2 agents instead of just 1 (at what BP is this necessary)? **When BP >160/90 mm Hg**
- What medication can be used for patients with a >10% risk of ASCVD as a form of primary prevention? **Aspirin 81 mg**
- What are some medications used for coronary heart disease? **Aspirin, statins, ACE inhibitors, ARBs, B-blockers**
Lifestyle Mods and Intro to Oral Diabetes Medications
What are the AADE 7 Self-Care Behaviors?

What are some patient specific factors that may influence individual nutrition goals?
What are the AADE 7 Self-Care Behaviors?

- Healthy eating
  - Food insecurity is when pt doesn’t have consistent access to nutritious food
- Being active
- Monitoring blood glucose and pertinent labs
- Taking medication – adherence
- Problem solving
- Healthy coping
- Reducing risks

What are some patient specific factors that may influence individual nutrition goals?

**Personal/cultural preference, health literacy, access to healthy food, willingness/ability to make the behavioral change, barriers to change**
What is the primary difference between simple and complex carbs in the ability to impact blood glucose?

We want patients to get most of their carbohydrates from what type of food group?

Can measure carbs in either portions or grams
  - Portions: what is the normal portion size for most carbs? What about pasta?
  - Grams: How many grams are in one serving?

How many carb servings are recommended per meal?

The “plate method” divides a plate up into sections based on how much of each food group you should be eating? What are the different sections and food groups?

What is the equation for net carbs?

What is the primary difference between glycemic index and glycemic load?
What is the primary difference between simple and complex carbs in the ability to impact blood glucose? Simple carbs cause a very rapid surge in blood glucose levels whereas complex carbs cause a gradual rise in blood glucose levels.

We want patients to get most of their carbohydrates from what type of food group? Non-starchy vegetables.

Can measure carbs in either portions or grams.
- Portions: what is the normal portion size for most carbs? Normal is ½ cup, for pasta it is 1/3 cup.
- Grams: How many grams are in one serving? 15 grams.

How many carb servings are recommended per meal? 3-4 servings.

The “plate method” divides a plate up into sections based on how much of each food group you should be eating? What are the different sections and food groups? ½ plate for non-starchy vegetables, ¼ plate for protein, ¼ plate for starches.

What is the equation for net carbs? Total carbs – fiber = net carbs.

What is the primary difference between glycemic index and glycemic load? Glycemic index is the ability for a certain TYPE of carbohydrate to raise blood glucose while glycemic load looks at how much a certain SERVING of a specific carbohydrate will raise blood glucose.
▪ What is the goal weight loss for diabetic patients?
▪ What are two diets that diabetic patients can try to utilize?
▪ Which types of fats should be avoided?
▪ What is the recommended alcohol limit for diabetic patients?
▪ Patients should try to limit sodium intake to less than ________
▪ What is the goal weight loss for diabetic patients? **7% wt. loss**

▪ What are two diets that diabetic patients can try to utilize? **DASH or Mediterranean**

▪ Which types of fats should be avoided? **Trans and saturated fats**

▪ What is the recommended alcohol limit for diabetic patients? **1 drink daily for women, 2 drinks daily for men**

▪ Patients should try to limit sodium intake to less than **2300 mg**
Physical Activity Goals

- What is the recommended amount of moderate/vigorous aerobic activity patients should be getting?
  - How about vigorous training in younger patients?
- How often should patients do resistance (strength) training?
- What is the recommended time children with diabetes or pre-diabetes should be engaging in physical activity?
- What are some diabetes complications that may impact patient’s ability to perform physical activity?
Physical Activity Goals

- What is the recommended amount of moderate/vigorous aerobic activity patients should be getting? **150 min/week**
- How about vigorous training in younger patients? **75 min/week**
- How often should patients do resistance (strength) training? **2-3 times a week**
- What is the recommended time children with diabetes or pre-diabetes should be engaging in physical activity? **60 minutes a day**
- What are some diabetes complications that may impact patient’s ability to perform physical activity? **Neuropathy and retinopathy**
** a lot of this is going to be repeat of previous slide information. But repetition is GOOD for learning
• What is the medication class and mechanism of action (hint, there are 3 ways this drug helps control diabetes)?

• How much does this drug reduce A1C and fasting blood glucose levels (FBG)?

• What are some common adverse effects of this drug?

