Diabetes Update 2009
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Objectives

- Review normal glucose metabolism
- Discuss pathophysiology of diabetes mellitus, type 2
- Review types of pharmacotherapy used to treat DM-2
- New treatment modalities
- Prevention strategies
Normal Physiology

**DEMAND**

Beta-Cell Workload

**SUPPLY**

Beta-Cell Response

**Physiology of Glucose Control**

Uptake of glucose & suppression of hepatic glucose production

Insulin-stimulated glucose uptake

Uptake and storage of excess glucose as TGs & suppression of lipolysis
Metabolic Defects in Diabetes

Pancreas

Progressive Insulin Secretory Defect

Hyperglycemia

Liver

Muscle

↑ Hepatic Glucose Production

↓ Glucose Uptake = Insulin Resistance

Insulin Resistance

Progressive Insulin Secretory Defect

The Pathogenesis of Type 2 Diabetes
An Imbalance of Beta-Cell Workload and Beta-Cell Response

- ↑ Insulin resistance
  - Obesity
  - ↑ Food intake
  - ↑ Rate of nutrient absorption
  - ↑ Glucagon secretion
    - ↑ Hepatic glucose output

Increased Beta-Cell Workload

→ Decreased Beta-Cell Response

↓ Insulin secretion in response to elevated glucose
↓ First-phase insulin response

Hyperglycemia
Natural History of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Year of Diabetes</th>
<th>Glucose (mg/dL)</th>
<th>Relative Function (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-10</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>-5</td>
<td>150</td>
<td>50</td>
</tr>
<tr>
<td>0</td>
<td>200</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>250</td>
<td>-50</td>
</tr>
<tr>
<td>10</td>
<td>300</td>
<td>-100</td>
</tr>
<tr>
<td>15</td>
<td>350</td>
<td>-150</td>
</tr>
<tr>
<td>20</td>
<td>400</td>
<td>-200</td>
</tr>
<tr>
<td>25</td>
<td>450</td>
<td>-250</td>
</tr>
<tr>
<td>30</td>
<td>500</td>
<td>-300</td>
</tr>
</tbody>
</table>

*IFG = impaired fasting glucose

Adapted from International Diabetes Center (IDC) Minneapolis, Minnesota

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Pathophysiology of Type 2 Diabetes

- Excess glucose production
- Defective β-cell secretion
- Resistance to the action of insulin
- Excessive lipolysis
- Reduced glucose uptake
# Pharmacologic Classes of Agents to Control Hyperglycemia in DM

## Class

<table>
<thead>
<tr>
<th>(---)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones—e.g., rosiglitazone, pioglitazone</td>
<td>Bind to peroxisome proliferator activated receptor-gamma (PPARγ) in muscle, fat and liver to decrease insulin resistance</td>
</tr>
<tr>
<td>Insulin secretagogues—e.g., sulfonylureas</td>
<td>Stimulate pancreatic β-cells to increase insulin output</td>
</tr>
<tr>
<td>Biguanides—e.g., metformin</td>
<td>Target liver to decrease glucose production</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors—e.g., acarbose &amp; miglitol</td>
<td>Inhibit intestinal enzymes that break down carbohydrates, which delays carbohydrate absorption</td>
</tr>
<tr>
<td>Insulin</td>
<td>Target insulin-sensitive tissue to increase glucose uptake</td>
</tr>
</tbody>
</table>

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## Pharmacologic Intervention in Type 2 Diabetes

- **Acarbose**
  - Supress hepatic glucose production
  - Reduce excessive lipolysis

- **Sulfonylureas**
  - Insulin (I)
  - Enhanced glucose uptake

- **Metformin**
  - Insulin (I)

- **Probable sites of rosiglitazone action**
  - Glucose (G)
  - Carbohydrate digestive enzymes

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Glucose (G) / Carbohydrate digestive enzymes
Current Therapies Do Not Influence Beta-Cell Failure

- Long-term glycemic control not easily attained or maintained
- Polypharmacy with oral agents with complementary mechanisms may be necessary to achieve long-term control

Rosiglitazone Increases Islet Area and Density in Pancreatic Islets of \( db/db \) Mice

- Improvements in pancreatic islet insulin content and morphology observed in models of type 2 DM

Source: UKPDS. *Lancet* 1998
Activation of PPARγ Alters Expression of Specific Genes

Co-repressors (SMRT, N-COR, etc.)

