Pathology of the Endocrine Pancreas 2018-19

Topics
- Diabetes mellitus
- Pancreatic endocrine tumors

Objectives
- Define the criteria for diagnosing Diabetes Mellitus
- Compare and contrast Diabetes Mellitus, Type 1 and Type 2
- Explain how the presence elevated blood sugars leads to the known macro and micro vascular complications of DM
- Describe the most common neuroendocrine tumors of the pancreas
Review FHB Lectures
Endocrinology 10 and 11
• “normal” blood sugar maintained 70-120mg/dl
• Glucose homeostasis regulation
  – Glucose production - Liver
  – Glucose uptake and utilization – peripheral tissues
    • Skeletal muscle
    • Counter-regulatory hormones
      • Glucagon

Classification
• Diabetes mellitus, type 1
• Diabetes mellitus, type 2
• Secondary - due to other causes
  – Genetic defects in beta cell function
  – Diseases of exocrine function (cystic fibrosis)
  – Drug induced (ie steroids)
• Gestational diabetes mellitus
  – Glucose intolerance during pregnancy

Epidemiology

EPIDEMIC
• #1 cause of
  – Kidney failure
  – Nontraumatic lower limb amputations
  – New cases of blindness among American adults
• Major factor in heart disease and stroke
Diabetes Mellitus Diagnostic Criteria (ADA)

- **Random** glucose >200 mg/dL
  - +Classical signs and symptoms
    - Polyuria, polydypsia, unexplained weight loss
- **Fasting** glucose ≥126 mg/dL
- **Abnormal glucose tolerance test**
  - Carbohydrate load (75g glucose dissolved in water)
  - 2 hours later Blood glucose >200mg/dL
- **HgbA1C ≥ 6.5 percent**

*must be confirmed by a repeat test

Increased Risk for DM

- Impaired fasting glucose – Fasting plasma glucose 100 to 125 mg/dL
- Impaired glucose tolerance – Two-hour plasma glucose value during a 75g OGTT between 140 and 199 mg/dL
- Hemoglobin A1C – A1C 5.7 to 6.4 percent

Diabetes Mellitus, Type 1

- Autoimmune
- Pancreatic β cell destruction
  - Insulin DEFICIENCY
- 5-10% cases of diabetes
- Most common subtype when diagnosed <20 years old
- Major linkage to MHC Class I and II genes
  - HLA-DR3 or HLA-DR4 haplotypes
Type I Diabetes Mellitus
Pathogenesis

- Autoimmune
  - Failure of self-tolerance in T-cells
  - Activated T-cells cause β-cell injury
    - CD8 CTLs directly injure β cells
    - TH1 cell injury via cytokines
  - Antibodies
  - Islet auto-antigens
    - Insulin
    - β-cell enzyme glutamic acid decarboxylase (GAD)
    - Islet cell autoantigen 512

"Insulitis" - Chronic inflammation within islet
Insulin deficiency. Pathogenesis of diabetic ketoacidosis secondary to relative insulin deficiency and counterregulatory hormone excess. GFR = glomerular filtration rate.

Diabetes Mellitus, Type 2

- Peripheral Insulin RESISTANCE
- Inadequate secretory response of insulin
- “Relative insulin deficiency”
- 90-95% cases
- Overweight
  - Metabolic Syndrome
- “Adult onset”

Diabetes Mellitus, Type 2 Pathogenesis

- Multifactorial
- Environment
  - Sedentary lifestyle
  - Obesity
- Strong genetic predisposition
  - Not clearly defined
    - Polymorphisms in genes associated with insulin secretion
Increased Free Fatty Acids (FFAs)
- Overwhelm intracellular fatty oxidation pathways
- Toxic intermediates
  - Alterate signaling through insulin-receptor pathways

Adipokines (proteins secreted by adipose tissue)
- Glucose lowering adipokines (leptin, adiponectin) decreased in obesity

Inflammation
- Proinflammatory cytokines secreted in response to excess FFAs and glucose
  - Act at major sites of insulin action

Amyloid deposition in islets
Protein = amylin
Nonketotic Hyperosmolar Coma

- Rare
- Extreme hyperglycemia (>600)
- Serum hyperosmolarity
- Dehydration, free water deficit
- Somnolence, confusion, coma, seizures
- Prototypic patient: NH residents, impaired thirst mechanism, decreased water access

Summary Type 1 vs Type 2 DM

**Onset**
- Type 1: Childhood, adolescence
- Type 2: Usually adults

**Type 1 DM**
- Normal weight or weight loss
- Progressive decrease in insulin levels
- Circulating islet cell autoantibodies
- DKA in absence of insulin therapy

