Diabetes Mellitus
Pharmacology Review

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Objectives

1. Review the epidemiology and pathophysiology of diabetes.

2. Review the diagnostic criteria, treatment goals, and monitoring parameters for type 2 diabetes mellitus.

3. Review signs and symptoms of hypoglycemia and hyperglycemia.

4. List and describe pharmacological treatment options.
   - Place in therapy, efficacy, hypoglycemia risks, effects on weight, adverse effects, and costs
Epidemiology

- Diabetes mellitus: 7th leading cause of death in US
- 9.3% or 29.1 million people in US have diabetes
- Estimated total cost related to diabetes: $245 billion
- Common forms of diabetes:
  - Type 1: absolute insulin deficiency (cannot be prevented)
  - Type 2: progressive insulin deficiency (self management is key)
  - Gestational: diagnosed in the 2nd or 3rd trimester of pregnancy
- Type 2 - leading cause of:
  - Neuropathy (44%)
  - Nephropathy (60% of non-traumatic lower-limb amputations)
  - Retinopathy (28.4%)

Pathophysiology: Pancreas

- **Exocrine**: involves breakdown of carbohydrates, proteins, and fat
- **Endocrine**: regulates utilization of food for energy and storage
  - Pancreatic hormones involved with regulating blood glucose (BG):
    - ALPHA CELLS $\rightarrow$ GLUCAGON $\star$
    - BETA CELLS $\rightarrow$ INSULIN $\uparrow$ & AMYLIN $\downarrow$
Pathophysiology: Low Blood Sugar

Glycogenolysis | Breakdown of glycogen $\rightarrow$ glucose
Gluconeogenesis | Synthesis of lactate, amino acids, and glycerol $\rightarrow$ glucose
Pathophysiology: High Blood Sugar

Amylin release
Slows gastric emptying & enhances satiety

Beta Cells
Insulin release
Storage & Energy

Glucose

Liver
glycogen

Insulin

Pancreas

Muscle Cells

Glucose

STOMACH

STORAGE & ENERGY
What is an A1C?

- **Glycosylated hemoglobin (A1C)**
  - Test reflect average BG over the past 2-3 months.
  - Normal A1C 5.6% or less
  - Not influenced by daily BG changes
  - Obtain A1C if not available within last 3 months

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>Mean plasma glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>126</td>
</tr>
<tr>
<td>7</td>
<td>154</td>
</tr>
<tr>
<td>8</td>
<td>183</td>
</tr>
<tr>
<td>9</td>
<td>212</td>
</tr>
<tr>
<td>10</td>
<td>240</td>
</tr>
<tr>
<td>11</td>
<td>269</td>
</tr>
<tr>
<td>12</td>
<td>298</td>
</tr>
</tbody>
</table>

### Diagnostic criteria

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Pre-diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting* Blood glucose (mg/dL)</td>
<td>99 or less</td>
<td>100 to 125</td>
<td>126 or greater</td>
</tr>
<tr>
<td>2 hour blood glucose during an OGTT** (mg/dL)</td>
<td>139 or less</td>
<td>140 to 199</td>
<td>200 or greater</td>
</tr>
<tr>
<td>Patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random blood glucose</td>
<td>-</td>
<td>-</td>
<td>200 or greater</td>
</tr>
<tr>
<td>Hgb A1C (%)</td>
<td>5.6 or less</td>
<td>5.7 to 6.4</td>
<td>6.5 or greater</td>
</tr>
</tbody>
</table>

*Fasting*: no caloric intake for at least 8 hours  
**OGTT**: 75 gram oral glucose tolerance test

Treatment Goals

- Prevent the onset of acute and chronic complications
  - **Acute complications:** Hypoglycemia, hyperglycemia (crisis)
  - **Chronic complications:**
    - **Microvascular** (small vessels)
      - Neuropathy
      - Retinopathy
      - Nephropathy
    - **Macrovascular** (large vessels)
      - Coronary heart disease
      - Stroke
      - Peripheral vascular disease

- Goals: A1C, blood pressure, & cholesterol
- Lifestyle modifications
## A1C Goals

