Week 5, Lecture 8

Landmark Studies in Diabetes
Landmark studies

- DCCT – Diabetes Control and Complications Trial
  In type 1 diabetes New England Journal of Medicine, 329(14), September 30, 1993.

- UKPDS – United Kingdom Prospective Diabetes Study

- Among apparently healthy-glucose intolerance/high risk
- The Da Qing IGT and Diabetes Study
- Finnish Diabetes Prevention Study

- The Diabetes Prevention Program
THE GLUCOSE HYPOTHESIS

TREATMENT THAT NORMALIZES GLUCOSE LEVELS WILL PREVENT OR DELAY THE LONG-TERM COMPLICATIONS OF DIABETES
DCCT
Retinopathy Results

Primary Prevention

<table>
<thead>
<tr>
<th>Year of Study</th>
<th>Conventional</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>375</td>
<td>342</td>
</tr>
<tr>
<td>1</td>
<td>220</td>
<td>202</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>

Secondary Intervention

<table>
<thead>
<tr>
<th>Year of Study</th>
<th>Conventional</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>348</td>
<td>354</td>
</tr>
<tr>
<td>1</td>
<td>324</td>
<td>335</td>
</tr>
<tr>
<td>2</td>
<td>128</td>
<td>136</td>
</tr>
<tr>
<td>3</td>
<td>79</td>
<td>93</td>
</tr>
</tbody>
</table>

P<0.001

DCCT Research Group
NEJM 1993;342:381
The Da Qing IGT and Diabetes Study

• 577 with IGT.
• Subjects were randomized by clinic into a clinical trial, either to a control group or to one of three active treatment groups: diet only, exercise only, or diet plus exercise.
• 6 years of follow-up

Pan 1997 Diabetes Care
Finnish Diabetes Prevention Study

• 522 middle-aged, overweight subjects (172 men and 350 women; mean age, 55 years.
• Mean BMI = 31.
• All with impaired glucose tolerance.
• Randomized to intervention and control.
• Average follow-up 3.2 yrs.

Tuomilehto 2001 NEJM
Finnish Diabetes Prevention Study
Lifestyle Intervention Strategies

- Weight loss
- Reduce total/saturated fats, and use vegetable oils rich in mono
- Increase in fiber intake
- Increase intakes of whole-grain products, vegetables, fruits, low-fat milk and meat products, soft margarines
- Moderate exercise for at least 30 minutes per day

Tuomilehto 2001 NEJM
<table>
<thead>
<tr>
<th>Goal</th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction &gt;5%</td>
<td>43</td>
<td>13</td>
<td>0.001</td>
</tr>
<tr>
<td>Fat intake &lt;30% of energy intake</td>
<td>47</td>
<td>26</td>
<td>0.001</td>
</tr>
<tr>
<td>Saturated-fat intake &lt;10% of energy intake</td>
<td>26</td>
<td>11</td>
<td>0.001</td>
</tr>
<tr>
<td>Fiber intake ≥15 g/1000 kcal</td>
<td>25</td>
<td>12</td>
<td>0.001</td>
</tr>
<tr>
<td>Exercise ≥4 hr/wk‡</td>
<td>86</td>
<td>71</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Nutrient intakes were calculated from three-day food records.

† P values were determined by the chi-square test for the difference between the groups.

‡ Exercise frequency was reported by the subjects who chose one of the four categories described in Table 3. The goal identified here was a frequency in category 2 or higher.
The Diabetes Prevention Program
A Randomized Clinical Trial
to Prevent Type 2 Diabetes
in Persons at High Risk

The DPP Research Group
Institutions and Investigators

Pennington Biomedical Research Center

George Bray

U. of Chicago Hospitals

David Ehrmann

Thomas Jefferson U.

Pamela Watson

U. of Miami School of Medicine

Ronald Goldberg

U. of Texas Health Science Center

Steven Haffner

U. of Colorado Health Sciences Center

Richard Hamman

Joslin Diabetes Center

Edward Horton

U. of Washington

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U. of Tennessee

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Medstar Clinical Research Center
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Washington U. School of Medicine
Neil White

Johns Hopkins U
Christopher Saudek

U. of New Mexico School of Medicine
David Schade
Institutions and Investigators

Albert Einstein College of Medicine
U. of Pittsburgh Medical Center
U. of Hawaii
Southwest American Indian Center for Diabetes Prevention
U. of California Los Angeles
George Washington University (Coordinating Center)

