TYPE 2 DIABETES MELLITUS: NEW HOPE FOR PREVENTION

Robert Dobbins, M.D. Ph.D.
Learning Objectives

- Recognize current trends in the prevalence of type 2 diabetes.
- Learn differences between type 1 and type 2 diabetes.
- List risk factors for type 2 diabetes.
- Understand how type 2 diabetes can be prevented or delayed.
- Introduce the concept of pre-diabetes.
Definition

Diabetes mellitus: A chronic disorder characterized by a deficiency of insulin secretion and/or insulin effect, which causes hyperglycemia, disturbances of carbohydrate, fat and protein metabolism, and a constellation of chronic complications.
### Diagnostic Criteria

<table>
<thead>
<tr>
<th></th>
<th>Fasting Glucose</th>
<th>Random</th>
<th>OGTT (2 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;110 mg/dl (5.5 mM)</td>
<td>&lt;140 mg/dl (7.7 mM)</td>
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<tr>
<td>IFG/IGT</td>
<td>111-125 mg/dl</td>
<td></td>
<td>140-200 mg/dl</td>
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<tr>
<td>Diabetes</td>
<td>≥126 mg/dl (7.0 mM)</td>
<td>&gt;200 mg/dl (11.1 mM)</td>
<td>&gt;200 mg/dl (11.1 mM)</td>
</tr>
</tbody>
</table>

*Confirmation on a second day by any of the above methods*
Two Flavors of Diabetes

Type 1

Type 2
Features of Type 1 Diabetes

- 80% occur before age 20
- May occur at any age
- Insulin deficient
  - autoimmune pathogenesis, HLA linked
  - less commonly non-immune mediated
- Ketosis prone
- Normal insulin sensitivity
Features of Type 2 Diabetes

- Most common after age 40
- Abdominal obesity present in 90%
- Insulin resistance/hyperinsulinemia
- Ketosis resistant
- Hypertension common
- High VLDL, low HDL cholesterol
- Accelerated atherosclerosis
- High in risk in many ethnic groups
Prevalence of Diagnosed Diabetes Mellitus

Patients with Diabetes (millions)

- 1960
- 1970
- 1980
- 1990
- 2000

0
5
10
15
20

Graph showing the increase in patients with diabetes mellitus from 1960 to 2000.
DM 10.2 million
Undiagnosed 5.4 million
IGT / Pre-Diabetes 13.4 million
At-Risk 40 million

Harris et al., Diabetes Care, 1998
Risk Factors for Type 2 Diabetes

- Age > 40
- Family history of diabetes
- Ethnicity
- Obesity; abdominal fat distribution
- GDM, or infant > 9 lbs
- Hypertension, hyperlipidemia
- Previous Impaired Glucose Tolerance
# Body Mass Index

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<th>Height</th>
<th>Weight</th>
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<tbody>
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<table>
<thead>
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<th>Height</th>
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<td>245</td>
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<td>250</td>
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- Body Mass Index (BMI) is a measure of body fat based on height and weight that applies to adult men and women.
- It is calculated using the formula: BMI = weight (kg) / height^2 (m^2).
- A BMI of 18.5 to 24.9 is considered healthy.
- A BMI of 25 to 29.9 is considered overweight.
- A BMI of 30 or higher is considered obese.
Correlation BMI and Fat Mass

\[ r = 0.956 \]

\[ y = 15.5 + 1.28x \]
Prevalence of Type 2 DM by Body Mass Index

% with Type 2 DM

BMI

<25 25-30 30-35 >35
Age 20-54

<25 25-30 30-35 >35
Age 55-74

<25 25-30 30-35 >35
Age 20-54

<25 25-30 30-35 >35
Age 55-74
Increasing Prevalence of Obesity in the United States

Mokdad et al., JAMA, 2001
Increasing Prevalence of Type 2 DM in the United States

