**PHARMACOLOGICAL TREATMENT OF DM**

ZIAD KAHWASH, M.D.

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**Pathogenesis of Hyperglycemia in Type 2 Diabetes**

- **Insulin resistance**: Defects in Insulin Signaling
  - Increased glucose production
  - Insufficient glucose disposal

Liver

Pancreas (skeletal muscle)

**Pancreatic β-cell Dysfunction in Type 2 Diabetes**

- Loss of 1st phase of insulin secretion in acute insulin response to IV glucose vs. IV Arginine

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Palmer et al. JCI 1976;56:565-570.
**Multihormonal Regulation of Glucose Homeostasis in Healthy People**

- **Gut L-Cells**: GLP-1
- **K-Cells**: GIP

**Portal Vein**
- **Liver**: Insulin, Amylin, Glucagon

**Pancreas**
- **β-Cells**: Insulin
- **α-Cells**: Glucagon

**Systemic Circulation**

**Ingestion of food**
- Release of gut hormones (Incretins)
- Insulin from beta cells (GLP-1 and GIP)

**Blood glucose**
- Glucose uptake by muscle
- Glucose production by liver

**GI tract**
- Active GLP-1 & GIP
- Inactive GLP-1 and GIP

**Amylin is Co-Secreced with Insulin from Pancreatic β-Cells in Healthy People**

- **Plasma Amylin (pM)**
  - 0: 7 am, 12 noon, 5 pm, Midnight
  - 5: Meal

- **Plasma Insulin (pM)**
  - 0: 7 am, 12 noon, 5 pm, Midnight
  - 5: Meal

Patterns of Body Fat Distribution

Abdominal (android) Lower body (gynoid)

Visceral Fat Distribution:
Normal vs. Type 2 Diabetes

Normal Type 2 Diabetes

Accumulation of excess visceral fat in abdominal adipose tissue and "ectopic" deposition of triglyceride and fatty acids in liver and skeletal muscle cells leads to tissue insulin resistance.
Association Between Visceral Fat and Insulin Resistance

Acanthosis Nigricans
Common Clinical Sign of Insulin Resistance

Definition of Type 2 Diabetes

- Type 2 diabetes mellitus encompasses a range of metabolic abnormalities, defined primarily by hyperglycemia, and frequently associated with cardiovascular risk factors.
- Whether or not the patient requires exogenous insulin to achieve metabolic control does not of itself classify individuals as either type 1 or type 2.
  - Type 2 patients may require insulin for glucose control or not.
  - Type 1 patients are designated insulin-dependent, since they always require insulin to prevent ketoacidosis.
Natural History of Type 2 Diabetes

Onset of Diabetes

Genetics
Environment
- nutrition
- obesity
- exercise

Insulin resistance
Hyperinsulinemia
↓ HDL Cholesterol
↑ Triglycerides

IGT/IFG

Complications

Atherosclerosis
Hyperglycemia
Hypertension
Retinopathy
Nephropathy
Neuropathy
Blindness
Renal Failure
Coronary Disease
Amputation

Disability

Ongoing Hyperglycemia

Onset of Diabetes

IGT/IFG

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Disability

Ongoing Hyperglycemia

“Eat less and exercise more? That’s the most ridiculous fad diet I’ve heard of yet!”
Progressive Care Approach: Type 2 Diabetes

- **Step 1:** Nutrition therapy, exercise, lifestyle changes
- **Step 2:** Add oral agents
  - monotherapy
  - early use of combination therapy
- **Step 3:** Add basal insulin to oral agents
- **Step 4:** Intensify insulin therapy

Therapies for Type 2 Diabetes – Sites of Action

- **Liver**
  - ↑ glucose output
- **Gut**
  - dietary glucose
  - ↓ incretins
- **Skeletal Muscle**
  - ↓ Glucose uptake

Thiazolidinediones: PPARγ agonists (a.k.a. TZDs or ‘glitazones’)

- **Rosiglitazone** (Avandia®)
- **Pioglitazone** (Actos®)
Thiazolidinediones act via PPARγ Receptors

