Pathophysiology of Type 1 Diabetes
Type 1 Diabetes Mellitus

- Characterized by absolute insulin deficiency
- Pathophysiology and etiology
  - Result of pancreatic beta cell destruction
    - Prone to ketosis
  - Total deficit of circulating insulin
  - Autoimmune
  - Idiopathic
Type of Diabetes in Youth by Race/Ethnicity and Etiology

**SEARCH for Diabetes in Youth Study**
(N=2291)

<table>
<thead>
<tr>
<th>Etiologic Categories</th>
<th>NHW</th>
<th>Hispanic</th>
<th>AA</th>
<th>API</th>
<th>AI</th>
<th>Total</th>
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<tbody>
<tr>
<td>Non-autoimmune + IR</td>
<td>6.2</td>
<td>28.3</td>
<td>40.1</td>
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<td>67.8</td>
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<td>3.2</td>
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<tr>
<td>Autoimmune + IR</td>
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<td>15.1</td>
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<td>33.3</td>
<td>16.1</td>
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</tbody>
</table>

AA, African American; AI, American Indian; API, Asian/Pacific Islander; IR, insulin resistant; IS, insulin sensitive; NHW, non-Hispanic white.

Type 1 Diabetes Pathophysiology

- β-cell destruction
  - Usually leading to absolute insulin deficiency
- Immune mediated
- Idiopathic

CD8, cluster of differentiation 8; FasL, Fas ligand; IFN-γ, interferon γ; IL-1, interleukin 1; MHC, major histocompatibility complex; NO, nitric oxide; TNF-α, tumor necrosis factor α.

Pathophysiologic Features of Type 1 Diabetes

- Chronic autoimmune disorder
  - Occurs in genetically susceptible individuals
  - May be precipitated by environmental factors

- Autoimmune response against
  - Altered pancreatic β-cell antigens
  - Molecules in β-cells that resemble a viral protein

- Antibodies
  - Approximately 85% of patients: circulating islet cell antibodies
  - Majority: detectable anti-insulin antibodies
  - Most islet cell antibodies directed against GAD within pancreatic β-cells

GAD, glutamic acid decarboxylase.
Trends in T1D Immunophenotype at Diagnosis

- Prevalence of IA-2A and ZnT8A has increased significantly, mirrored by raised levels of IA-2A, ZnT8A, and IA-2β autoantibodies (IA-2βA).
- IAA and GADA prevalence and levels have not changed.
- Increases in IA-2A, ZnT8A, and IA-2βA at diagnosis during a period of rising incidence suggest that the process leading to type 1 diabetes is now characterized by a more intense humoral autoimmune response.

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

Autoimmune Basis for Type 1 Diabetes

Models for Pathogenesis of T1D

Models for Pathogenesis of T1D

Models for Pathogenesis of T1D: Fertile Field Hypothesis

How Type 1 Diabetes Might Arise

Insulin and Glucose Metabolism

**Major Metabolic Effects of Insulin**

- Stimulates glucose uptake into muscle and adipose cells
- Inhibits hepatic glucose production

**Consequences of Insulin Deficiency**

- Hyperglycemia $\rightarrow$ osmotic diuresis and dehydration
Major Metabolic Effects of Insulin and Consequences of Insulin Deficiency

- **Insulin effects**: inhibits breakdown of triglycerides (lipolysis) in adipose tissue
  - Consequences of insulin deficiency: elevated FFA levels

- **Insulin effects**: inhibits ketogenesis
  - Consequences of insulin deficiency: ketoacidosis, production of ketone bodies

- **Insulin effects in muscle**: stimulates amino acid uptake and protein synthesis, inhibits protein degradation, regulates gene transcription
  - Consequences of insulin deficiency: muscle wasting