<table>
<thead>
<tr>
<th>A1C goal</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7%</td>
<td>Most adult non-pregnant patients</td>
</tr>
<tr>
<td>&lt; 6.5%</td>
<td>More stringent goal for selected patients if they can achieve goal without any significant hypoglycemia or adverse effects</td>
</tr>
<tr>
<td>&lt; 8%</td>
<td>Less stringent goal for selected patients with a h/o severe hypoglycemia, limited life expectancy, extensive comorbid conditions in whom the general goal is difficult to attain</td>
</tr>
</tbody>
</table>

### Blood Glucose Goal (mg/dL)

<table>
<thead>
<tr>
<th>Blood Glucose</th>
<th>Goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Prandial</td>
<td>80-130</td>
</tr>
<tr>
<td>2 hour post prandial</td>
<td>&lt; 180</td>
</tr>
</tbody>
</table>

## Blood Pressure Goals

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA/JNC-8</td>
<td>BP &lt; 140/90 mm Hg</td>
</tr>
<tr>
<td></td>
<td>If tolerated</td>
</tr>
<tr>
<td></td>
<td>*BP &lt; 130/80 mm Hg</td>
</tr>
</tbody>
</table>

**Treatment regimen including either**

- Angiotensin-converting enzyme (ACE) inhibitors: Enalapril, Lisinopril
- Angiotensin receptor blocker (ARB): Candesartan, Valsartan, Irbesartan

Cholesterol Goals

- If not performed/available within past year obtain:
  - Fasting lipid profile and liver function tests as needed

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Goals</th>
</tr>
</thead>
</table>
| ADA        | LDL: < 100 mg/dL  
            | CVD: LDL < 70 mg/dL  
            | TG: < 150 mg/dL |
| AHA/ACC    | DM 40 - 75 years old: ↓LDL by 30 – 49%  
            | 10 year CVD risk ≥ 7.5%: ↓LDL by 50%  
            | TG: < 150 mg/dL |

**Treatment**

- HMG CoA Reductase Inhibitors: Rosuvastin, Atorvastatin, Pravastatin

Lifestyle Modifications

- **Weight loss of 7%**
- **Diet**
  - Individualize dietary plan
  - Low fat or fat free dairy
  - ↑ omega-3 fatty acids intake
  - ↑ dietary fiber intake
  - Limit alcohol consumption
  - Limit sodium intake
  - Nutrition Label

- **Physical activity**
  - Moderate intensity exercise for at least 150 minutes per week
  - Reduce sedentary time
  - Resistance exercise at least twice a week

Signs/Symptoms of Hypoglycemia

- BG < 70 mg/dL
- **Treatment**
  - **Oral** (15 gram of carbohydrate)
    - 4-8 oz. fruit juice
    - 6-12 oz. regular (not diet) soda
    - 1-2 bottles dextrose liquid
  - **IV Access**
    - Dextrose 50% IV (25 mL), then D₅W infusion
  - **No IV Access**
    - Glucagon 1 mg IM once

http://www.womenshealthyfitnesstips.com/what-is-hypoglycemia
Signs/Symptoms of Hyperglycemia

- Symptoms develop slowly over several days or weeks
- BG: 50 mg/dL to >1000 mg/dL
- Hyperglycemic crisis
  - Diabetic Ketoacidosis
  - Hyperosmolar Hyperglycemic State
- Treatment (Emergency)
  - IV fluids
  - Potassium replacement
  - Insulin therapy
  - Sodium bicarbonate

[Image: HYPERGLYCEMIA (High Blood Glucose)]

Causes: Too much food, too little insulin or diabetes pills, illness, or stress.
Onset: Often starts slowly. May lead to a medical emergency if not treated.

