Diabetes, Genetics and the State of Comprehensive Diabetes Care

There, and Back again*

*Bilbo Baggins

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Outline: Diabetes 2011

- Definitions
- Epidemiology
- Lifestyle Modifications
- Key Pharmacologic Agents
- Goals of Therapy
- Insulin
- Combination Therapy
- Thoughts about Compliance/Adherence
Case Presentation

- “When he came to the hospital, he was emaciated, weak and dejected; his thirst was unquenchable; and his skin dry, hard, and harsh to the touch, like rough parchment.”
- J.L. 12/15/22
- wt 15 lb, age 3 yrs
- J.L. after insulin
  2/15/23, wt 29 lb

- Before and after pictures of another 1922 patient, thought too indelicate for lay viewing
Type 1-diabetes: Beta-cells are destroyed by the immune system

Once diabetic – always diabetic

Beta-cells do not come back?
## Comparison of IDDM - Type I - with NIDDM - Type II

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
<th>monogenic diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>usually &lt;30</td>
<td>usually &gt;40*</td>
<td>infancy to adulthood</td>
</tr>
<tr>
<td><strong>Ketosis – Coma</strong></td>
<td>Common</td>
<td>Rare</td>
<td>rare</td>
</tr>
<tr>
<td><strong>Body Weight</strong></td>
<td>Nonobese</td>
<td>Obese 80%</td>
<td>either</td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>0.5%</td>
<td>4-5%</td>
<td>0.1% ?</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>HLA</td>
<td>Non-HLA</td>
<td>monogenic</td>
</tr>
<tr>
<td><strong>Twins</strong></td>
<td>40-50%</td>
<td>95-100%</td>
<td></td>
</tr>
<tr>
<td><strong>Islet Cell Ab</strong></td>
<td>50-85%</td>
<td>&lt;10%</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Insulin</td>
<td>Diet, Pills, Insulin</td>
<td></td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td><em>Frequent</em></td>
<td><em>Frequent</em></td>
<td></td>
</tr>
</tbody>
</table>

=> Type 2 in Children:
Exploding incidence, associated with obesity

=> Type 1 ½; Type 3 ???
MODY

- Monogenic diabetes = maturity onset diabetes of youth
- Heterogeneous disorder
- Non ketotic
- Autosomal dominant
- Autoimmunity absent
- Onset < 25 yo, freq childhood/adolescence
- Primary defect in function of beta cells, in insulin secretion (not insulin action)
- May account for 1-5% cases of diabetes in industrialized countries
- Up to 10% of patients classified as type 1 but without high risk HLA may have MODY

DIABETES: INABILITY TO UTILIZE FUEL

Signs and Symptoms

- Polyphagia
- Polydipsia
- Polyuria
- Wt loss
- Hyperglycemia
- glycosuria
### Diagnosis Guidelines

<table>
<thead>
<tr>
<th>Category</th>
<th>FPG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;110</td>
</tr>
<tr>
<td>Impaired Fasting Glucose* (IFG)</td>
<td>110 – 125</td>
</tr>
<tr>
<td>Diabetes</td>
<td>&gt;126</td>
</tr>
</tbody>
</table>

*Not to be confused with impaired glucose tolerance (IGT): 2 h OGTT 75 g at 140–200 mg/dL*
Plasma Glucose Normally Maintained in Narrow Range

Glucose and Insulin Profiles After Oral Glucose Challenge

Glucose Contributions to HbA1c

\[ \text{HbA}_{1c} = \text{Normal about 4-6\%} \]

Fasting Glucose influenced by:
- Hepatic glucose production
- Hepatic sensitivity to insulin

Postprandial Glucose influenced by:
- Preprandial glucose
- Insulin secretion
- Glucose load from meal
- Insulin sensitivity in peripheral tissues
Schematic Representation: Benefit of Lowering HbA$_{1c}$ (Type 1 and Type 2 Composite Data)