• What are patient risk factors for getting lactic acidosis while on metformin? What lab values are used to show that a patient has lactic acidosis?

• What is the initiating dose for metformin (immediate release)? What is the maximum effective dose? How many times a day can this drug be administered (for both immediate release and extended release)?

• How often can the dose be titrated?

• What is a contraindication for using this drug (hint: renal function)?
What is the medication class and mechanism of action (hint, there are 3 ways this drug helps control diabetes)? **Biguanide. Decreases hepatic glucose production, decreases intestinal absorption of glucose, and increases insulin sensitivity**

How much does this drug reduce A1C and fasting blood glucose levels (FBG)? **Reduces A1C by 1-2% and reduces FBG by 50-70 mg/dL**

What are some common adverse effects of this drug? **Gastric upset, diarrhea, flatulence, nausea/vomiting**

What are patient risk factors for getting lactic acidosis while on metformin? What lab values are used to show that a patient has lactic acidosis? If pt is in sepsis, is dehydrated, has renal/liver failure, has acute/complicated heat failure, is over 80 years old. Lab values are low pH, elevated lactate levels, increased anion gap.

What is the initiating dose for metformin (immediate release)? What is the maximum effective dose? How many times a day can this drug be administered (for both immediate release and extended release)? **Initiate at 500 mg daily. Max effective dose is 2000 mg daily (although the accepted max dose is 2550 mg daily). Can be administered up to 3 times daily (up to 2 times daily for extended release).**

How often can the dose be titrated? **Every week as tolerated**

What is a contraindication for using this drug (hint: renal function)? **eGFR <30 mL/min. Should not be initiated with eGFR 30-45 mL/min.**
Thiazolidinediones (TZDs)

- What is the mechanism of action (hint, there are 3 ways this drug helps control diabetes)?
- How much does this drug reduce A1C and fasting blood glucose levels (FBG)?
- When should patients expect to see improvements in glycemic control?
- For each statement state whether it pertains to pioglitazone or rosiglitazone:
  - Dosed once a day
  - Dosed twice a day
  - Peak of action at 1 hour
  - Peak of action at 2-4 hours
  - Extensive liver metabolism
- What is a black box warning for these drugs? What is a contraindication to using them? What needs to be periodically monitored for patients on these drugs?
- What is the initiating dose and maximum dose for each TZD?
- What are some common adverse effects of TZDs?
Thiazolidinediones (TZDs)

- What is the mechanism of action (hint, there are 3 ways this drug helps control diabetes)? Activates the PPAR gamma receptor in the nucleus, which activates insulin receptors. Overall, TZDs increase insulin sensitivity, increase glucose uptake in muscle and adipose, and inhibit gluconeogenesis.

- How much does this drug reduce A1C and fasting blood glucose levels (FBG)? Reduces A1C by 0.5-1.5% and reduces FBG by 30-60 mg/dL.

- When should patients expect to see improvements in glycemic control? 4-12 weeks.

- For each statement state whether it pertains to pioglitazone or rosiglitazone:
  - Dosed once a day – pioglitazone
  - Dosed twice a day – rosiglitazone
  - Peak of action at 1 hour – rosiglitazone
  - Peak of action at 2-4 hours – pioglitazone
  - Extensive liver metabolism – both

- What is a black box warning for these drugs? What is a contraindication to using them? What needs to be periodically monitored for patients on these drugs? BBW for increased risk of congestive heart failure. Contraindicated in patients with NYHA Class III or IV CHF. LFTs need to be taken at initiation of TZDs and periodically during therapy.

- What is the initiating dose and maximum dose for each TZD?
  - Pioglitazone: Start at 15 mg daily, max is 45 mg daily
  - Rosiglitazone: Start at 2 mg daily, max is 8 mg daily

- What are some common adverse effects of TZDs? Edema, weight gain, change in lipids, increased risk upper respiratory infections.
▪ What is the mechanism of action (hint, there are 3 ways this drug helps control diabetes)? How much do these drugs reduce A1C and fasting blood glucose levels (FBG)?

▪ Name the second generation sulfonylureas

▪ State the starting dose and maximum EFFECTIVE dose for each agent along with the number of times they are dosed each day

▪ Which agent comes in an extended release form?

▪ What is/are the preferred agent(s) in patients with poor renal function and/or cardiovascular issues? Which agent cannot be used with CrCL< 60 mL/min? What enzyme metabolizes these drugs?

