Pathophysiology of Diabetes: beyond insulin and glucagon

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Endocrine Pancreas

- The pancreas is both an endocrine (produces hormones) and an exocrine gland (produces digestive enzymes)
- Houses the islets of Langerhans
  - Secretion of hormones that regulate carbohydrate metabolism
  - Cells
    - Alpha—glucagon
    - Beta—insulin and amylin
    - Delta—somatostatin and gastrin
    - F cells—pancreatic polypeptide

McCance & Heuther. Pathophysiology: The Biological Basis for Disease in Adults and Children. 7th ed. 2015
### Endocrine Pancreas

<table>
<thead>
<tr>
<th><strong>Glucagon</strong></th>
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<tbody>
<tr>
<td>- Secretion is promoted by decreased blood glucose levels</td>
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<tr>
<td>- Stimulates glycogenolysis, gluconeogenesis, and lipolysis</td>
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<tr>
<th><strong>Somatostatin</strong></th>
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<tr>
<td>- Essential in carbohydrate, fat, and protein metabolism</td>
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<tr>
<td>- Possible involvement in regulating alpha and beta cell secretions</td>
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<table>
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<tr>
<th><strong>Amylin (aka Islet Amyloid Polypeptide (IAPP))</strong></th>
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<tbody>
<tr>
<td>- A 37-residue peptide hormone</td>
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<td>- Co-secreted with insulin from the pancreatic β-cells in the ratio of approximately 100:1</td>
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<td>- Plays a role in glycemic regulation by slowing gastric emptying and promoting satiety, thereby preventing post-prandial spikes in blood glucose levels</td>
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<th><strong>Insulin</strong></th>
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<td>- Synthesized from proinsulin; proinsulin is composed of an A chain and a B chain connected by a C peptide.</td>
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<tr>
<td>- Secretion is promoted by increased blood glucose levels, amino acids, free fatty acids, GI hormones, and parasympathetic stimulation of beta (β cells)</td>
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<td>- Facilitates the rate of glucose uptake into the cells</td>
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<td>- Anabolic hormone</td>
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<td>- Synthesis of proteins, lipids, and nucleic acids</td>
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</table>

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Other hormones involved in glucose metabolism

- Growth hormone
- Thyroid hormone
- Cortisol

Incretins: GLP-1 and GIP

- Synthesized in the cells of small intestine
  - GLP-1 (Glucagon-like peptide-1) from L-cells
  - GIP (Gastric inhibitory peptide, aka glucose-dependent insulino- tropic peptide) from K-cells
- Incretin effect: postprandial enhancement of insulin secretion by factors from the gut
  - Insulin response to oral stimulation exceeds that of intravenous
  - Incretin secretion stimulated by CHO in small intestine

- GLP-1 reduces gastric emptying, resulting in a slower rate of absorption of nutrients and may directly reduce food intake
- GLP-1 inhibits glucagon release from the α-cells; GIP is a weaker inhibitor
Glucose Control Is a Multi-organ Process

- Central nervous system
  - Food intake and satiety
  - Hormone regulation
- Peripheral target tissues
  - Glucose uptake and utilization
  - Gluconeogenesis
    - Liver and kidneys
- Pancreas
  - β cells: insulin secretion
  - α cells: glucagon secretion
- Digestive system
  - Glucose absorption
  - Incretin hormones

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Carbohydrate Metabolism Regulation - Traditional Perspective

- Glucose and other metabolites in the bloodstream
- Energy expenditure
- Feeding behavior

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Carbohydrate Metabolism Regulation - Contemporary Perspective

- GLP-1
- Ghrelin
- Amylin
- Adiponectin
- Leptin
- Insulin
### Pathophysiology of Diabetes

A syndrome of disordered glucose metabolism due to either a deficiency of insulin secretion or insulin resistance or a combination of both.

### Diabetes Mellitus

- A syndrome of disordered glucose metabolism due to either a deficiency of insulin secretion or insulin resistance or a combination of both.

