Role of the Pharmacist in the Treatment of Diabetes

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Primary Care Clinical Pharmacist

Objectives

• Discuss the Prevalence of Diabetes in USA
• Brief Discussion of Metabolic Causes of Type 2 Diabetes
• Review Pharmacologic Treatment of Diabetes Mellitus Type 2
• Discuss the role of Pharmacogenomics in Medication Management
• Discuss the future role of the pharmacists as members of interprofessional teams in management of Diabetes
Diabetes Statistics- ADA (2007)

- **Total:** 23.6 million children and adults in the United States—7.8% of the population—have diabetes.
- **Diagnosed:** 17.9 million people
- **Undiagnosed:** 5.7 million people
- **Pre-diabetes:** 57 million people
- **New Cases:** 1.6 million new cases of diabetes are diagnosed in people aged 20 years and older each year.

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**Insulin Resistance**

Type 2 diabetes
Aging
Obesity/ sedentary lifestyle

Other associated conditions
Genetics

Other conditions:
- acromegaly
- Cushing’s disease
- lipodystrophy
- anti-insulin receptors

Olefsky JM. In: Endocrinology. 2nd ed. 1989;1369-1388.
The Insulin Resistance Syndrome

**Clinical Manifestations**
- Central obesity
- Glucose intolerance
- Hypertension
- Atherosclerosis
- Polycystic Ovary Syndrome

**Biochemical Abnormalities**

<table>
<thead>
<tr>
<th>Carbohydrate:</th>
<th>Lipid:</th>
<th>Fibrinolysis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin resistance</td>
<td>High TG</td>
<td>Increased PAI-1</td>
</tr>
<tr>
<td>Hyperinsulinemia</td>
<td>Low HDL-C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Small, dense LDL particles</td>
<td></td>
</tr>
</tbody>
</table>

Pathophysiology of type 2 diabetes

- Defective β-cell secretion
- Excess glucose production
- Resistance to the action of insulin
- Excessive lipolysis
- Reduced glucose uptake

Insulin Resistance and β-Cell Dysfunction Produce Hyperglycemia in Type 2 Diabetes

β-Cell Dysfunction

- Pancreas
  - Islet β-Cell Degranulation; Reduced Insulin Content
  - Reduced Plasma Insulin
  - Increased Glucose Output

Insulin Resistance

- Elevated Plasma FFA
- Increased Lipolysis
- Muscle
- Adipose Tissue

Hyperglycemia

-> Decreased Glucose Transport & Activity (expression) of GLUT4

Endothelial Dysfunction & Insulin Resistance

Pharmacology-
The Domain of the Clinical Pharmacist

DM Type 1 vs. DM Type 2

Type 1
- Lean Patient
- Usually younger patient
- Ketonuria present
- Large loss of weight
- Family Hx Type 1
- Hyperglycemic with symptoms
- May have positive islet cell antibodies

Type 2
- Overweight
- Family Hx Type 2
- Native American, African American, Hispanic, Asian
- Nonketotic with hyperglycemia
- PCOS
- Waist circumference >35” in women >40” in men
Diabetes Medication Therapy…
Educational Points for Providers/ Patients
TYPE 2 DIABETES — A PROGRESSIVE DISEASE

Progressive Decline of β-Cell Function in the UKPDS


UKPDS

Effect of Treatment on HbA1c

Adapted from UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:837-853, with permission.
TYPE 2 DIABETES . . . A PROGRESSIVE DISEASE
Natural History of Type 2 Diabetes

Oral Pharmacotherapy

- **Sulfonylureas** - Original 1st Line Oral Agents
  - 1st Generation - Chlorpropamide
- Sulfonylureas- 2nd Generation (50-200 times more potent than 1st generation)
  - Glyburide ➔ long half-life; caution in elderly
    (Diabeta, Micronase,Glynase)
    - Excreted in urine and bile
  - Glipizide - shorter t½;
    - Metabolized in Liver (90%) and Kidney (10%)
  - Glimepiride – properties of 2 previous medications
Sulfonylurea- Mechanism of Action

Beta cell membrane surface
Sulfonylurea binds
Potassium channel

Sulfonylurea- Mechanism of Action

Calcium channel

Gavin, S Medscape Image accessed 2/05
**Sulfonylureas: Mechanism of Action**

1. Intestine glucose absorption
2. Muscle and adipose tissue: glucose uptake
3. Pancreas: insulin secretion
4. Liver: hepatic glucose output