**Type 2 DM**
- Usualy adults
- 80% obese
- Increased blood insulin (early), normal or moderate decrease in insulin (late)
- No islet cell autoantibodies
- Nonketotic hyperosmolar coma more common

Type 1 vs Type 2 DM

**Genetics**
- Type 1: Major linkage to MHC class I and II genes
- Type 2: No HLA linkage; candidate diabetogenic and obesity related genes

**Pathogenesis**
- Type 1: Dysfunction in regulatory T-cells
- Type 2: Insulin resistance in peripheral tissues; overall failure of β-cell compensation
- Multiple obesity related factors linked to insulin resistance
Type I vs Type 2 DM

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Pathology</th>
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<tbody>
<tr>
<td>• Insulitis</td>
<td>• No insulitis</td>
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<tr>
<td>• B-cell depletion, islet atrophy</td>
<td>• Amyloid deposition in islets</td>
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<td>• Mild β-cell depletion</td>
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Chronic Complications of Diabetes Mellitus

- Macrovascular Disease
  - MI
  - Stroke
  - LE ischemia
- Microvascular Disease
  - Retinopathy
  - Nephropathy
  - Neuropathy

Pathogenesis of Complications

- Persistent Glucotoxicity
  - Major pathways
    - Formation of Advanced Glycation End Products (AGES)
    - Activation of Protein Kinase C
    - Intracellular hyperglycemia
    - Generation of fructose-6-phosphate
Formation of Advanced Glycation End Products (AGEs)

- **Nonenzymatic glycosylation (glycation)**
  - Glucose covalently attaches to multiple intra and extracellular proteins nonenzymatically
    - ie Cellular basement membrane proteins
  - Glycation ~ proportion to severity of hyperglycemia

Formation of Advanced Glycation End Products (AGEs)

- Initial glycation products (Schiff bases) labile, can dissociate
- Over time labile products undergo complex chemical rearrangements to form stable **advanced glycosylation end-products (AGEs)**
  - AGE formation permanently alters protein structure, function

Deposition of extracellular matrix
Increase vascular stiffness
Increase vascular permeability

**Cardiovascular Diabetology** 2008 7:29  doi:10.1186/1475-2840-7-29
Result...

- Thickening of basement membranes
- Microangiopathy
- Large vessel injury - atherosclerosis

Hemoglobin A1C

- Hemoglobin formed in new RBCs enters circulation with minimal glucose attached
- Red cells freely permeable to glucose
- Glycation of hemoglobin irreversible
- Glycated Hgb (Hemoglobin A1c) levels serve as marker for glycemic control
  - Goal <7%

Activation of Protein Kinase C

- Protein Kinase C = Enzyme influencing multiple cellular processes
- Intracellular hyperglycemia results in activation of Protein Kinase C
- Downstream effects:
Activation of Protein Kinase C

• Production of VEGF
• Decreased expression of endothelial nitric oxide synthase
  – Elevated endothelin-α (vasoconstrictor) and decreased NO (vasodilator)
• Production of profibrinogenic factors (TGF-β)
  – Increased deposition of extracellular matrix and basement membrane material
• Increased Plasminogen Activator Inhibitor (PAI-1)
  • Reduce fibrinolysis and possible vascular occlusive episodes
• Production of proinflammatory cytokines by vascular endothelium

Result...

• Changes in retinal and renal blood flow, contractility, permeability
  – Retinopathy, Nephropathy
• Promotes hypertension and atherogenesis

Increase in Intracellular Glucose

\[
\text{Glucose + NADPH \rightarrow Sorbitol + NADP}
\]

• Excess glucose metabolized by aldose reductase to sorbitol via NADPH co-factor
  – NADPH also required by enzyme glutathione reductase which regenerates glutathione
  • Glutathione = Key in antioxidant mechanisms

• Note: hyperglycemia induces glucose uptake in tissues that do not depend on insulin – nerves, lenses, blood vessels
Result...

- Intracellular oxidative stress
  - Neuronal affect = peripheral neuropathy

- Increased sorbitol may create osmotic gradient
  - Ocular lens swelling

Generation of fructose-6-phosphate

- Hyperglycemia leads to increased flux of glucose through hexosamine pathway resulting in increased production fructose-6-phosphate
  - End result: Increased production of N-acetyl glucosamine
    - Excess proteoglycans produced
    - Pathologic changes in gene expression
      - Increased TGF, PAI-1
    - Exacerbation of end organ damage

Ophthalmic Complications
Diabetic Retinopathy

- Preproliferative - microvascular changes/hypoxia lead to increased production of VEGF and retinal angiogenesis

- Proliferative - retinopathy caused by new vessel formation on disc, retina, and elsewhere
  - Can lead to hemorrhage and vitreous detachment