▪ What are two major side effects of these drugs?

▪ What are contraindications to these drugs?

▪ What is the difference between primary and secondary failure?
What is the mechanism of action (hint, there are 3 ways this drug helps control diabetes)? *Causes beta cells in pancreas to secrete insulin, sensitizes cells to insulin, and decreases glucose production by the liver*.

How much does this drug reduce A1C and fasting blood glucose levels (FBG)? *Reduces A1C by 1-2% and reduces FBG by 50-70 mg/dL*.

Name the second generation sulfonylureas: *Glipizide, glimepiride, glyburide (non-micronized and micronized; micronized not really used)*.

State the starting dose and maximum EFFECTIVE dose for each agent along with the number of times they are dosed each day:
- **Glipizide**: 5 mg start; 20 mg max effective
- **Glimepiride**: 0.5-1 mg start; 4 mg max effective
- **Glyburide**: 2.5 mg start; 10 mg max effective

Which agent comes in an extended release form? *Glipizide*.

What is/are the preferred agent(s) in patients with poor renal function and/or cardiovascular issues? Which agent cannot be used with CrCL<60 mL/min? *Glipizide and glimepiride are drugs of choice. Cant use glyburide with CrCL<60 mL/min*.

What enzyme metabolizes these drugs? *CYP2C9*.

What are two major side effects of these drugs? *Hypoglycemia and weight gain*.

What are contraindications to these drugs? *Type 1 diabetes, ketoacidosis, and can’t use glyburide with Bosentan (drug used to treat pulmonary artery hypertension)*.

What is the difference between primary and secondary failure? *Primary means the pt never had a response to the drug. secondary means they initially responded well to therapy but are now no longer responding to it*.
▪ What is the mechanism of action? How much do these drugs reduce A1C and fasting blood glucose levels (FBG)?

▪ What is the main difference between these drugs and sulfonylureas?

▪ What are the two meglitinides discussed in lecture?

▪ What is the starting dose for each agent? What is a major counseling point for patients in regard to the timing of dosing?

▪ Which agent does not need dose adjusting for renal or hepatic failure?

▪ What are major side effects of these agents?

▪ What are contraindications to these drugs?
- What is the mechanism of action? How much do these drugs reduce A1C and fasting blood glucose levels (FBG)?
  - Increases insulin release from beta cells of the pancreas. Reduces A1C by 1-2% and reduces FBG by 50-70 mg/dL.

- What is the main difference between these drugs and sulfonylureas? The half-life. These drugs have half-life of 1-3 hrs and duration of action 4-6 hrs. Sulfonylureas have longer half-lives and durations of action.

- What are the two meglitinides discussed in lecture? Repaglinide, Nateglinide.

- What is the starting dose for each agent? What is a major counseling point for patients in regard to the timing of dosing? Repaglinide is 0.5 mg TID if A1C<8% and 1-2mg TID if A1C >8%. Nateglinide is 120 mg TID (can do 60 mg TID if close to A1C goal). MUST dose with meals 15-30 minutes before eating.

- Which agent does not need dose adjusting for renal or hepatic failure? Nateglinide.

- What are major side effects of these agents? Hypoglycemia (though not as severe as with sulfonylureas), weight gain, headache, dizziness (nateglinide), diarrhea, upper respiratory infection.

- What are contraindications to these drugs? Use with gemfibrozil (repaglinide), type 1 diabetes, and ketoacidosis.
What is the mechanism of action? How much do these drugs reduce A1C and fasting blood glucose levels (FBG)?

What is the recommended dose of Januvia and how does this change based off renal function? Does this drug need to be taken with food? What is an important drug interaction to counsel patients about (hint; it’s another diabetes drug)?

Which agent is usually the most tolerated in terms of adverse effects?

What is the recommended dose of saxagliptan and how does this change based off renal function?

Which agents need to be dosed after dialysis?

What is the recommended dose of linagliptan and how does this change based off renal function?

What is the recommended dose of alogliptan and how does this change based off renal function?

What are some shared side effects of these drugs? What are two unique adverse effects of saxagliptan?

