Chapter 11

Prediction of Type 1A Diabetes: The Natural History of the Prediabetic Period
Greenbaum et al Diabetes June 11, 2012
Fall in C-peptide During First 2 Years From Diagnosis: Evidence of at Least Two Distinct Phases From Composite TrialNet Data.
“Stages” in Development of Type 1A Diabetes

1. Genetic Predisposition
2. Overt immunologic abnormalities
3. Normal insulin release
4. Progressive loss of insulin release
5. Glucose normal
6. Overt diabetes
7. C-peptide present
8. Minimal C-peptide

Eisenbarth 2012
nPOD 6052-02 Tail: 12 yo 1 year diabetes
-Lobular Pseudoatrophic Islets

Glucagon/anti-CD3 Staining
Insulin and Ki67 Staining
RISING HbA1c PRECEDES DIABETES

Stene et al DAISY Study Pediatric Diabetes 7:247-253
TRIGGERING QUESTIONS

• Is there an environmental trigger?
• Does autoantibody appearance mark triggering?
• Time lag between trigger and insulitis?
• Time lag between insulitis and beta cell killing?
• “Best Model”
  Kilham Rat Virus (Multiple Other viruses)
  ACTIVATION INNATE IMMUNITY BY VIRUS
  SPECIFIC MHC AND SPECIFIC TCR (Mordes et al)
  ANTI-INFLAMMATORY PREVENTS (Zipris et al)
Non-Radioactive Electrochemiluminescent Insulin Autoantibody Assay

Yu et al Diabetes Nov 2011
Progression to Diabetes Among Children Positive for Anti-Islet Autoantibodies

Steck et al Diabetes Care 2011
Predicted Onset Age =
2.6 - 1.3 * log(mean IAA) = 0.8 * age first Ab+
MEAN LOG IAA vs Time to DM from age Islet Ab first +

R2 = 0.37  P < 0.001

Steck et al Diabetes Care 2011
Age 1st Islet Ab+ vs Age DM Onset

Steck et al Diabetes Care 2011

R² = .47  p < .0001
Progressive Loss C-peptide Post Diagnosis (SEARCH Diab Care 2009)

DCCT
Fast $\geq 0.23$ ng/ml
ACCELERATED LOSS OF PEAK C-PEPTIDE AFTER DIAGNOSIS OF TYPE 1A DIABETES (“WAITING” FOR CONFIRMATORY ORAL GLUCOSE TOLERANCE TEST)

Sosenko et al, Diabetes Care August 2008
New Onset Type 1 DM: Loss of Insulin Secretion (ISR area(AUC)) related to early (peak<45 min) versus delayed secretion Mixed Meal  Steele et al Diabetes 53:26, 2004
Type 1 diabetes risk stratification models based on islet autoantibody characteristics

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stratification based on</strong></td>
<td><strong>Stratification based on</strong></td>
<td><strong>Stratification based on</strong></td>
<td><strong>Stratification based on</strong></td>
</tr>
<tr>
<td><strong>Number of islet autoantibodies (IAA, IA-2A, GADA)</strong></td>
<td><strong>High titre of IAA (&gt;3rd quart.) and IA-2A (&gt;1st quart.)</strong></td>
<td><strong>High risk characteristics:</strong> High titre IA-2A (&gt;1st quart.) and IgG2 or IgG4 IA-2A and IgG2, IgG3 or IgG4 IAA</td>
<td><strong>Status of IA-2A and IA-2βA</strong></td>
</tr>
<tr>
<td><strong>Category 1</strong></td>
<td><strong>Category 1</strong></td>
<td><strong>Category 1</strong></td>
<td><strong>Category 1</strong></td>
</tr>
<tr>
<td>One autoantibody</td>
<td>Neither IAA nor IA-2A at high titre</td>
<td>No high risk characteristic</td>
<td>IA-2A negative</td>
</tr>
<tr>
<td><strong>Category 2</strong></td>
<td><strong>Category 2</strong></td>
<td><strong>Category 2</strong></td>
<td><strong>Category 2</strong></td>
</tr>
<tr>
<td>Any two autoantibodies</td>
<td>One of IAA or IA-2A at high titre</td>
<td>One high risk characteristic</td>
<td>IA-2A positive and IA-2βA negative</td>
</tr>
<tr>
<td><strong>Category 3</strong></td>
<td><strong>Category 3</strong></td>
<td><strong>Category 3</strong></td>
<td><strong>Category 3</strong></td>
</tr>
<tr>
<td>All three autoantibodies</td>
<td>Both of IAA and IA-2A at high titre</td>
<td>Any two high risk characteristics</td>
<td>IA-2AβA positive</td>
</tr>
<tr>
<td><strong>Shaded Categories:</strong> 10-year diabetes risk &gt;50% (high-risk categories)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Achenbach et al., Diabetologia (2006) 49:2969-2976*
Type 1 diabetes risk stratification considering changes in model risk category on follow-up

