DRUGS USED IN MANAGEMENT OF DIABETES

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INSULIN BIOSYNTHESIS

• Preproinsulin $\rightarrow$ Proinsulin (RER)
• Secretory granules formed in Golgi apparatus
  – package proinsulin and Ca-dependent endopeptidases
• Insulin, C-peptide and Amylin released from $\beta$-cells
SIGNIFICANCE OF INSULIN and Zinc INTERACTION

• Insulin exists as monomer, dimer and hexamer coordinated with zinc
• Insulin stored in secretory granules as hexamer
  – Long acting insulin higher percent of hexamer form
• Biologically active form is monomer
  – Short acting insulin preparations maintain monomer form
Significance of Insulin and Zinc

- Monomer and dimer diffuse easily
- Hexamer poorly diffuses
Insulin Stimulation by Glucose
GLUCOSE

K

G

G6P

ATP

Insulin

Ca

Voltage-dependent Ca channel

ATP-dependent

Beta Cell
INSULIN SECRETION

- Insulin release requires increased intracellular calcium in β-cells
- A rise in plasma glucose following a meal induces increases ATP/ADP ratio
  - causes inhibition of ATP-sensitive K channel & depolarization of the cell
  - Results in activation of voltage-dependent Ca channel, influx of Ca
  - Rise in intracellular Ca and ↑PI turnover
- Results in Insulin release
AGENTS THAT STIMULATE INSULIN RELEASE

- Glucose principal stimulus for insulin
  - better response oral than IV
- Gastrin, Secretin, Amino acids, Fatty acids
- Glucagon, GLP-1
- Sulphonylureas - glyburide
- Metaglinide - Repaglinide
- Vagal stimulation
- Isoproterenol
INSULIN RELEASE INHIBITED BY:

- DIAZOXIDE
- SOMATOSTATIN
- $\alpha_2$-AGONIST
- $\beta_2$-ANTAGONIST
Classification of Diabetics

• **Type I**
  – 10% of diabetics in US
  – low circulating insulin levels
  – Prone to ketoacidosis

• **Type II**
  – 85-90% of diabetics
  – normal to elevated insulin levels
  – Decreased density of peripheral insulin receptors- associated with obesity
# Insulin Preparations

<table>
<thead>
<tr>
<th>TYPE</th>
<th>Protein</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin Aspart</td>
<td></td>
<td>5-15 min</td>
<td>30-90 min</td>
<td>&lt;5 h</td>
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<tr>
<td>Insulin Glulisine</td>
<td></td>
<td></td>
<td>30-120 min Lispro</td>
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<tr>
<td>Insulin Lispro</td>
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</tr>
<tr>
<td><strong>Short Acting</strong></td>
<td></td>
<td>30-60 min</td>
<td>2-3 h</td>
<td>5-8 h</td>
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<tr>
<td>Regular Insulin</td>
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<tr>
<td><strong>Intermediate</strong></td>
<td>Protamine</td>
<td>1-4 h</td>
<td>4-10 h</td>
<td>10-18 h</td>
</tr>
<tr>
<td><strong>Acting</strong></td>
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<tr>
<td>NPH Insulin</td>
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<tr>
<td><strong>Long Acting</strong></td>
<td></td>
<td>1.5-4 h</td>
<td></td>
<td>6-23 h</td>
</tr>
<tr>
<td>Insulin Detemir</td>
<td></td>
<td></td>
<td></td>
<td>24 h</td>
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<tr>
<td>Insulin Glargine</td>
<td></td>
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</table>
Insulin preparations
Rapid Insulin Analogues
ASPART, GLULISINE & LISPRO

- **RAPID ACTING INSULIN ANALOGUES**
  - Developed for greater flexibility in timing
  - Postprandial hyperglycemia
    - More effective in lowering glucose than regular insulin
  - ASPART, GLULISINE & LISPRO

- **Inj sc, IV, insulin pump**
- **Compatible with NPH**
DIFFERENCES FOR
Rapid Insulin Analogues

