Epidemiology and Pathophysiology of Type 2 Diabetes and Obesity

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Diabetes in the USA

• >26 million Americans with diabetes in 2011
• About 10% have type 1 diabetes
• Many more with either IGT, IFG or both
• Many Americans today with the metabolic syndrome at risk for diabetes

The epidemic continues…

CDC 2008; National Diabetes Fact Sheet and the National Diabetes Surveillance System;
http://apps.nccd.cdc.gov/DDTSTRS/default.aspx
Actual and Projected Diagnosed Diabetes in the United States, 1990-2050

Number (millions)

Year

6.6 8.0 12.0 15.8 20.5 28.8 36.4 42.8 48.3


County-level Estimates of Diagnosed Diabetes among Adults aged ≥ 20 years:
United States 2009

www.cdc.gov/diabetes
Estimated lifetime risk of developing diabetes for individuals born in the United States in 2000

Narayan et al, JAMA, 2003

Type 2 Diabetes in Children and Adolescents
Diagnostic Blood Tests

<table>
<thead>
<tr>
<th>RPG</th>
<th>FPG</th>
<th>OGTT</th>
<th>HbA1c or A1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random plasma glucose</td>
<td>Fasting plasma glucose</td>
<td>Oral glucose tolerance test</td>
<td>Glycated hemoglobin Average of blood glucose over 2-3 months</td>
</tr>
<tr>
<td>Any time, irrespective of meals</td>
<td>Before breakfast (8-h fast)</td>
<td>1 or 2 hours after drinking a medically formulated glucose drink</td>
<td>Any time, irrespective of meals</td>
</tr>
<tr>
<td>≥200 mg/dL plus signs/symptoms</td>
<td>≥126 mg/dL</td>
<td>≥200 mg/dL</td>
<td>≥6.5%?</td>
</tr>
</tbody>
</table>

Diagnosis must be confirmed with a second glucose measurement on another day

New criterion (ADA, 2009)
No confirmation necessary

Increasing Problem of Obesity and Diabetes in the United States

Obesity*

<table>
<thead>
<tr>
<th>Year</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>17.9%</td>
</tr>
<tr>
<td>2006</td>
<td>34.3%</td>
</tr>
</tbody>
</table>

92% increase

Diabetes

<table>
<thead>
<tr>
<th>Year</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>6.5%</td>
</tr>
<tr>
<td>2007</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

20% increase

*BMI ≥30 kg/m².

Type 2 Diabetes

Why Is It Important?

Clinical Impact of Diabetes Mellitus

Heart disease and stroke
- Account for 65% of deaths
- 2- to 4-fold increase in cardiovascular disease death rates

Kidney disease
- Diabetes is leading cause of ESRD
- Accounts for 44% of cases

Blindness
- Diabetic retinopathy causes 12,000 to 24,000 new cases of blindness/year
- Serves as leading cause of new cases of blindness in adults 20-74 years of age

Amputations
- More than 60% of nontraumatic lower-limb amputations occurs in people with diabetes
- 10-fold increase in amputation rate

ESRD, end-stage renal disease.
Diabetes Is a Cardiovascular Disease Risk Equivalent

<table>
<thead>
<tr>
<th>DM=diabetes mellitus; MI=myocardial infarction.</th>
</tr>
</thead>
</table>

Costs of Diabetes in the United States in 2007:
174 Billion

Direct Costs
$116 billion

- $31 billion Excess general medical costs
- $58 billion Diabetes-related complications
- $27 billion Diabetes care / management

Indirect Costs
$58 billion

- 15 million work days absent
- 120 million work days with reduced performance
- 445,000 cases of unemployment disability in 2007
  - 107 million work days lost due to diabetes-related unemployment disability
- Lost productivity due to premature, diabetes-related death: $26.9 billion

Type 2 Diabetes

How Do We Minimize Its Impact?

Historic Rationale for Improving Glycemia: Microvascular Risk Reduction

Estimated 37% decrease in microvascular risk for each 1% decrement in HbA1c (P<0.0001)

Lasting Benefits of Early, Intensive Intervention: UKPDS “Legacy Effect”

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Relative Risk Reduction (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Diabetes Endpoint</td>
<td>-</td>
<td>0.029</td>
</tr>
<tr>
<td>Microvascular Disease</td>
<td>-</td>
<td>0.0099</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>-</td>
<td>0.014</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>-</td>
<td>0.007</td>
</tr>
</tbody>
</table>


Early vs Late Intervention in Type 2 Diabetes

Early diagnosis and intensive glucose control therapy from the start are the key to long-term risk reduction in diabetes

UKPDS 80: Goal: FPG <108 mg/dL; Intervention endpoint: 7.0%; Follow-up: 7.7%; N=4209; 17 yr; Newly diagnosed with T2DM: No

Yes
Mortality Risk from the ACCORD Study

Steady increase of risk from an A1c of 6 to 9% in the intensive strategy.

Riddle M. Diab Care 33, 983-90, 2010

ADA 2011

Type 2 Diabetes

How Successful Are We at Controlling Hyperglycemia?
AACE “State of Diabetes in America”: 67% of Patients Have an A1C >6.5%

SDI data; top 10% with A1C >6.5%
SDI data; % with A1C >6.5%
HEDIS data; % with A1C >9.0%

SDI = Surveillance Data Inc.; HEDIS = Health Plan Employer Data and Information Set


Pathophysiology of Diabetes
Natural History of Type 2 Diabetes

Adapted from International Diabetes Center (IDC) Minneapolis, Minnesota.

Lifestyle changes – diet and...