Which two agents have a safety alert for increased risk of heart failure?
**DPP-IV Inhibitors**

- **What is the mechanism of action? How much do these drugs reduce A1C and fasting blood glucose levels (FBG)?** Inhibit the enzyme DPP-IV, which normally degrades GLP-1 and glucose-dependent insulinotropic peptide (GIP). These are called incretins and help control blood glucose after meals. DPP-IV inhibitors work by reversible inhibition.
  - Sitagliptan/alogliptan/linagliptan – reduces A1C by 0.5-0.8% and FBG by 20-40 mg/dL
  - Saxagliptan – reduces A1C by 0.5% or if used in combo therapy 0.5-0.8%.

- **What is the recommended dose of Januvia and how does this change based off renal function?** Does this drug need to be taken with food? What is an important drug interaction to counsel patients about (hint; it's another diabetes drug)?
  - Januvia: 100 mg daily. If CrCL 30-50 mL/min give 50 mg daily. If CrCL < 30 mL/min give 25 mg daily. Can be taken with or w/out food. Caution with sulfonylureas or insulin b/c increased risk of hypoglycemia.

- **What is the recommended dose of saxagliptan and how does this change based off renal function?**
  - 2.5-5 mg daily; if CrCL < 50 mL/min then 2.5 mg daily

- **Which agents need to be dosed after dialysis?** Saxagliptan

- **What is the recommended dose of linagliptan and how does this change based off renal function?**
  - 5 mg daily, no dose adjustment in renal failure

- **What is the recommended dose of alogliptan and how does this change based off renal function?**
  - 25 mg daily; if CrCL 30-60 mL/min then 12.5 mg daily; if CrCL < 30 mL/min then 6.25 mg daily

- **What are some shared side effects of these drugs? What are two unique adverse effects of saxagliptan?** Nasopharyngitis, headache, upper resp. tract infection. Unique to saxa are UTI and peripheral edema

- **Which two agents have a safety alert for increased risk of heart failure?** Alogliptan and saxagliptan
What is the mechanism of action? How much do these drugs reduce A1C and fasting blood glucose levels (FBG)?

What are the three agents mentioned in lecture?

Which agent has an FDA approved indication for reducing risk of cardiovascular death?

What is the major way these agents are metabolized?

How often are these drugs dosed?

Which agent needs to be taken before the first meal of the day?

These agents are not recommended for patients with an eGFR < ______ and are contraindicated for patients with an eGFR < ______

What are some side-effects common to all these agents? Which agent increases risk for bone fracture? Which agent has been shown to cause bladder cancer in rare cases?

SGLT2 Inhibitors
What is the mechanism of action? How much do these drugs reduce A1C and fasting blood glucose levels (FBG)? Block reabsorption of filtered glucose by inhibiting SGLT2 transporter. Reduce A1C by 0.8-0.9% and FBG by 25-30 mg/dL.

What are the three agents mentioned in lecture? Canagliflozin, empagliflozin, dapagliflozin.

Which agent has an FDA approved indication for reducing risk of cardiovascular death? Empagliflozin.

What is the major way these agents are metabolized? Glucuronidation.

How often are these drugs dosed? Once daily.

Which agent needs to be taken before the first meal of the day? Canagliflozin.

These agents are not recommended for patients with an eGFR < 45 mL/min and are contraindicated for patients with an eGFR < 30 mL/min.

What are some side-effects common to all these agents? Which agent increases risk for bone fracture? Which agent has been shown to cause bladder cancer in rare cases? UTIs, genital mycotic infections, dehydration/increased urination, and ketoacidosis. Canagliflozin increases bone fracture risk. Dapagliflozin had incidence of bladder cancer.

SGLT2 Inhibitors
What is the mechanism of action? How much do these drugs reduce A1C and fasting blood glucose levels (FBG)?

What are the two agents mentioned in lecture?

How are these medications dosed?

What are some common side-effects of these drugs?

What are contraindications to using these drugs?
What is the mechanism of action? How much do these drugs reduce A1C and fasting blood glucose levels (FBG)? Competitive inhibitor of pancreatic amylases and brush border alpha glucosidases. Delays the breakdown and absorption of carbohydrates. Has dose-dependent reduction of post-prandial glucose/insulin peaks.

What are the two agents mentioned in lecture? Acarbose and miglitol.

How are these medications dosed? TID with meals.

What are some common side-effects of these drugs? GI – flatulence, abdominal pain, diarrhea.