**Blood glucose**

**Insulin resistance**


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**Biguinides**

- **Metformin**: (Glucophage, Glucophage XR)-
  - maximum effective dose= 2000mg/ day
- **Contraindications:**
  - Creatinine >1.4 women ; >1.5 Men ,
  - Active liver disease, binge drinkers .
- **May cause diarrhea or vomiting** .
- **Combination metformin/sulfonylurea**
  - Glucovance, Metaglip
Metformin: Mechanism of Action

1. Intestine glucose absorption
   - Insulin resistance
   - Blood glucose

2. Muscle and adipose tissue: glucose uptake
   - Metformin glucose utilization
   - Insulin resistance

3. Pancreas: insulin secretion

4. Liver: hepatic glucose output
   - Metformin ↓ HGO


TZDs Decrease Insulin Resistance at Target Tissues

- Decrease excessive fat breakdown
- Reduce free fatty acids
- Improve insulin-mediated glucose uptake
- Improve insulin sensitivity
- Suppress excessive glucose production
- ? Improve insulin secretion, defect in pancreas

Carbohydrate Digestive enzyme Glucose
Thiazolidinediones- Mechanism of Action

1. Intestine: glucose absorption
   - Intestine: glucose absorption secondary to digestion of carbohydrate
   - Insulin resistance
   - Blood glucose

2. Muscle and adipose tissue: glucose uptake
   - Insulin resistance
   - Blood glucose

3. Liver: hepatic glucose output
   - Insulin resistance
   - Blood glucose

4. Pancreas: insulin secretion

**α-Glucosidase Inhibitors: Mechanism of Action**

- **Liver**:
  - Lipoprotein metabolism
  - Increased adiponectin C-III (pp)
  - Increased adiponectin A-1, B-1
  - Increased fatty acid transporter protein 1 (pp)
  - Increased fatty acid translocase/CD36 (pp)
  - Decreased inflammation
  - Decreased pro-inflammatory protein (pp)
  - HIF-1α (pp, by means of interleukin-6)

- **Skeletal muscle**
  - Fatty acid metabolism
    - Increased CPT-1 (pp)
    - Increased GLUT-4
    - Increased phosphorylated 3-kinase
    - Increased PDK-4

- **Adipose tissue**
  - Adipocyte differentiation (pp)
  - Fatty acid uptake and storage (pp)
  - Increased fatty acid transport protein 1
  - Increased high-mobility group A protein
  - Other effects (pp)
    - Increased adiponectin
    - Decreased 1,25-cholecalciferol
    - Interleukin-6
  - Increased LP (pp)
  - Glucose uptake (pp)
  - Increased HIF-2α
  - Increased free fatty acids (pp)
  - Increased GLUT-4
  - Increased MAPK
  - Increased PI3K
  - Increased PI3K

**Vascular wall**

- Adhesion molecules
  - Decreased intracellular adhesion molecule-1 (pp)
  - Decreased vascular cell adhesion molecule-1 (pp)
  - Inflammation
    - Increased nuclear factor-kB (pp)
    - Decreased oxidative stress (pp)
  - Decreased endothelial (pp)

**Cytokine activity**

- Increased A20 (pp)
- Increased Jak-2 (pp)

**Other**

- Decreased TNF-α (pp)
- Decreased IL-6 (pp)
- Decreased interleukin-6 (pp)
- Decreased MAP-3 (pp)
- Decreased MCP-1 (pp)
- Decreased tissue factor (pp)

Yki-Jarvinen, NEJM 2004; 351: 1106-18

Amatruda JM. In: Diabetes Mellitus. 1996.
Oral therapy for type 2 diabetes: sites of action

Pharmacokinetics of Insulin Preparations

<table>
<thead>
<tr>
<th>Insulin Preparation</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>lispro, aspart</td>
<td>&lt;15 min</td>
<td>1-2 hr</td>
<td>3 hr</td>
</tr>
<tr>
<td>Regular</td>
<td>0.5-1 hr</td>
<td>2-3 hr</td>
<td>2-5 hr</td>
</tr>
<tr>
<td>NPH/Lente</td>
<td>2-4 hr</td>
<td>6-10 h</td>
<td>10-12 hr</td>
</tr>
<tr>
<td>70/30, 50/50</td>
<td>0.5-1 h</td>
<td>2-10 h</td>
<td>10-12 hr</td>
</tr>
<tr>
<td>H’log 75/25, N’log 70/30</td>
<td>&lt;15 min</td>
<td>1-8 hr</td>
<td>10-12 hr</td>
</tr>
<tr>
<td>Ultralente</td>
<td>4 hr</td>
<td>Varies</td>
<td>14-18 hr</td>
</tr>
<tr>
<td>Ins. Glargine</td>
<td>1-2 hr</td>
<td>Flat</td>
<td>24 hr</td>
</tr>
<tr>
<td>Ins. Detemir</td>
<td>1-2 hr</td>
<td>Flat</td>
<td>24 hr</td>
</tr>
</tbody>
</table>
**INSULIN TACTICS**