PPAR = peroxisome proliferator-activated receptor

**Ligand**
- Fibrates
- Thiazolidinediones
- Fatty Acids

**Receptor**
- PPARα
- PPARγ
- PPAGγ

**Effect**
- Lipoprotein Expression
- Peroxisome Proliferation
- Lipid Synthesis
- Carbohydrate Metabolism


Thiazolidinediones: Effect on Glucose and Insulin

<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>Insulin (µU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>450</td>
<td>200</td>
</tr>
</tbody>
</table>

Before TZD

Rosiglitazone dose is 4–8 mg/day; pioglitazone is 15–45 mg/day
The glucose lowering effects are similar
TZDs are metabolized in the liver and are safe in patients with renal failure
Major side effects
- Fluid retention
  - Usually causes harmless peripheral edema
  - Use cautiously if at all in patients with a history of CHF
  - Fluid retention is mediated by PPARγ effect in renal tubules
- Weight gain
  - Due to effects on adipose differentiation and fat storage
  - Generally 2-3 kg over a 6 month to 1 year period
  - Can be minimized by caloric restriction

**Metformin: Mechanism of Action**

- Major effect is ↓ hepatic glucose production
- Metformin is the only available biguanide drug
- Enhances insulin sensitivity to a degree
  - not as robust as that observed withTZDs
- Works independently of the pancreas and reduces circulating insulin levels (called insulin “sparing”)
- Metformin activates AMP kinase and alters glucose and lipid metabolism

**Clinical Use of Metformin**

- Metformin lowers insulin levels and does not cause hypoglycemia
- In combination with sulfonylureas, hypoglycemia may occur
- Metformin is started at 500 mg twice a day with a meal
  - For 1-2 weeks when initiating therapy, patients may have diarrhea
  - GI side effects occur in 30% of patients overall, and 4% of patients need to discontinue therapy
- To alleviate the GI side-effects:
  - slow titration
  - take with food
  - extended release form of metformin may have better GI tolerance
- Metformin helps limit weight gain
  - ? Due to anorexia, nausea

**Acarbose: Lowers Peak of Postprandial Glucose**

![Graph comparing postprandial glucose levels between placebo, acarbose, sulfonylurea, and metformin](image)

*P<0.01; †P<0.019; ‡P<0.026

α-Glucosidase Inhibitors: Clinical Considerations

- Acarbose (Precose®) and Miglitol (Glyset®)
  - Have a similar clinical spectrum of activity and side-effect profile
  - Dosing is three times daily at the start of each main meal
    - Initial dose is 25 mg dose
    - Gradually increase to 50 to 100 mg three times a day
  - Clinical effect is modest, fall in the HbA1c of only ~0.5%
  - No added risk of hypoglycemia
  - Major side effects are gastrointestinal
    - Flatulence (80%), diarrhea (27%), nausea and vomiting (7-28%)
    - As the absorption of complex carbohydrates is delayed, they can appear in the colon where enteric bacteria generating gaseous by-products

(Anti-)Social Effects of α-Glucosidase Inhibition

Insulin Secretory Pathway in the Pancreatic β-Cell

- Glucose transport and phosphorylation
  - Glucose-6-P
  - Glycolysis
  - Glycogen
  - ATP (ATP/ADP)
  - Mitochondrial metabolism
  - Gene transcription
  - Granule formation and trafficking
  - Insulin secretion
  - Voltage-dependent Ca²⁺ channel
  - ATP-dependent K⁺ channel
  - Sulfurylurea receptor
  - Meglitinides
  - Sulfonylurea receptor
  - GLUT2
  - K⁺ channel
Insulin Secretion Enhancers: Mechanism of Action

- Bind to a unique component of the K-ATP channel system and increase insulin secretion
- To a greater or lesser extent, insulin secretion is coupled to circulating glucose levels
- Sulfonylureas are given once or twice a day to act over a 24 hr period
- The shorter-acting agents (meglitinites –repaglinide and nateglinide) have a shorter half-life in the circulation
  - Used for meal-time increase in insulin secretion

Insulin Secretion Enhancers - Sulfonylureas

- Widely used SU include glipizide sustained-release system (Glucotrol XL®) and glimepiride (Amaryl®).
  - Once-a-day dosing with improved safety profile
  - Glimepiride offers several advantages over older members of this class
    - reduced episodes of hypoglycemia
    - limited weight gain
    - no dose adjustment in elderly patients or in renal insufficiency

