PHARMACOTHERAPY OPTIONS IN DIABETES

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Describe the pathogenesis of different types of diabetes and their sequelae of complications

Make connections between pathophysiology of disease state and pharmacology of treatment

Compare and contrast the clinical utility of various insulin preparations

Recommend pharmacologic treatment strategies for different types of diabetic patients
KEY CONCEPTS

- DM is a group of metabolic disorders of fat, carbohydrate, and protein metabolism that results from defects in insulin secretion, insulin action, or both.

- Type 1 and Type 2 forms are associated with microvascular and macrovascular complications.

- Incidence of T2DM is increasing.

KEY CONCEPTS

- Intensive glycemic control is paramount for reduction in microvascular complications

- T1DM treatment necessitates insulin therapy

- T2DM often necessitates combination therapy (oral antihyperglycemics and insulin)

- Aggressive management of CVD risk factors in T2DM is necessary to reduce mortality

KEY CONCEPTS

- Prevention - to date, medications have been less effective than lifestyle modifications to prevent progression to T2DM

- Knowledge of meal patterns, activity levels, PK of insulin, pharmacology of oral agents are all essential to individualized treatment plans

- Patient education and ability to demonstrate self-care and adherence to lifestyle and pharmacological interventions are crucial to success

DIABETES - BY THE NUMBERS

- 18.2 million Americans - 1/3 undiagnosed
- $132 Billion - economic burden in 2002
- #1 Cause - Blindness and ESRD
- 82,000 amputations/year - lower extremity, non-traumatic
- 75% of deaths in DM - caused by CVD

Type 1 - destruction of pancreatic β-cells results in absolute deficiency of insulin

Glycogen and protein breakdown, causing keto-acidosis

Muscle unable to use glucose due to low insulin

 Increased glucose due to low insulin

Decreased insulin in the blood vessels

CLASSIFICATION OF DM

- Type 2 - characterized by insulin resistance and sometimes lack of insulin secretion


CLASSIFICATION OF DM

- Gestational - glucose intolerance that is first recognized during pregnancy
  - Complicates 7% of all pregnancies in US
  - Most women return to normoglycemia postpartum
  - 30%-50% will develop T2DM
  - Insulin (regular and NPH) are mainstays of therapy

## Drug-induced hyperglycemia or DM

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Glucose</th>
<th>Mechanism/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitors</td>
<td>Slight reduction</td>
<td>Improves insulin sensitivity</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Reduction</td>
<td>Reduces hepatic glucose production</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Increase</td>
<td>May inc. insulin resist.</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Increase</td>
<td>Impairs insulin action</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Increase</td>
<td>Unclear</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Increase</td>
<td>Decrease insulin secretion</td>
</tr>
<tr>
<td>Clozapine &amp; olanzapine</td>
<td>Increase</td>
<td>Unclear; weight gain</td>
</tr>
</tbody>
</table>

The liver is primarily responsible for maintaining glucose homeostasis.

Glucose output is regulated by the reciprocal balance of insulin and glucagon.
CONSEQUENCES OF INSULIN DEFICIENCY

- Reduced inhibition of gluconeogenesis and overproduction of glucose by the liver

DKA - diabetic ketoacidosis

Defects in insulin secretion

Insulin resistance involves these tissues:
- Liver - continues to make its own glucose, too
- Muscle - primary site of insulin resistance
- Fat - chronically elevated free fatty acids (FFAs)

T2DM AND OBESITY

- Estimated Diabetes Diagnoses age > 20 years in the United States, 2009

[Map of the United States showing the age-adjusted percent of estimated diabetes diagnoses from 2009, with different colors representing different percentage ranges.]

CDC.gov/diabetes [Accessed 1 July 2015]
Estimates of Obesity in Adults age > 20 years in the United States, 2009

Age-adjusted percent

CDC.gov/diabetes [Accessed 1 July 2015]
SYNDROME

Obesity

Hypertension

Diabetes

Dyslipidemia

KEY POINTS ON GLUCOSE CONTROL

Always include a cardiovascular risk factor reduction program

- Smoking cessation + other healthy lifestyle habits
- Blood pressure control
- Lipid management (priority to Statins)
- Antiplatelet therapy (if nec.)