What are contraindications to using these drugs? IBD, colonic ulceration, intestine obstruction, cirrhosis, chronic intestinal diseases.
Hypoglycemia

- Hypoglycemia is considered blood glucose less than ______
- Name some common signs/symptoms of hypoglycemia
- For initial hypoglycemic treatment, how many grams of carbohydrate should you give and when should you re-check blood glucose? When should you repeat treatment?
- How many grams of carbohydrates should you give when BG is < 50 mg/dL?
- What are examples of fast-acting carbohydrates?
- How do you administer a glucagon emergency kit?
- What is used in hospital to correct severe hypoglycemia?
Hypoglycemia

- Hypoglycemia is considered blood glucose less than 70 mg/dL
- Name some common signs/symptoms of hypoglycemia
  - Shaking, sweating, blurry vision, confusion, hunger, irritability, tachycardia, headache, fatigue
- For initial hypoglycemic treatment, how many grams of carbohydrate should you give and when should you re-check blood glucose? When should you repeat treatment? 15 grams, recheck in 15 minutes. Repeat tx if BG still under 70 mg/dL
- How many grams of carbohydrates should you give when BG is < 50 mg/dL? 30 grams
- What are examples of fast-acting carbohydrates? Glucose tablets, hard candies, juice, glucose gel, glass of milk
- How do you administer a glucagon emergency kit? 1 mg SQ, IM, IV in butt, thigh, or upper arm. Can repeat in 15 min. when pt responds, give a carb snack.
- What is used in hospital to correct severe hypoglycemia? Dextrose IV 25 grams
Injectable Diabetes Medications
- For which patients is insulin therapy indicated?
- Onset, duration of action, strength, source, and analog are all examples of _________ properties of insulin
- Explain the two phase kinetics of insulin. How is this replicated with therapy?
- What is the ceiling dose for insulin?
- Which form of diabetes (Type I or Type II) usually requires higher doses of insulin?
- Which form of diabetes (Type I or Type II) is dependent on insulin therapy?
Insulin Action

- For which patients is insulin therapy indicated? *Patients who have Type I diabetes or patients with Type II diabetes on optimized oral therapy who are not meeting their target goals*

- Onset, duration of action, strength, source, and analog are all examples of **pharmacokinetic** properties of insulin

- Explain the two phase kinetics of insulin. How is this replicated with therapy? *In response to glucose consumption, there is an initial first phase of an acute spike in insulin levels. This lasts a few minutes and is followed by a sustained steady release of insulin (phase II) while the glucose is still present. Therapy replicates this by using both a rapid-acting and basal insulin therapy*

- What is the ceiling dose for insulin? *There is no ceiling dose. Patient will use as much as it takes to get blood glucose under control*

- Which form of diabetes (Type I or Type II) usually requires higher doses of insulin? *Type II*

- Which form of diabetes (Type I or Type II) is dependent on insulin therapy? *Type I*
Insulin Preparations

- Match the insulin type with it’s duration of action:
  - Insulin aspart
  - Insulin detemir
  - Novolin R
  - Insulin glargine
  - Humulin N
  - Insulin lispro
  - Insuline degludec
  - Insulin glulisine
  - Humulin R
  - Novolin N
  - Insulin glargine U300
  - Humulin R U500
  - A. Rapid acting
  - B. Short acting/Regular
  - C. Intermediate acting/NPH
  - D. Long acting
  - E. Concentrated regular insulin
  - F. Ultra long-acting
Insulin Preparations

- Match the insulin type with its duration of action:
  - Insulin aspart (A)
  - Insulin detemir (D)
  - Novolin R (B)
  - Insulin glargine (D)
  - Humulin N (C)
  - Insulin lispro (A)
  - Insuline degludec (F)
  - Insulin glulisine (A)
  - Humulin R (B)
  - Novolin N (C)
  - Insulin glargine U300 (F)
  - Humulin R U500 (E)
  
  A. Rapid acting
  B. Short acting/Regular
  C. Intermediate acting/NPH
  D. Long acting
  E. Concentrated regular insulin
  F. Ultra long-acting
Match the generic insulin name with the brand name (this is more for your knowledge in practice rather than the exam)

- Insulin glulisine
- Insulin glargine
- Insulin lispro
- Insulin degludec
- Insulin detemir
- Insulin aspart
- Insulin glargine U300

