Differentiation of Diabetes by Pathophysiology, Natural History and Prognosis

Do we know what diabetes is?

1921
Diabetes mellitus
Diagnosed by measuring one metabolite- glucose
Diabetes prevalence 0.1%

1960
Adult Onset
Juvenile Onset
Diabetes prevalence 1.5%

1990
Type 2
LADA
Type 1
LADA: Latent autoimmune diabetes in adults
Diabetes prevalence 3%

2015
Type 2 ??
LADA
Type 1
Diabetes prevalence 7%

Stages of Type 2 Diabetes

Reprinted with permission from Lebovitz H. Diabetes Reviews. 1999;7:139
**Why Change the T1D Diagnostic Criteria?**

- Provides a framework to inform benefit/risk evaluation for regulatory, reimbursement, and clinical care with interventions to prevent symptomatic T1D
- Improves the design of prevention trials
- Catalyzes risk screening and increases enrollment in natural history and prevention clinical trials
- Earlier diagnosis has current benefits
  - Decreased risk of DKA and hospitalization at diagnosis
  - Greater levels of residual functional beta cell mass at time of initiation of insulin replacement may lead to long-term benefit

**Early Stages of Type 1 Diabetes: Diagnostic Criteria**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Stage #1 Autoreactivity Normoglycemia Presymptomatic</th>
<th>Stage #2 Autoreactivity Dysglycemia Presymptomatic</th>
<th>Stage #3 New Onset Symptomatic T1D</th>
</tr>
</thead>
</table>
| Diagnostic Criteria | • Multiple AutoAbs  
• No impaired glucose tolerance or impaired fasting glucose  
• FPG ≥100 mg/dL or ≥110 mg/dL  
• 2hPG ≥140 mg/dL; min 2hPG ≥200 mg/dL  
• Random plasma glucose >200 mg/dL  
• HbA1c >5.7% or >5.9%  
• Increasing HbA1c (10%) | • Multiple AutoAbs  
• Glycogenic impaired glucose tolerance and/or impaired fasting glucose  
• FPG ≥100 mg/dL or ≥110 mg/dL  
• 2hPG ≥140 mg/dL; min 2hPG ≥200 mg/dL  
• Random plasma glucose >200 mg/dL  
• HbA1c >5.7% or >5.9%  
• Increasing HbA1c (10%) | • Clinical Symptoms |

**T1D incidence is Rising 3-5% per Year**

**Islet Autoantibodies in T1D**

1st generation assays
- ICA
- Insulin autoantibodies

2nd generation (RIA, ELISA)
- ZnT8A
- IA-2A
- GADA
- mIAA

3rd generation (ECL, etc.)
- ECL-IA-2A
- ECL-GADA
- ECL-IAA
Variables Affecting Rate of Progression from Stage 1 to Stage 3

- Number of autoantibodies
- Autoantibody specificities
- Autoantibody titer
- Age of autoantibody seroconversion (< 3 yrs general population children; younger vs older relatives)
- HLA (HLA DR3/DR4-DQ8), non-HLA genes

**Type 1 Diabetes Risk Screening:**

Screening for Stage 1

- Relatives: Adults, Children (TrialNet)
- Universal Childhood Screening
  - HLA risk screening at birth followed by screening for multiple islet autoantibodies in HLA at-risk cohort (TEDDY)
  - Universal screening for multiple islet autoantibodies of population-based young children (FR1DA)

**Many Type 1 Diabetes Preventions Have Been Successful in NOD Mice**

- >400

May, 2016

Courtesy of Amanda Prange and Mark Atkinson
**Human T1D Prevention Studies Have Had Very Limited Impact**

- DPT-1 Parenteral Insulin: No effect
- DPT-1 Oral Insulin: No effect**
- TrialNet Oral Insulin: Ongoing
- ENDIT Nicotinamide: No effect
- DIPP Nasal Insulin: No effect
- INIT-II Nasal Insulin: Ongoing
- TRIGR Casein hydrolysate: No effect on abs
- NIP Docosahexaenoic Acid: No effect
- PRE-Point Oral Insulin: Immunologic hints