Diabetes Care 2015;38:140-149; Diabetologia 2015;58:429-442
TREATMENT IS NOT ONE SIZE FITS ALL

Approach to the management of hyperglycemia

**PATIENT / DISEASE FEATURES**

- Risks potentially associated with hypoglycemia and other drug adverse effects
  - low to high
- Disease duration
  - newly diagnosed to long-standing
- Life expectancy
  - long to short
- Important comorbidities
  - absent to severe
- Established vascular complications
  - absent to severe
- Patient attitude and expected treatment efforts
  - highly motivated, adherent, excellent self-care capacities to less motivated, non-adherent, poor self-care capacities
- Resources and support system
  - Readily available to limited

**Approach to management**

HbA1c 7%

Usually not modifiable

Potentially modifiable

*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;58:429-442
**ACTIVITY OF INSULIN**

- **Liver**
  - Suppression of glucose production

- **Muscle**
  - Stimulates glucose uptake

- **Fat**
  - Potent anti-lipolytic effect, marked reduction in FFA

\[ \text{[FFA]}_{\text{plasma}} \quad \Leftrightarrow \quad \text{Glucose Uptake} \quad \downarrow \quad \text{Glucose Production} \]

*FFA - free fatty acid*

*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;58:429-442

**ACTIVITY OF INSULIN**

- Suppression of glucose production
- Stimulates glucose uptake
- Potent anti-lipolytic effect, marked reduction in FFA

Reapply the principles

**Diabetes Care** 2015;38:140-149; *Diabetologia* 2015;58:429-442
INSULIN

- Biphasic process of insulin secretion
  1. A rapid increase of insulin after ingestion of food (BOLUS) ~minutes
  2. Next slow increase of insulin over a longer duration (BASAL) ~hours

- The goal of insulin therapy is to mimic this process
- Can be administered IV, IM, Sub-Q, or INH
- HYPOglycemia and weight gain

IV - intravenous
IM - intramuscular
Sub-Q - subcutaneous
INH - inhaled

Regular crystalline insulin naturally associates into hexamers upon Sub-Q injection

Absorption
- Hexamer → dimers → monomers → capillaries

http://www.uic.edu/classes/bios/bios100/lecturesf04am/lect15.htm

Analogs rapidly dissociate into monomers
pH change & microprecipitates slowly dissolve into monomers & dimers
All are modified human insulin molecules
U-100 = 100 units/mL  U-500 = 500 units/mL
## Insulin Pharmacokinetics

<table>
<thead>
<tr>
<th>Type of Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Pregnancy Category</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Aspart</td>
<td>15-30min</td>
<td>1-2 hr</td>
<td>3-5 hr</td>
<td>B</td>
<td>$$$$$</td>
</tr>
<tr>
<td>Lispro</td>
<td>15-30min</td>
<td>1-2 hr</td>
<td>3-4 hr</td>
<td>B</td>
<td>$$</td>
</tr>
<tr>
<td>Glulisine</td>
<td>15-30min</td>
<td>1-2 hr</td>
<td>3-4 hr</td>
<td>B</td>
<td>$$$$$</td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>30-60min</td>
<td>2-3 hr</td>
<td>3-6 hr</td>
<td>B</td>
<td>$</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>NPH</td>
<td>2-4 hr</td>
<td>4-6 hr</td>
<td>8-12 hr</td>
<td>B</td>
<td>$</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detemir</td>
<td>3-4 hr</td>
<td>3-9 hr *</td>
<td>6-23 hr **</td>
<td>B</td>
<td>$$$$$</td>
</tr>
<tr>
<td>Glargine</td>
<td>4-5 hr</td>
<td>------</td>
<td>12-24 hr</td>
<td>C</td>
<td>$$$$$</td>
</tr>
</tbody>
</table>

INSULIN PHARMACOKINETICS

- Long (Detemir)
- Long (Glargine)

Insulin level vs. Hours after injection for different types of insulin:
- Short (Regular)
- Long (Degludec)
INHALED INSULIN AFREZZA®

- Regular Insulin powder for inhaler
- Peak onset: 45 mins - 1 hr
- Duration: 2.5 - 3 hrs
- Insulin Naïve: start 4 units INH at beginning of each meal
- NOT a substitute for basal insulin

Acute bronchospasm has been observed in patients with asthma and COPD using inhaled insulin. Use is contraindicated in patients with chronic lung disease. Before initiating inhaled insulin, perform a detailed medical history, physical exam, and spirometry (FEV₁) to identify potential lung disease in all patients.

Add ≥ 2 rapid insulin* injections before meals (‘basal-bolus’)

- **Start:** 4U, 0.1 U/kg, or 10% basal dose/meal. If A1c<8%, consider ↓ basal by same amount.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly to achieve SMBG target.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

If not controlled, consider basal-bolus.