- A. Humalog (U-100, U-200)
- B. Novolog
- C. Apidra
- D. Lantus
- E. Levemir
- F. Toujeo U-300
- G. Tresiba (U-100, U-200)
- Match the generic insulin name with the brand name (this is more for your knowledge in practice rather than the exam)
  - Insulin glulisine (C)
  - Insulin glargine (D)
  - Insulin lispro (A)
  - Insulin degludec (G)
  - Insulin detemir (E)
  - Insulin aspart (B)
  - Insulin glargine U300 (F)
  - A. Humalog (U-100, U-200)
  - B. Novolog
  - C. Apidra
  - D. Lantus
  - E. Levement
  - F. Toujeo U-300
  - G. Tresiba (U-100, U-200)
Rapid Acting Insulin

- Please state the following for rapid-acting insulin:
  - Onset
  - Peak
  - Duration of action
  - When to dose
Rapid Acting Insulin

- Please state the following for rapid-acting insulin:
  - Onset – 10-20 min
  - Peak – 30-90 min
  - Duration of action – 3-5 hours
  - When to dose – immediately before meals
Regular (Short-Acting) Insulin

- Please state the following for short-acting insulin:
  - Onset
  - Peak
  - Duration of action
  - When to dose

- What are some times you would be worried about hypoglycemia with this type of insulin?
Regular (Short-Acting) Insulin

- Please state the following for short-acting insulin:
  - Onset – 30-60 min
  - Peak – 2-4 hours
  - Duration of action – 5-8 hours
  - When to dose – 20-40 min before meals

- What are some times you would be worried about hypoglycemia with this type of insulin? Late postprandial onset especially if meal is delayed. Also if exercise after a meal.
Intermediate Acting Insulin

- Please state the following for intermediate-acting insulin:
  - Onset
  - Peak
  - Duration of action
  - When to dose

- What are some times you would be worried about hypoglycemia with this type of insulin?
Intermediate Acting Insulin

- Please state the following for intermediate-acting insulin:
  - Onset – 1-3 hours
  - Peak – 8 hours
  - Duration of action – 12-16 hours
  - When to dose – twice daily

- What are some times you would be worried about hypoglycemia with this type of insulin? **At the time of the insulin peak**
Long-Acting Insulin

- Please state the following for long-acting insulin:
  - Onset
  - Peak
  - Duration of action
  - When to dose (glargine vs. detemir)
  - How often can you dose adjust?
Please state the following for long-acting insulin:

- Onset – 1 hour
- Peak – no peak (very flat peak with detemir)
- Duration of action – 24 hours (20-26 hrs with detemir, depending on the dose)
- When to dose (glargine vs. detemir) – Once a day at same time each day for glargine. Once OR twice a day for detemir (may benefit to receive another dose if elevated pre-dinner BG)
- How often can you dose adjust? Every 3 days
State if the following are characteristics of Toujeo or Tresiba:

- Onset of 6 hours
- Onset of 90 minutes
- True “24 hr” insulin that allows flexibility in dosing
- Make take up to 5 days to effectively lower glucose

How often can the dose be titrated for these insulins?

**Ultra Long-Acting Insulin**
State if the following are characteristics of Toujeo or Tresiba:

- Onset of 6 hours – Toujeo
- Onset of 90 minutes – Tresiba
- True “24 hr” insulin that allows flexibility in dosing – Tresiba
- Make take up to 5 days to effectively lower glucose – Toujeo

How often can the dose be titrated for these insulins?
Every 5 days

Ultra Long-Acting Insulin
• What does the first number and the second number refer to in mixed insulins (for example, Humalog Mix 75/25)

• What are some advantages and disadvantages to mixed insulins?

• Please state when you would “see” the effect in BG levels from various insulin preparations (for example, with a rapid acting insulin in the morning, would you see that reflected in the post-breakfast levels or the pre-lunch level?)
  • Morning bolus insulin
  • Morning basal insulin
  • Evening bolus insulin
  • Evening basal insulin

• How long can insulin usually be stored at room temp?
What does the first number and the second number refer to in mixed insulins (for example, Humalog Mix 75/25)? The first number tells you the percent long-acting (or intermediate) and the second number tells you the percent rapid-acting (or short-acting).

What are some advantages and disadvantages to mixed insulins? Advantage is less frequent administration (easier to adhere) and disadvantage is they are hard to titrate.