5.1% = 10.2 million people
7.3% = 15 million people

Mokdad et al., JAMA, 2001
Risk Factors for Type 2 Diabetes

Percent of Nondiabetic Individuals

Number of Risk Factors
Microvascular Complications

- **Diabetic retinopathy**
  - background retinopathy
  - macular edema
  - proliferative retinopathy

- **Diabetic nephropathy**

- **Diabetic neuropathy**
  - distal symmetrical polyneuropathy
  - mononeuropathy (peripheral, cranial nerves)
  - autonomic neuropathy
Diabetic Retinopathy
Macrovascular Complications

Complications
- Coronary Heart Disease
- Cerebrovascular Disease
- Peripheral Vascular Disease

Risk Factors
- Dyslipidemia
- Hypertension
- Smoking
- Family history
- Hyperglycemia
Complications of Diabetes
Magnitude of the Problem

- Diabetic retinopathy: most common cause of blindness before age 65
- Nephropathy: most common cause of ESRD
- Neuropathy: most common cause of non-traumatic amputations
- 2-3 fold increase in cardiovascular disease
Mortality Due to Diabetes Mellitus is Steadily Increasing
Prevention of Diabetic Complications

- Weight reduction
- Exercise
- Control glycemia
- Improve lipid profile
- Smoking cessation
- Treat Hypertension
- Daily aspirin therapy
Any Diabetes Related Endpoint (cumulative)

1401 of 3867 patients (36%)

- Conventional (1138)
- Intensive (2729)

Risk reduction 12%
(95% CI: 1% to 21%)

p=0.029
Any Diabetes Related Endpoint (cumulative )

1401 of 3867 patients (36%)

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- Intensive (2729)

Risk reduction 12% (95% CI: 1% to 21%)
p=0.029

Diabetes Prevention

Diabetes Treatment
Prevention is the Key
Come and get it!
Exercise
Every Little Bit Helps
Prevention of Type 2 Diabetes
Finnish Diabetes Prevention Study Group

- 522 subjects
- 2:1 female:male ratio
- Age - 40-65 years
- Weight - BMI > 25
- Impaired glucose tolerance with plasma glucose of 140-200 mg/dl 2h after ingesting 75 gm of oral glucose
- Exclusions - diabetes, chronic illness, psychological or physical disabilities

Tuomilehto et al., NEJM, 2001
Design of Interventions
Finnish Diabetes Prevention Study Group

- Randomized to two study groups
- Control Group
  - 2-page leaflet on diet and exercise
  - Nutritionist reviewed a 3-day food diary
- Intervention Group
  - Individualized, detailed diet/exercise advice
  - Nutrition appointments every 2-3 months
  - 3-day food diary completed every 3 months
  - Supervised, progressive, individually-tailored physical training sessions

Tuomilehto et al., NEJM, 2001
Success Achieving Treatment Goals
Finnish Diabetes Prevention Study Group

<table>
<thead>
<tr>
<th>Goal of Intervention</th>
<th>Intervention Group</th>
<th>Control Group</th>
</tr>
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<tbody>
<tr>
<td>Weight Reduction (&gt;5% of body weight)</td>
<td>43</td>
<td>13</td>
</tr>
<tr>
<td>Fat Intake (&lt;30% of energy intake)</td>
<td>47</td>
<td>26</td>
</tr>
<tr>
<td>Saturated Fat Intake (&lt;10% of energy intake)</td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td>Fiber Intake (&gt;15 g / 1000 kcal)</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>Exercise (&gt;4 hours / week)</td>
<td>86</td>
<td>71</td>
</tr>
</tbody>
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Tuomilehto et al., NEJM, 2001
Prevention of Type 2 Diabetes

Finnish Diabetes Prevention Study Group

Tuomilehto et al., NEJM, 2001
Prevention of Type 2 Diabetes
Finnish Diabetes Prevention Study Group

Tuomilehto et al., NEJM, 2001
Prevention of Type 2 Diabetes
Diabetes Prevention Program Research Group