Adapted from International Diabetes Center (IDC) Minneapolis, Minnesota.
EVERYTIME I FEEL LIKE EXERCISING……

I JUST LIE DOWN UNTIL THE FEELING PASSES……
Normal Insulin and Glucagon Response in the Postprandial Period

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Glucose (mg/dL)</th>
<th>Insulin (µU/mL)</th>
<th>Glucagon (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>60</td>
<td>120</td>
</tr>
<tr>
<td>60</td>
<td>100</td>
<td>80</td>
<td>110</td>
</tr>
<tr>
<td>120</td>
<td>80</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>180</td>
<td>60</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>240</td>
<td>40</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Pancreatic islet
α-cells
β-cells
Islet boundary

Photomicrograph courtesy of Michael Sarras, PhD, Rosalind Franklin University of Medicine and Science


b-Cell Mass in Type 2 Diabetes Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>NGT (n=31)</th>
<th>IFG (n=19)</th>
<th>Type 2 Diabetes (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Cell Volume (%)</td>
<td>3.0±0.5</td>
<td>2.0±1.0</td>
<td>1.0±0.5</td>
</tr>
</tbody>
</table>

*P<0.05 vs NGT
†P<0.001 vs NGT

Increased Beta-Cell Apoptosis Occurs in Type 2 Diabetes

*p<0.05. Islet cell death was assessed by an ELISA method, which evaluates the cytoplasmic histone-associated DNA fragments. After incubation absorbance of samples was read spectrophotometrically. Data obtained from pancreatic islets isolated from 6 T2DM organ donors and 10 nondiabetic cadaveric organ donors. Adapted from Marchetti P et al. J Clin Endocrinol Metab. 2004;89:5535–5541.

In Type 2 Diabetes, The α-Cell Mass is Increased

GLP-1 – Effects in Humans
Understanding the Potential of Incretins

Normal GLP-1 secretion
- Stimulated by food intake
- Diminished in IGT, diabetes
- Response to GLP-1 preserved even in diabetes

CNS: promotes satiety and reduction of appetite

Liver:
\[ \text{glucagon} \]
- Reduces hepatic glucose output

Beta cell:
- Enhances glucose-dependent insulin secretion

Stomach:
- Regulates gastric emptying

Alpha cell:
\[ \text{glucagon} \]
- Secretion post-meal


The Kidney Supports Three Key Functions in Glucose Handling

1. Kidney Glucose Production in the Renal Cortex
   - Glucose filtered = 180 g/day
   - In Healthy Subjects

2. Kidney Glucose Utilization in the Renal Medulla
   - Glucose reabsorbed = 180 g/day

3. Kidney Glucose Reabsorption in Nephrons

FFA=free fatty acid
CNS Regulation of Weight

- Weight is controlled via a multi-level system involving gut and adipose origin hormones which input into the CNS and affect hunger, sensory perception, cognition, emotion and behavior.

NEUROTRANSMITTER ABBREVIATION

- POMC Proopiomelanocortin
- CART Cocaine and Amphetamine regulated transcript
- Alpha MSH alpha melanocyte stim hormone
- MC3R,MC4R Melanocortin 3,4 receptors
- NPY Neuropeptide Y
- AgrP Agouti related peptide
- Y1R Y5R Receptors for NPY AgRP
- MCH Melanin Concentrating Hormone
HUNGER SIGNALING 1

<table>
<thead>
<tr>
<th>ANOREXIGENS</th>
<th>OREXIGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPOTHALAMUS (Arcuate Nucleus)</td>
<td>HYPOTHALAMUS (Arcuate Nucleus)</td>
</tr>
<tr>
<td>POMC, Alpha MSH</td>
<td>NPY</td>
</tr>
<tr>
<td>CART</td>
<td>AgRP</td>
</tr>
<tr>
<td>Serotonin</td>
<td></td>
</tr>
<tr>
<td>HYPOTHALAMUS (Paraventricular Nucleus)</td>
<td>HYPOTHALAMUS (Lateral)</td>
</tr>
<tr>
<td>CRH, TRH, CART</td>
<td>MCH</td>
</tr>
<tr>
<td>Neurotensin, Neurotrophic factor</td>
<td>Orexin/Hypocretin</td>
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</table>

HUNGER SIGNALING 2

<table>
<thead>
<tr>
<th>ANOREXIGENS</th>
<th>OREXIGENS</th>
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<tbody>
<tr>
<td>GUT</td>
<td>GUT</td>
</tr>
<tr>
<td>CCK</td>
<td>Ghrelin</td>
</tr>
<tr>
<td>GIP</td>
<td></td>
</tr>
<tr>
<td>PYY</td>
<td></td>
</tr>
<tr>
<td>Oxyntomodulin</td>
<td></td>
</tr>
<tr>
<td>GLP1</td>
<td></td>
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HUNGER SIGNALING 3

<table>
<thead>
<tr>
<th>ANOREXIGENS</th>
<th>OREXIGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANCREAS</td>
<td></td>
</tr>
<tr>
<td>Pancreatic Polypeptide</td>
<td></td>
</tr>
<tr>
<td>ADIPOSE TISSUE</td>
<td></td>
</tr>
<tr>
<td>Leptin</td>
<td></td>
</tr>
<tr>
<td>Adiponectin</td>
<td></td>
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Pathogenesis of Type 2 Diabetes
An Evolving Concept

- Impaired Insulin Secretion
- Increased Glucagon Secretion
- Increased Lipolysis
- Increased Glucose Reabsorption
- Decreased Incretin Effect
- Decreased Glucose Uptake
- Increased HGP