• ASPART
  – fastest absorption inj 5 min prior to eating (monomer configuration)
• LISPRO
  – 15 min prior to meal or just after meal
• GLULISINE
  – 15 min prior to meal or 20 min of starting to eat
Short Acting Human Insulin

• Short Acting- Regular
• Inject IV, IM, sc
• Onset 30-60 min, peak 2 h, last 8 h
• Inject 30-60 min prior to meal (breakfast)
• Compatible with NPH
# Insulin Preparations

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<tr>
<td>Aspart, Lispro &amp; Glulisine</td>
<td>5-15 min</td>
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</tr>
<tr>
<td>Degludec</td>
<td>1.5 h</td>
<td></td>
<td>42 h</td>
<td></td>
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LONG ACTING Insulin Analogues
- constant flat level, no peak

• **INSULIN DETEMIR**
  – Deletion of last AA on Beta Chain
  – Added Fatty acid - increase plasma binding
  – Inj sub-cutaneous, inj alone

• **INSULIN GLARGINE**
  – Two arginine added to terminal end of Beta chain
  – Substitution of 1 glycine for asparginine at A21 and 2 arginines added at end of B chain
  – Prep at pH 4, rapidly neutralized at injection site & precipitates depot release

• **Foreign protein, allergies occur long term safety not known**
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Insulin Glargiline, Detemir & Degludec

- Human Insulin Analogue
- Onset within 1.5 h, no peak but effect for 24 h is constant
- Provides constant levels of insulin

Therapeutic options: Insulins

![Graph showing insulin levels over time](image)
INSULIN ACTION AFFECTED BY:

• **Blood flow** (skin temperature, hot shower, etc.)
• **Insulin preparation** (short, intermediate and long acting) and mixing preps
• **Physical activity**
• **Site of injection faster absorption**
  - abdomen > arm > thigh > buttocks
SITUATIONS THAT ALTER INSULIN REQUIREMENTS

• **INCREASE INSULIN:**
  - Surgery, Trauma (burns, broken bone), Stress
  - Hyperthyroidism
  - Infection, fever

• **DECREASE INSULIN:**
  - Nausea and vomiting (decreased caloric intake)
  - Hypothyroidism
  - Renal impairment (↓insulin clearance)
  - Liver dysfunction (↓insulin clearance)
ADVERSE EFFECTS

• Hypoglycemia One of the most common side effects
  – Symptoms include sweating, hunger, tremor, nervousness, dizziness, confusion
  – Cause, incorrect dose or timing with meals, ↑ activity

• Redness and swelling at injection site

• Lipohypertrophy
Insulin used to avoid Hyperglycemia

• Hyperglycemia associated with loss of appetite, thirst, drowsiness and/or fruity smell to breath

• Causes
  – too little insulin, ↑stress or ↑calories
SPECIAL CONSIDERATIONS

• TYPE II WITH INTERMITTENT INSULIN REQUIREMENT
  – Surgery
  – ICU use insulin

• GESTATIONAL DIABETES
PRAMLINTIDE
Synthetic AMYLIN Analogues

• MECHANISM
  – Amylin released by Beta cells with insulin
  – Decreases postprandial glucose levels by inhibiting glucagon secretion
  – Decreases hepatic glucose output
  – Slows gastric emptying
  – Decreases appetite centrally
    • Less caloric intake and some weight loss

• USE
  – Type 1 and 2 Diabetics
  – Inj sub-cutaneous
Pramlintide – ADVERSE EFFECTS