SYMPTOMS:
- NEED TO URINATE OFTEN
- DRY SKIN
- HUNGRY
- BLURRY VISION
- DROWSY
- SLOW-HEALING WOUNDS

WHAT CAN YOU DO?
- CHECK BLOOD GLUCOSE
- CALL YOUR HEALTHCARE PROVIDER

Call your healthcare provider if your blood glucose levels are higher than normal for 3 days and you don't know why.

http://www.usd497.org/Page/6728/
Approach to the Management of Hyperglycemia

## Agents Available

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide*</td>
<td>metformin</td>
</tr>
<tr>
<td>Sulfonylureas*</td>
<td>glyburide, glipizide, glimperide</td>
</tr>
<tr>
<td>Thiazolidinediones*</td>
<td>pioglitazone, rosiglitazone</td>
</tr>
<tr>
<td>DDP-4 inhibitors*</td>
<td>sitagliptin, saxagliptin, linagliptin</td>
</tr>
<tr>
<td>GLP-1 receptor agonists*</td>
<td>exenatide, liraglutide</td>
</tr>
<tr>
<td>SGLT2 inhibitors*</td>
<td>canagliflozin, dapagliflozin, empagliflozin</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>repaglinide, nateglinide</td>
</tr>
<tr>
<td>Alpha glucosidase inhibitors</td>
<td>acarbose, miglitol</td>
</tr>
<tr>
<td>Amylin agonist</td>
<td>pramlintide</td>
</tr>
<tr>
<td>Insulins*</td>
<td>rapid acting, short acting, intermediate acting, long acting, premixed, concentrated insulin*</td>
</tr>
</tbody>
</table>

* Commonly used
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>↓ A1C %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>1% - 2%</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1% - 2%</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>0.5% - 1.5%</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.5% - 1.4%</td>
</tr>
<tr>
<td>Amylin agonist</td>
<td>0.5% - 1.0%</td>
</tr>
<tr>
<td>GLP-1 Receptor agonists</td>
<td>0.5% - 1.0%</td>
</tr>
<tr>
<td>Alpha glucosidase inhibitors</td>
<td>0.5% - 0.8%</td>
</tr>
<tr>
<td>DDP-4 inhibitors</td>
<td>0.5% - 0.8%</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>0.3% - 1.0%</td>
</tr>
</tbody>
</table>
Site of Action: Pharmacological Agents

Adapted from Jennifer Trujillo 2003
Implementation Strategies

Monotherapy + Lifestyle Changes

- Metformin – preferred 1st line agent
- Alternative: sulfonylurea, meglitinides, pioglitazone, or DPP-4 Inhibitor

Dual Therapy

- Second oral agent (SU, TZD, DPP-4 inhibitor, SGLT-2 inhibitor)
- GLP-1 Agonist
- Insulin

Triple Therapy

- Third oral agent (SU, TZD, DPP-4 inhibitor, SGLT-2 inhibitor)
- GLP-1 Agonist
- Insulin >>> Better Response

Abbreviations: SU – sulfonylurea, TZD – thiazolidinediones
### Mono-therapy

- **Efficacy**
- **Hypo risk**
- **Weight**
- **Side effects**
- **Costs**

### Dual therapy

- **Efficacy**
- **Hypo risk**
- **Weight**
- **Side effects**
- **Costs**

### Triple therapy

### Combination injectable therapy

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**Metformin**

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin +</th>
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<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Thiazolidinedione</td>
<td>DPP-4 inhibitor</td>
<td>SGLT2 inhibitor</td>
<td>GLP-1 receptor agonist</td>
<td>Insulin (basal)</td>
</tr>
<tr>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>moderate risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high</td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>neutral</td>
<td>GI</td>
<td>high</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>edema, HF, fx</td>
<td>rare</td>
<td>rare</td>
<td>GI, dehydration</td>
<td>high</td>
</tr>
<tr>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>hyponatremia</td>
<td>variable</td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Thiazolidinedione</td>
<td>DPP-4 inhibitor</td>
</tr>
<tr>
<td>or DPP-4i</td>
<td>or SGLT2i</td>
<td>or GLP-1-RA</td>
</tr>
<tr>
<td>or Insulin</td>
<td>or SGLT2i</td>
<td>or GLP-1-RA</td>
</tr>
<tr>
<td>or Insulin</td>
<td>or DPP-4i</td>
<td>or GLP-1-RA</td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-

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Drug therapy considerations

- Place in therapy
- Efficacy ↓ A1C
- Hypoglycemia risk
- Effect on weight
- Adverse effects
- Cost
Biguanides

