Type 1 and Type 2 Diabetes

Disease Overview
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β- and α-Cells in the Pancreas of Normal Individuals

<table>
<thead>
<tr>
<th>β-Cells</th>
<th>α-Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprise about 70%-80% of the endocrine mass of the pancreas</td>
<td>Comprise about 15% of the endocrine mass of the pancreas</td>
</tr>
<tr>
<td>Located in the central portion of the islet</td>
<td>Located in the periphery of the islet</td>
</tr>
<tr>
<td>Produce insulin and amylin</td>
<td>Produce glucagon</td>
</tr>
<tr>
<td>Insulin released in response to elevated blood glucose levels</td>
<td>Glucagon released in response to low blood glucose levels</td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Non-autoimmune + IR</th>
<th>Non-autoimmune + IS</th>
<th>Autoimmune + IR</th>
<th>Autoimmune + IS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHW-Hispanic</td>
<td>22.9</td>
<td>42.7</td>
<td>18.0</td>
<td>19.5</td>
</tr>
<tr>
<td>Hispanic</td>
<td>28.5</td>
<td>42.7</td>
<td>18.5</td>
<td>19.5</td>
</tr>
<tr>
<td>AA</td>
<td>45.7</td>
<td>45.7</td>
<td>18.5</td>
<td>19.5</td>
</tr>
<tr>
<td>API</td>
<td>28.5</td>
<td>42.7</td>
<td>18.0</td>
<td>19.5</td>
</tr>
<tr>
<td>AI</td>
<td>18.0</td>
<td>19.5</td>
<td>19.5</td>
<td>19.5</td>
</tr>
<tr>
<td>Total</td>
<td>22.9</td>
<td>42.7</td>
<td>18.0</td>
<td>19.5</td>
</tr>
</tbody>
</table>

Type 1 Diabetes Pathophysiology

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

**Autoimmune Reaction**

**Macrophage**

**Dendritic cell**

**β-cell Destruction**

**Inflammation**

- T cell
- TNF-α
- IFN-γ
- FasL

**Autoimmune Response**

- Class I MHC
- Class II MHC

**CD8+ T cell**


- **b-cell destruction** – Usually leading to absolute insulin deficiency
- **Immune mediated**
- **Idiopathic**

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

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

Clinical Presentation of Type 2 Diabetes

- Age ≥45 years
- Family history of T2D or cardiovascular disease
- Overweight or obese
- Sedentary lifestyle
- Non-Caucasian ancestry
- Previously identified IGT, IFG, and/or metabolic syndrome
- PCOS, acanthosis nigricans, or NAFLD
- Hypertension (BP >140/90 mmHg)
- Dyslipidemia (HDL-C <35 mg/dL and/or triglycerides >250 mg/dL)

Risk Factors for Prediabetes and Type 2 Diabetes

- History of gestational diabetes
- Delivery of baby weighing >4 kg (>9 lb)
- Antipsychotic therapy for schizophrenia or severe bipolar disease
- Chronic glucocorticoid exposure
- Sleep disorders
  - Obstructive sleep apnea
  - Chronic sleep deprivation
  - Night shift work
Development of Type 2 Diabetes Depends on Interplay Between Insulin Resistance and β-Cell Dysfunction

