Alterations in Pancreatic Function

Marcela Brissova
County-level Estimates of Diagnosed Diabetes among Adults aged ≥ 20 years:
United States 2009

Age-adjusted percent
0 - 6.3
6.4 - 7.5
7.6 - 8.8
8.9 - 10.5
≥ 10.6

www.cdc.gov/diabetes
<table>
<thead>
<tr>
<th></th>
<th>TYPE 1</th>
<th>TYPE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SYNONYMS</strong></td>
<td>IDDM, JODM</td>
<td>NIDDM, AODM</td>
</tr>
<tr>
<td><strong>AGE OF ONSET</strong></td>
<td>Usually &lt; 30</td>
<td>Usually &gt; 30</td>
</tr>
<tr>
<td><strong>KETOSIS</strong></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>BODY WEIGHT</strong></td>
<td>Non-Obese</td>
<td>Obese (80%)</td>
</tr>
<tr>
<td><strong>PREVALENCE</strong></td>
<td>0.5%</td>
<td>2-5%</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td>Insulin</td>
<td>Diet, Oral Agents, Insulin</td>
</tr>
</tbody>
</table>
Classification of Diabetes

- Type 1 diabetes
- Type 2 diabetes
- Other types of diabetes
Classification of Diabetes

• Type 1 diabetes
  – Immune-mediated
  – Idiopathic
Glucose Flux in Type 1 Diabetes

Liver

Glucose production, storage

Glucose

Insulin

Glucagon

Muscle, Fat

Glucose utilization

Pancreatic Islet

X
Incidence of Chronic Diseases in US Children (age <16 years)

New cases per 100,000 children per year

IDDM
Peptic ulcer
Cystic fibrosis
Juvenile rheumatoid arthritis
Multiple sclerosis
Nephrotic syndrome
Muscular dystrophy
Lupus erythematosus
Total cancers
Leukemia
Brain
Lymphoma
Other cancers

Cancer

Diabetes Care 16:841, 1993
Humoral and Cellular Autoimmunity in Type 1 Diabetes

Normal Islet  Pancreatic Islet in Type 1 Diabetes

Islet Cell Autoantibodies

(BB rat; photograph by A. Like)
Geographic Differences in Type 1 Diabetes

![Bar chart showing annual incidence per 100,000 for different countries.]

- Sardinia
- Finland
- Canada
- UK (Oxford)
- United States
- Kuwait
- Denmark
- Poland
- Venezuela
- China
Temporal Model of Type 1 Diabetes

- Genetic Susceptibility
- Triggering Event
- Markers of Autoimmune Process
- Progressive Loss of Beta Cells

Time (months or years)

Beta Cell Mass

100 %

10 %

No Diabetes

Clinical Diabetes
Classification of Diabetes

• Type 1 diabetes
  – Immune-mediated
  – Idiopathic

• Type 2 diabetes
Glucose Flux in Type 2 Diabetes

- Liver
  - Increased glucose production

- Glucose
- Insulin Glucagon
- Pancreatic Islet
  - Impaired insulin secretion

- Muscle, Fat
  - Insulin resistance
  - Reduced glucose utilization

- Increased glucose production
- Impaired insulin secretion
“Normal” Populations Have a Range of Glucose Sensitivity

- White Males
- Prepubertal
- White Females
- Aged, High-Carbohydrate
- Mexican American
- Second Trimester
- Puberty
- Aged, Ad Lib
- Obese
- Third Trimester

*Insulin Sensitivity Index (SI; x 10^-4 min^-1/μU/mL)*

*Diabetes 38 (1989), pp. 1512-1527*
Relationship of Insulin Secretion and Insulin Sensitivity

Harrison’s, Principles of Internal Medicine, 2005
Genome Wide Association Studies and Type 2 Diabetes

- 19 validated T2DM genes
- T2DM genetic loci occur mainly at SNPs coding proteins involved in β cell function and not insulin resistance
- 14 T2DM genes have been shown to influence glucose or incretin stimulated insulin secretion
- 7 variants with the greatest association with diabetes risk (TCF7L2, CDKAL1, HHEX, CDKNA2B, IGF2BP2, SLC30A8, JAZF1) all affect β-cell insulin secretion
Classification of Diabetes

