30 YEARS AND COUNTING
THE LONG-TERM EXPERIENCE OF THE
DIABETES CONTROL AND COMPLICATIONS TRIAL (DCCT)
1982-1993
AND
EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS (EDIC)
1994-………..

OBJECTIVES
• BE FAMILIAR WITH THE LANDMARK DIABETES CONTROL AND COMPLICATION TRIAL (DCCT)
AND EDIC, THE LONG-TERM FOLLOW-UP PROGRAM.
• DESCRIBE THE MAJOR OUTCOMES OF THE DCCT AND THE IMPLICATIONS FOR THE CLINICAL
CARE OF INDIVIDUALS WITH TYPE 1 DIABETES.
• BE AWARE OF THE ON-GOING BENEFITS FOR THE PARTICIPANTS IN THE “INTENSIVE CONTROL
ARM” 20 YEARS AFTER THE DCCT ENDED.
• KNOW AND UNDERSTAND THE CONCEPT OF “METABOLIC MEMORY” (GOOD CONTROL FOR
ANY PERIOD OF TIME HAS LASTING POSITIVE BENEFITS).

DISCLOSURES
DANIEL ESTEN HALE, MD, HAS NO RELATIONSHIPS WITH COMMERCIAL
COMPANIES TO DISCLOSE RELEVANT TO THIS PRESENTATION

COSTS OF DIABETES (2012)
• DIRECT COSTS OF DIABETES $200 BILLION/YEAR
  ~ 2/3 OF THE COST OF WORLD WAR 2 (IN 1945 $)
  ~ 1/5 OF THE COST OF WORLD WAR 2 (IF USING 2012$)
  ~ 1/3 OF THE DEPARTMENT OF 2012 DEFENSE BUDGET
  ~ TOTAL FEDERAL BUDGET FOR PUBLIC SCHOOL EDUCATION
  ~ 2X ANNUAL FEDERAL BUDGETS FOR THE AFFORDABLE CARE ACT
  ~ 6X THE ENTIRE NATIONAL INSTITUTES OF HEALTH BUDGET
• INDIRECT COSTS ~$400 BILLION (MISSING DAYS OF WORK, DECREASED PRODUCTIVITY, ETC.)

“PEOPLE COSTS”
DEATHS DUE TO DIABETES ~ 200,000/YEAR IN THE US
• 4X THE NUMBER OF US SOLDIERS WHO WERE KILLED IN VIETNAM
• 2X THE NUMBER OF US SOLDIERS WHO WERE KILLED IN WW I
• ½ THE NUMBER OF US SOLDIERS WHO WERE KILLED IN WW II

COMPlications just 1 of many
• RETINOPATHY - 600,000
• 2X THE NUMBER OF US SOLDIERS INJURED IN VIETNAM
• 3X THE NUMBER OF US SOLDIERS INJURED IN WW I
• THE TOTAL NUMBER OF US SOLDIERS INJURED IN WW II

A FOCUS ON TYPE 1 DIABETES
• 1.25M AMERICANS ARE LIVING WITH T1D
• 200,000 YOUTH (LESS THAN 20 YEARS OLD)
• 1.1 MILLION ADULTS (20 YEARS OLD AND OLDER)
• 40,000 PEOPLE ARE DIAGNOSED EACH YEAR IN THE U.S.
• 5 MILLION PEOPLE IN THE U.S. ARE EXPECTED TO HAVE T1D BY 2050
• 6% OF AMERICANS HAVE T1D
• BETWEEN 2001 AND 2009 THERE WAS A 21% INCREASE IN THE PREVALENCE OF T1D IN PEOPLE UNDER AGE
20 IN THE US AND THIS IS OCCURRING INTERNATIONALLY AS WELL
• DESPITE MAJOR ADVANCES IN CARE, T1D IS ASSOCIATED WITH AN ESTIMATED LOSS OF LIFE EXPECTANCY OF
UP TO 13 YEARS5
COMPETING IDEAS

CONCEPT 1  GLUCOSE INDEPENDENT COMPLICATIONS
"EAT, DRINK AND BE MERRY FOR TOMORROW WE WILL DIE"
- EARLY PHASE – HYPERGLYCEMIA
- LATE PHASE – ALL OF THE SYSTEMIC COMPLICATIONS

CONCEPT 2  GLUCOSE DEPENDENT COMPLICATIONS
- "IT IS ALL ABOUT THE SUGAR"
- CHRONIC HYPERGLYCEMIA LEADS TO ALL (OR ALMOST ALL) OF THE COMPLICATIONS