Established Oral Agents for Type 2 Diabetes

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Potential 24h Benefit</th>
<th>Potential Problems</th>
<th>Main Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Secretion Enhancers</td>
<td>Augmented insulin secretion</td>
<td>Relatively rapid onset of action</td>
<td>Weight gain, hypoglycemia</td>
<td>Hepatic disease</td>
</tr>
<tr>
<td>Biguanides (metformin)</td>
<td>Reduced hepatic glucose production</td>
<td>Less weight gain</td>
<td>Gastrointestinal side-effects</td>
<td>Renal insufficiency, CHF, elderly</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Enhanced insulin sensitivity</td>
<td>Reduced insulin resistance, cardiovascular protection</td>
<td>Fluid retention, weight gain</td>
<td>Abnormal liver function, CHF</td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>Delayed gut absorption of carbohydrates</td>
<td>Reduced postprandial glucose</td>
<td>Flatulence, can be severe</td>
<td>Gastrointestinal disease</td>
</tr>
</tbody>
</table>
Overweight T2DM (presumed insulin resistant)

Metformin → Sulfonlurea ↔ TZDs

Add ≥ GLP-1 agonist or DPP-4 inhibitor?
Add Bedtime NPH or basal insulin

? D/C SU and GLP-1 agents

INTENSIFIED INSULIN REGIMEN

Goal: A1c < 6.5%

Educational Goals

Insulin in Diabetes Mellitus

Understand the currently available formulations of insulin and how they are used in the management of type 1 and type 2 diabetes.

Major Physiologic Functions of Insulin

Liver
- ↓ glucose output
- ↓ gluconeogenesis
- ↓ glycogenolysis

Skeletal Muscle
- ↑ glucose uptake and metabolism
- ↑ stimulate amino acid uptake
- ↓ protein degradation

Adipose
- ↑ glucose uptake and metabolism
- ↓ hydrolysis of triglycerides and FFA release
Advantages
- Can control all patients
- Flexibility in dosing
- Pen devices improve compliance
- Novel long and short-acting insulins provide clinical benefit

Disadvantages
- Injections required
- Hypoglycemia
- Weight gain

Who Needs Insulin Therapy?
- **Type 1 Diabetes** - ALL patients need:
  - Basal insulin always to prevent ketoacidosis
  - Mealtime insulin for glycemic control
- **Type 2 Diabetes**
  - Hyperglycemia despite maximally effective doses of oral agents
  - Significant hyperglycemia at presentation
  - Acute injury, stress, infection
  - High glucose and unexpected weight loss
    - suggests insulin deficiency
  - Surgery
  - Pregnancy - only insulin is indicated

Available Human Insulins and Analogs

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting</td>
<td>lispro, aspart, glulisine</td>
<td>15 min</td>
<td>1 h</td>
<td>3-5 h</td>
</tr>
<tr>
<td>Short-acting</td>
<td>regular (soluble, crystalline)</td>
<td>30-60 min</td>
<td>2-4 h</td>
<td>6-8 h</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td>neutral protamine Hagedorn (NPH)</td>
<td>2-4 h</td>
<td>4-10 h</td>
<td>12-16 h</td>
</tr>
<tr>
<td>Basal insulin</td>
<td>glargine</td>
<td>2 h</td>
<td>(peakless)</td>
<td>20-24 h</td>
</tr>
<tr>
<td></td>
<td>detemir</td>
<td>3 h</td>
<td>(peakless)</td>
<td>14 h</td>
</tr>
</tbody>
</table>

The time course of action of any insulin may vary in different individuals, or at different times in the same individual.
Regular and Rapid-Acting Insulin Preparations

- **“Regular” insulin**
  - Crystalline hexameric zinc insulin

- **Rapid-Acting Analogs**
  - lispro (Humalog®); aspart (Novolog®); glulisine (Apidra®)
  - Synthetic structurally altered derivatives of human insulin
  - More easily dissociated from insulin/zinc hexamer
  - More rapidly absorbed from subcutaneous space

Physiologic Serum Insulin Secretion Profile

Physiologic Insulin Secretion Profile

- Insulin therapy must match the physiological secretion of insulin
  - Basal insulin delivery
    - Suppresses ketogenesis and hepatic glucose output
    - Nearly constant levels
    - ~50% of insulin requirements
  - Bolus insulin delivery
    - Limits hyperglycemia after meals
    - ~10-20% of daily insulin needs prior to each meal
    - Need rapid delivery into bloodstream as food is absorbed, and
    - Rapid reduction of insulin as blood glucose falls post-prandially
Plasma Insulin (mU/mL)

Normal Insulin Pattern
Bolus Insulin
Basal Insulin

Breakfast
Lunch
Dinner

Skyler J. Kelley’s Textbook of Internal Medicine 2000.