Short-acting Insulin Analogues: 
*Lispro* and *Aspart*

**Plasma Insulin Profiles**

![Graphs showing plasma insulin profiles for Lispro and Aspart](image)


**Glucagon-Like Peptide-1 (GLP-1)**

Is an Important Incretin Hormone

- The “incretin effect” started the search
- Incretins
  - Gut hormones that enhance insulin secretion in response to food
  - Glucose-dependent insulin secretion
- GLP-1
  - Secreted from L cells of the intestines
  - Most well-characterized incretin
  - Diminished in type 2 diabetes
- Glucagon
  - Secreted from pancreatic alpha cells
  - Counterregulatory hormone to insulin
  - Elevated in type 2 diabetes

GLP-1 Modulates Numerous Functions in Humans

GLP-1: Secreted upon the ingestion of food

Promotes satiety and reduces appetite

α cells:
↓ Postprandial glucagon secretion

β cells:
Enhances glucose-dependent insulin secretion

Liver:
↓ Glucagon reduces hepatic glucose output

Stomach:
Helps regulate gastric emptying


Innovations in Diabetes Therapy

- Amylin
  - Stimulates secretion of insulin during episodes of elevated glucose
  - Does not promote secretion during low blood glucose levels
  - Improved safety profile over sulfonylureas
Amylin Is Co-Secreted With Insulin

Healthy adults; n = 6

Pramlintide Mimics Three Important Actions of Amylin That Impact Glucose Appearance

<table>
<thead>
<tr>
<th>Action</th>
<th>Amylin*</th>
<th>Pramlintide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibits inappropriately high postprandial glucagon secretion</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Slows gastric emptying</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Promotes satiety and reduces caloric intake</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

** For use in Type 1 and Type 2 Diabetics

*All amylin studies were performed in animals
Pramlintide Acetate Prescribing Information, 2005
Role of the Pharmacist

The Future of Pharmaceutical Care…

Project: Development of the Center for Innovation in Pharmacy Practice (CIPP) at the University of South Florida-College of Pharmacy
Role of the Pharmacist

- Provide medication expertise to patients and healthcare providers
- Serve as the “Trained Intermediary” between patients and providers (Tennessee lawsuit)
- Concurrent intervention with healthcare professionals to achieve optimal prescribing/administration
- Documentation of adverse effects and contraindications

Role of the Pharmacist

- Discharge medication counseling/documentation to achieve desired outcomes
- *Oversight of medication administration systems to achieve desired outcomes and enhance safety*
- Engage in Outcomes Data Collection and Research (IN-SCHAPE)
- Doctor of Pharmacy training is enhanced to provide Patient-Centered Disease state management (heart failure, diabetes, etc…)
Adverse Drug Reactions

- Over 106,000 people in the US die yearly from adverse reactions to correctly prescribed doses of drugs
- In top 6 leading causes of death in the US
- $4.3 billion per year cost in excess medical care

http://gale.genetics.utah.edu/units/pharma/phxwhatis/

A New Way to Practice Medicine?

- Currently, medications prescribed through “trial and error”
- With pharmacogenomics, individualizing prospective drug therapy to:
  - Maximize effectiveness
  - Minimize side effects
From “Genetics” to “Genomics”

**Genetics**
The science of heredity; refers to a single gene and its effects.

**Genomics**
The study of the entire genome including the complex interactions among multiple genes as well as between genes and the environment.

Use of Genetic Information

- To guide drug development and prescribing (pharmacogenomics)
  - Based on disease characteristics (somatic mutations)
    - HIV, OncotypeDx
  - Based on individuals’ genetic variation (inherited mutations)
    - depression-CYP450
- To predict disease risk
- Development of gene-based therapies
Come Join Us!!! IN-SHAPE Members will be available to:
- Provide Information about **Heart Attack and Stroke Prevention**
- Discuss options for Prevention and Treatment of **Heart Attack** and **Stroke**

Let’s all Get IN-SHAPE!!!
Participant Report of Diabetes

- Average BG: 105 ± 46 mg/dL
- Average A1c: 6.7 ± 1.3%
- 6% (12/201) reported a diagnosis of diabetes
- 36% (27/74) stated no diagnosis of diabetes, but screened positive for at least pre-diabetes
One More Important Question.........

Are we making a difference......

- Pharmacists are uniquely positioned to make important clinical medication management decisions in patient care.

- Inter-professional Healthcare teams = Improved Health Outcomes in the Future!