Model 1 | Model 2 | Model 3 | Model 4
---|---|---|---
P = 0.02 | P < 0.001 | P < 0.001 | P < 0.001

Stable low-risk category | Changed from low-risk to high-risk category | Stable high-risk category | Changed from high-risk to low-risk category

Follow up (years)

Diabetes-free survival (%)

Achenbach et al., Diabetologia (2006) 49:2969-2976
Sustained beta cell apoptosis in patients with long-standing type 1 diabetes: indirect evidence for islet regeneration?

Meier et al, Diabetologia 2005

% Insulin/Pancreatic Area

Diabetes

Control
Time Course of Beta Cell Loss

Linear, Chronic Model
Eisenbarth (NEJM 1986, 314:1360)

Benign: Malignant Model
Lafferty (J Aut 1997, 10:261)

Random Loss Model
Palmer (Diabetes 1999, 48:170)
Time Course Beta Cell Loss

Linear: Eisenbarth
NEJM 1986, 314:1360

Prodrome > Acute
Lafferty; J Aut 1997, 10:261

Random: Palmer
Diabetes 1999, 48:170
Stages in Development of Type 1 Diabetes

- Genetically at Risk
- Beta Cell Mass
- Genetic Predisposition
- Insulitis
- Beta Cell Injury
- "Pre"-Diabetes
- Diabetes
- Newly Diagnosed Diabetes

J. Skyler
T1DM- a slowly progressive T-cell mediated autoimmune illness

Genetic susceptibility

Inciting Event(s)

“Silent” \(\beta\) Cell Loss

Diabetes Onset

“Brittle” Diabetes

Islet Cell Mass

100% +

Strong association with MHC class II (DQ in particular)

We cannot easily/accurately measure islet mass in vivo or ex vivo

No accepted norm for the islet number within a human pancreas

Infectious agent(s)? Etiology if true?

Environmental toxin(s)?

Absence of childhood illness?

Combination of factors?

Age of exposure?

\(\beta\) cell Mass??

0%

Time (years)

What is the “slope” of the \(\beta\) cell loss?

Is recovery possible once process begins?

What underlies the effect of age on slope of \(\beta\) cell loss?

Why does the \(\beta\) cell destruction typically occur slowly (in contrast to graft rejection)?

\(\beta\) cell loss can \(\beta\) cell exclusively regenerate immune mediated loss?