Harry Shamoon
Rena Wing
Richard Arakaki
William Knowler
Mohammed Saad
Sarah Fowler
<table>
<thead>
<tr>
<th>Central Resources</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle core</td>
<td>Univ. Pittsburgh</td>
</tr>
<tr>
<td>Medication resource group</td>
<td>Albert Einstein</td>
</tr>
<tr>
<td>Central biochemistry lab</td>
<td>Univ. Washington</td>
</tr>
<tr>
<td>ECG reading center</td>
<td>Wake Forest Univ.</td>
</tr>
<tr>
<td>Carotid US reading center</td>
<td>New England Medical Center</td>
</tr>
<tr>
<td>CT scan reading center</td>
<td>Univ. of Colorado Health Sciences Center</td>
</tr>
<tr>
<td>Nutrition coding center</td>
<td>Univ. South Carolina</td>
</tr>
<tr>
<td>Quality of well being center</td>
<td>Univ. California San Diego</td>
</tr>
<tr>
<td>Drug distribution center</td>
<td>McKesson Biosciences</td>
</tr>
<tr>
<td>Community outreach/media</td>
<td>Matthews Media Group</td>
</tr>
<tr>
<td>Clinical monitoring group</td>
<td>ACRN</td>
</tr>
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</table>
Sponsors

• National Institute of Diabetes & Digestive & Kidney Diseases
• Other NIH Institutes, Offices
  National Center on Minority Health and Health Disparities
  National Institute of Child Health and Human Development
  National Institute on Aging
  National Center for Research Resources, GCRC Program
  Office of Research on Women’s Health
• Other Federal Agencies
  Indian Health Service
  Centers for Disease Control and Prevention
• American Diabetes Association
Sponsors

• Industrial grant support
  Bristol-Myers Squibb
  Warner-Lambert.

• Additional Support
  LifeScan, Inc
  Health O Meter
  Hoechst Marion Roussel, Inc.
  Merck-Medco Managed Care, Inc
  Merck & Co.
  Nike Sports Marketing
  Slim Fast Foods Co.
  Quaker Oats Co.
Feasibility of Preventing Type 2 Diabetes

- There is a long period of glucose intolerance that precedes the development of diabetes
- Screening tests can identify persons at high risk
- There are safe, potentially effective interventions that can address modifiable risk factors
Modifiable Risk Factors for Type 2 Diabetes

- Obesity
- Body fat distribution
- Physical inactivity
- Elevated fasting and 2 hr glucose levels
DPP Primary Goal

• To prevent or delay the development of type 2 diabetes in persons with impaired glucose tolerance (IGT)
DPP Secondary Goals

- Reduce cardiovascular disease (CVD) events
- Reduce CVD risk factors
- Reduce atherosclerosis
Study Design

- 3-group randomized clinical trial
- 27 clinical sites
- Standardized across clinics:
  - Common protocol and procedures manual
  - Staff training
  - Data quality control program
Diabetes Prevention Program Clinics

Map of the United States showing the locations of Diabetes Prevention Program Clinics.
Eligibility Criteria

- Age $\geq 25$ years
- Plasma glucose
  - 2 hour glucose 140-199 mg/dl (7.8- <11.1 mmol/L) and
  - Fasting glucose 95-125 mg/dl (5.3- <7.0 mmol/L)
- Body mass index $\geq 24$ kg/m$^2$
- All ethnic groups
  - goal of up to 50% from high risk populations
Screening and Recruitment

Number of participants

- **Step 1 screening**: 158,177
- **Step 2 OGTT**: 30,985
- **Step 3 start run-in**: 4,719
- **Step 3 end run-in**: 4,080
- **Step 4 randomization**: 3,819*

*3,234 in 3 arm study (585 in troglitazone arm)

The DPP Research Group, *Controlled Clin Trials*
Study Interventions

Eligible participants

Randomized

Standard lifestyle recommendations

- Intensive Lifestyle (n = 1079)
- Metformin (n = 1073)
- Placebo (n = 1082)
Primary Outcome: Diabetes

- Annual fasting plasma glucose (FPG) and 75 gm Oral Glucose Tolerance Test
  - FPG > 126 mg/dL (7.0 mmol/L) or
  - 2-hr > 200 mg/dL (11.0 mmol/L),
  - Either confirmed with repeat test

- Semi-annual FPG
  - > 126 mg/dL, confirmed
Lifestyle Intervention

An intensive program with the following specific goals:

• > 7% loss of body weight and maintenance of weight loss
  – Dietary fat goal -- <25% of calories from fat
  – Calorie intake goal -- 1200-1800 kcal/day

• > 150 minutes per week of physical activity
Lifestyle Intervention Structure

• 16 session core curriculum (over 24 weeks)
• Long-term maintenance program
• Supervised by a case manager
• Access to lifestyle support staff
  – Dietitian
  – Behavior counselor
  – Exercise specialist
The Core Curriculum

• 16 session course conducted over 24 weeks

• Education and training in diet and exercise methods and behavior modification skills

• Emphasis on:
  – Self monitoring techniques
  – Problem solving
  – Individualizing programs
  – Self esteem, empowerment, and social support
  – Frequent contact with case manager and DPP support staff
Post Core Program