Genes & environment

Insulin resistance

Genes & environment

Normal β-cell function

Compensatory hyperinsulinemia

No diabetes

Insulin resistance

Abnormal β-cell function

Relative insulin deficiency

Type 2 diabetes


Etiology of β-cell Dysfunction

Genetic predisposition

Obese phenotype

Lean phenotype

Increased FFA

Oxidative stress and glucotoxicity

Cellular lip synthesis and glucotoxicity

Hyperglycemia

Progressive β-cell failure and type 2 diabetes


Pathophysiology of Type 2 Diabetes

Organ System

Defect

Major Role

Pancreatic beta cells

Decreased insulin secretion

Muscle

Increased endogenous glucose secretion

Liver

Increased endogenous glucose secretion

Contributing Role

Adipose tissue

Increased FFA production

Digestive tract

Decreased incretin effect

Pancreatic alpha cells

Increased glucagon secretion

Kidney

Increased glucose reabsorption

Nervous system

Neurotransmitter dysfunction


Tissues Involved in T2D Pathophysiology

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Normal Metabolic Function</th>
<th>Defect in T2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Role</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic beta cells</td>
<td>Secretes insulin</td>
<td>Decreased insulin secretion</td>
</tr>
<tr>
<td>Muscle</td>
<td>Metabolizes glucose for energy</td>
<td>Insufficient glucose uptake</td>
</tr>
<tr>
<td>Liver</td>
<td>Secretes glucose during fasting periods to maintain brain function; major site of gluconeogenesis (glucose production in the body)</td>
<td>Increased endogenous glucose secretion</td>
</tr>
<tr>
<td>Contributing Role</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>Secretes glucose, which stimulates hepatic glucose production between meals and also helps suppress insulin secretion during fasting periods</td>
<td>Increased FFA production</td>
</tr>
<tr>
<td>Digestive tract</td>
<td>Digests and absorbs carbohydrates and secretes incretin hormones</td>
<td>Decreased incretin effect</td>
</tr>
<tr>
<td>Pancreatic alpha cells</td>
<td>Secretes glucagon, which stimulates hepatic glucose production and also helps suppress insulin secretion during fasting periods</td>
<td>Increased glucagon secretion</td>
</tr>
<tr>
<td>Kidney</td>
<td>Releases glucose from renal filtrate to maintain glucose at steady-state levels; also an important site for glucose reabsorption</td>
<td>Increased glucose reabsorption</td>
</tr>
<tr>
<td>Brain</td>
<td>Releases glucose for brain and nerve function</td>
<td>Neurotransmitter dysfunction</td>
</tr>
</tbody>
</table>


Natural History of Type 2 Diabetes

Years from diagnosis

Insulin resistance

Insulin secretion

Insulin resistance

Diabetes

Macrovascular complications

Microvascular complications

Postprandial glucose

Fasting glucose

Probiotics

Type 2 diabetes


Figure courtesy of CADRE.
β-cell Loss Over Time

Data points from obese UKPDS population, determined by HOMA model.

Hyperglycemia in Type 2 Diabetes Results from Abnormal Insulin and Glucagon Dynamics

Normal Glucose Homeostasis and Pre- and Postmeal Insulin and Glucagon Dynamics

Acute Insulin Response Is Reduced in Type 2 Diabetes

Defective Insulin Action in Type 2 Diabetes

Elevated Fasting Glucose in Type 2 Diabetes Results From Increased HGP
The Incretin Effect Is Diminished in Type 2 Diabetes

Normal Glucose Tolerance (n=8)

Type 2 Diabetes (n=14)

Plasma Glucose (mg/dL)

0 60 120 180 240

IV Glucose

Oral Glucose

GLP-1

• Released from L cells in ileum and colon
• Stimulates insulin release from β-cell in a glucose-dependent manner
• Potent inhibition of gastric emptying
• Potent inhibition of glucagon secretion
• Reduction of food intake and body weight
• Significant effects on β-cell growth and survival

GIP

• Released from K cells in duodenum
• Stimulates insulin release from β-cell in a glucose dependent manner
• Minimal effects on gastric emptying
• No significant inhibition of glucagon secretion
• No significant effects on satiety or body weight
• Potential effects on β-cell growth and survival

Actions of GLP-1 and GIP

Renal Glucose Reabsorption in Type 2 Diabetes

• Sodium-glucose cotransporters 1 and 2 (SGLT1 and SGLT2) reabsorb glucose in the proximal tubule of kidney
  – Ensures glucose availability during fasting periods
• Renal glucose reabsorption is increased in type 2 diabetes
  – Contributes to fasting and postprandial hyperglycemia
  – Hyperglycemia leads to increased SGLT2 levels, which raises the blood glucose threshold for urinary glucose excretion

Renal Glucose Handling of Glucose

(180 L/day) (90 mg/dL) x 162 g glucose per day

Glucose

SGLT2

90% of glucose

10% of glucose

SGLT1

S3

S1

Renal Glucose Excretion

Increased SGLT2 Protein Levels Change Glucose Reabsorption and Excretion Thresholds

Reabsorption

Excretion

TmG

TmG

Blood Glucose Concentration (mg/dL)

Blood Glucose Concentration (mg/dL)

Hypothalamic Dopaminergic Tone and Autonomic Imbalance

In diabetes:
Low dopaminergic tone in hypothalamus in early morning

Sympathetic tone
HPA axis tone
Hepatic gluconeogenesis
FFA and TG
Insulin resistance
Inflammation/hypercoagulation

Impaired glucose metabolism
Hyperglycemia
Insulin resistance
Adverse cardiovascular pathology


ADDICTION

Changes to DSM in new edition: no longer dichotomy between abuse and dependence
Addiction now the preferred term instead of dependence.
Addiction now seen as a continuum.

