Clinical Presentation of Type 2 Diabetes
Risk Factors for Prediabetes and 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)

- 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

BP, blood pressure; HCL-C, high density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes.

Development of Type 2 Diabetes Depends on Interplay Between Insulin Resistance and β-Cell Dysfunction

Etiology of β-cell Dysfunction

Genetic predisposition

Lean phenotype
- IGT, IFG
  - Oxidative stress and glucotoxicity

Obese phenotype
- Elevated FFA
  - Initial glucolipoadaptation (increased FFA usage)
    - Hyperglycemia
  - Cellular lipid synthesis and glucolipotoxicity
    - Glucolipotoxicity and glucotoxicity

Progressive β-cell failure and type 2 diabetes

Progression to Type 2 Diabetes: “Falling Off the Curve”

EMBS, estimated metabolic body size; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

# Pathophysiology of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Role</strong></td>
<td></td>
</tr>
<tr>
<td>Pancreatic beta cells</td>
<td>Decreased insulin secretion</td>
</tr>
<tr>
<td>Muscle</td>
<td>Inefficient glucose uptake</td>
</tr>
<tr>
<td>Liver</td>
<td>Increased endogenous glucose secretion</td>
</tr>
<tr>
<td><strong>Contributing Role</strong></td>
<td></td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>Increased FFA production</td>
</tr>
<tr>
<td>Digestive tract</td>
<td>Decreased incretin effect</td>
</tr>
<tr>
<td>Pancreatic alpha cells</td>
<td>Increased glucagon secretion</td>
</tr>
<tr>
<td>Kidney</td>
<td>Increased glucose reabsorption</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Neurotransmitter dysfunction</td>
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</tbody>
</table>

DeFronzo RA. *Diabetes*. 2009;58:773-795
## Tissues Involved in T2D Pathophysiology

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Normal Metabolic Function</th>
<th>Defect in T2D</th>
</tr>
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<tbody>
<tr>
<td><strong>Major Role</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic beta cells</td>
<td>Secrete insulin</td>
<td>Decreased insulin secretion</td>
</tr>
<tr>
<td>Muscle</td>
<td>Metabolizes glucose for energy</td>
<td>Inefficient glucose uptake</td>
</tr>
<tr>
<td>Liver</td>
<td>Secretes glucose during fasting periods to maintain brain function; main site of gluconeogenesis (glucose production in the body)</td>
<td>Increased endogenous glucose secretion</td>
</tr>
<tr>
<td><strong>Contributing Role</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adipose tissue (fat)</td>
<td>Stores small amounts of glucose for its own use. When fat is broken down, glycerol is released, which is used by the liver to produce glucose</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>Secrete glucagon, which stimulates hepatic glucose production between meals and also helps suppress insulin secretion during fasting periods</td>
<td>Increased glucagon secretion</td>
</tr>
<tr>
<td>Kidney</td>
<td>Reabsorbs glucose from renal filtrate to maintain glucose at steady-state levels; also an important site for gluconeogenesis (glucose production)</td>
<td>Increased glucose reabsorption</td>
</tr>
<tr>
<td>Brain</td>
<td>Utilizes glucose for brain and nerve function Regulates appetite</td>
<td>Neurotransmitter dysfunction</td>
</tr>
</tbody>
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T2D, type 2 diabetes.
DeFronzo RA. *Diabetes*. 2009;58:773-795
Natural History of Type 2 Diabetes

- Fasting glucose
- Postprandial glucose
- β-Cell function
- Insulin resistance
- Insulin secretion

Years from diagnosis

-10 -5 0 5 10 15

Onset Diagnosis

Macrovascular complications

Microvascular complications

Prediabetes

Type 2 diabetes

Fasting glucose

Postprandial glucose

β-Cell function

Insulin resistance

Insulin secretion

Figure courtesy of CADRE.

β-cell Loss Over Time

Dashed line = extrapolation based on Homeostasis Model Assessment (HOMA) data.

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

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

Just enough glucose to meet metabolic needs between meals

<table>
<thead>
<tr>
<th></th>
<th>Premeal</th>
<th>Postmeal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (µU/mL)</td>
<td>↓ Insulin</td>
<td>↑ Insulin</td>
</tr>
<tr>
<td>Glucagon (pg/mL)</td>
<td>↑ Glucagon</td>
<td>↓ Glucagon</td>
</tr>
<tr>
<td>Glucose (mg %)</td>
<td>↑ HGP</td>
<td>↓ HGP</td>
</tr>
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</table>

Just enough glucose to meet metabolic needs between meals

Modest postprandial increase with prompt return to fasting levels

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

Acute Insulin Response Is Reduced in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Normal (n=85)</th>
<th>Type 2 diabetes (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>80</td>
</tr>
<tr>
<td>30</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>60</td>
<td>80</td>
<td>50</td>
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<td>120</td>
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Plasma IRI (µU/ml)

IRI, immunoreactive insulin.

Defective Insulin Action in Type 2 Diabetes

T2D, type 2 diabetes.
Elevated Fasting Glucose in Type 2 Diabetes Results From Increased HGP

FPG, fasting plasma glucose; HGP, hepatic glucose production; T2D, type 2 diabetes.

The Incretin Effect Is Diminished in Type 2 Diabetes

Normal Glucose Tolerance (n=8)

Type 2 Diabetes (n=14)

*P≤.05.

Actions of GLP-1 and GIP

**GLP-1**
- Released from L cells in ileum and colon
- Stimulates insulin release from $\beta$-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 $\beta$-cell growth and survival

**GIP**
- Released from K cells in duodenum
- Stimulates insulin release from $\beta$-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 $\beta$-cell growth and survival

Drucker DJ. Diabetes Care 2003;26:2929-2940.
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

Normal Renal Handling of Glucose

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

90% of glucose

10% of glucose

No Glucose

Increased SGLT2 Protein Levels Change Glucose Reabsorption and Excretion Thresholds

Reabsorption

Excretion

Reabsorption increases

Excretion threshold increases

Tm,

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