- Hypoglycemia - serious concern
- Cannot mix insulin and pramlintide in same syringe
  - Patient error comparing ug for Pramlintide and Units for insulin
- Avoid use in non-compliant patients
  - Must eat or hypoglycemia will be severe
- Cannot use diabetics with gastroparesis
# Drug Treatment in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Action</th>
<th>Drug Class</th>
<th>Agents</th>
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<tbody>
<tr>
<td>Stimulate Insulin Release</td>
<td>Sulphonylureas</td>
<td>Chlorpropamide, Glyburide</td>
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<tr>
<td></td>
<td>Meglitinides</td>
<td>Repaglinide, Nateglinide</td>
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<tr>
<td>Decrease hepatic glucose</td>
<td>Biguanides</td>
<td>Metformin</td>
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<tr>
<td>Decrease Carbohydrate absorption</td>
<td>α-glucosidase inhibitors</td>
<td>Acarbose, Miglitol</td>
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<tr>
<td>Peripheral cell Insulin sensitizers</td>
<td>Thiazolidinediones</td>
<td>Pioglitazone, rosiglitazone</td>
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<tr>
<td>Amylin analogs</td>
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<td>Pramlintide</td>
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<tr>
<td>Glucagon-like analog</td>
<td>Glucagon Like Peptide 1 agonist</td>
<td>Exanatide &amp; Liraglutide</td>
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<td>Dipeptidyl Peptidase IV (DPP-4) Inhibitor</td>
<td>Dipeptidyl Peptidase IV Enzyme Inhibitor</td>
<td>Alogliptin, Sitagliptin, Saxagliptin</td>
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</tbody>
</table>
ORAL HYPOGLYCEMIC AGENTS

• SULPHONYLUREAS
  – 1st Generation Tolbutamide, Chlorpropamide
  – 2nd Generation Glyburide, Glimepiride

• METAGLINIDIES
  – Repaglinide & Nateglinide

• Use Type 2 Diabetics-not prone to ketosis
SULPHONYLUREAS
Chlorpropamide, Glimepiride & Glyburide

• Pancreas
  – stimulate insulin release
  – bind to receptor near K channel to decrease conductance of ATP sensitive K channel
    • ↑intracellular Ca stimulates insulin release

• Extrapancreatic
  – Decrease hepatic gluconeogenesis
  – Increase glucose transporters & peripheral insulin receptor numbers
SULPHONYLUREAS
Chlorpropamide, Glimepiride & Glyburide

- FIRST GENERATION
  Tolbutamide
  Chlorpropamide
  Acetohexamide

- SECOND GENERATION
  Glyburide
  Glipizide
  Glicazide
  Glimepiride
First & Second Generation Sulphonylureas

• 1st generation: Chlorpropamide & Tolbutamide
  – more binding displacement drug interactions
  – enhances ADH activity, more water retention

• Second generation: Glimepiride & Glyburide
  – more potent
  – less binding displacement interactions
  – Less water retention
SULPHONYLUREAS
Chlorpropamide, Glimepiride & Glyburide

- USE Type II diabetes
  - not susceptible to ketosis
- Can be combined with insulin for better glycemic control or metformin
SULPHONYLUREAS
Chlorpropamide

- Central Diabetes Insipidus
  - Chlorpropamide only
  - Enhances action of ADH
  - Used in individuals that cannot tolerate desmopressin
Adverse Effects of Sulphonylureas

- All can induce hypoglycemia
- Contraindicated in ketoacidosis
- Chlorpropamide
  - water retention
  - alcohol induced flushing
  - cholestatic jaundice
Drug Interactions

- **Azole antifungals, miconazole and itraconazole**
  - induce hypoglycemia
  - decrease sulphonylurea clearance
- **Propranolol**
  - Inhibit glycogenolysis
  - Mask symptoms of hypoglycemia
- **Aspirin and NSAIDs**
  - Binding displacement of first generation
Metaglinides
REPAGLINIDE & NATEGLINIDE

• Mechanism
  – Stimulates insulin release
  – Interact with K channel to cause depolarization
  – Action similar to sulphonylureas but structurally dissimilar to sulphonylureas

• Used in Type II diabetics
REPAGLINIDE

- Used in Type II diabetics
- Can be taken 0-30 min prior to a meal
- Peak effect within 1 h
- Cleared in 3-4 h, short duration
- Used in combination with metformin
- Do not use with sulphonylureas (similar mechanism)
Adverse Effects of Repaglinide