- Type 1 diabetes
- Type 2 diabetes
- Other types of diabetes
  - Maturity Onset Diabetes of The Young (MODY)
  - Neonatal diabetes
  - Gestational diabetes (GDM)
  - Endocrinopathies—acromegaly, Cushing's syndrome, glucagonoma
  - Drug- or chemically-induced - glucocorticoids, atypical antipsychotics
# Features of Monogenic Diabetes

<table>
<thead>
<tr>
<th>Type</th>
<th>Gene Mutation</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODY1</td>
<td>HNF-4α</td>
<td>Respond to SU</td>
</tr>
<tr>
<td>MODY2</td>
<td>Glucokinase</td>
<td>Mild fasting hyperglycemia; rare complications; diet</td>
</tr>
<tr>
<td>MODY3</td>
<td>TCF1/HNF-1α</td>
<td>Progressive; may require insulin; respond to SU</td>
</tr>
<tr>
<td>MODY4</td>
<td>Pdx1/IPF1</td>
<td>Pancreatic agenesis</td>
</tr>
<tr>
<td>MODY5</td>
<td>TCF2/HNF-1β</td>
<td>Renal (cysts, dysplasia), uterine, and GU disorders</td>
</tr>
<tr>
<td>MODY6</td>
<td>NeuroD1</td>
<td>3 cases; may require insulin</td>
</tr>
<tr>
<td>MODY7</td>
<td>KLF11</td>
<td>Regulator of Pdx1 (MODY4)</td>
</tr>
<tr>
<td>MODY8</td>
<td>Carboxyl ester lipase</td>
<td>&gt;50% diabetic mutation carriers require insulin</td>
</tr>
<tr>
<td>MODY9</td>
<td>Pax4</td>
<td>Progressive; may require insulin</td>
</tr>
<tr>
<td>MODY10</td>
<td>Insulin</td>
<td>Associated with neonatal diabetes, &lt; 1% cases</td>
</tr>
</tbody>
</table>

**MODY = Maturity Onset Diabetes of Young**
Pancreatic Exocrine and Endocrine Cells Share Common Heritage

Figure – M. Gannon, adapted
MODY and Type 2 Diabetes are Different

[Graph showing glucose levels over 24 hours for Normal, Glucokinase-related MODY, Type 2 diabetes, with arrows indicating breakfast, lunch, and dinner times.]
## MODY and Type 1 Diabetes are Different

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MODY</th>
<th>Type 1 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Onset</td>
<td>Adolescence, young adult</td>
<td>Childhood, adolescence, young adult</td>
</tr>
<tr>
<td>Family history</td>
<td>80-90% (dominant pattern)</td>
<td>&lt; 25%</td>
</tr>
<tr>
<td>Body habitus</td>
<td>Not obese</td>
<td>Not obese</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>Absent</td>
<td>Antibodies +</td>
</tr>
<tr>
<td>Insulin deficiency</td>
<td>Partial (no DKA)</td>
<td>Almost complete</td>
</tr>
</tbody>
</table>
MODY and Type 2 Diabetes are Different

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MODY</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inheritance</td>
<td>Monogenic</td>
<td>Polygenic</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>Childhood, adolescence, young adult</td>
<td>Usually age 40-60 years</td>
</tr>
<tr>
<td>Penetration</td>
<td>80-90%</td>
<td>Variable (10-40%)</td>
</tr>
<tr>
<td>Body habitus</td>
<td>Not obese</td>
<td>Obese (80%)</td>
</tr>
<tr>
<td>Features of Metabolic Syndrome</td>
<td>Absent</td>
<td>Often present</td>
</tr>
</tbody>
</table>
Neonatal Diabetes

- Occurs in first six months of life
- Due to gain-of-function mutations in SUR or Kir6.2 subunits of ATP-sensitive potassium channel (Kir6.2 > SUR1)
- Mutations prevent ATP from closing channel so glucose does not stimulate insulin secretion
- Phenotypically looks like type 1 diabetes (insulin deficiency)
Kir6.2 Mutations and Neonatal Diabetes

Yellow shows site of mutations on the intracellular side of the Kir6.2 protein

Some of these mutations are inherited; some are sporadic.

