Diabetes Mellitus and the Elderly individual with I/DD

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Brief Early History

- 400 B.C.
  - Hindus described “honeyed urine”
- 17th Century
  - This is the period marked with the discovery of the sweetness of urine (by Oxford Physician Thomas Willis) and glycosuria itself but the reason behind it was not established
- 19th Century
  - The concept of excessive glucose production was that of Frenchman Claude Bernard
  - Czech researcher Pavlov discovers the link between the nervous system and gastric secretion
  - In 1869 German student Paul Langerhans was studying the pancreas and preliminarily found what later became known as the Islets of Langerhans
  - 1889 Austrians von Mering and Minkowski determined the effect that removing the pancreas has on digestion

Later
Foundations

- Canada 1921
  - Frederick Banting and Charles Best discovered insulin
- Britain 1936
  - Sir Harold Himsworth proposed theory of insulin insensitivity
- Britain 1955
  - Frederick Sanger discovered the structural formula of insulin
- USA 1957
  - Rosalind Yalow and Solomon Berson discovered technique of immunoassay
- Britain 1969
  - Dorothy Hodgkin elucidated the physical structure of insulin

Diabetes Overview

- Insulin resistance
- Metabolic syndrome
- Definitions
- Etiology
- Epidemiology
- Risk factors, diagnoses and tests

- Complications
- Treatment and management goals
- Pharmacologic agents
- Future advances
- Summary
Insulin Resistance

Obesity/ sedentary lifestyle
Aging
Type 2 diabetes
Genetics
Other conditions
Other associated conditions

Metabolic Syndrome Increases Risk for CHD and Type 2 Diabetes

- High LDL-C
- Metabolic Syndrome
- Type 2 Diabetes
- Coronary Heart Disease
# ATP III: Metabolic Syndrome

Diagnosis is established when ≥ 3 of these risk factors are present

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abdominal obesity</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td><strong>HDL-C</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td>≥130/≥80 mm Hg*</td>
</tr>
<tr>
<td><strong>Fasting glucose</strong></td>
<td>≥110 mg/dL</td>
</tr>
</tbody>
</table>

ATP III: Metabolic Syndrome
WHO Definition of Metabolic Syndrome

- Insulin resistance
  - Type 2 diabetes, impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)
- Plus any 2 of the following:
  - Elevated blood pressure (>140/90 and/or medication)
  - Plasma triglycerides ≥150 mg/dL
  - HDL <35 mg/dL (men); <40 mg/dL (women)
  - BMI >30
  - Urinary albumin >20 mcg/min; Alb/Cr >30 mcg/mL

IFG and IGT is considered serum blood glucose of 100 mg/dL - 125 mg/dL
Diabetes Differentiation

Definition of Diabetes

- “A metabolic disorder characterized by chronic hyperglycemia with disturbances in carbohydrate, fat and protein metabolism caused by defects in insulin secretion, insulin action, or both.”

Diabetes Mellitus in the US: Health Impact of the Disease

Type 2 Diabetes

- 6th leading cause of death
- Life expectancy: 5 to 10 yr
- Cardiovascular disease
- Blindness
- Renal failure
- Nerve damage in 60% to 70% of patients

Haines ST. Pharmacotherapy 2003;23:1227-31
Diabetes Facts

- ~13 million people in the U.S. are diagnosed with diabetes
- 60 million people in the U.S. have metabolic syndrome
- 1.3 million (≥ 20 years) newly diagnosed cases of diabetes each year
- 90-95% of those with diabetes are type 2
- Sixth leading cause of death in U.S. in 2001
- ~ 80% of people with type 2 diabetes are overweight
Diabetes Facts
In Elderly Settings

- 25% of residents in nursing homes have diabetes
- In long-term care residents with diabetes:
  - 80% have cardiovascular disease
  - 69% have 2 or more chronic conditions
  - 56% have hypertension
  - 39% have senile dementia
  - 33% have impaired vision
  - 6% are blind
  - 2.8% have kidney failure
Diabetes Incidence in the Elderly (≥ 65 years)

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of cases (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>6</td>
</tr>
<tr>
<td>2010</td>
<td>6</td>
</tr>
<tr>
<td>2020</td>
<td>8</td>
</tr>
</tbody>
</table>
Types of Diabetes

- Pre-Diabetes
  - Impaired fasting glucose (100 – 125 mg/dL)
  - Impaired glucose tolerance (100 – 125 mg/dL)
  - 20.1 million Americans