Rosiglitazone

PPAR

AGGTCA X AGGTCA

PPRE (DR-1)

Lipoprotein lipase, PEPCK, αP2

Co-activators (SRC-1, PGC-1, etc.)

Retinoic Acid

Model of Multihormonal Regulation

Plasma Glucose

Rate of glucose appearance

Rate of glucose disappearance

Food intake

Gastric Emptying

Amylin

Insulin

Model derived from animal studies
Amylin the Hormone

- Reported in 1987
- 37-amino acid peptide
- Co-located and co-secreted with insulin from pancreatic β-cells
- Deficient in diabetes

Effect of Amylin on Postprandial Glucose Excursions

- In animal models, 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

References:
Effect of Amylin on Postprandial Glucose Excursions

- 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 and body weight

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

GLP-1 secreted upon the ingestion of food

† Beta-cell response

Beta cells:
Enhances glucose-dependent insulin secretion

Promotes satiety and reduces appetite

↓ Beta-cell workload

Alpha cells:
↓ Postprandial glucagon secretion

Liver:
↓ Glucagon reduces hepatic glucose output

Stomach:
Helps regulate gastric emptying

Adapted from Breiner DJ. Diabetes. 1996;45:159-169
Glucagon-Like Peptide-1 (GLP-1)
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 small intestine
  - Most well-characterized incretin
  - Diminished in type 2 diabetes
- Glucagon
  - Secreted from pancreatic alpha cells
  - Counterregulatory hormone to insulin
  - Elevated in type 2 diabetes


The Incretin Effect
Beta-Cell Response to Oral vs IV Glucose

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

Mean (SEM); *P<0.05
Data from Neustiz MA, et al. J Clin Endocrinol Metab. 1986;63:492-498

Incretin Effect
**The Beginning**

- **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 Mimics Many Properties of GLP-1**

<table>
<thead>
<tr>
<th></th>
<th>GLP-1</th>
<th>Exenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>↑ Glucose-dependent insulin secretion</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>↓ Glucagon secretion</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>↓ Hepatic glucose output</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Regulates gastric emptying</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>↓ Rate of nutrient absorption</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>↓ Food intake</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>↓ Plasma glucose acutely to near-normal levels</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Resistant to DPP-IV degradation</strong></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>Duration in plasma following a subcutaneous (SC) injection</strong></td>
<td>Short</td>
<td>Long</td>
</tr>
</tbody>
</table>

Adapted from Nielsen LL, et al. Regul Pept 2014;177:71-89

See Important Safety Information included in this presentation
Leveraging the Therapeutic Potential of GLP-1

- GLP-1
  - Short half-life (<2 minutes)
    - Rapidly degraded by dipeptidyl peptidase-IV (DPP-IV)
- DPP-IV inhibition
  - Could extend endogenous GLP-1 half-life
- Incretin mimetics
  - Mimic many of the glucoregulatory effects of GLP-1
  - Resistant to DPP-IV
    - GLP-1 analogs
    - Exenatide

Acutely Improving Beta-Cell Response
BYETTA Restored First-Phase Insulin Response

Insulin (pM/kg/min)

Healthy Controls (n = 12)

Type 2 Diabetes (n = 13)

Placebo

BYETTA

Data from Pekosz F, et al. Diabetologia 2004;47(suppl 1):A279
Summary of Pathophysiology

- **Type 1 diabetes**
  - The main abnormality is insulin deficiency

- **Type 2 diabetes**
  - Both insulin deficiency and insulin resistance contribute

- **Glucotoxicity and lipotoxicity**
  - Poor metabolic control worsens insulin deficiency and insulin resistance