Relative Risk of Complications

Hemoglobin A$_{1c}$

Average Glucose

Reduced Risk of Complications

Slide adapted from Kendall D, International Diabetes Center, Minneapolis.
Lowering HbA\textsubscript{1C} Reduces Risk of Complications

United Kingdom Prospective Diabetes Study (UKPDS)

*Percent risk reduction per 0.9% decrease in HbA\textsubscript{1C}; UKPDS. Lancet. 1998;352:837-853.
Good Glycemic Control (Lower HbA$_1c$) Reduces Incidence of Complications

<table>
<thead>
<tr>
<th></th>
<th>DCCT</th>
<th>Kumamoto</th>
<th>UKPDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>9 → 7%</td>
<td>9 → 7%</td>
<td>8 → 7%</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>63%</td>
<td>69%</td>
<td>17-21%</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>54%</td>
<td>70%</td>
<td>24-33%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>60%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Macrovascular disease</td>
<td>41%*</td>
<td>–</td>
<td>16%*</td>
</tr>
</tbody>
</table>

* not statistically significant


The epidemic of type 2 diabetes

<table>
<thead>
<tr>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>inactivity</td>
</tr>
<tr>
<td>Abdominal fat</td>
</tr>
<tr>
<td>Excess calories</td>
</tr>
<tr>
<td>World-wide distribution</td>
</tr>
</tbody>
</table>
Age-adjusted Percentage of U.S. Adults Who Were Obese or Who Had Diagnosed Diabetes

Obesity (BMI ≥30 kg/m²)

1994

No Data  <14.0%  14.0-17.9%  18.0-21.9%  22.0-25.9%  ≥26.0%

2000

No Data  <4.5%  4.5-5.9%  6.0-7.4%  7.5-8.9%  ≥9.0%

2008

No Data  <14.0%  14.0-17.9%  18.0-21.9%  22.0-25.9%  ≥26.0%


Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2008

44 Million Patients With Diabetes by 2034: $336 Billion

Epidemiology/Health Services Research
ORIGINAL ARTICLE

Projecting the Future Diabetes Population Size and Related Costs for the U.S.

ELBERT S. HUANG, MD, MPH
AMIRRAN BASH, PhD
MICHAEZ ORGEADY, PhD
JAMES C. CASETTA, MA

OBJECTIVE — We developed a novel population-level model for projecting future direct spending on diabetes. The model can be used in the federal budget process to estimate the costs implications of alternative policies.

RESEARCH DESIGN AND METHODS — We constructed a Markov model simulating individuals’ movement across different BMI categories, the incidence of diabetes and screening, and the natural history of diabetes and its complications over the next 25 years. Prevalence and incidence of obesity and diabetes and the direct spending on diabetes care and complications are projected. The study population is 24- to 85-year-old patients characterized by the Centers for Disease Control and Prevention’s National Health and Nutrition Examination Survey and National Health Interview Survey.

RESULTS — Between 2000 and 2034, the number of people with diagnosed and undiagnosed diabetes will increase from 23.7 million to 44.1 million. The obesity distribution in the population without diabetes will remain stable over time with ~65% of individuals of the population being overweight or obese. During the same period, annual diabetes-related spending is expected to increase from $113 billion to $336 billion (2007 dollars). For the Medicare-eligible population, the diabetes population is expected to rise from 8.2 million in 2000 to 14.6 million in 2034; associated spending is estimated to rise from $45 billion to $171 billion.

CONCLUSIONS — The diabetes population and the related costs are expected to at least double in the next 25 years. Without significant changes in public or private strategies, this population and cost growth are expected to add a significant strain to an overburdened health care system.

Diabetes Care 32:2225–2229, 2000

Content courtesy of the American Diabetes Association.

kovler diabetes center
Step 1

- Always remember the benefits of exercise!