- Type 1 Diabetes
  - Affects 5 to 10% of people with diabetes

- Type 2 Diabetes
  - Affects 90 to 95% of people with diabetes

- Gestational Diabetes
  - Affects 7% of pregnant women (more than 200,000 cases per year)
# Type 1 Versus Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td>Onset typically &lt; 20 years</td>
<td>Onset typically &gt; 30 years</td>
</tr>
<tr>
<td></td>
<td>Normal weight</td>
<td>Often overweight</td>
</tr>
<tr>
<td></td>
<td>Anti-islet cell antibodies</td>
<td>No anti-islet cell antibodies</td>
</tr>
<tr>
<td></td>
<td>Ketoacidosis common</td>
<td>Ketoacidosis rare</td>
</tr>
<tr>
<td></td>
<td>Decreased blood insulin</td>
<td>Normal or increased blood insulin</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>50% concordance in twins</td>
<td>90%-100% concordance in twins</td>
</tr>
<tr>
<td></td>
<td>HLA-D linked</td>
<td>No HLA association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>About 40% chance of inheriting from a first degree relative</td>
</tr>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>Autoimmunity, immunopathologic mechanisms</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td></td>
<td>Severe insulin deficiency due to pancreatic failure</td>
<td>Relative insulin deficiency</td>
</tr>
<tr>
<td><strong>Islet Cells</strong></td>
<td>Inflammatory reaction early</td>
<td>No inflammatory reaction</td>
</tr>
<tr>
<td></td>
<td>Marked atrophy and fibrosis</td>
<td>Focal atrophy and amyloid deposits</td>
</tr>
<tr>
<td></td>
<td>β-cell depletion and/or failure</td>
<td>Mild β-cell depletion</td>
</tr>
</tbody>
</table>

Adapted from: Robbins Pathologic Basis of Disease. 1999
Latent Autoimmune Diabetes of Adulthood

- Adult at diagnosis -- usually over 25 years of age
- Initial presentation -- non-obese type 2 diabetes
- Initially controlled with diet with/without diabetes medications
- Insulin dependency within a short period
- Presence of pancreatic antibodies
- Low C-peptide levels
- Unlikely to have a family history of type 2 diabetes
Etiologic Classification

- Genetic defects of beta-cell function
- Genetic defects in insulin action
- Diseases of the exocrine pancreas
- Endocrinopathies
- Drug- or chemical-induced
- Physiologic stress (e.g., infection)
- Uncommon forms of immune-mediated diabetes
- Other genetic syndromes sometimes associated with diabetes
Type 1 Diabetes

GENETIC PREDISPOSITION

- HLA-linked genes and other genetic loci

Immune response against normal beta-cells
AND/OR
Immune response against altered beta cells

ENVIRONMENTAL INSULT

- Viral Infection: Molecular mimicry by viral antigen evokes autoimmune attack of similar beta-cell antigen
AND/OR
Damage to β cells

AUTOIMMUNE ATTACK

- Beta-cell destruction

TYPE 1 DIABETES

Adapted from: Robbins Pathologic Basis of Disease. 1999
Type 2 Diabetes

GENETIC PREDISPOSITION

- Multiple genetic defects

ENVIRONMENT

- Obesity

PRIMARY BETA-CELL DEFECT

- Deranged insulin secretion

PERIPHERAL TISSUE INSULIN RESISTANCE

- Inadequate glucose utilization

Hyperglycemia

Beta-cell exhaustion

TYPE 2 DIABETES

Adapted from: Robbins Pathologic Basis of Disease. 1999
Risk Factors for Type 2 Diabetes

**NONMODIFIABLE**
- Genetic factors
- Age
- Ethnicity
- Family history
- Gestational diabetes
- Delivery of baby > 9lbs
- Polycystic ovarian disease
- Previous impaired glucose tolerance

**MODIFIABLE**
- Obesity (BMI > 25 kg/m²)
- Physical activity
- Hypertension (≥ 140/90 mm Hg)
- Increased triglycerides and/or low cholesterol

Matrex, International Diabetes Center. Type 2 diabetes practice guidelines 2000
AACE. Consensus conference on guidelines for glycemic control. Endocr Prac 2001
Metabolic Staging of Type 2 Diabetes

Obesity

Peripheral insulin resistance

Hyperinsulinemia

Impaired glucose tolerance

Defective glucorecognition and decreased insulin secretion

Early diabetes

Beta-cell failure

Late diabetes

Insulin Resistance and Hyperinsulinemia

- Insulin Resistance
- Insulin Production
- Blood Glucose

Onset of diabetes
Beta-cell failure
Hyperglycemia (125 mg/dL)

Years of Diabetes

-20 -15 -10 -5 0 5 10 15 20 25
Insulin Resistance and Hyperinsulinemia (cont’d)

