Pathophysiological Approach to Drug Therapy in Type 2 Diabetes Mellitus

Rattan Juneja, MD
Senior Medical Advisor
Eli Lilly and Company

Disclosures

• Employee: Eli Lilly and Company, Indianapolis, IN

Objectives

• List the criteria for the diagnosis of Diabetes Mellitus
• Categorize different types of Diabetes Mellitus
• Understand how we regulate glucose under physiological circumstances
• Discuss the physiology of Insulin Secretion
• Describe the pathophysiologic alterations that contribute to hyperglycemia in Type 2 Diabetes Mellitus
• Discuss Treatment Options for Type 2 Diabetes based on pathophysiology

Classification of Glucose Levels

Data from The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow up Report Diabetes Care. 2003;26:3160-3167.

Classification of Diabetes

Glucose Tolerance Categories

<table>
<thead>
<tr>
<th>Glucose Tolerance Categories</th>
<th>FPG</th>
<th>2-Hour PG on OGTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>116 mg/dL</td>
<td>7.0 mmol/L</td>
</tr>
<tr>
<td>Impaired Fasting Glucose</td>
<td>160 mg/dL</td>
<td>7.6 mmol/L</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>126 mg/dL</td>
<td>200 mg/dL</td>
</tr>
</tbody>
</table>

Data from The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow up Report Diabetes Care. 2003;26:3160-3167.
Definition of Type 2 Diabetes

- Comprises a heterogeneous group of metabolic diseases
- Fundamental problem is impaired insulin secretion and/or action
- Result is
  - hyperglycemia (high glucose)
  - ...and complications related to this
  - defects in lipid metabolism
  - ... and complications related to this

How Do We Regulate Glucose?
Plasma glucose changes only when appearance (Ra) does not match disappearance (Rd).

In diabetes, appearance is increased and disposal is impaired.

Therapies may address Ra, Rd, or both.

**Hepatic Glucose Production**

- **Gluconeogenesis**
  - Production of glucose from non-glucose sources
  - Occurs when there is hepatic insulin resistance and increased free fatty acid oxidation

- **Glycogenolysis**
  - Breakdown of the stored form of glucose in the liver (glycogen)
  - This is primarily driven by glucagon - a hormone produced from the pancreatic α cells

**Insulin Increases and Glucagon Falls in Response to Meals in Normal Subjects**

- Glucose
- Insulin
- Glucagon

**The Role of Incretins in Type 2 Diabetes**
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

Modulation of Insulin and Glucagon Levels: The Enteroinsular Axis

The Incretin Effect

Non-Diabetic Subjects (n=8)

<table>
<thead>
<tr>
<th>Time, min</th>
<th>IR Insulin, mU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>30</td>
<td>0.6</td>
</tr>
<tr>
<td>60</td>
<td>0.5</td>
</tr>
<tr>
<td>120</td>
<td>0.4</td>
</tr>
<tr>
<td>180</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Glucose-Stimulated Secretion of Insulin

Kidney and Glucose Homeostasis

Site of glucose filtration
Filters 180 g/d; almost all is reabsorbed
Reabsorbed by the SGLT-1 and SGLT-2 co-transporters in the proximal tubules
Amount excreted in the urine is <0.5 g/d

Renal Glucose Reabsorption
**Normal Glucose Homeostasis**

- Renal Glucose Reabsorption
- HGO-Glycogenolysis
- HGO-Gluconeogenesis
- Insulin resistance (Glucose Uptake)
- Insulin Deficiency (Glucose Uptake)
- Glucose Intake (Food)

**Pathophysiology of Type 2 Diabetes**

Role of Insulin Resistance

**Role of Free Fatty Acids in Hyperglycemia**

- Adipose tissue insulin resistance
- Lipolysis
- FFA mobilization
- FFA oxidation
- Glucose utilization
- Hyperglycemia


**Pathophysiology of Type 2 Diabetes**

Role of Insulin Deficiency
**Pathogenesis of Type 2 Diabetes**

*Falling Off the Curve*

- Insulin level
- Normal curve
- Type 2 diabetes
- Resistant
- Sensitive

**The Incretin Effect in Subjects Without and With Type 2 Diabetes**

- Control Subjects (n=8)
- Patients With Type 2 Diabetes (n=14)

**Increased Excretion Threshold and Increased Glucose Reabsorption Exacerbates Hyperglycemia in Type 2 Diabetes**

- Subjects With T2D
- Healthy Subjects
- Normal Threshold
- Increased Threshold

**The Kidneys in Patients with Diabetes**

- Increased glucose flux across the glomerular Basement Membrane
- Upregulation of SGLT-2 transporters to handle the increased flux
- Renal threshold increases from 180 mg/dl to ~240 mg/dl
- Excess Glucose instead of being excreted is reabsorbed
- Plasma glucose therefore increases.

**Mechanism of Action**

- Increase the removal of glucose via SGLT-2 inhibitors

**Structural Changes in Islets With Type 2 Diabetes**
**Insulin and Amylin**

**Mealtime Secretory Excursions**

Adapted from Koda et al. Diabetologia 1995.

**AMYLIN: SUMMARY**

**Insulin and Glucagon Dynamics in Response to Meals Are Abnormal in Type 2 Diabetes**


**The Relationship Between Insulin Secretion and Insulin Action During the Development of Type 2 Diabetes**

Adapted with permission from Weyer C et al. J Clin Invest. 1999;104;787–794.

**Pathogenesis of T2DM: The Ominous Octet**

Appropriate Intensive Risk Factor Management Today, Protect Patients Against Consequences Tomorrow

Manage Risk Factors Intensively Today

Protect Patients Against Consequences Tomorrow

Ezetimibe
Elevated LDL
Statins
Medication Compliance
Weight Loss
Exercise
Smoking Cessation
Lifestyle & Dietary Modifications

Hypertensive Renal Failure
Stroke
CHD
Heart Failure
Diabetic Renal Disease
End Stage Renal Disease
Statins
Thrombosis Risk
ASA
Clopidogrel
Warfarin
ARBs
ACEIs
Combination Therapy
Diuretics

Waist circumference
Blood pressure
Blood glucose
Triglycerides
HDL-cholesterol
LDL-cholesterol
Insulin resistance
Thrombotic risk

Current Therapies Often Address Individual Risk Factors

A Guide to Selecting Treatment: NIH Guidelines

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BMI Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet, physical activity, behavior therapy</td>
<td>25–28.9</td>
</tr>
<tr>
<td>Yes with comorbidities</td>
<td>Yes</td>
</tr>
<tr>
<td>Pharmaco-therapy</td>
<td></td>
</tr>
<tr>
<td>Weight-loss surgery</td>
<td></td>
</tr>
</tbody>
</table>

NIH = National Institutes of Health.

The Natural Progression of Diabetes

Diabetes Disease Progression

Beta-cell function

Normal
Type 2 (progressive)
Type 1

Oral Agents
(Potentiated/SUs, TZDs, GLP-1R Agonists, SGLT2 Inhibitors, DPP-IV Inhibitors, GLP-1 Agonists, SGLT2 Inhibitors, DPP-IV Inhibitors, GLP-1 Agonists)
Fasting Oral Agents
Mealtime Insulin
Pramlintide
Incretin Mimetics

Questions?