Limitations of Regular + NPH Insulin

Breakfast
Lunch
Dinner

Skyler J. Kelley’s Textbook of Internal Medicine 2000.

Glargine vs NPH Insulin Action Profiles by Glucose Clamp

End of observation period

Adding Insulin to Oral Agents in Type 2 Diabetes: synergistic and Complementary Effects

- **Metformin**
  - Improves insulin sensitivity at the liver
  - Reduces hepatic glucose production

- **Thiazolidinediones**
  - Improve insulin action in peripheral tissues
  - Enhance glucose uptake

- **Sulfonylureas / Repaglinide / Nateglinide**
  - Enhance meal-mediated insulin release

- **α-glucosidase inhibitors**
  - Decrease postprandial glucose absorption

**Inhaled insulin: Exubera®**

- **Benefits**
  - No injection needed
  - Post-prandial control

- **Concerns**
  - Only provides short-acting coverage
  - Associated with mild, non-progressive changes in lung function
  - Baseline and follow-up pulmonary testing is required
  - Not appropriate for smokers – they absorb too much insulin (!)
  - Small changes in dosing not as easy as injections
  - Long-term safety (> 2 yrs) not established
The Incretin Effect
Beta-Cell Response to Oral vs IV Glucose

Crossover of Healthy Subjects (n = 6)
- Oral Glucose
- Intravenous (IV) Glucose

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Plasma Glucose (mg/dL)</th>
<th>C-peptide (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0.5</td>
</tr>
<tr>
<td>60</td>
<td>100</td>
<td>1.5</td>
</tr>
<tr>
<td>120</td>
<td>200</td>
<td>2.0</td>
</tr>
<tr>
<td>180</td>
<td>200</td>
<td>0.5</td>
</tr>
</tbody>
</table>

INCRETINS
- Are intestinal hormones released after meal ingestion
- Play an important role in normal glucose homeostasis
- Physiologically help regulate insulin release in a glucose-dependent manner
- Diminished in type 2 diabetics

GLP-1 and GIP Are Incretin Hormones

<table>
<thead>
<tr>
<th>GLP-1 (glucagon-like peptide 1)</th>
<th>GIP (glucose-dependent insulinoctropin polypeptide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Released from L cells in ileum and colon 1,2</td>
<td>Released from K cells in duodenum 1,2</td>
</tr>
<tr>
<td>Stimulates insulin release from beta cells in a glucose-dependent manner 1,2</td>
<td>Stimulates insulin release from beta cells in a glucose-dependent manner 1</td>
</tr>
<tr>
<td>Inhibits gastric emptying 1,2</td>
<td>Has minimal effects on gastric emptying 2</td>
</tr>
<tr>
<td>Reduces food intake and body weight</td>
<td>Has no significant effects on satiety or body weight</td>
</tr>
<tr>
<td>Inhibits glucagon secretion from alpha cells in a glucose-dependent manner 1</td>
<td>Does not appear to inhibit glucagon secretion from alpha cells 2</td>
</tr>
</tbody>
</table>

GLP-1 Effects in Humans
Understanding the Natural Role of Incretins

GLP-1 secreted upon the ingestion of food

↓ Beta-cell workload
Promotes satiety and reduces appetite

↓ Beta-cell response

Alpha cells: Pancreatic glucagon secretion
Liver: 24-hour glucose tolerance, hepatic glucose output
Stomach: Helps regulate gastric emptying

Beta cells: Ectopic glucagon-like insulin secretion


Intestinal GLP-1 release
GLP-1 inactive (>80% of pool)