Substance use disorder requires 2 of following:
tolerance inability to stop
withdrawal problems excessive spending or effort
use more than intended to obtain
reduced involvement continued use

What is addiction?
• heroin addiction
• cocaine addiction
• alcohol addiction ("alcoholism")
• marijuana addiction
• amphetamine addiction
• nicotine addiction

What is addiction?
• sex addiction??
• gambling addiction??
• food addiction??
• shopping addiction????
• internet addiction????
• cell phone addiction????

Vulnerability
Why do some people become addicted while others do not?

True or False
Prescription medications are the most abuse substances in the United States?
True or False

It is safer to abuse prescription medications than street drugs?

True or False

Most people who abuse prescription drugs get them from a drug dealer?

Where do People Obtain Prescription Drugs?

70% of people who abuse prescription medicine get them from a FRIEND or RELATIVE

DA Neurotransmitter

DA Pathway

Activation of the reward pathway by addictive drugs
### DOPAMINE RECEPTOR
1. Decreased in DM2  
2. Control Food Intake  
3. Energy Expenditure  
4. Glucose Metabolism  
5. Increase Resistance  
6. Control Insulin Secretion (acute +, chronic -)  
7. Insulin and DA ReUptake (acute +, chronic -)  
8. Increase Liver Production Glucose  
9. Lipid Metabolism Increase Lipolysis, FFA

### Dopamine Related
1. Schizophrenia/ Depression  
2. Restless Leg Syndrome  
3. ADHD  
4. Prolactinoma  
5. Nausea, Vomiting  
6. Parkinson and other Movement disorders  
7. Obesity?  
8. Metabolic Syndrome?

### Pharmacologic Use
1. Movement Disorders  
2. Prolactinomas  
3. Nausea, Vomiting  
4. Motility Disorders  
5. Mood Disorders  
6. Psychotic Disorders  
7. ADHD  
8. Pain

### ALCOHOL
1. Increase in CARB intake  
2. Increased Hypoglycemia  
3. Decrease hypoglycemia awareness  
4. Confusion over hypoglycemia  
5. Chronic use increase nerve damage  
6. Blurry vision Vasodilation of eye vessels  
7. Decrease activity of secretague  
8. Dyslipidemia

### SMOKING
1. Increase Vascular Disease  
2. Increase Cancer  
3. Decrease Control  
4. Increase Renal Disease  
5. Increase Neuropathic Pain  
6. Increased Amputations

### STIMULANTS
1. Hyperglycemia  
2. Hypoglycemia  
3. Weight Loss  
4. Insulin Resistance  
5. Increase MI and CVA
**Benzodiazepine**
1) Insulin Resistance  
2) Increase Sedentary Life  
3) Increase Metabolic Syndrome  
4) Weight Gain

**Narcotics**
1) Increase Insulin Resistance  
2) Decrease Insulin Secretion  
3) Change in appetite  
4) Memory Change  
5) Mood change  
6) Weight Change  
7) Bowel Habit Change

**CANNABIS**
1) Decrease in Glucose in Intoxication  
2) Increase in Fat Deposition  
3) Increase Appetite  
4) Short Term Memory Loss with Decrease compliance  
5) Decrease coordination

**ANTIPSYCHOTICS**
1) Increase Insulin Resistance  
2) Decrease Insulin secretion  
3) Increase Weight Mainly Central  
4) Dyslipidemia  
5) Increase Prolactin  
6) Increase DM  
7) Cardiovascular Disease

**ACTION POINTS**
1) Avoid Dopamine Altering Medication  
2) Aggressive Life Intervention to Minimize Effects  
3) Pharmacologic Therapy  
4) Seek Professional and Spiritual Help

**OPEN DISCUSSION**