David Harlan
<table>
<thead>
<tr>
<th></th>
<th>NORMAL</th>
<th>IMPAIRED</th>
<th>DIABETES</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>$&lt; 6.4$</td>
<td>$5.7-6.4$</td>
<td>$\geq 6.5$</td>
</tr>
<tr>
<td>FASTING</td>
<td>$&lt; 100 \text{ mg%} (5.6 \text{ mM})$</td>
<td>$100-125$</td>
<td>$\geq 126 \text{ mg% (7 mM)}$</td>
</tr>
<tr>
<td>ORAL GTT</td>
<td>$&lt; 140 \text{ mg% (7.8 mM)}$</td>
<td>$140-199$</td>
<td>$\geq 200 \text{ mg% (11.1 mM)}$</td>
</tr>
</tbody>
</table>
Gestational Diabetes (>=2 high)
100-g or 75-g Glucose

<table>
<thead>
<tr>
<th></th>
<th>mg/dl</th>
<th>mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>100-g Glucose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>95</td>
<td>5.3</td>
</tr>
<tr>
<td>1-h</td>
<td>180</td>
<td>10</td>
</tr>
<tr>
<td>2-h</td>
<td>155</td>
<td>8.6</td>
</tr>
<tr>
<td>3-h</td>
<td>140</td>
<td>7.8</td>
</tr>
<tr>
<td><strong>75-g Glucose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>95</td>
<td>5.3</td>
</tr>
<tr>
<td>1-h</td>
<td>180</td>
<td>10</td>
</tr>
<tr>
<td>2-h</td>
<td>155</td>
<td>8.6</td>
</tr>
</tbody>
</table>
“Stages” in Development of Type 1A Diabetes

- Genetic Predisposition
- Overt immunologic abnormalities
- Normal insulin release
- Progressive loss insulin release
- Glucose normal
- Overt diabetes
- C-peptide present
- No C-peptide
Intravenous Glucose Tolerance Test (IVGTT) 1+3 minute insulin


Discordant Triplets at Risk for Diabetes

Antibody Positive Initial Test

Antibody Positive

Intravenous Glucose Tolerance Test (IVGTT) 1+3 minute insulin

Age

“Biochemical” Autoantibody Assays

- Insulin
- Glutamic Acid Decarboxylase
- ICA512 (IA-2)
DPT-1 Ancillary Biochemical Ab

- **Cytoplasmic ICA Positive** (3.4%)
  1/2 Negative for GAD/ICA512/Insulin Ab
  0.9% = 1 Biochemical Ab
  1.1% >=2 Ab

- **Cytoplasmic ICA Negative** (96.6%)
  3.3% =1 “Biochemical Ab
  0.3% >=2 Ab

- Staging: Only 12% eligible ICA+/Bioch -

- Future Trials Likely without ICA
Progression to Diabetes vs Number of Autoantibodies (GAD, ICA512, Insulin)

Verge et al. Diabetes, 1996;45;926
Gestational Diabetes: Risk at 2 years Type 1 Diabetes by Autoantibodies
ICA, GAD65, ICA512(IA-2)

Sensitivity GAD=63%; Sensitivity 3 Abs=82%

LADA: Latent Autoimmune Diabetes Adults in UKPDS study

% GAD +

AGE

25-34 55-65

Insulin by 6 Years

ICA+ GAD65+ 0 Ab

Turner et al. Lancet 1997;350:1288-93
## Caveats of IVGTT Testing

<table>
<thead>
<tr>
<th>Caveat</th>
<th>Suggestion</th>
</tr>
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<tbody>
<tr>
<td>&quot;First&quot; Test lack response young children</td>
<td>Repeat Abnormal Tests</td>
</tr>
<tr>
<td>Lack Carbohydrate</td>
<td>Dietary Preparation similar to OGTT</td>
</tr>
<tr>
<td>Type 1A and insulin resistance may coexist</td>
<td>Subtract 2X fasting insulin</td>
</tr>
<tr>
<td>Can be &lt;1&lt;sup&gt;st&lt;/sup&gt; Percentile in adults years prior to DM</td>
<td>Long-term follow up</td>
</tr>
<tr>
<td>Subset normals &lt;1&lt;sup&gt;st&lt;/sup&gt; %</td>
<td>In absence Abs low risk</td>
</tr>
<tr>
<td>Variation e.g. puberty</td>
<td>Repeat tests; caution in interpreting changes</td>
</tr>
</tbody>
</table>
First-phase insulin release during the intravenous glucose tolerance test as a risk factor for type 1 diabetes (DPT)