THE PROBLEM

- NO WAY TO ADEQUATELY MEASURE GLUCOSE ON A FREQUENT BASIS AT HOME
- NO WAY TO OPTIMIZE GLYCEMIC CONTROL IN THE HOME SETTING
- NO WAY TO ASSESS GLYCEMIC CONTROL OBJECTIVELY
- FEW STANDARDS FOR ASSESSING KEY OUTCOMES, ESPECIALLY THE EARLIEST CHANGES

A HISTORY LESSON OF DIABETES MANAGEMENT

A compelling need to have a means to simply, accurately and quickly to measure blood glucose at home

A HISTORY OF HGB A1C

<table>
<thead>
<tr>
<th>YEAR</th>
<th>EVENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1958</td>
<td>Hgb A1c separated from other forms of hemoglobin</td>
</tr>
<tr>
<td>1968</td>
<td>Characterized as a glycoprotein</td>
</tr>
<tr>
<td>1969</td>
<td>Increase in diabetes first described</td>
</tr>
<tr>
<td>1975</td>
<td>Reactions leading to its formation were characterized</td>
</tr>
<tr>
<td>1976</td>
<td>The potential use for assessing glycemic control proposed</td>
</tr>
<tr>
<td>1977-1980</td>
<td>Validation of Hgb A1c as objective assessment of glycemic control</td>
</tr>
<tr>
<td>1992</td>
<td>DCA 2000 Hgb A1c machine introduced into clinical use</td>
</tr>
</tbody>
</table>
Thus by ~1980

- Reliable tools to assess and monitor glucose at home
- Home glucose monitors
- Demonstration that multiple daily injections or pumps could substantially improve glycemic control
- Objective tool (HbA1c) to assess glycemic control and agreement on its validity
- Validated tools to assess many of the known complications
  - Questionnaires
  - Fundal photography
  - Provocative testing
  - Assays of metabolites in blood and urine

The "Glucose" Hypothesis

- Achieving near normal glycemic control can ameliorate the long-term complications of diabetes
- Compared to conventional therapy, does an intensive treatment program designed to achieve glycemic control as close to the nondiabetic ranges as safely possible prevent or delay the appearance of early background retinopathy (primary prevention) and prevent or delay the progression to more advanced forms of retinopathy (secondary intervention)

Inclusion Criteria

- Ages 13-39 years with type 1 diabetes based on clinical criteria and with fasting C-peptide concentrations of < 0.2
- General good health with no cardiovascular disease, no hypertension, dyslipidemia, or neuropathy
- Primary prevention
  - Duration of diabetes: from 1-5 years
  - No evidence of retinopathy on fundus photography
  - Albumin excretion < 30 mg/24 hours

Secondary intervention

- Duration of diabetes from 1-15 years
- At Least 1 microaneurysm in each eye
- Albumin excretion < 200

Participants – DCCT and EDIC

- 1441 participants at DCCT start
- 1422 participants at DCCT end (98.6% of the original cohort)
- 1284 participants at EDIC year 18 (year 28 since start)
- 89.1% of the original cohort
- 93% of those still living

- Groups matched for gender, age, etc
- Slightly more males than females
- Age at DCCT start 27 ± 7 years
- Duration of diabetes at DCCT start ~5 years
- ~50% primary prevention and ~50% secondary intervention
- ~18% cigarette smokers

Characteristics at start

- BMI: 23 (<2% with BMI > 30)
- Systolic blood pressure: 114 ± 11
- Diastolic blood pressure: 73 ± 8
- Retinopathy: ~50% (secondary intervention group)
- Renal function:
  - Albumin excretion < 30: ~90%
  - Albumin excretion 30-<300: ~10%
- Neuropathy: ~6%

Additional characteristics at start

- HbA1C: 9.1%

- Lipids
  - Total cholesterol: 175 mg/dL
  - HDL cholesterol: 50 mg/dL
  - LDL cholesterol: 110 mg/dL
  - Triglycerides: 80 mg/dL
**PROTOCOL - DCCT**

- **GOAL** – ABSENCE OF FREQUENT OR SEVERE HYPOGLYCEMIA
- **HGB A1C < 2 SD ABOVE THE MEAN VALUE OF 6.05%**
- **MEASURED MONTHLY AT AID ADJUSTMENT IN INTENSIVE (INT) GROUP**
- **MEASURED QUARTERLY AS A PROCESS OUTCOME FOR BOTH CONTROL (CON) AND INT GROUPS**