<table>
<thead>
<tr>
<th>Medications</th>
<th>Metformin (Glucophage), Metformin ER (Glucophage XR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combinations</td>
<td>Pioglitazone (Actoplus Met®), Rosiglitazone (Avandamet®), Canagliflozin (Invokamet®), Sitagliptin (Janumet®)</td>
</tr>
</tbody>
</table>

- **Mechanism of action**: decrease hepatic glucose production

- **Advantages**
  - Place in therapy: 1st line agent
  - ↓ A1C 1 to 2%
  - Helps with fasting BG
  - Favorable Lipid Profile: ↓ TG, ↓ LDL, and ↑ HDL
  - Costs: Low

- **Effect on weight**: weight neutral, possible weight loss

- **Risk of hypoglycemia**: Low
Biguanides

- **Disadvantages**
  - Monitor renal function
  - IV Contrast Media – risk of lactic acidosis
    - Discontinue at the time of IV contrast media
    - Restart after 48 hours after normal serum creatinine levels are achieved

- **Adverse effects**
  - Metallic taste in mouth
  - Vitamin B12 deficiency, Lactic acidosis risk (rare)
  - GI side effects (bloating, gas, diarrhea, upset stomach, nausea)
    - Titrate slowly & take with food to minimize GI effects

- **Contraindications**
  - SCr > 1.4 mg/dL for women, SCr > 1.5 mg/dL for men
  - Age > 80 yo, Hepatic impairment, Congestive Heart Failure
## Sulfonylureas

### Mechanism of action:
Stimulate release of insulin from pancreas

### Advantages
- Place in therapy: 2\textsuperscript{nd} to 3\textsuperscript{rd} line agent
- ↓ A1C 1 to 2%
- Helps with both fasting and prandial BG
- Costs: low

### Effect on weight:
weight gain (≥ 2 kg)

### Risk of Hypoglycemia
- Glyburide (higher risk)

### Medications

<table>
<thead>
<tr>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide (Diabeta®, Micronase®), Glipizide (Glucotrol ®), Glimepiride (Amaryl®)</td>
</tr>
</tbody>
</table>

### Combinations

<table>
<thead>
<tr>
<th>Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide &amp; Metformin (Metaglip®), Glyburide &amp; Metformin (Glucovance®), Pioglitazone &amp; Glimepiride (Duetact®), Rosiglitazone &amp; Glimepiride (Avandaryl®)</td>
</tr>
</tbody>
</table>
Sulfonylureas

- **Disadvantages**
  - Hastens beta cell dysfunction
  - Special precaution in the elderly: **Glipizide is the preferred agent**

- **Adverse effects**
  - Rash, headache, nausea/vomiting, photosensitivity
  - Weight gain: Glimepiride has less weight gain
  - Hypoglycemia: higher risk with glyburide

- **Contraindications**
  - Hypersensitivity to sulfonamides
  - Patients prone to hypoglycemia
  - Renal impairment/dysfunction: **Glipizide is the preferred agent**
Thiazolidinediones

<table>
<thead>
<tr>
<th>Medications</th>
<th>Pioglitazone (Actos®), Rosiglitazone (Avandia®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combinations</td>
<td>rosiglitazone + metformin (Avandamet®), rosiglitazone + glimperide (Avandaryl®), pioglitazone + metformin (Actoplus Met®), pioglitazone + glimperide (Duetact®)</td>
</tr>
</tbody>
</table>

- **Mechanism of action**: increase insulin sensitivity in cells
- **Advantages**
  - Place in therapy: 2nd to 3rd line agent
  - ↓ A1C 0.5 to 1.4%
  - Helps with fasting and prandial BG
  - Favorable lipid profile: Pioglitazone ↓ LDL, TG
    Slight increase in HDL
- **Effect on weight**: weight gain (5 to 10 lbs)
- **Risk of hypoglycemia**: low

Thiazolidinediones

- **Disadvantages**
  - Maximal effects takes 2-3 months
  - Avandia linked to increase TG and higher risk of MI/CHF
  - Actos linked to increase risk of bladder cancer
  - Cost: high