Chase et al. J. Peds 138,244; 2,001

![Graph showing 1+3 Minute Insulin (uU/ml) for different age groups: ICA Negative and ICA Positive]
FPIR in pre-diabetic relatives with initial FPIR > 50mU/L

Years prior to diabetes

Melbourne Pre-Diabetes Study (Colman PG & Harrison LC)
Insulin Secretion (IVGTT) in Obese Child (BMI 30 to 35) Progressing to Diabetes: Type 1 + Type 2 with Elevated Fasting Insulin
Lack of Progression to DM of ICA+ 0602+ Relatives
Melbourne Data: Dual Parameter Prediction
Time to DM=$-.12+1.35\ln(IVGTT)-.59\ln(IAA)$

<2.5 $N=11$  5  3  1  0
>2.5 $N=70$  53  42  32  24  13  6  Proc AAP:110:126-135
Normal but increasing hemoglobin A1c levels predict progression from islet autoimmunity to overt type 1 diabetes: Diabetes Autoimmunity Study in the Young (DAISY). Stene Pediatr Diabet 2005
Blood glucose values in Control vs. Daisy children

Diabetes Autoimmunity Study in the Young

General population cohort

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Number</th>
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<tbody>
<tr>
<td>High risk</td>
<td>293</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>429</td>
</tr>
<tr>
<td>Average - low risk</td>
<td>347</td>
</tr>
<tr>
<td>All</td>
<td>1,069</td>
</tr>
<tr>
<td>Relatives</td>
<td>1,491</td>
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</tbody>
</table>

Sibling/offspring cohort

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Number</th>
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</thead>
<tbody>
<tr>
<td>High risk</td>
<td>72</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>220</td>
</tr>
<tr>
<td>Average - low risk</td>
<td>401</td>
</tr>
<tr>
<td>All</td>
<td>693</td>
</tr>
<tr>
<td>Relatives</td>
<td>1,007</td>
</tr>
</tbody>
</table>

screened = 21,713
DAISY Interviews and Clinical

Interviews: diet, infections, immunizations, allergies, stress

Visits

Clinical Visits: blood sample for GAA, IAA, ICA512, ICA DNA, throat and rectal swabs, saliva sample
Prediction of Autoantibody Positivity and Progression to Type 1 Diabetes: DAISY study
Barker et al. J Clin Endocrinol Metab 89:3896, 2004

162 Positive

50 False +
1/3

112 Confirmed +

50 Transient
1/3

58(4) Persistent
1/3

28 X1+

22 >1+

24 Diabetic

28 Not DM

1/3 of Multiple Time+ are Transient
(22/(22+24+28))

2/3 High Risk Diabetes

Of 1,972 = 8.2%
DAISY AUTOANTIBODIES: Initial Test <Age 1

Percent with Persistent Autoantibodies (GAA/IAA/ICA512)

- 3/4 SOC: 15 9 5 4
- 3/4 NEC: 151 110 67 18
- -3/4 SOC: 69 56 39 16 3
- -3/4 NEC: 492 300 208 110

p < .0001

12/27/97
Relatives (SOC) vs. Population (NEC) Persistent vs. Transient AutoAb

Yu et al. JCEM 85: 2421, 2000
Mature high-affinity immune responses to (pro)insulin anticipate the autoimmune cascade that leads to type 1 diabetes. Achenbach et al, J.Clin Invest 2004, 114:589
Candidate environmental causes of type 1 diabetes

