Diagnosis of Type 1 Diabetes
## Differential Diagnosis of Type 1 and Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual clinical course</td>
<td>Insulin-dependent</td>
<td>Initially non-insulin-dependent</td>
</tr>
<tr>
<td>Usual age of onset</td>
<td>&lt;20 years (but ~50% over 20 years)</td>
<td>&gt;40 years but increasingly earlier</td>
</tr>
<tr>
<td>Body weight</td>
<td>Often lean but ~50% overweight or obese</td>
<td>Usually obese</td>
</tr>
<tr>
<td>Onset</td>
<td>Often acute</td>
<td>Subtle, slow</td>
</tr>
<tr>
<td>Ketosis prone</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Family history</td>
<td>≤15% with 1st-degree relative</td>
<td>Common</td>
</tr>
<tr>
<td>Frequency of HLA-DR3, DR4, DQB1*0201, *0302</td>
<td>Increased</td>
<td>Not increased</td>
</tr>
<tr>
<td>Islet autoantibodies (GADA, ICA, IA-2A, IAA, ZNT8A)</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

GADA, glutamic acid decarboxylase; HLA, human leukocyte antigen; IAA, autoantibodies to insulin; IA-2A, tyrosine phosphatase insulinoma antigen; ZnT8A, zinc transporter 8.

*Needs to be refined for nonwhite population groups.

### Classifying Diabetes

<table>
<thead>
<tr>
<th>High-risk HLA*</th>
<th>IAA+ GADA+ IA-2A+ or ZnT8A+</th>
<th>Autoantibody negative at onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR3/4, DQ1B1*0302, DR4/4, DR4/8, DR3/3 (10% of T1D population)</td>
<td></td>
<td>C-peptide (ng/mL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>HLA+</td>
<td>T1aD = 80%</td>
<td></td>
</tr>
<tr>
<td>HLA-</td>
<td></td>
<td>T1bD 5%</td>
</tr>
</tbody>
</table>

GADA, glutamic acid decarboxylase; HLA, human leukocyte antigen; IAA, autoantibodies to insulin; IA-2A, the tyrosine phosphatase insulinoma antigen; ZnT8A, zinc transporter 8; T1aD, type 1 (immune-mediated) diabetes; T1bD, type 1 (idiopathic) diabetes; T2D, type 2 diabetes.

*Needs to be refined for nonwhite population groups.

Rewers M. *Diabetes Metab J.* 2012;36:90-97.
Etiologic Classification of Diabetes

- **Insulin deficient**
  - **Immune mediated**
    - **Type 1a**
      - Typical (HLA-DR3, 4, or 9)
      - Slow progressing
      - LADA
      - APS1, IPEX
    - **Type 1b**
      - Fulminant
      - Idiopathic
  - **Nonimmune mediated**
    - Typical (~5% – 20% of all DM)

- **Insulin deficient/resistant**
  - **Monogenic**
    - MODY
      - HNF4A
      - GCK
      - HNF1A, 1B
      - PDX1
      - NeuroD1
  - **Polygenic**
    - PNDM
      - KCNJ11
      - ABCC8
      - INS
      - PTF1A
      - EIF2AK3

Rewers M. *Diabetes Metab J.* 2012;36:90-97.
Genetic Defects of β-Cell Function

- Chromosome 12, HNF-1α (MODY3)
- Chromosome 7, glucokinase (MODY2)
- Chromosome 20, HNF-4α (MODY1)
- Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
- Chromosome 17, HNF-1β (MODY5)
- Chromosome 2, NeuroD1 (MODY6)
- Mitochondrial DNA

Immune-Mediated Diabetes (T1a Diabetes)

**β-Cell Destruction**
- Variable rate
  - Rapid in infants and children (primarily)
  - Slow in adults (primarily)

**Immune Markers**
- Islet cell autoantibodies
- Autoantibodies to insulin
- Autoantibodies to GAD (GAD65)
- Autoantibodies to the tyrosine phosphatases IA-2 and IA-2b

When fasting hyperglycemia is first detected, 85% – 90% of individuals have ≥1 autoantibody

Genetic Markers

• Strong HLA associations, with linkage to the DQA and DQB genes
• Influenced by the DRB genes
• HLA-DR/DQ alleles can be either predisposing or protective

HLA, human leukocyte antigen.
Symptoms and Severity of T1D at Presentation

EURODIAB (N=1260)

Presenting Symptoms

- Polyuria: 96%
- Weight Loss: 61%
- Fatigue: 52%

DKA at Presentation

- Severe DKA: 42%
- DKA: 9%
  - 33% with pH 7.1-7.3
  - 9% with pH <7.1

DKA, diabetic ketoacidosis; T1D, type 1 diabetes.

T1D Age at Diagnosis Among Youth

SEARCH for Diabetes in Youth
Youth Age ≤19 Years, 2012

Cases per 100,000 youths/year

Individuals ≥20 years of age may also develop T1D.

Immunological Changes and Incidence of Type 1 Diabetes

• Rising incidence of T1D is associated with altered immunophenotype at diagnosis
• Prevalence of IA-2A and ZnT8A has increased significantly
• IAA and GADA prevalence and levels have not changed
• Suggests T1D is now characterized by a more intense humoral autoimmune response

IAA, autoantibodies to insulin; GADA, GAD; IA-2A, islet antigen-2; T1D, type 1 diabetes; ZnT8A, zinc transporter 8.
Ketoacidosis in T1D

- First manifestation of T1D in many patients, especially children and adolescents
- May be precipitated by infection or environmental triggers
  - Rapid change from modest fasting hyperglycemia to severe hyperglycemia
- In some patients (especially adults), residual β-cell function may prevent ketoacidosis for many years
  - Once patients become insulin dependent (with low or undetectable plasma C-peptide), they are at risk for ketoacidosis

T1D, type 1 diabetes.
T1D and Obesity

- Although T1D patients are rarely obese when they present, the presence of obesity is not incompatible with T1D

T1D, type 1 diabetes.
T1D: Clinical Course

• Typically characterized by the acute onset of the classic symptoms of diabetes
  – Polyuria, polydipsia, weight loss

• Course of autoimmune diabetes characterized by ongoing β-cell destruction

• Exogenous insulin required for survival
  – T1D should be identified as soon as possible to avoid high morbidity due to a delay in insulin treatment

T1D, type 1 diabetes.
T1D and Susceptibility to Other Autoimmune Diseases

- Addison’s disease
- Autoimmune hepatitis
- Celiac sprue
- Graves’ disease
- Hashimoto’s thyroiditis
- Myasthenia gravis
- Pernicious anemia
- Vitiligo
Idiopathic Diabetes (Type 1b Diabetes)

- No known etiology
- Strongly inherited
  - No immunological evidence for β-cell autoimmunity and no HLA association
  - More common with African or Asian ancestry
- Patient presentation
  - May have permanent insulinopenia
  - Prone to ketoacidosis, with varying degrees of insulin deficiency between episodes

Fulminant T1D

- Presentation
  - Extremely high glucose levels with diabetic ketoacidosis
  - On average only 4 days of hyperglycemia
  - Normal or near-normal A1C

- Often preceded by common cold–like and gastrointestinal symptoms
- Sometimes associated with pregnancy
- Pancreatic enzymes often elevated

T1D, type 1 diabetes.