Neovascularization
Up to Date 2017
Diabetic Nephropathy Review

- Renal vascular lesions
  - Hyaline arteriosclerosis
- Glomerular lesions
  - Capillary Basement Thickening
  - Diffuse mesangial sclerosis
  - Nodular glomerulosclerosis (Kimmelstiel-Wilson lesion)
- Pyelonephritis

Diabetic Kidney - Review

Diabetic Nephropathy

- Pathogenetic mechanisms include
  - glomerular hyperfiltration
    - dilatation of the afferent (precapillary) glomerular arteriole plays important role in hyperfiltration by raising both intraglomerular pressure and renal blood flow
  - increased production of AGEs
  - hypoxia-inflammation
  - activation of cytokines
Neuropathy

• Peripheral
  – Distal symmetric sensory symptoms
    • Feet > hands
  – Predisposition to ulcer formation; increase risk infection and gangrene

• Autonomic
  – Late manifestation
    • Postural hypotension
    • Incomplete bladder emptying
    • Gastroparesis
Diabetes and Pregnancy

• “Pre-gestational” or “Overt DM”
  – Women with pre-existing DM become pregnant

• Gestational Diabetes
  – Previously euglycemic
  – Develop impaired glucose tolerance, diabetes first time in pregnancy
  – Typically resolves following delivery
    • Majority develop overt DM in 10-20 years

Pregnancy in DM
Newborn/Child Sequela

• Preconception hyperglycemia
  – Increased risk of low birth weight, congenital malformations

• Hyperglycemia later in pregnancy
  – Increased birth weight (macrosomia)
  – Obesity
  – Diabetes later in life

Pancreatic Islet Cell Tumors
Pancreatic Islet Cell Tumors

- aka pancreatic endocrine neoplasms
- Relatively uncommon
- Can be
  - benign or malignant
  - functioning or nonfunctioning
  - single or multiple
  - an individual tumor or part of a multiple endocrine tumor complex

β-Cell Tumors

- Insulinoma (Hyperinsulinism)
  - Most solitary
  - About 90% benign
  - Arise in β-cells

Insulinoma

- Typically mild hypoglycemia
- Clinical triad:
  - glucose < 50mg/dl
  - CNS symptoms; Attacks occur with fast or exercise
  - Resolve with feeding, glucose
- Can have β-cell tumors without hypoglycemia
  - Can also have hyperinsulinism with diffuse islet cell hyperplasia (nesidoblastosis)

Note: Insulinomas are not very common; there are other more common reasons for hypoglycemia.
Insulinomas

- Clinico-pathologic correlation
  - Laboratory findings
    - High circulating levels of insulin
    - High insulin:glucose ratio
  - Surgical removal followed by reversal of hypoglycemia
Gastrinomas

- Gastrin producing cells found in pancreas, duodenum, and in peripancreatic tissue

Gastrinomas

- Clinico-pathologic correlation
  - Zollinger-Ellison Syndrome
    - Hypergastrinemia stimulates gastric acid secretion
    - Peptic Ulceration
    - Ulcers in 90 to 95% of patients
      - Duodenal: gastric ulcers 6:1
      - Multiple
      - Unusual places – jejunum
    - Diarrhea frequently part of ZE syndrome

Gastrinomas

- Treatment
  - Control of gastric acid secretion
  - Excision of neoplasm
    - Tumors often locally invasive
    - Total resection eliminates ZE syndrome
  - Hepatic metastases - shortened life expectancy
Rare(er) Endocrine Tumors of the Pancreas

- Glucagonomas: α-cell tumors presenting with a skin rash, necrolytic migratory erythema, mild diabetes mellitus, often middle aged and older women, diarrhea, high glucagon levels

- Vasoactive Intestinal Polypeptide (VIPoma): severe secretory diarrhea
  - activation of cellular adenylate cyclase, cAMP production results in net fluid and electrolyte secretion into lumen resulting in secretory diarrhea, hypokalemia

Review Questions

- An increase is the number and size of islets is characteristic of non-diabetic newborns of diabetes mothers. Why?

- A patient undergoes lab testing after an overnight fast. Blood sugar is 122 mg/dL. What is your diagnosis?

A 77-year-old man is found unresponsive. On physical examination he has decreased skin turgor. Laboratory studies show a blood glucose of 799 mg/dL. Urinalysis reveals no ketosis or proteinuria, though there is 4+ glucosuria. Which of the following is the most likely diagnosis?
A. Glucagon secreting neuroendocrine tumor
B. Diabetes mellitus type 1
C. Diabetes mellitus type 2
D. Ingestion of many cans of sugary soda