- IR
- IP
- BG

Onset of diabetes

-5 - 0 - 5 - 10 - 15 - 20

-20 -15 -10 -5

Years of Diabetes

-20 -15 -10 -5

Impaired fasting glucose
Abnormal glucose concentrations

Hyperglycemia
Retinopathy
Nephropathy

Hypertension, Dyslipidemia, Atherosclerosis

Blindness
Renal failure
CHD
Amputation
Diabetes Trends in Adults in the US 1992

Mokdad AH et al. JAMA 2003;1:289
Haines ST. Pharmacotherapy 2003;23:1227-31
Obesity Trends in Adults in the US 1992

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Haines ST. Pharmacotherapy 2003;23:1227-31
Clinical Diagnosis

- **Signs**
  - Polyuria
  - Polydipsia
  - Polyphagia
  - Slow healing wounds
  - Weight loss
  - Recurrent infections
  - Hyperglycemia

- **Symptoms**
  - Blurred vision
  - Fatigue
  - Itching

Haines ST. Pharmacotherapy 2003;23:1227-31
Tests for Diabetes

- Fasting Plasma Glucose (FPG)
  - Preferred in clinical settings
  - Easiest and fastest to perform
  - Most accurate and the least expensive
  - If < 126 mg/dL with suspicion of diabetes then OGTT should be performed
  - Fasting defined as no consumption of food/beverage (other than water) for at least 8 hours before testing

- Oral Glucose Tolerance Test (OGTT)
  - Plasma glucose levels following a 75 gm anhydrous glucose load

- Casual Plasma Glucose (non-fasting)
  - Any time of day without regard to time since last meal
  - If < 200 mg/dL perform FPG and/or OGTT
### Criteria for Diagnosis

<table>
<thead>
<tr>
<th>Stage of Glycemic Control</th>
<th>Plasma Glucose Level (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasting Plasma Glucose</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt;100</td>
</tr>
<tr>
<td>IFG or IGT</td>
<td>≥ 100 &lt; 126</td>
</tr>
<tr>
<td>Diabetes</td>
<td>≥ 126</td>
</tr>
</tbody>
</table>

IFG=impaired fasting glucose  
IGT=impaired glucose tolerance

Glucose Tolerance Categories

Plasma glucose (mg/dL)

0 100 120 140 160 180 200 220 240

FPG

2-h PPG (OGTT)

Normal

IFG

IGT

Diabetes Mellitus

A1C test

- % glycosylation of hemoglobin related to the concentration of blood glucose in contact with RBC over their 120 day lifespan
- Average blood glucose control for past 2 to 3 months
- Not used for diagnosis
- Necessary for monitoring blood glucose and affect of treatment
- Minimum 2 times yearly, more if poor control or start of new medication
- Measure of overall control
# A1C Levels and Corresponding Plasma Glucose Levels

## How to Compare

<table>
<thead>
<tr>
<th>A1C</th>
<th>Blood Sugar (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4%</td>
<td>60</td>
</tr>
<tr>
<td>5%</td>
<td>90</td>
</tr>
<tr>
<td>6%</td>
<td>120</td>
</tr>
<tr>
<td>7%</td>
<td>150</td>
</tr>
<tr>
<td>8%</td>
<td>180</td>
</tr>
<tr>
<td>9%</td>
<td>210</td>
</tr>
<tr>
<td>10%</td>
<td>240</td>
</tr>
<tr>
<td>11%</td>
<td>270</td>
</tr>
<tr>
<td>12%</td>
<td>300</td>
</tr>
<tr>
<td>13%</td>
<td>330</td>
</tr>
</tbody>
</table>


Plasma Glucose Versus Whole Blood Glucose Goals

- These values are for nonpregnant adults with diabetes. Treatment goals should be individualized. Patients with comorbid disease, the very young, the elderly, and others with unusual conditions or circumstances may warrant different treatment goals.

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>Normal</th>
<th>Goal</th>
<th>Action suggested when:</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6</td>
<td>&lt; 7</td>
<td>&gt; 8</td>
<td></td>
</tr>
</tbody>
</table>

Plasma values (mg/dL) – values calibrated to plasma glucose

<table>
<thead>
<tr>
<th>Average preprandial glucose</th>
<th>&lt; 110</th>
<th>90-130</th>
<th>&lt; 90 or &gt; 150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average bedtime glucose</td>
<td>&lt; 120</td>
<td>110 - 150</td>
<td>&lt; 110 or &gt; 180</td>
</tr>
</tbody>
</table>

Whole blood values (mg/dL) – measurement of capillary blood glucose

<table>
<thead>
<tr>
<th>Average preprandial glucose</th>
<th>&lt; 100</th>
<th>80 - 120</th>
<th>&lt; 80 or &gt; 140</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average bedtime glucose</td>
<td>&lt; 110</td>
<td>100 - 140</td>
<td>&lt; 100 or &gt; 160</td>
</tr>
</tbody>
</table>
Health Care Costs of Diabetes