Change to premixed insulin* twice daily

- **Start:** Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

If not controlled, consider basal-bolus.

Add 1 rapid insulin* injections before largest meal

- **Start:** 4U, 0.1 U/kg, or 10% basal dose. If A1c<8%, consider ↓ basal by same amount.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

If not controlled, consider basal-bolus.

Basal Insulin (usually with metformin +/- other non-insulin agent)

- **Start:** 10U/day or 0.1-0.2 U/kg/day
- **Adjust:** 10-15% or 2-4 U once-twice weekly to reach FBG target.
- **For hypo:** Determine & address cause; ↓ dose by 4 units or 10-20%.

If not controlled after FBG target is reached (or if dose > 0.5 U/kg/day), treat PPG excursions with meal-time insulin. (Consider initial GLP-1-RA trial.)

- **Start:** 4U, 0.1 U/kg, or 10% basal dose/meal. If A1c<8%, consider ↓ basal by same amount.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

If not controlled, consider basal-bolus.

Diabetes Care 2015;38:140-149; Diabetologia 2015;58:429-442
TARGETS OF ORAL ANTIHYPERGLYCEMICS

Pancreas
- Beta-cell dysfunction
- Sulfonylureas
- Meglitinides
- Incretin drugs

Muscle and fat
- Incretin drugs
- Biguanides
- Meglitinides
- Sulfonylureas
- TZDs

Liver
- Hepatic glucose overproduction
- Biguanides
- TZDs
- Incretin Drugs

Gut
- Alpha-glucosidase inhibitors
- Biguanides

Glucose level

MOA: enhances insulin sensitivity of both hepatic and muscle tissues; decreased hepatic glucose production and intestinal absorption of glucose
- Activates AMP-kinase
- Activates GLUT-4 transporter

No direct effect on pancreatic β-cells
METFORMIN

- Pharmacokinetics
  - Onset: days; maximum effects up to 2 weeks
  - Half-life: 4-9 hours
  - Renal elimination (relaxed recommendations)

- Efficacy
  - HbA1c reduction 1-2%
  - Weight loss
  - Reduce LDL & TG, Increase HDL (↓ CVD events)

- Dosing
  - 500mg PO once daily to BID with meals
  - Max: 2550mg per day

- Side FX
  - Diarrhea
  - Nausea/Vomiting
  - Flatulence

LDL - low density lipoprotein
HDL - high density lipoprotein
TG - triglycerides
CVD - cardiovascular disease


**SULFONYLUREAS (SFU)**

- **MOA:**
  - Stimulates insulin release from pancreatic β-cells
  - Reduces glucose output from the liver
  - Increases insulin sensitivity at peripheral sites

http://content.onlinejacc.org/article.aspx?articleid=1124475

SFU’S

- **Pharmacokinetics**
  - Hepatic metabolism + or - renal clearance
  - Glyburide has longest half-life of 2nd generation

- **Efficacy**
  - HbA1c reduction 1-2%
  - Reduction of microvascular complications

- **Dosing**
  - Lower dosages recommended for elderly and/or hepatic/renal impairment
  - Titrate every 1-2 weeks
  - Give with food!

- **Side FX**
  - HYPOglycemia
  - Weight gain

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**Diabetes Care** 2015;38:140-149;  
**Diabetologia** 2015;58:429-442


THIAZOLIDINEDIONES (TZD)

- **MOA:**
  - Binds to PPAR-γ receptor on adipocytes
  - Indirect enhancement of insulin sensitivity

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http://www.cmaj.ca/content/172/2/213/F6.expansion.html
**THIAZOLIDINEDIONES (TZD)**

- **Pharmacokinetics**
  - Well-absorbed with/without food
  - Metabolized liver
  - Active metabolites provide 24hr activity
  - Max Effect seen in 3-4 months

- **Efficacy**
  - HbA1c reduction 1-1.5% after ≥ 6 months

- **Dosing**
  - Actos 15mg PO once daily; max 45mg
  - Decrease insulin dose ~20% if initiated

- **Side FX**
  - Weight Gain
  - Fluid Retention/Heart Failure
  - Loss of bone mineral density
  - Bladder Cancer?