- Hypoglycemia
- Contraindicated in Diabetic with ketoacidosis
- Lower dose of Repaglinide in individuals taking erythromycin or ketoconazole (inhibit Cyp 3A4), greater risk of hypoglycemia
BIGUANIDES-METFORMIN

• Use Type II Diabetics
  – One of Most commonly prescribed drugs in Type II Diabetes
  – can be combined with sulphonylurea, insulin, Meglitinides, acarbose and thiazolinediones

• Similar to phenformin
  – withdrawn due to risk of lactic acidosis
METFORMIN

• **Mechanism**
  - decreases hepatic glucose production
  - increases peripheral insulin sensitivity  
    • Promotes peripheral glucose uptake
  - decreases intestinal glucose absorption
• **Has no effect on insulin release**
  - (no hypoglycemia)
• **Does not cause weight gain**
• **Lowers LDL-C**
Metformin Adverse Effects

- GI vomiting, flatulence, cramping, diarrhea in 30%
- Decreased Vitamin B12 absorption in some people
- Avoid alcohol ingestion with Metformin
  - May enhance risk of lactic acidosis
Metformin Contraindications

• Ketoacidosis or history of lactic acidosis
  – Any situation that can worsen lactic acid production
  – Liver disease
• Renal disease, associated with impaired renal lactate clearance & increase lactate production
• Congestive heart failure
Other Uses of Metformin

• Polycystic ovary disease and infertility related to obesity
• Associated with insulin resistance, menstrual irregularity, high LH and androgens
• Metformin
  – Improves insulin resistance
  – Lower circulating insulin levels decrease androgen levels
  • Insulin inhibits hepatic synthesis of sex hormone binding globulin (higher androgen free fraction)
ACARBOSE & MIGLITOL

• Mechanism of Action
• Competitive reversible inhibitor of intestinal amylase & α-glucosidase
  – Reduces absorption of starches & disaccharides
• Site of Action is intestine
  less than <2% reaches blood
ACARBOSE

• USE
  – Taken just **before** meal
  – Used in Type II diabetics
  – Used in monotherapy or in combination with sulphphonylureas, insulin, metformin, repaglinide, thiazolinediones
Acarbose & Miglitol
Adverse Effects

• Most involve GI tract
  – Flatulence, abdominal pain and diarrhea (20-70% of individuals)
  – Acarbose higher incidence and severity
• ACARBOSE -Monitor ALT levels
THIAZOLIDINEDIONES
PIOGLITAZONE & ROSIGLITAZONE

• Mechanism
  – Increases glucose uptake into skeletal muscle
  – Agonists at nuclear receptors (PPARγ peroxisome proliferator activated receptors) which stimulate transcription of insulin responsive genes
  – Decreases hepatic glucose production

• Use in Type II Diabetes
  – can be used with insulin, metformin, repaglinide or sulphonylureas

• *Does not stimulate pancreatic insulin release (no hypoglycemia)*
Concerns for drug class-THIAZOLIDINEDIONES

• Troglitazone withdrawn March 2000 by FDA due to hepatotoxicity; over 65 deaths in patients using troglitazone
  – Must monitor liver function enzymes (ALT)

• Rosiglitazone associated with a 30% higher risk of myocardial infarct
  – Restricted used
Adverse Effects of Pioglitazone and Rosiglitazone

• **Hepatic dysfunction, Elevated transaminase levels**
  – must monitor baseline liver function and every 2 months for first 12 months

• **Edema & weight gain**
  – associated with all thiazolidinediones
  – **BLACK BOX WARNING**: Worsen congestive heart failure and edema
  – Contraindicated Heart Failure Class III & IV

• **Use with caution**
  – Presence of liver disease or cardiac failure
Glucagon Like Peptide-1 (GLP-1) Agonists Exenatide, Liraglutide & Dulaglutide

- GLP-1 (incretin hormones) secreted by intestinal cells with a meal
- Suppresses compensatory glucagon release stimulated by insulin secretion
- Stimulates glucose dependent insulin release
GLP-1 Agonists
Exenatide, Liraglutide & Dulaglutide