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Diabetes Mellitus in the US: Health Impact

- 7th leading cause of death

- Heart disease and stroke: 2X to 4X increase

- Nerve damage in 60% to 70% of patients

- Blindness

- Renal failure

- Amputation

Type 2 Diabetes

Two Principal Defects

Genes

Insulin resistance

± Environment

IGT

Glucose

Toxicity

Type 2 diabetes

Genes

β-cell dysfunction/ failure

± Environment

IGT

Glucose

Toxicity

Prevention

- Diabetes Prevention Trial
  - Participants had signs of early insulin resistance
  - Three treatment strategies
    - Education alone
    - Medication (insulin sensitizer)
    - Increase physical activity
  - Exercise had greater impact than Rx
    - Type and frequency of exercise

CURRENT AMERICAN DIET

In 1970 Americans spent $6 Billion on Fast Food
In 2000 Americans spent $110 Billion on Fast Food
that is more than Higher Education, Personal Computers, Software, Movies, Videos & Recorded Music Combined!
ARE VITAMINS THE ANSWER?

In the 1960’s the availability and use of vitamins increased. It seemed to make sense in correcting our nutritional problems.

What do we know about vitamins?

WHAT ARE VITAMINS?

- Described as “key nutrients” in food
- Deficiencies associated with disease
- Synthetic forms easily manufactured
Vitamin Deficiencies

- Vitamin A: loss of night vision
- Vitamin B: dry scaly skin, inflammation
- Vitamin C: scurvy, vascular fragility, fatigue, increased susceptibility to illness
- Vitamin D: fragile bones
- Vitamin E: infertility, miscarriages

SO IF WE REPLACE THESE MISSING OR LACKING VITAMINS, WILL WE ELIMINATE THESE PROBLEMS?

- Isolated or synthetic vitamins have not consistently shown reversal of these problems.
- Surprisingly, there is a lot of emerging research showing safety concerns of vitamins.
SOME ANTIOXIDANT SUPPLEMENTS LINKED TO LETHALITY.

JAMA 2007; 297: 842-857

This study only included vitamin supplements and these findings should not be translated to potential effects of fruit and vegetable sources of similar vitamins.

WHOLE FOODS ARE BEST.

- NUTRIENTS IN FOODS ARE BEST
  JAMA JULY 20, 2005

- ESSENTIAL NUTRIENTS: FOOD OR SUPPLEMENTS, WHERE SHOULD THE EMPHASIS BE?
  JAMA, 2005; 294: 351- 58
STUDY RESULTS

◆ MEDITERRANEAN DIET:
  – LENGTHENS LIFE
    British Medical Journal April 8, 2007
  – DECREASES ALZHEIMER’S
    Arch Neurol. 2006; 63: 1402-08
MEDITERRANEAN DIET

- Fruit, veggies, berries
- Whole grains, nuts, seeds
- Legumes, eggs, sheep and goat cheese
- Olive oil and avocado
- Lean meats and fish
- Moderate red wine

Fruits & Vegetables

- Fruits and Veggies contain all the Vitamins, Minerals, Anti-oxidants, Phytonurients, enzymes that our bodies need every day – we need them in a rainbow of color.
USDA Guidelines

The new USDA guidelines
9-13 Servings of Fruits and Vegetables a day!

www.mypyramid.com
Biggest Health Challenges Today

- We are not eating enough Fruits & Vegetables
- Lower nutrient content in F&V today
- Food Prep – Folate and Folic Acid are destroyed in cooking.
- Accept health consequences of poor nutrition

WHOLE FOOD SUPPLEMENTS

- They are fruit and vegetable juices processed carefully into a powder concentrate and then usually put into a capsule or tablet form.
- They are considered a ‘food’ and are labeled as food and not as a ‘supplement’ – thus do not contain isolated, synthetic or fragmented vitamins or minerals.
WHOLE FOOD SUPPLEMENTS

- Can help bridge the gap between what we should eat and what we do

- For more information:
  - www.ejlovesjuiceplus.com
and the
The shape of things
to come