The doctor said he needed more activity. So I hide his T.V. remote three times a week.
Exercise Therapy

1. Warm-up 5-10 minutes
2. Stretching 5-10 minutes
3. Walking 30 minutes
4. Cool down 5-10 minutes
5. Weight training (light weights/high reps)
Exercise

- Improves sense of well-being
- Improves muscle tone
- Lowers blood sugar
- Lowers blood pressure and heart rate
- Lowers bad cholesterol (total and LDL)
- Improves good cholesterol (HDL and particle size)
- May not have a large effect on weight loss
- May improve heart function, memory
● Exercise programs (absent contraindications) should include the following:
  – ≥150 min/week moderate-intensity aerobic activity (50%–70% maximum heart rate)
    AND
  – resistance training 3 times/week
The total amount of carbohydrate you eat affects blood glucose levels more than the type.
To the Rescue...

Content courtesy of the American Diabetes Association.
Diet Insights Help Any Drug Therapy

- Work with your nutritionist to understand protein, carbohydrate, fats, and fiber
- Know how much water to drink
- Consider a diet high in complex carbohydrate and fiber
- Some people can benefit by a diet reduced in starches and simple carbohydrate
- Fruit can be a source of sugar
  - Too much sugar!

Content courtesy of the American Diabetes Association.
Carbohydrate Counting

- Technique based on the concept that most meal-related glucose increase is due to the carbohydrate content
- Patients count either
  - Carbohydrate choices (milk, fruit, breads, sweets, starchy vegetables)
  - Grams of “total carbohydrates” on food label
- Providers prescribe insulin-to-carbohydrate ratio
  - Start with 1 unit per choice or 1 unit per 15 grams
  - Typical dose is 2-4 units per choice in type 2 diabetes
- Titrate based on postprandial glucose monitoring
- Generally, start with lispro/aspart/glulisine administered before meals
Encourage weight loss for all overweight/obese individuals; even modest weight loss reduces insulin resistance
  - make lifestyle changes the primary approach to weight loss
  - physical activity important for weight loss and maintenance
• Reduce calorie and fat intake
  - saturated fat should be <7% of total calories
  - minimize *trans* fat
• Monitor carbohydrate consumption to achieve glycemic control
• Customize nutrition counseling to each patient
• Limit alcohol intake
• Supplementation with antioxidants and chromium is not recommended

Oral Agents for Diabetes

- First line treatment is meal planning, weight loss, and exercise
- Sometimes these measures are not enough to bring blood glucose levels down near the normal range
- Oral agents work best when used with meal planning and exercise
  - 3 therapies working together to lower blood glucose levels
## Four Goals of Diabetes Management

<table>
<thead>
<tr>
<th>FOCUS</th>
<th>MEASUREMENT</th>
<th>GOAL</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUCOSE</td>
<td>A1C</td>
<td>&lt;7.0%</td>
<td>Every 3-6 months</td>
</tr>
<tr>
<td></td>
<td>Before meal, bedtime, and mid-sleep finger-prick glucose</td>
<td>70-130 mg/dL</td>
<td>As needed to ensure control and to avoid hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>1-2 hours after meal finger-prick glucose</td>
<td>&lt;180 mg/dL</td>
<td>As needed to ensure control</td>
</tr>
<tr>
<td>BLOOD</td>
<td>Office blood pressure</td>
<td>&lt;130/80 mm Hg</td>
<td>Every visit</td>
</tr>
<tr>
<td>PRESSURE</td>
<td>Apolipoprotein B (ApoB-100)</td>
<td>&lt;90 mg/dL (≤80 mg/dL with vascular disease, smoking, fam hx of CAD, HTN)</td>
<td>Annually; more often while adjusting treatment</td>
</tr>
<tr>
<td></td>
<td>-or- Non-HDL cholesterol (total cholesterol – HDL chol.)</td>
<td>&lt;130 mg/dL (≤100 mg/dL with vascular disease, smoking, famil history of early CAD, HTN)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-or- LDL cholesterol (requires fasting)</td>
<td>&lt;100 mg/dL (≤70 mg/dL with vascular disease, smoking, family history of early CAD, HTN)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HDL cholesterol</td>
<td>&gt;40 mg/dL (&gt;50 mg/dL for women)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triglycerides (requires fasting)</td>
<td>&lt;150 mg/dL</td>
<td></td>
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</tbody>
</table>