**INTENSIVE GROUP**
- 4 OR MORE GLUCOSE CHECKS PER DAY, INCLUDING 3AM AT LEAST ONCE EACH WEEK
- SPECIFIC GOALS FOR PREPRANDIAL AND POSTPRANDIAL LEVELS
- 3 OR MORE INJECTIONS PER DAY (MULTIPLE DAILY INJECTIONS, MDI) OR PUMP (R, NPH, LENTE, ULTRA)

**CONTROL GROUP**
- 1 OR 2 DAILY DOSES OF INSULIN
- DAILY URINE OR SELF-MONITORED BLOOD GLUCOSE (SMBG)
- IF HGB A1C >13.5% THE REGIMEN WAS ADJUSTED

**DCCT MEASURES**

- **RETINOPATHY** - 7 FIELD STEREOSCOPIC AND FUNDUS PHOTOGRAPHY 6 MONTHS
- **RENAL FUNCTION** - ALBUMIN EXCRETION AND SERUM CREATININE
- **NEUROPATHY** - HISTORY, EXAMINATION AND NERVE CONDUCTION BASELINE, YEAR 5, STUDY END
- **CARDIOVASCULAR** - HISTORY ANNUAL
- **RISK FACTORS** - HGB A1C 3 MONTHS

**EDIC MEASURES**

- **RETINOPATHY** - 7 FIELD STEREOSCOPIC AND FUNDUS PHOTOGRAPHY ¼ EACH YEAR, ALL IN YEAR 4
- **RENAL FUNCTION** - ALBUMIN EXCRETION AND SERUM CREATININE ALTERNATE YEARS
- **NEUROPATHY** - HISTORY, EXAMINATION AND NERVE CONDUCTION YEAR 13/14
- **CARDIOVASCULAR** - HISTORY ANNUAL
- **RISK FACTORS** - HGB A1C ANNUAL

**ADDITIONAL CHARACTERISTICS AT DCCT END/EDIC START**

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>INT</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>23 (&lt;2% WITH BMI &gt;30)</td>
<td>26.6</td>
</tr>
<tr>
<td>SYSTOLIC BLOOD PRESSURE</td>
<td>114 ± 11</td>
<td>116</td>
</tr>
<tr>
<td>DIASTOLIC BLOOD PRESSURE</td>
<td>73 ± 8</td>
<td>74</td>
</tr>
<tr>
<td>NO RETINOPATHY</td>
<td>~30% (INTERVENTION)</td>
<td>28%</td>
</tr>
<tr>
<td>RETINAL EXCISION</td>
<td>~30%</td>
<td>89%</td>
</tr>
<tr>
<td>ALBUMIN EXCISION</td>
<td>20 – 100</td>
<td>8.8</td>
</tr>
<tr>
<td>NEUROPATHY</td>
<td>~6%</td>
<td>9.3</td>
</tr>
<tr>
<td>HGB A1C</td>
<td>9.1%</td>
<td>7.3%</td>
</tr>
<tr>
<td>TOTAL CHOLESTEROL</td>
<td>175 MG/DL</td>
<td>178</td>
</tr>
<tr>
<td>HDL CHOLESTEROL</td>
<td>50 MG/DL</td>
<td>51</td>
</tr>
<tr>
<td>LDL CHOLESTEROL</td>
<td>110 MG/DL</td>
<td>112</td>
</tr>
<tr>
<td>TRIGLYCERIDES</td>
<td>80 MG/DL</td>
<td>82</td>
</tr>
</tbody>
</table>

**ADDITIONAL CHARACTERISTICS AT DCCT END/EDIC START**

- **BMI**
  - INT: 23 (<2% WITH BMI >30)
  - CON: 26.6, 25.0
- **Systolic Blood Pressure**
  - INT: 114 ± 11
  - CON: 116, 115
- **Diastolic Blood Pressure**
  - INT: 73 ± 8
  - CON: 74, 74
- **No Retinopathy**
  - INT: ~30% (INTERVENTION)
  - CON: 28%, 17%
- **Retinal Excision**
  - INT: ~30%
  - CON: 89%, 82%
- **Albumin Excision**
  - INT: 20 – 100
  - CON: 8.8, 14.0%
- **Neuropathy**
  - INT: ~6%
  - CON: 9.3, 17.5%
- **HGB A1C**
  - INT: 9.1%
  - CON: 7.3%
  - INT: 9.1%
**GLYCEMIC GOALS FOR DCCT**

- 40% reached 6.05% or less at least once during the trial.
- Median quarterly HbA1C was 7.0% in the intensive group vs 9% in the conventional group.
- Less than 3% cross over between the groups in terms of management (with the exclusion of pregnancy where tight control was mandated).
- Once DCCT was completed, the difference in HbA1C between the 2 groups dissipated.