### Epidemiology of Diabetes

- 29.1 million people with DM in US (9.3% of population)
- 1.25 million with type 1 and ~28 million with type 2 (with health care costs nearing $274 billion)
  - 2 million people under age 21 have T2DM
  - 11.8 million or 25% of those over 65 y.o. have DM

Types

- Type 1 DM: due to pancreatic islet B cell destruction caused by either an autoimmune process (type 1A) or idiopathic (type 1B)
- Type 2 DM: due to insulin resistance with a defect in compensatory insulin secretion
- Gestational diabetes
- LADA (latent autoimmune diabetes of adulthood)
- MODY types 1-13 (maturity-onset of diabetes of youth)
- Cystic Fibrosis Related Diabetes (CFRD)

Type 1 Diabetes Mellitus (T1D)

- Type 1A
  - Presence of antibodies to insulin, islet cell antibodies (ICA), glutamic acid decarboxylase (GAD), IA-2A, zinc transporter 8 (ZnT8)
  - Stage 1—+ autoimmunity; normoglycemia
  - Stage 2—+ autoimmunity; glucose intolerance
  - Stage 3—+ autoimmunity; symptomatic
- Type 1B
  - idiopathic

Epidemiology

- Approximately 1.25 million individuals with type 1 diabetes
- Overall prevalence of type 1 diabetes has been increasing steadily
- Lifetime prevalence of type 1 diabetes
  - United States: ~0.4%
  - High-incidence countries such as Finland and Sweden: 1%


Incidence of Type 1 diabetes

- Incidence increases by 3.4% each year
- 50% of patients diagnosed before age 20
- 50% of patients diagnosed after age 20
  - Often mistaken for type 2 diabetes—may make up 10% to 30% of individuals diagnosed with type 2 diabetes
  - Autoimmune process slower and possibly different


Pathophysiology of T1D

- T1D is a genetic and autoimmune disease

T1D and Immunity

- T1D is linked to HLA (human leukocyte antigen) class II complex
- HLA (aka Major Histocompatibility Complex) class II is expressed by antigen presenting cells (APCs)
  - APCs are B cells, macrophages, and dendritic cells
  - APCs take an antigen and incorporate it onto the cell surface
    - B cells make antibodies
    - T-helper cells interact with the APC

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Type 1 DM and Genetics

- Polygenic disease
- **IDDM1** (HLA genes): located on chromosome 6p21.3 (HLA DR-DQ haplotypes)
  - HLA-DR3, HLA-DR4, HLA-DQ2, and HLA-DQ8 are positively associated with T1D, while HLA-DR15, HLA-DR14, or HLA-DR7 plus HLA-DQ6, HLA-DQ5, or HLA-DQ3 are negatively associated (protective)
- **INS** (aka **IDDM2 or ILPR**): located on chromosome 11p15.5—codes for insulin


- **PTPN2**: located on chromosome 1p13—enzyme that regulates T cell activation and signaling
- **CTLA-4**: located on chromosome 2q33; codes for molecules involved in T-cell regulation
- 50+ other genes implicated in T1DM
  - Many associated with interferon, interleukins, and T-cells


Gene and Environment

Current theory involves having both the gene and an environmental trigger
  - Viral infection; enteroviruses
  - Diet: early introduction of lactose, gluten
  - Hygiene theory
  - Gut microbiome
Progression of type 1 diabetes

Data from Devendra D et al. BMJ. 2004; 328: 750-754.