• USE
  – Type 2 diabetes, inj sub-cutaneous
  – Liraglutide 1x/day, Exenatide 2x/day
    Dulaglutide 1x/wk

• ADVERSE EFFECTS
  – Hypoglycemia
  – Pancreatitis

• Black Box Warning thyroid cancer
  Contraindicated with family history
Dipeptidyl Peptidase IV (DPP-4) Inhibitors
ALOGLIPTIN, SAXAGLIPTIN & SITAGLIPTIN

• **Mechanism**
  – DPP-4 degrades GLP-1 (incretin hormones)
  – DPP-4 Inhibitor will increase GLP-1 half-life

• **USE**
  – Type 2 diabetics

• **ADVERSE EFFECTS**
  – Hypoglycemia
  – Lower initial dose of sulphonylureas or megatinilides when adding DPP-4 inhibitors
MORE SIGNIFICANT ADVERSE EFFECTS WITH Dipeptidyl Peptidase IV (DPP-4) Inhibitors ALOGLIPTIN, SAXAGLIPTIN & SITAGLIPTIN

- Pancreatitis
  - Must discontinue immediately
- Worsen Renal impairment
- Elevate Liver enzymes
INHIBITOR OF SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT2)
CANAGLIFLOZIN & DAPAGLIFLOZIN

- INHIBITOR OF SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT2)
- Reduce glucose reabsorption from the lumen at the proximal tubule
- Primary site of reabsorption of filtered glucose
- Lower plasma glucose by increase renal glucose excretion
CANAGLIFLOZIN & DAPAGLIFLOZIN

- Used for Type II diabetes
- Monotherapy with diet and exercise
- Combined with metformin
SGLT2 Inhibitor Side effects and contraindications

• Contraindicated in patients with severe renal impairment
• Increased incidence of genitourinary infections
  – Worse in females
  – Bacteria and yeast
• Hyperkalemia worse with K sparing diuretics
• Hypotension (osmotic diuresis causing volume contraction)
Figure 1. Glucose reabsorption from the glomerular filtrate through a proximal tubule epithelial cell into the blood. Reprinted by permission from Macmillan Publishers Ltd: Kidney Int. 2009;75:1272-1277. © 2009 www.nature.com/kifjournal/v75/n12/fig_tab/ki200987f1.html#figure-title.
Source: Reference 7.
DRUG THERAPY IN DIABETES

Impaired insulin secretion

- Sulphonylureas and Metaglinides
- DPP-4 Inhibitors & GLP-1 Agonists

↓Excess hepatic glucose production

- Metformin, Sulphonylurea, Thiazolidinediones, Pramlinitide

Hyperglycemia

↑Decreased muscle uptake of glucose

- Canagliflozin & Dapagliflozin

↑Urinary glucose excretion
## Drug Therapy in Diabetes

<table>
<thead>
<tr>
<th>Can Induce hypoglycemia</th>
<th>Must monitor Hepatic enzymes</th>
<th>Weight gain &amp; water retention</th>
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<tr>
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<td>GLP-1 Agonists</td>
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</table>
Agents to Increase Blood Glucose

- Diazoxide oral route
- Glucagon (iv)
Glucagon & Diazoxide

• **Diazoxide**
  – given orally to raise blood glucose
  – keeps the ATP sensitive K channel open to prevent an influx of Ca through the voltage dependent Ca channel
  – used to regulate glucose in patients with insulin secreting tumors

• **Glucagon**
  – IV, IM, SC for hypoglycemia
  – Use prior to glucose IV Sol’ns
  – Radiograph (IV, IM) relaxes GI tract
INSULIN RECEPTOR BINDING

• $\alpha$-subunit external and binds insulin

• $\beta$-subunit is transmembrane

• Insulin binding increases kinase activity
# INSULIN ANALOGUES

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<td>Lys</td>
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[Glutamic acid]