Please state when you would “see” the effect in BG levels from various insulin preparations (for example, with a rapid acting insulin in the morning, would you see that reflected in the post-breakfast levels or the pre-lunch level?)

- Morning bolus insulin – pre-lunch glucose levels
- Morning basal insulin – pre-dinner glucose levels
- Evening bolus insulin – bedtime glucose levels
- Evening basal insulin – next morning glucose levels

How long can insulin usually be stored at room temp? Same amount of time the opened insulin can be kept in the fridge. Usually, it’s around 28 days but varies based on the formulation.
What angle should the needle be inserted?

Which sites can insulin be injected?

What is an important counseling point to tell patients to avoid injection site reactions?
What angle should the needle be inserted? **90 degrees**

Which sites can insulin be injected? **Abdomen, arm, upper thigh, butt**

What is an important counseling point to tell patients to avoid injection site reactions? **Rotate injection sites**
Insulin Adverse Effects

- What are some adverse effects that can occur with insulin administration?
  - What is Somogyi phenomenon?
  - What is the Dawn effect?
- What is weight gain associated with?
- What is lipohypertrophy and how does it occur?
- What is lipoatrophy?
Insulin Adverse Effects

- What are some adverse effects that can occur with insulin administration? **Hypoglycemia, weight gain**
  - What is Somogyi phenomenon? **Nocturnal hypoglycemia** (around 2-3 am) followed by rebound hyperglycemia
  - What is the Dawn effect? **Early morning cortisol/epinephrine release** causing elevated fasting blood glucose in the morning

- What is weight gain associated with? **Insulin dose** (higher = more wt. gain)

- What is lipohypertrophy and how does it occur? **Thickened skin lesions at injection site** due to pt not rotating injection site

- What is lipoatrophy? **Immune mediated reaction** that causes skin atrophy at injection site
Initiating Insulin – Tx Naïve Patients (Type I Diabetes)

▪ What is the weight-based dosing regimen for insulin initiation? What percent should come from bolus insulin vs basal insulin?

▪ How does the regimen change for mixed insulins?
Initiating Insulin – Tx Naïve Patients (Type I Diabetes)

- What is the weight-based dosing regimen for insulin initiation? What percent should come from bolus insulin vs basal insulin? 0.5 units/kg/day. Give 20% bolus at each meal and 40% basal.
  - So 20% times 3 meals a day is 60%. Plus 40% basal = 100%.

- How does the regimen change for mixed insulins? 0.5 units/kg/day with 2/3 dose before breakfast and 1/3 dose before dinner.
Initiating Insulin for Patients Who Failing Oral Therapy (Type II DM)

- Which insulin type should be initiated and at what dose?
- How do you switch a patient from once daily NPH to long-acting insulin? What about twice daily NPH?
- How do you switch a patient from long-acting insulin to NPH?
- How about converting between regular insulin and rapid-acting?
Initiating Insulin for Patients Who Failing Oral Therapy (Type II DM)

- Which insulin type should be initiated and at what dose? Basal insulin at 10 units or 0.1-0.2 units/kg

- How do you switch a patient from once daily NPH to long-acting insulin? What about twice daily NPH? Once daily is a 1:1 ratio switch. With going from BID NPH to long-acting, you reduce the total dose by 20%

- How do you switch a patient from long-acting insulin to NPH? Consider 20% total dose reduction. Give NPH BID with 2/3 dose in morning and 1/3 dose in evening

- How about converting between regular insulin and rapid-acting? It’s always a 1:1 ratio
If a patient’s total insulin dose is 50 units, calculate the insulin-to-carbohydrate ratio

- If this same patient is eating a meal with total carbs of 100 g, how much insulin should they use?

Insulin sensitivity factor

- The “1800 rule” is used for which type of insulin?
- The “1500 rule” is used for which type of insulin?

If pt has total 50 units of insulin (rapid-acting), what is the insulin sensitivity factor and what does this mean?
Other Insulin Regimens

- If a patient’s total insulin dose is 50 units, calculate the insulin-to-carbohydrate ratio: \( \frac{500}{50} = 10 \). Therefore, 1 unit = 10 grams carbs.
- If this same patient is eating a meal with total carbs of 100 g, how much insulin should they use? \( \frac{1 \text{ unit}}{10 \text{ g}} = \frac{x \text{ unit}}{100 \text{ g}} \). \( x = 10 \) units of insulin.