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**THIAZOLIDINEDIONES (TZD)**

- Pure PPAR-γ agonist
  - LDL
  - HDL
  - TG
  - May have inc risk for CVD events

- Mixed PPAR-γ and α
  - LDL
  - HDL
  - TG
  - Heart Failure
  - Edema
  - Fractures

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**Rosiglitazone**

**Pioglitazone**

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**Dipeptidyl Peptidase 4 Inhibitors (DPP-4)**

- **MOA:**
  - Inhibit DPP-4 expressed on most cell types
  - Prolongs activity of incretin hormones
- Glucagon-like peptide 1 (GLP-1) based therapy
In healthy individuals, (1) ingestion of food results in (2) release of gastrointestinal peptides (GLP-1 and GIP) as well as (3) pancreatic beta cell hormones (insulin and amylin). GLP-1 and amylin, in particular, have inhibitory effects on (4) gastric emptying, (5) glucagon release, and (6) appetite. (7) Following the absorption of food, GLP-1 and GIP promote insulin secretion, otherwise known as the incretin effect. In diabetes, these steps are disrupted.

GLP-1: glucagon-like peptide 1; GIP: gastric inhibitory peptide.
DIPEPTIDYL PEPTIDASE 4 INHIBITORS (DPP-4)

- **Pharmacokinetics**
  - Sita, Saxa, Alo all cleared renal
  - Lina cleared enterohepatic

- **Efficacy**
  - HbA1c reduction 0.5 - 0.75%

- **Dosing**
  - Once daily dosing for all
  - Reduce dose by ½ or ¾ for moderate - severe renal impairment

- **Side FX**
  - Well-tolerated
  - Acute pancreatitis?
Exendin-4 Protein mimics activity of GLP-1

Discovered and synthesized from the saliva of the Gila Monster
Enhances glucose-dependent insulin secretion, delays gastric emptying, reduces post-prandial glucose and food intake.


http://flipper.diff.org/app/items/5477
Glucagon-like peptide-1 receptor agonist (GLP-1 RA)

- Pharmacokinetics
  - Minimal systemic metabolism
  - Immediate release form: half-life ~2 hrs
  - Extended release form: half-life ~2 weeks

- Efficacy
  - HbA1c reduction 1-2%
  - Superior to TZD, DPP-4 Inhibs, Lantus**

- Dosing
  - Exenatide (Byetta®) sub-q twice daily
  - Liraglutide (Victoza®) sub-q once daily

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST (GLP-1 RA)

- Long-acting formulations
- Usually synthesized so that they bind to plasma proteins (albumin)
  - Ext Release Exenatide (Bydureon®) 2mg sub-q once weekly
  - Albiglutide (Tanzeum®) 30mg sub-q once weekly
  - Dulaglutide (Trulicity®) 0.75mg sub-q once weekly
  - Structurally modified to prevent degradation by DPP-4.

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST (GLP-1 RA)

- **Side FX**
  - Weight loss (can even be an indication)
  - Acute pancreatitis
  - Injection site reactions

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Liraglutide and dulaglutide causes dose-dependent and treatment dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown if the drug causes these or medullary thyroid carcinoma (MTC) in humans. Contraindicated in patients with personal or family history of MTC or multiple endocrine neoplasia syndrome type 2. Counsel patients on potential risk and inform them of symptoms of thyroid tumors (mass in neck, dysphagia, dyspnea, persistent hoarseness.

Dungan K. GLP-1 Ras in the treatment of T2DM.
SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS (SGLT2)
SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS (SGLT2)
Healthy eating, weight control, increased physical activity & diabetes education

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Dual therapy</th>
<th>Triple therapy</th>
<th>Combination injectable therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td><strong>Efficacy</strong></td>
<td><strong>Efficacy</strong></td>
<td><strong>Efficacy</strong></td>
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<tr>
<td>Hypo risk</td>
<td>Hypo risk</td>
<td>Hypo risk</td>
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<td>Weight</td>
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<tr>
<td>Side effects</td>
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<tr>
<td>Costs</td>
<td>Costs</td>
<td>Costs</td>
<td>Costs</td>
</tr>
</tbody>
</table>

**Metformin**
- high
- low risk
- neutral/loss
- GI / lactic acidosis
- low

If HbA1c 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- & disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin</th>
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<td>Metformin</td>
</tr>
</tbody>
</table>

If HbA1c 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- & disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin</th>
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<td>Metformin</td>
<td>Metformin</td>
</tr>
</tbody>
</table>

If HbA1c 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-i:

Metformin + Basal Insulin + Mealtime Insulin or GLP-1-RA
QUESTIONS?