DIRECT COSTS:
$92 Billion

INDIRECT COSTS:
$40 Billion

Lifetime Costs of Diabetes

- **Neuropathy/LEA**
- **Renal disease**
- **Eye disease**
- **New coronary heart disease**
- **General diabetes-related care**

### Graph Details
- **X-axis:** Age at Diagnosis of Diabetes (Y)
- **Y-axis:** Cost ($)
- **Legend:**
  - Yellow: Neuropathy/LEA
  - Grey: Renal disease
  - White: Eye disease
  - Red: New coronary heart disease
  - Green: General diabetes-related care

### Data Points
- **Maintained A1C (%)**
  - 6
  - 8
  - 10
  - 12
## Select Diabetes Interventions: Cost-effectiveness

<table>
<thead>
<tr>
<th></th>
<th>Intensive glycemic control</th>
<th>Intensive hypertension control</th>
<th>Reduction in serum cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard treatment ($)</strong></td>
<td>10,785</td>
<td>11,030</td>
<td>10,756</td>
</tr>
<tr>
<td><strong>Cost of intervention ($)</strong></td>
<td>12,213</td>
<td>3,708</td>
<td>15,942</td>
</tr>
<tr>
<td><strong>Cost of complications ($)</strong></td>
<td>33,271</td>
<td>28,902</td>
<td>36,505</td>
</tr>
<tr>
<td><strong>Total cost ($)</strong></td>
<td>56,270</td>
<td>43,641</td>
<td>63,204</td>
</tr>
<tr>
<td><strong>Incremental cost effectiveness ratio ($)</strong></td>
<td>41,384</td>
<td>-1,959</td>
<td>51,889</td>
</tr>
</tbody>
</table>
Leading Causes of Death in the US, 2001

Causes of Deaths

Heart Disease
Malignant Neoplasms
Cerebrovascular
Chronic Lower Resp. Disease
Influenza & Pneumonia
Diabetes Mellitus
Alzheimer's disease
Nephritis
Unintentional injury
Septicemia
All Others

% of All Deaths

Long-Term Complications of Diabetes

- Retinopathy
- Cataracts
- Glaucoma
- Microangiopathy
- Cerebral Vascular Infarcts
- Hemorrhage
- Coronary Heart Disease
- Myocardial Infarction
- Nephropathy
- Peripheral Vascular Disease
- Peripheral Neuropathy
- Gangrene
- Infections
- Amputations

Adapted from: Robbins Pathologic Basis of Disease. 1999
## Complications of Diabetes

<table>
<thead>
<tr>
<th>Complications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular Disease</strong></td>
<td>Leading cause of diabetes related deaths</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>Risk is increased by two to four times</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>97% have lipid abnormalities contributing to higher rates of cardiovascular disease</td>
</tr>
<tr>
<td><strong>High Blood Pressure</strong></td>
<td>Incidence is 73%</td>
</tr>
<tr>
<td><strong>Blindness</strong></td>
<td>Retinopathy is the leading cause of new blindness in adults aged 20-74 years</td>
</tr>
<tr>
<td><strong>Kidney Disease</strong></td>
<td>Nephropathy is the leading cause of end stage renal disease (44% of new cases)</td>
</tr>
<tr>
<td><strong>Nervous System Disease</strong></td>
<td>60% to 70% have mild to severe form of damage</td>
</tr>
<tr>
<td><strong>Amputations and Peripheral Neuropathy</strong></td>
<td>Leading nontraumatic cause of lower limb amputations and foot ulcerations</td>
</tr>
<tr>
<td><strong>Acute-Life Threatening Events</strong></td>
<td>Diabetic ketoacidosis, hyperosmolar nonketonic coma, more susceptible to infections (e.g. pneumonia and influenza)</td>
</tr>
</tbody>
</table>

Microvascular Complications

Hyperglycemia

Eye
- Retinopathy
- Cataract
- Glaucoma

Kidney
- Nephropathy
  - Microalbuminuria
  - Gross albuminuria
- Kidney failure

Nerves
- Neuropathy
  - Peripheral
  - Autonomic
- Amputation

Death and/or disability

Eye

Kidney

Nerves
Macrovascular Complications

**Metabolic injury to large vessels**

- **Heart**
  - Coronary artery disease
    - Acute coronary syndrome (e.g., MI)
    - CHF

- **Brain**
  - Cerebrovascular disease
    - TIA
    - CVA
    - Cognitive impairment

- **Extremities**
  - Peripheral vascular disease
    - Ulceration
    - Gangrene
    - Amputation
Questions?