**Insulin sensitivity factor**
- The “1800 rule” is used for which type of insulin? **Rapid-acting**
- The “1500 rule” is used for which type of insulin? **Short-acting**
- If pt has total 50 units of insulin (rapid-acting), what is the insulin sensitivity factor and what does this mean? ISF = 36. This means blood glucose will be lowered by 36 mg/dL for every unit of insulin.
Managing Insulin

- Should insulin be continued when patient is vomiting/not eating?
- What are some physical signs/symptoms of ketoacidosis (don’t need to know lab values)?
- What are the goals of ketoacidosis treatment?
- What is the difference between ketoacidosis and hyperglycemic hyperosmolar state?
- What are some complications that can occur in gestational diabetes and which diabetes treatment is recommended?
  - What are the A1c and FBG goals?
Managing Insulin

- Should insulin be continued when patient is vomiting/not eating? Yes at least should be getting 50% of normal dose

- What are some physical signs/symptoms of ketoacidosis (don’t need to know lab values)? Increased resp. rate, nausea, vomiting, dehydration, polyuria, fruity breath

- What are the goals of ketoacidosis treatment? Restore circulatory volume and tissue perfusion, correct electrolyte imbalances, treat underlying cause. Use NaCl IV fluid to restore volume, IV insulin to tx underlying cause, potassium correction to prevent cardiac complications, and admin of various electrolytes

- What is the difference between ketoacidosis and hyperglycemic hyperosmolar state (HHS)? Patients with HHS are not acidotic and have much greater fluid losses

- What are some complications that can occur in gestational diabetes and which diabetes treatment is recommended? Heavy birth weight, birth defects, and HTN in the mother
  - What are the A1c and FBG goals? A1C 6-6.5% and FBG < 95 mg/dL
For which patients would a GLP-1 agonist be indicated?

What is a black box warning for use of GLP-1 agonists?

What are precautions to consider with GLP-1 agonists?

Which formulation is short-acting, how often is it dosed, and does it impact fasting BG or post-prandial BG more?

Results of the LEADER trial showed that death from cardiac events was less in patients that were taking ____________

When would a patient be indicated for Soliqua? Xultophy?
For which patients would a GLP-1 agonist be indicated? Used as adjunctive therapy to diet/exercise but is not first-line. Can be used with another oral agent (metformin) esp if pt concerned for hypoglycemia and weight gain.

What is a black box warning for use of GLP-1 agonists? Thyroid cancer.

What are precautions to consider with GLP-1 agonists? Pancreatitis, hypoglycemia, renal impairment.

Which formulation is short-acting, how often is it dosed, and does it impact fasting BG or post-prandial BG more? Byetta, dosed once a day, impacts PPG more.

Results of the LEADER trial showed that death from cardiac events was less in patients that were taking liraglutide.

When would a patient be indicated for Soliqua? Xultophy? Adjunctive therapy in pts not controlled on <60 units basal insulin for Soliqua. For Xultophy, adjunctive therapy for pts not controlled on <50 units basal insulin or not controlled on liraglutide.
Amylin

- What are the three main mechanisms of action of amylin?
- What are some advantages and disadvantages to amylin therapy?
- What needs to be done with the bolus insulin dose before initiation of amylin?
- When should patients dose amylin? Can this be given at the same time as other oral medications?
- When can the dose be titrated up?
- Can amylin analog and insulin be mixed and administered together?
- What is a boxed warning for this drug?
What are the three main mechanisms of action of amylin? Regulates gastric emptying time, reduces appetite/food intake, and decreases hepatic glucose output.

What are some advantages and disadvantages to amylin therapy? Advantage is weight loss and decreased glucose excursion. Disadvantages are GI side effects, risk of hypoglycemia, and not super effective at lowering A1C.

What needs to be done with the bolus insulin dose before initiation of amylin? Reduce bolus dose by 50%.

When should patients dose amylin? Can this be given at the same time as other oral medications? Administer prior to major meals. Want to separate from oral meds (1 hr prior, 2 hrs after).

When can the dose be titrated up? Every 3 days.

Can amylin analog and insulin be mixed and administered together? No.

What is a boxed warning for this drug? Hypoglycemia.