NEJM 350:1838, 2006
Neonatal Diabetes

- Sometimes neonatal diabetes can be treated with a sulfonylureas.
- Closes the ATP-sensitive potassium channel or alters sensitivity to closure by ATP generated by glucose metabolism.
Neonatal Diabetes

- **Sulfonylureas** (glyburide, glipizide)
  - Drugs used to treat type 2 diabetes
  - Not effective in type 1 diabetes because beta cells have been destroyed
  - Bind to SUR (sulfonylurea receptor) part of the ATP-sensitive potassium channel
  - Binding closes ATP-sensitive potassium channel and leads to insulin secretion
What do we know about human islet function?

- Available for basic research and clinical transplantation through NIH and JDRF supported distribution program
- Isolated from normal and T2DM cadaveric donors
Differences between Human and Mouse Islets

- Architecture
- Cell composition
- Proliferative capacity
- Susceptibility to injury
- Expression of heat-shock proteins, antioxidant enzymes
- Expression of principal glucose transporter, GLUT-1 vs GLUT-2
Interspecies Differences in Islet Architecture

Human islet

Mouse islet

β cells/α cells/δ cells
Interspecies Differences in Islet Architecture

Mouse

Non-human primate

Human

Brissova et al., J Histochem Cytochem (2005) vol. 53 (9) pp. 1087-97
Adult Human Islets Have Fewer β Cells and are Heterogeneous in Composition


Brissova et al., J Histochem Cytochem (2005) vol. 53 (9) pp. 1087-97
Human Islets Release Less Insulin in Response to Glucose Than Mouse Islets

Human islets (n=14)

Mouse islets (n=4)
...from Human to Mouse
Phenotypic Characterization of MODY4

- Hyperglycemic clamp

NM - subjects with Pdx1 mutation
NN - subjects without Pdx1 mutation
Impaired Glucose Tolerance in Pdx1^{+/−} Mice

Brissova et al., JBC, 2002
Islet Genes Regulated by Pdx1

- Insulin
- GLUT2
- Islet amyloid polypeptide (IAPP)
- Glukokinase
- Somatostatin
β Cell Genes Have Differential Sensitivity to Level of Pdx1 Activity

Pancreatic peptide content

<table>
<thead>
<tr>
<th>Gene</th>
<th>Insulin Content/ Pancreatic Protein µg/mg</th>
<th>Glucagon Content/ Pancreatic Protein ng/mg</th>
<th>IAPP Content/ Pancreatic Protein ng/mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pdx1+/+</td>
<td>17.5 ± 1.6 (n = 9)</td>
<td>365 ± 31 (n = 13)</td>
<td>411 ± 46 (n = 14)</td>
</tr>
<tr>
<td>Pdx1+/-</td>
<td>18.0 ± 3.5 (n = 12)</td>
<td>470 ± 40a (n = 10)</td>
<td>278 ± 33a (n = 15)</td>
</tr>
</tbody>
</table>

ap < 0.05 compared with Pdx1+/+

Brissova et al., JBC, 2002
Effect of Reduced Pdx1 Expression on β Cell Function

- **Pdx1 Expression**
  - Transcription Factors
  - IAPP
  - GLUT2
  - GK

- **Other β cell Gene(s)**

- **Glucose-Stimulated Insulin Secretion**
Insulin Secretion

Insulin Secretory Responses of \textit{in situ} Perfused Pdx1\textsuperscript{+/−} Pancreas

- Reduced responses to glucose, KIC and KCl pointed to defects in mitochondrial function and/or intracellular calcium levels.

- Preserved insulin response to GLP-1 suggested that insulin exocytosis is normal in Pdx1\textsuperscript{+/−} β cells.

Brissova et al., JBC, 2002
Perifusion of Isolated Pdx1\textsuperscript{+/-} Islets