Genetic predisposition
Antibodies
Glucose
normal
Overt diabetes
At risk
Progressive loss of insulin release
C-Peptide present
C-Peptide absent (?)
Time
Environmental trigger
New onset diabetes
•Variable insulitis
•β-cell injury
•Multiple β-cell antibodies
•Loss of first phase insulin response

Type 2 Diabetes Mellitus (T2DM)

♦ Initially, a disease of insulin resistance
♦ β cells produce excess insulin
♦ Eventually, the β cells "burn out" and stop producing insulin

Type 2 Diabetes Mellitus

♦ Risk factors
  • Obesity
  • Family h/o T2DM
  • Gestational diabetes
  • Latino, African American, Native American, Asian/Pacific Islanders
    – 15.9% for Native Americans
    – 13.2% for African Americans
    – 12.8% for Latinos
    – 9.0% for Asian Americans
    – 7.6% for non-Hispanic Whites

Impaired insulin production and secretion

Hyperinsulinemia, normal glucose tolerance

IR + declining insulin levels + impaired glucose tolerance

Type 2 diabetes

Two of the Underlying Defects in Type 2 Diabetes - IR and β-Cell Dysfunction

Macrovascular complications

Insulin resistance: associated conditions

Insulin resistance (IR)

β-cell dysfunction

Failure of β-cell to adapt to IR

Glucotoxicity

Genetic predisposition

Impaired responsiveness to insulin

Impaired insulin production and secretion

IR + declining insulin levels + impaired glucose tolerance

Type 2 diabetes

IR and β-cell Dysfunction From Pre-diabetes Through Diabetes

Macrovascular complications

Impaired glucose tolerance

Diabetes

Normal insulin

Insulin resistance

Insulin secretion

Fasting glucose

Postprandial glucose

Normal blood glucose

Insulin resistance: associated conditions

Atherosclerosis (endothelial dysfunction)

Dyslipidemia

HDL

LDL

TG

Decreased fibrinolytic activity

Acanthosis nigricans

Low-grade inflammation

Hypertension (pre-hypertension)

Impaired glucose tolerance

Obesity (central visceral)

Polycystic ovary disease

Defects in type 2 diabetes: the ‘ominous octet’

- Increased glucagon secretion
- Increased hepatic glucose production
- Decreased insulin secretion
- Hyperglycemia
- Increased lipolysis
- Increased glucose reabsorption
- Decreased glucose uptake

Adapted from DeFronzo Diabetes. 2009; 58(4): 773-795

Classic Signs and Symptoms of Diabetes

- Polyuria—due to osmotic diuresis
- Polydipsia—as above
- Polyphagia—lack of insulin causes a breakdown of protein and fat
- Weight loss
- Headache
- Tachycardia/palpitations
- Blurred vision

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Clinical Diagnosis

- Fasting glucose of 126 mg/dl or higher on more than one occasion
- Symptoms plus a random glucose of 200 mg/dl on any occasion
- 2 hour post load glucose ≥ 200 mg/dl
- HgA1c ≥ 6.5% (glucose~140mg/dL)

Impaired Fasting Glucose

- Fasting blood sugar of 100-125 mg/dl (5.6-6.9 mmol/l)

American Diabetes Association Standards of Medical Care in Diabetes. Classification and Diagnosis of Diabetes. Diabetes Care 2016; 39 (Suppl. 1): S13-S22

Impaired Glucose Tolerance

- An abnormal 2 hour postprandial blood sugar (140-199 mg/dl)

American Diabetes Association Standards of Medical Care in Diabetes. Classification and Diagnosis of Diabetes. Diabetes Care 2016; 39 (Suppl. 1): S13-S22

Gestational Diabetes Mellitus

- 2 hour GTT is considered positive if there are two or more abnormal values:
  - Fasting glucose ≥ 92 mg/dl
  - 1 hr. glucose ≥ 180 mg/dl
  - 2 hr. glucose ≥ 153 mg/dl

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Complications of Diabetes

- Microvascular Complications
  - Retinopathy
  - Nephropathy
  - Neuropathy

- Macrovascular Complications
  - Coronary Artery Disease
  - Cerebrovascular Disease
  - Peripheral Arterial Disease

Other co-morbidities

- Hypertension
- Dyslipidemia
- Obesity
- Sleep apnea
- Osteoporosis
- Hypogonadism
- Gastroparesis
- Fatty Liver Disease
- Memory Impairment
- Depression
- Periodontal Disease
- Pancreatitis
- Cancers

Questions?

Thank you for your participation!