- **Adverse effects**
  - Weight gain, fluid retention, edema
  - Hepatotoxicity
  - Risk of osteoporosis
  - **Black Box Warning:** NYHA III or IV Heart Failure

- **Contraindications**
  - Hepatic impairment
  - Existing fluid retention
  - Initiation in patients with NYHA Class III or IV HF
SGLT2 Inhibitors

- **SGLT2** = Sodium Glucose Cotransporter 2 (located in the kidneys)

- **Mechanism of action:** Blocks glucose reabsorption by the kidney, increases glucose urinary excretion

- **Advantages**
  - Place in therapy: 2nd to 3rd line agent
  - Efficacy: A1C↓ 0.3 to 1.0%
  - Helps with fasting & prandial BG
  - Reduction in blood pressure

- **Effects on weight:** weight loss

- **Risk of hypoglycemia:** low

**Medications**

| Medications | Canagliflozin (Invokana®), Dapagliflozin (Farxiga®), Empagliflozin (Jardiance®) |

SGLT2 Inhibitors

- **Disadvantages**
  - Requires renal adjustment
  - Adverse effects
  - Costs: high

- **Adverse effects**

<table>
<thead>
<tr>
<th>Endocrine &amp; Metabolic</th>
<th>Cardiovascular</th>
<th>Renal/Genitourinary</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hyperkalemia</td>
<td>• Hypotension</td>
<td>• Micturition frequency</td>
<td>• Pancreatitis</td>
</tr>
<tr>
<td>• Hypermagnesemia</td>
<td>o Orthostatic</td>
<td>• UTI</td>
<td>• Angioedema</td>
</tr>
<tr>
<td>• ↑ cholesterol</td>
<td>o Syncope</td>
<td>• Mycosis (yeast infection)</td>
<td></td>
</tr>
<tr>
<td>• Dehydration</td>
<td></td>
<td>• Renal impairment</td>
<td></td>
</tr>
</tbody>
</table>

- **Contraindications**
  - Avoid/discontinue if CrCl < 45 mL/min
  - Ensure patient is euvolemic
Pathophysiology: GI Hormones

- **GI hormones: Incretins**
  - Release throughout the day
  - ↑ levels in response to meals

- **Hormones**
  - GLP-1: Glucagon-Like Peptide 1
  - GIP: Glucose-dependent Insulinotropic Peptide
  - DPP-4: Dipeptidyl-peptidase 4

- **In the presence of food**
  - GLP-1 and GIP: signals beta cells to release insulin
  - GLP-1: signals alpha cells to inhibit glucagon release
  - DPP-4 enzymes: break down GLP-1 and GIP
DPP-4 Inhibitors

Mechanism of action
- Prevents DPP-4 enzymes from breaking down GLP-1 & GIP
- Indirectly: stimulate release of insulin from pancreas, decrease glucagon secretion, slows gastric emptying, and enhances satiety

Advantages
- Place in therapy: 2nd to 3rd line agent
- Efficacy: A1C ↓ 0.5 to 0.8%
- Helps with prandial BG

Effect on weight: weight neutral

No risk of hypoglycemia

| Medications  | Sitagliptin (Januvia®), Saxagliptin (Onglyza®), Linagliptin (Tradjenta®), Alogliptin (Nessina®) |
DPP-4 Inhibitors

- **Disadvantages**
  - Januvia, Onglyza, and Nessina require renal adjustment
  - Costs: high

- **Adverse effects**
  - Angioedema
  - Headache
  - Upper respiratory tract infection, nasopharyngitis
  - Risk of pancreatitis

- **Contraindications**
  - History of pancreatitis
GLP-1 Receptor Agonists

- **Mechanism of action**: Stimulate release of insulin from pancreas, decreases glucagon secretion, slows gastric emptying, and enhances satiety

- **Advantages**
  - Place in therapy: 2nd to 3rd line agent
  - ↓ A1C 0.5 to 1.1%
  - Helps with fasting and prandial BG
  - Favorable lipid profile

- **Effect on weight**: modest weight loss

- **No risk of hypoglycemia**

<table>
<thead>
<tr>
<th>Medications</th>
<th>Exenatide (Byetta®), Exenatide Extended Release, (Bydureon®), Liraglutide (Victoza®)</th>
</tr>
</thead>
</table>
GLP-1 Receptor Agonists