**Other Studies in Recent-Onset T1D**

- Metabolic Control Study: No effect
- DPP-4 Inhibitor + PPI: No effect

**Pilot Studies:**
- Low Dose IL-2: Safe
- Plasmid-Encoded Proinsulin: Safe
- T-regs: Safe
- Dendritic Cells: Safe

**Antigen-Based New Onset Studies**

- Oral Insulin France: No effect
- Oral Insulin Italy: No effect
- Oral Insulin US: No effect
- GAD Pilot: No effect (? subgroup)
- TrialNet GAD: No effect
- Diamyd EU GAD: No effect
- Diamyd US GAD: No effect
- Neurocrine Altered Peptide: No effect
- DiaPep-277 Heat Shock Protein: No effect (papers retracted for fraud)

**Use of Presymptomatic Stages of Type 1 Diabetes to Design Type 1 Diabetes Prevention Clinical Trials**

1. **Pre-Stage 1:** Individuals at-risk for T1D
   - General population: 0.4%
   - Individuals with high-risk genes: 4%
   - First-degree relatives: 3-8%
   - Interventions at birth/universal interventions
   - Interventions during pregnancy
   - Childhood interventions in highest-risk individuals

2. **Stage 1:** Autoimmunity/Normoglycemia/Presymptomatic T1D
   - Multiple T1D-associated islet autoantibodies with normal glycemic control
   - TrialNet Oral Insulin Prevention Trial
   - TrialNet Abatacept Prevention Trial
   - TrialNet Teplizumab Prevention Trial

3. **Stage 2:** Autoimmunity/Dysglycemia/Presymptomatic T1D
   - Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia
   - TrialNet Teplizumab Prevention Trial

4. **Stage 3:** Symptomatic T1D

**Immunomodulatory New Onset Studies**

- Cyclosporin France: Transient effect
- Cyclosporin Canada/EU: Transient effect
- Teplizumab Anti-CD3 Pilot: Transient effect
- Otelixizumab Anti-CD3 Pilot: Transient effect
- Abate Teplizumab: Transient effect
- Protège Teplizumab: Transient effect (25% endpoint)
- DEFEND Otelixizumab (2 trials): No effect
- Etanercept: ? Effect
- Mycophenolate Anti-CD25: No effect
- Rituximab Anti-CD20: Transient effect
- Abatacept CTLA4-Ig: Transient effect
- Canakinumab Anti-IL-1β: No effect
- Anakinra IL-1 Trap: No effect
- Thymoglobulin: No effect
- Alefacept CTLA4-Ig: Potential effect (25% endpoint)

**A Combination Therapy Approach May Be Required – One Potential Program**

- **Anti-Inflammatory Agents (e.g. Targeting IL1β or TNFα)**
- **Immunomodulation (e.g. Anti-CD3 or Anti-CD20 or Co-Stimulation Blockade or ATG)**
- **Drive T-regs (e.g. IL-2 or GCSF or T-reg infusion)**
- **Preserve Beta-Cell Health (e.g. GLP-1 Receptor Agonist)**

Slyker. Diabetes Care 2015;38:997-1007
Ant-inflammatory Agent – Etanercept and Anakinra

Immunomodulation

Alectuzumab

Preserve Beta-Cell Health – Liraglutide

Mobilize Stem Cells for Beta Cell Repair

Plerixafor

Conclusions

- T1D, a disease continuum, progresses through distinct presymptomatic stages
  - Stage 1 (multiple islet autoantibodies)
  - Stage 2 (islet autoantibodies with dysglycemia)
  - Stage 3 (symptomatic disease)
- Relative rate of progression to symptomatic T1D can be predicted with appreciable accuracy but needs to be further refined
- Screening and staging prior to symptomatic T1D:
  - Provides a framework to inform benefit/risk evaluation for regulatory, reimbursement, and clinical care
  - Catalyzes risk screening and will increase enrollment in natural history and prevention clinical trials
- Will provide a window of opportunity to delay, and ultimately prevent, symptomatic T1D

Module_1

Module_2

Module_3

Module_4

Heterogeneity of T2DM Within Populations: the Belfast Diet Study

Type 1 Diabetes TrialNet

Diabetes Prevention Trial – Type 1

Heterogeneity of T2DM Within Populations: the Belfast Diet Study

Insulin Sensitivity

Years from diagnosis

β-Cell function (%)
What determines disease progression in T2DM?