Screen for diabetes starting at age 30-45 every 3-5 years in everyone, earlier in those with risk factors

**Opportunistic** therapy of ABCs of diabetes

- Early treatment of hyperglycemia to achieve lowest possible without adverse consequences
  - Certainly <7%, probably <6%; at least in primary prevention, except the lessons from ACCORD in older patients with heart disease (7.5%)
  - Is there a particular role of non-hypoglycemic and nonobesogenic agents?
  - Is there a changing role for thiazolidinediones and secretagogues?
Opportunistic therapy of ABCs of diabetes (cont’d)

- Control blood pressure
  - Certainly <140/85 mm Hg; probably <130/80 mm Hg; possibly <120/80 mm Hg (probably not from ACCORD)
- Statins to control LDL <100 mg/dL, non-HDL <130 mg/dL
  - If triglycerides >200 mg/dL and HDL cholesterol <35 mg/dL, consider targeting dyslipidemia
  - What is the role of niacin?
  - Consider lower targets for those with family history of premature cardiovascular disease, hypertension and/or tobacco abuse

Aspirin for 10 year risk >10% and in secondary prevention

No tobacco
Welcome

We are pleased to announce the 6th Annual Chicago Diabetes Day that will take place on Saturday May 14th, 2011. This conference is intended to serve as a forum for basic and clinical investigators, clinicians, and pharmaceutical industry personnel in Chicago and the Midwest to meet, share information, and discuss common interests with the goal of fostering collaborations between institutions. Ample opportunities will exist throughout the day to meet with your colleagues. A poster session is planned for those who wish to share findings from current basic, clinical, or translational research. The top eight posters will receive an award of $100 each.

We are excited about this event and encourage you to attend what promises to be a stimulating and productive day.

The Organizing Committee

Registration

Registration is simple and complimentary. If you plan to attend, please reply to this email and type the words “will attend” in the subject line. You will receive an e-mail confirmation acknowledging your registration.

If you are unable to attend, type “will not attend” in the subject line.

You may also register by sending an e-mail with your name and institutional affiliation to:

zpaz@bsd.uchicago.edu

Program

8:30 AM Registration
8:55 AM Welcome and Introduction
  Graeme I. Bell, Ph.D.

9:00 AM From Stem-Cells to Insulin: How to Make a Beta-Cell
  Michael S. German, M.D.
  Department of Medicine
  University of California, San Francisco

10:00 AM Sexuality in Women and Men with Diabetes
  Stacy T. Lindau, M.D., M.A.P.P.
  Department of Obstetrics and Gynecology
  The University of Chicago

10:45 AM Endothelial Cell - Islet Cell Interactions: Roles in Islet Function and Regeneration
  Alvin C. Powers, M.D.
  Department of Medicine
  Vanderbilt University School of Medicine

11:30 AM Implications of Cross-Talk Between Insulin and Incretin Signaling Pathways in Pancreatic Beta-cells
  Rohit N. Kulkarni, M.D., Ph.D.
  Joslin Diabetes Center
  Harvard Medical School

12:15 PM Lunch and Poster Session
2:30 PM Awards for Posters
  Eight prizes of $100

Organizing Committee

Matthew Brady, Ph.D., University of Chicago
Joseph Bass, M.D., Ph.D., Northwestern University
Graeme I. Bell, Ph.D., University of Chicago
Marshall H. Chin, M.D., M.A.P.P., University of Chicago
David A. Ehrmann, M.D., University of Chicago
Louis H. Philipson, M.D., Ph.D., University of Chicago
Donald F. Steiner, M.D., University of Chicago
Terry G. Unrenman, M.D., University of Illinois at Chicago
Thank You!

Lilly Jaffe

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