- **Disadvantages**
  - Subcutaneous injection
  - GI side effects
  - Bydureon: Must reconstitute prior to use
  - Costs: high

- **Adverse effects**
  - GI side effects: nausea, vomiting, diarrhea
  - Post marketing: risk of pancreatitis and renal dysfunction
  - **Black Box Warning**: thyroid cell tumor

- **Contraindications**
  - History of pancreatitis, GI tract disorder (gastroparesis)
  - Exenatide: renal impairment (CrCl < 30 ml/min)
  - Liraglutide: personal or family history of medullary thyroid cancer
Meglitinides

| Medications | Nateglinide (Starlix®), Repaglinide (Prandin®) |

- **Mechanism of action**: Stimulate release of insulin from pancreas
- **Advantages**
  - Place in therapy: 2nd to 3rd line agent
  - ↓ A1C 0.5 to 1.5% (Nateglinide > Repaglinide)
  - Helps with prandial blood glucose
  - **Dosing flexibility**: Extra meal $\rightarrow$ extra dose; Skip a meal $\rightarrow$ skip a dose
  - Use in patients with renal impairment
- **Effect on weight**: weight gain
- **Risk of hypoglycemia**
  - Caution in the elderly

Meglitinides

- **Disadvantages**
  - Frequent dosing schedule
  - Requires separation from other medication by 1-2 hours
  - Costs: moderate

- **Adverse effects**
  - Upper respiratory infection, flu-like symptoms, dizziness
  - Hypoglycemia (less than sulfonylureas)
  - Weight gain (less than sulfonylureas)

- **Drug interactions:** Caution with use of repaglinide and gemfibrozil
alpha glucosidase inhibitors

| Medications | Acarbose (Precose®), Miglitol (Glyset®) |

- **Mechanism of action**: slows intestinal carbohydrate digestion and absorption

- **Advantages**
  - Place in therapy: 3rd to 4th line agent
  - ↓ A1C 0.5 to 0.8%
  - Helps with prandial BG
  - No systemic absorption

- **No hypoglycemia or weight gain**
  - When used as monotherapy

Product Information: GLYSET(R) oral tablets, miglitol oral tablets. Pfizer (per FDA), New York, NY, 2012.
alpha glucosidase inhibitors

- Disadvantages
  - Frequent dosing schedule
  - Requires separation from other medication by 1-2 hours
  - GI side effects
  - Cost: moderate

- Adverse effects
  - GI: flatulence, diarrhea, abdominal pain
  - Hepatotoxicity

- Contraindications
  - Inflammatory bowel disease
  - Colonic ulcerations
  - Intestinal obstructions
Amylin Agonist

Medication | Pramlintide (Symlin®)

- **Mechanism of action:** decreases glucagon secretion, slows gastric emptying, and enhances satiety

- **Advantages**
  - Place in therapy: adjunct to insulin therapy
  - ↓ A1C 0.5 to 1.0%
  - Can be used in type 1 or type 2 DM
  - Helps with prandial BG

- **Effect on weight:** weight loss (1 to 1.5 kg)

- **Risk of hypoglycemia**
  - If added on, ↓ dose of rapid, short acting, and premixed insulin by 50%

Amylin Agonist

- **Disadvantages**
  - Subcutaneous injection – inject 2 inches apart from site of insulin
  - Cannot be mixed with insulin
  - Cost: high

- **Adverse effects**
  - GI side effects: nausea, vomiting
  - Anorexia, headache
  - **Black Box Warning**: Severe hypoglycemia (within 3 hours – Type 1 DM)

- **Contraindications**
  - Gastroparesis
  - A1C > 9%
  - Patients prone to hypoglycemia
  - Patients with poor adherence or monitoring of BG
When to start insulin therapy

- A1C $\geq$ 9.5%
- Random glucose $> 300$ mg/dL
- Fasting glucose $> 250$ mg/dL
- Hyperglycemic symptoms
- +/- presence of urine ketones
- Oral medication options no longer effective
Insulin Regimens