**ADVERSE EFFECTS - HYPOGLYCEMIA**

- Severe Hypoglycemia: 62 events/100 patient years in intervention group (3 fold higher than in control).
- Hypoglycemia with coma or seizures: 16 events/100 patient years in intervention group (3 fold higher than in control).

No apparent adverse effect on rigorously and repeatedly measured cognitive functions in the adolescents or adults, during or after the DCCT.

**ADVERSE EFFECTS - WEIGHT GAIN**

- More individuals with weight gain in the intervention group.
- Mean difference in weight of 4.6 kg.
- Difference disappeared during EDIC.

**OUTCOMES**

- Ongoing monitoring by data safety and monitoring committee showed clear differences and the study was stopped about 1 year earlier than planned.

**% REDUCTION IN COMPLICATIONS FROM INTENSIVE MANAGEMENT**

- 3+Step Devel (Primary)
- 3+Step Progr (Secondary)
- Microalbuminuria
- Macroalbuminuria
- Neuropathy

**CHANGES IN HGB A1C AFTER THE END OF THE DCCT**
DIABETIC NEUROPATHIES

- Peripheral neuropathy, the most common type of diabetic neuropathy, causes pain or loss of feeling in the toes, feet, legs, hands, and arms.
- Autonomic neuropathy causes changes in digestion, bowel and bladder function, sexual response, and perspiration. It can also affect the nerve that serve the heart and control blood pressure, as well as nerves in the lungs and eyes. Autonomic neuropathy can also cause hypoglycemia unawareness.
- Focal neuropathy results in the sudden weakness of one nerve or a group of nerves, causing muscle weakness or pain. Any nerve in the body can be affected.

ASSESSMENT TOOLS

- Diabetic peripheral neuropathy (DPN)
  - Clinical symptoms and signs
  - Vibration perception
  - Michigan neuropathy screening instrument (MNSI)
  - Nerve conduction tests
- Cardiovascular autonomic neuropathy (CAN)
  - R to R variability during deep breathing, Valsava maneuver and postural testing

PREVALENCE OF DPN AND CAN

<table>
<thead>
<tr>
<th></th>
<th>Baseline (%)</th>
<th>DCCT End (%)</th>
<th>EDIC Year13-14 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically evident DPN</td>
<td>INT 16</td>
<td>14*</td>
<td>14*</td>
</tr>
<tr>
<td></td>
<td>CON 8</td>
<td>22</td>
<td>41</td>
</tr>
<tr>
<td>Abnormal Nerve Conduction</td>
<td>INT 31</td>
<td>28*</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>CON 34</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>Confirmed DPN</td>
<td>INT 7</td>
<td>8*</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>CON 5</td>
<td>17</td>
<td>35</td>
</tr>
<tr>
<td>CAN Composite</td>
<td>INT 4</td>
<td>7</td>
<td>37*</td>
</tr>
<tr>
<td></td>
<td>CON 5</td>
<td>10</td>
<td>25</td>
</tr>
</tbody>
</table>

* P < 0.001; ** p < 0.05

CARDIOVASCULAR OUTCOMES
COMPLICATIONS OF TYPE 1 DIABETES

- SHORT TERM
- LONG TERM
- MICROVASCULAR
- MACROVASCULAR

DIABETIC RETINOPATHY

600,000 people with diabetes have retinopathy
~2X the number of US soldiers injured in Vietnam
~3X the number of US soldiers injured in WW I
~the total number of US soldiers injured in WW II

CURRENT RECOMMENDATION

The current recommendation is to monitor for microalbuminuria (diabetic nephropathy).
DIABETIC NEUROPATHY

THE BENEFITS CONTINUE LONG AFTER

PEDIATRIC TYPE 2 DIABETES

CARDIOVASCULAR DISEASE RISK FACTORS

THE BENEFITS CONTINUE LONG AFTER PEDIATRIC TYPE 2 DIABETES