• Self-monitoring and other behavioral strategies

• Monthly visits
  – Must be seen in person at least every two months

• Supervised exercise sessions offered

• Periodic group classes and motivational campaigns

• Tool box strategies
  – Provide exercise videotapes, pedometers
  – Enroll in health club or cooking class
DPP Study Interventions: Criteria for Drug Treatment

- Efficacy
- Safety
- Tolerability - minimal side effects
- Acceptability - dose frequency
Interventions: Medications

Metformin- 850 mg per day escalating after 4 weeks to 850 mg twice per day

Placebo- Metformin placebo adjusted in parallel with active drugs
DPP Population

Caucasian
1768 (55%)

African American
645 (20%)

Hispanic American
508 (16%)

Asian/Pacific Islander
142 (4%)

American Indian
171 (5%)

The DPP Research Group, *Diabetes Care* 23:1619-29, 2000
The DPP Research Group, *Diabetes Care* 23:1619-29, 2000
Retention and Participation

- 99.6% of the study cohort alive at study end
- 93% completed study
- 93% of annual visits completed
- Average follow-up 2.8 years (range 1.8 - 4.6)
Lifestyle Intervention: Physical Activity Results

- 74% of volunteers assigned to intensive lifestyle achieved the study goal of \( \geq 150 \) minutes of activity per week at 24 weeks.

The DPP Research Group, *NEJM* 346:393-403, 2002
Mean Change in Leisure Physical Activity

The DPP Research Group, *NEJM* 346:393-403, 2002
The DPP Research Group, *NEJM* 346:393-403, 2002
The DPP Research Group, *NEJM* 346:393-403, 2002
Incidence of Diabetes

Placebo (n=1082)
Metformin (n=1073, p<0.001 vs. Placebo)
Lifestyle (n=1079, p<0.001 vs. Metformin, p<0.001 vs. Placebo)

Risk reduction
31% by metformin
58% by lifestyle

The DPP Research Group, *NEJM* 346:393-403, 2002
Effect of Treatment on Incidence of Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Metformin</th>
<th>Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong> of diabetes</td>
<td>11.0%</td>
<td>7.8%</td>
<td>4.8%</td>
</tr>
<tr>
<td>(percent per year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reduction</strong> in incidence</td>
<td>----</td>
<td>31%</td>
<td>58%</td>
</tr>
<tr>
<td>compared with placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number needed to treat</strong></td>
<td>----</td>
<td>13.9</td>
<td>6.9</td>
</tr>
<tr>
<td>to prevent 1 case in 3 years</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The DPP Research Group, *NEJM* 346:393-403, 2002
The DPP Research Group, *NEJM* 346:393-403, 2002
Mean Change in HbA$_{1c}$

The DPP Research Group, *NEJM* 346:393-403, 2002
Diabetes Incidence Rates by Sex

The DPP Research Group, *NEJM* 346:393-403, 2002
Diabetes Incidence Rates by Age

The DPP Research Group, *NEJM* 346:393-403, 2002
Diabetes Incidence Rates by Ethnicity

- Caucasian (n=1768)
- African American (n=645)
- Hispanic (n=508)
- American Indian (n=171)
- Asian (n=142)

Cases/100 person-yr

Lifestyle • Metformin • Placebo

The DPP Research Group, *NEJM* 346:393-403, 2002
Diabetes Incidence Rates by BMI

Body Mass Index (kg/m²)

- 24 - < 30 (n=1045)
- 30 - < 35 (n=995)
- ≥ 35 (n=1194)

Cases/100 person-yr

Lifestyle ▲ Metformin ■ Placebo ▲

The DPP Research Group, NEJM 346:393-403, 2002
Diabetes Incidence Rates by Fasting Glucose

The DPP Research Group, *NEJM* 346:393-403, 2002
Diabetes Incidence Rates by 2-hr Glucose

Cases/100 person-yr

Lifestyle  Metformin  Placebo

The DPP Research Group, *NEJM* 346:393-403, 2002
Normal Glucose at Annual Visits

Normal Fasting Glucose

- Lifestyle
- Metformin
- Placebo

- Years from Randomization

Normal 2-hour Glucose

- Years from Randomization

The DPP Research Group, *NEJM* 346:393-403, 2002
Consistency of Treatment Effects

- Lifestyle intervention was beneficial regardless of ethnicity, age, BMI, or sex
- The efficacy of lifestyle relative to metformin was greater in older persons and in those with lower BMI
- The efficacy of metformin relative to placebo was greater in those with higher baseline fasting glucose and BMI
Summary-1

- Both interventions were well accepted and safe
- Intensive lifestyle resulted in weight loss and increased activity level for the duration of the study
Summary-2

• Both interventions were effective in men and women and all ethnic groups

• Intensive lifestyle intervention was effective in all age groups, including those $> 60$ years of age
Summary-3

• Intensive lifestyle intervention reduced the development of diabetes by 58%

• Metformin reduced the development of diabetes by 31%

• Lifestyle was more effective than metformin