Glucose/ HbA1c

Aim of therapy

Accelerators

Brakes

Slow progression

Normal / no progression

Years

What does the Future Hold?

DPP Study Treatment Groups

Screen (156,177 people)

Randomize (3,819 people)

Standard lifestyle teaching

Intensive Lifestyle (1079 people)

Metformin (1073 people)

Placebo (1082 people)

Troglitazone 585 people Until 6/98

DPP Incidence of Diabetes

Risk reduction

31% by metformin

58% by lifestyle

DPPOS Incidence of Diabetes

Placebo

Metformin

Lifestyle

Cumulative incidence (%)
Regression vs. Progression

Glucose concentration assessed by annual 2h OGTT

Risk Factor Change from Baseline By Glucose Tolerance Category in Placebo Group


Change from Baseline By Glucose Tolerance Category

**Regression From Pre-Diabetes to Normal Glucose Regulation in the Diabetes Prevention Program**

Variables associated with regression:

- Lower baseline fasting and 2h glucose
- Younger age
- Higher insulin response
- Greater weight loss
- ILS

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**Diabetes Incidence in DPPOS: Effect of Achieving NGR**

Never reached NGR in DPP

Reached NGR at least once in DPP

P = 0.0001

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**Cumulative, Undiscounted, Per-participant Direct Medical Costs**

DPP/DPPOS Interventions Medical Care Received Outside the DPP/DPPOS

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**Discounted Incremental Cost-Effectiveness Ratios over 10 Years by Intervention Group – Health System Perspective**

<table>
<thead>
<tr>
<th></th>
<th>Lifestyle</th>
<th>Metformin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total direct medical costs</td>
<td>25,456</td>
<td>24,071</td>
<td>24,229</td>
</tr>
<tr>
<td>QALYs</td>
<td>5.99</td>
<td>5.88</td>
<td>5.87</td>
</tr>
<tr>
<td>Δ Cost v placebo</td>
<td>1,226</td>
<td>-159</td>
<td>—</td>
</tr>
<tr>
<td>Δ QALY v placebo</td>
<td>0.12</td>
<td>0.02</td>
<td>—</td>
</tr>
<tr>
<td>Δ Cost / Δ QALY</td>
<td>10,037</td>
<td>Cost-saving</td>
<td>—</td>
</tr>
</tbody>
</table>

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**Diabetes Incidence in DPPOS: Effect of Achieving NGR by Treatment**

**Delay and Prevention of Diabetes**


Herman et al. Diabetes Care 35:723-30, 2012

Herman et al. Diabetes Care 35:723-30, 2012


Herman et al. Diabetes Care 35:723-30, 2012
**“Real-World Translation”**

- Can we take what we know from DPP and bring it into many communities?
- What types of programs or treatments can and should be offered?
- Who will deliver these programs?
- Who will pay for them?

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**FOR IMMEDIATE RELEASE**
March 23, 2016
media@hhs.gov

- Independent experts confirm that diabetes prevention model supported by the Affordable Care Act saves money and improves health
- First ever preventive service model eligible for expansion under Medicare holds promise for employers, private insurers and patients

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**Translating the DPP/DPPOS Experience to the “Real World”**

- Franken-Lugar Health Reform Bill
  “Diabetes Prevention Amendment”
  - This amendment will authorize the Centers for Disease Control and Prevention (CDC) to train, recognize, and fund community based diabetes prevention programs.

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**Action on Capitol Hill**

- Medicare beneficiaries enrolled in the program lost about five percent of their body weight, which is enough to substantially reduce the risk of future diabetes. Average weight loss was 4.73 percent of body weight for participants attending at least four weekly sessions. Participants who attended at least nine weekly sessions lost an average of 5.17 percent of their body weight.
- Over 80 percent of participants recruited attended at least four weekly sessions.
- When compared with similar beneficiaries not in the program, Medicare estimated savings of $2,650 for each enrollee in the Diabetes Prevention Program over a 15-month period, more than enough to cover the cost of the program.
We must prevent diabetes or our health system will be consumed by it.