Non-insulin regimens

Basal insulin only (usually with oral agents)

Basal insulin + 1 (mealtime) rapid-acting insulin injection

Pre-mixed insulin twice daily

Basal insulin + ≥2 (mealtime) rapid-acting insulin injections

Number of injections
1
2
3+

Regimen complexity
Low
Mod.
High

Flexibility
More flexible
Less flexible
# Types of Insulin

<table>
<thead>
<tr>
<th>Effect</th>
<th>Insulin Categories</th>
<th>Generic (Brand)</th>
<th>Onset of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prandial</td>
<td>Rapid Acting</td>
<td>insulin lispro (Humalog®)</td>
<td>10 to 20 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>insulin aspart (Novolog®)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>insulin glulisine (Apidra®)</td>
<td></td>
</tr>
<tr>
<td>Prandial</td>
<td>Short Acting</td>
<td>insulin regular (Novolin R®, Humulin R®)</td>
<td>20 to 60 minutes</td>
</tr>
<tr>
<td>Basal</td>
<td>Intermediate Acting</td>
<td>insulin NPH (Novolin N®, Humulin N®)</td>
<td>2 to 6 hours</td>
</tr>
<tr>
<td>Basal</td>
<td>Long Acting</td>
<td>insulin glargine (Lantus®)</td>
<td>1 hour</td>
</tr>
<tr>
<td></td>
<td></td>
<td>insulin detemir (Levemir®)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>insulin degludec (Tresiba®)</td>
<td></td>
</tr>
<tr>
<td>Prandial + Basal</td>
<td>Premixed Insulin</td>
<td>Insulin lispro 75/25 (Humalog Mix 75/25®)</td>
<td>20 to 60 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insulin lispro 50/50 (Humalog Mix 50/50®)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insulin aspart 70/30 (Novolog Mix 70/30®)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NPH/regular 70/30 (Humulin or Novolin Mix 70/30®)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NPH/regular 50/50 (Humulin Mix 50/50®)</td>
<td></td>
</tr>
</tbody>
</table>
Insulin Duration of Action

Graph showing the plasma insulin levels over time for different types of insulin:
- Aspart, lispro, glulisine (black line)
- Regular (blue line)
- NPH (purple line)
- Detemir (green line)
- Glargine (red line)

The x-axis represents hours, ranging from 0 to 24, and the y-axis represents plasma insulin levels.
## Special Types of Insulin

<table>
<thead>
<tr>
<th>Effect</th>
<th>Insulin Categories</th>
<th>Generic (Brand)</th>
<th>Onset of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prandial</td>
<td>Inhaled Rapid Acting</td>
<td>insulin human (Afrezza)</td>
<td>~ 50 minutes</td>
</tr>
<tr>
<td>Prandial + Basal</td>
<td>Concentrated Short Acting</td>
<td>insulin regular (Humulin R – U 500)</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Basal</td>
<td>Concentrated Long Acting</td>
<td>insulin glargine (Toujeo)</td>
<td>6 hours</td>
</tr>
</tbody>
</table>
Insulin Injection Sites

Remember to rotate the injection site!

Self Monitoring of Blood Glucose

- **Self Monitoring of Blood Glucose (SMBG)**
  - Use as a guide to treatment decision
  - Access appropriate SMBG technique
  - Frequency and timing dictated by the patient’s needs and goals
  - Important for patients on insulin to monitor asymptomatic hypoglycemia and hyperglycemia
  - Patients on multiple-dose insulin or insulin pump should do SMBG:
    - prior to meals, snacks, and at bedtime
    - occasionally after meals
    - prior to exercise and critical tasks such as driving
    - when suspecting/treating low blood glucose
  - Educated patients to record SMBG readings (log sheet, electronic)
Summary

- Individualize glycemic targets & glucose lowering therapies
- Unless contraindicated, metformin is 1st line agent
- After metformin therapy, combination therapy with 1 to 2 oral agents or an injectable is reasonable
- Patients ultimately will require insulin therapy alone or combination with other agents to maintain glucose control
- Monitor for adverse effects and signs/symptoms of hypoglycemia & hyperglycemia
Questions?