- 3234 subjects
- 2:1 female:male ratio
- Age - >25 years
- Weight - BMI > 24
- Impaired glucose tolerance on an OGTT or impaired fasting glucose
- Exclusions - diabetes, chronic illness, taking medications altering insulin sensitivity

DPPRG, NEJM, 2002
Design of Interventions

Diabetes Prevention Program Research Group

- Randomized to three study groups
- Control Group
  - standard lifestyle recommendations with an annual dietitian visit and placebo medication
- Drug Treatment Group
  - standard lifestyle recommendations
  - Metformin or Rosiglitazone
- Intensive Lifestyle Modification Group
  - diet/exercise/behavior modification curriculum
  - monthly case-manager visits and group sessions

DPPRG, NEJM, 2002
Success Achieving Treatment Goals
Diabetes Prevention Program Research Group

DPPRG, NEJM, 2002
Prevention of Type 2 Diabetes
Diabetes Prevention Program Research Group

DPPRG, NEJM, 2002
Prevention of Type 2 Diabetes
Summation of Clinical Trials

■ Goals
- Lose weight - 10-20 pounds is enough
- Increase activity to walking 30 min/day or going to a gym 3 days/week

■ Results
- One case of diabetes is prevented for every 7-8 people who participate in an intensive lifestyle intervention program for 3 years
- Achieving all diet and exercise goals virtually stalls the progression to diabetes
Pre-diabetes: A serious, treatable medical condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Without intervention, nearly one-half of these individuals progress to clinical diabetes in five years.

For info see http://www.diabetes.org/main/info/pre-diabetes.jsp
Type 2 Diabetes Screening Program
Conditions that must be met

- Disease represents a significant burden
- Natural history of the disease is understood
- The disease can be recognized at a preclinical (asymptomatic) stage
- Sensitive and specific screening tests are available
- Early detection and treatment improve outcomes
- Testing and treatment are cost-effective
- Systematic procedures can be adopted
Socioeconomic Costs of Diabetes Mellitus

- Diabetes costs the U.S. economy $105 billion annually.
- One out of every ten U.S. healthcare dollars is spent for diabetes.
- One of four Medicare dollars pays for care in individuals suffering from diabetes.
Actual Therapy

Years from randomisation

Conventional Policy
accept < 15 mmol/L

Intensive Policy
aim for < 6 mmol/L

proportion of patients

0 20 40 60 80 100

diet alone

additional non-intensive pharmacological therapy

intensive pharmacological therapy
Pathophysiology-based Therapy for Type 2 Diabetes

- **Defect in insulin sensitivity**
  - exercise
  - weight reduction
  - thiazolidinediones
  - metformin

- **Defect in insulin secretion**
  - sulfonylureas (mild defect)
  - insulin (severe defect)
Pathophysiology-based Therapy for Type 2 Diabetes

- **Increased hepatic glucose output**
  - metformin > thiazolidinediiones
  - insulin (sulfonylurea)

- **Carbohydrate absorption (post-prandial hyperglycemia)**
  - acarbose
Prevention of Diabetic Complications

- Optimize glycemic control
- Control hypertension < 135/85 mm Hg
- Screen at diagnosis, then annually for microalbuminuria
- Use angiotensin converting enzyme inhibitor when microalbuminuria is reproducible
Prevention of Diabetic Complications

- Ophthalmoscopic exam of the eye every 3-6 months with a formal exam annually
- Determine the fasting lipid profile each year and treat to LDL <100
- Prescribe 325 mg aspirin to be taken daily
Diagnostic Criteria for Diabetes

- Symptoms of diabetes +
  casual glucose $> 200$ mg/dl (11.1 mmol/l)
- FPG $\geq 126$ mg/dl (7.0 mmol/l)
- 2h PG $> 200$ mg/dl (11.1 mmol/l) during OGTT

*Confirmation on a second day by any of the above methods*