• **Definite (rare cases)**
  - congenital rubella

• **Putative**
  - enteroviruses
  - rotaviruses
  - components of infant diet
    • gluten
    • cow’s milk
<table>
<thead>
<tr>
<th>Study</th>
<th>Autoimmunity</th>
<th>Diabetes</th>
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<tbody>
<tr>
<td>Frisk 1992</td>
<td></td>
<td>CVB1-5 IgM</td>
</tr>
<tr>
<td>Dahlquist 1995</td>
<td></td>
<td>CVB2-4 IgM</td>
</tr>
<tr>
<td>Hyoty 1995</td>
<td>IgM, IgG CVB</td>
<td>CVB IgM, IgG</td>
</tr>
<tr>
<td>Clements 1995</td>
<td></td>
<td>EV RNA</td>
</tr>
<tr>
<td>Graves (DAISY) 1996,2000</td>
<td>No EV RNA (RNA 12%:18%)</td>
<td>No EV RNA</td>
</tr>
<tr>
<td>Hyoty (DIPP) 2000 (&lt;6mos.)</td>
<td>EV Ab: 57%:31% EV RNA: 29% 6%</td>
<td></td>
</tr>
</tbody>
</table>
Autoantibody development and enteroviral RNA in a HLA-DR3/4,DQB1*0302 sibling

SD score

ECHO 16

GAA
IAA
ICA512
TG IgA

Age [yrs]

0.8  1.1  1.4  1.8  2.4  2.7  3.0  3.3  3.6  3.8  4.2  4.9  5.5
EV-  EV+  EV-  EV+  EV+  EV-  EV+  EV+  EV-  EV-  EV-  EV-
Beta-cell autoimmunity and presence of enteroviral RNA in serum, saliva and stool

Graves PM, DAISY, 1999

Prevalence of EV RNA

<table>
<thead>
<tr>
<th></th>
<th>Relatives</th>
<th>High risk children from the general population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>3/13</td>
<td>3/14</td>
</tr>
<tr>
<td>Controls</td>
<td>3/13</td>
<td>6/28</td>
</tr>
</tbody>
</table>

0% 10% 20% 30%
DIPP Protocol

Main Cohort (n=38,000)

• Newborns screened for genetic risk
• High risk babies followed serially for ICA (n=81)
• ICA-positive children randomized to nasal insulin or placebo
Trials to Prevent Type 1 Diabetes

- Trialnet/DPT-1
- ENDIT
- TRIGR
- DIPP
Development of islet autoantibodies in 1610 offspring of mothers or fathers with T1D

Walter et al, Diabetologia 2003 (updated 2004)
Development of islet Abs
- HLA DR-DQ and INS VNTR genotypes

Walter et al, Diabetologia 2003 (updated 2004)
Development of islet Abs - proband

- Both parents or parent + sibling
- Father only
- Mother only

$P = 0.05$

$P < 0.0001$
Progression from multiple islet Abs to diabetes
- No effect of HLA DR-DQ or proband

A. Ziegler
Islet autoantibody appearance in BABYDIAB offspring

A. Ziegler

Age (years)

Any islet Abs (7.8%)
Multiple islet Abs (3.7%)
Single islet Abs

Hummel et al., Ann Intern Med, June 2004
Progression to multiple Abs is necessary for disease

A. Ziegler

Hummel et al., Ann Intern Med, June 2004
Progression

- Insulin
- GAD
- IA-2
First antibody is insulin/proinsulin
IAA affinity is high in children who develop multiple islet Abs

$P<0.0001$

Achenbach, J Clin Invest, 2004

A. Ziegler
IAA affinity is relatively stable during follow-up
Progression to multiple islet autoantibodies in children is related to IAA affinity

IAA positive follow-up (years)

% with multiple islet abs

IAA affinity high

IAA affinity low

$P = 0.0004$

A. Ziegler
Risk for developing islet Abs in relation to birth autoantibody status in offspring of T1D mothers

\[ P = 0.007 \]

- POS GADA or IA2A at birth
  - n = 476

- NEG GADA and IA2A at birth
  - n = 244

Father T1D

Koczwara et al, Diabetes 2004

A. Ziegler