DPP-4 = Dipeptidyl Peptidase-IV

Inhibition of DPP-4 Increases Active GLP-1

Active GLP-1

DPP-IV inhibitor

GLP-1 inactive

Exenatide

- Synthetic version of salivary protein found in the Gila monster
- More than 50% overlap with human GLP-1
  - Binds to known human GLP-1 receptors on beta cells (in vitro)
  - Resistant to DPP-IV inactivation

Following injection, exenatide is measurable in plasma for up to 10 hours

Exenatide (Byetta®)

- FDA-approved on April 28, 2005
- Indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking
  - Metformin (MET)
  - Sulfonylurea (SFU)
  - Thiazolidinedione (TZD)
- But have not achieved adequate glycemic control

Exenatide Sustained A1C Reductions
Open-Label Extension – Combined

<table>
<thead>
<tr>
<th>Time (wk)</th>
<th>Placebo-Controlled</th>
<th>Open-Label Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-2.0</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>-1.5</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

Baseline A1C
- Placebo 8.2%
- 5 µg Exenatide 8.0%
- 10 µg Exenatide 8.3%
Exenatide Continued to Reduce Weight
Open-Label Extension - Combined

Baseline Weight
Placebo Controlled
Open-Label Extension

Time (wk)

Exenatide BID 5 µg and 10 µg

ITT; Overall incidence ≥ 5% and incidence of exenatide > placebo
Exenatide Prescribing Information, 2005

Other Adverse Events
Large Phase 3 Clinical Studies - Combined

Results of 30-Week Exenatide Studies

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N = 483)</th>
<th>Exenatide BID 5 µg and 10 µg (N = 963)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>18%</td>
<td>44%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4%</td>
<td>13%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td>Feeling Jittery</td>
<td>4%</td>
<td>9%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3%</td>
<td>6%</td>
</tr>
</tbody>
</table>

General Prescribing Considerations

How Supplied

- 2 fixed-dose prefilled pens
  - 5 mg per dose
  - 10 mg per dose
- 60 doses per pen (30-day supply)
Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels rise in response to a meal. Concentrations of the active intact hormones are increased by JANUVIA™ (sitagliptin phosphate), thereby increasing and prolonging the actions of these hormones.

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide.

JANUVIA provided significant improvements in A1C, FPG, and 2-hr PPG vs placebo when added to patients inadequately controlled on metformin monotherapy.

Adverse Reactions

Overall:
Incidence of adverse reactions and discontinuation rates with JANUVIA in both monotherapy and combination therapy were similar to placebo.

Incidence of hypoglycemia with JANUVIA was similar to placebo (1.2% vs 0.9%).

Incidence of selected GI adverse reactions in patients treated with JANUVIA vs placebo was as follows:

- Abdominal pain (2.3%, 2.1%)
- Nausea (1.4%, 0.6%)
- Diarrhea (3.0%, 2.3%)

In patients inadequately controlled on metformin monotherapy:

Compared with placebo plus metformin.

Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

Difference from placebo.
Amylin has been shown to:

- Suppress postprandial glucagon secretion
  - glucagon is an important determinant of hepatic glucose production
  - postprandial glucagon is abnormally elevated in diabetes
- Regulate gastric emptying
  - regulates rate of gastric emptying from stomach to small intestine
  - rate of gastric emptying is an important determinant of early glucose excursion postprandially
- Reduce food intake (central effect) and body weight
An analog of amylin that overcomes the tendency of human amylin to:
- Aggregate, form insoluble particles
- Adhere to surfaces
- Pharmacokinetic and pharmacodynamic properties similar to human amylin

Pramlintide (analog of amylin)

Human amylin

Pramlintide (analog of amylin)

Adapted from Westermark P, et al. Proc Natl Acad Sci 1990; 87: 5036-5040

- Inhibits glucagon secretion from α-cells
- Helps to reduce hepatic glucose production
- Slows gastric emptying
  - Accounts for dose-related side-effect of nausea
  - Also has CNS effects on satiety
  - Reduces food intake and body weight
- Major glucose effects are improved post-prandial control

Pramlintide acetate is given at mealtimes and is indicated for:
- Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and have failed to achieve desired glucose control despite optimal insulin therapy.
- Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.
“To lengthen thy Life, lessen thy Meals”

Benjamin Franklin
in Poor Richard’s Almanack,
Philadelphia, June 1733