Diabetes: The Basics

Objectives

- Describe the diagnostic criteria for diabetes
- Identify patient characteristics and attributes that increase risk for diabetes
- Describe the societal importance of diabetes and diabetes risk factors
- Discuss the co-morbidities and complications of diabetes

Diabetes

- Metabolic disorders of fuel homeostasis
  - Characterized by:
    - Hyperglycemia
    - Altered lipid metabolism
  - Caused by:
    - Inadequate (or no) insulin secretion and/or
    - Defects in insulin action
  - Results in:
    - Hyperglycemia
    - Chronic complications
Symptoms of Hyperglycemia

- Increased thirst (polydipsia)
- Increased urination (polyuria)
- Increased appetite (polyphagia)
- Weight loss
- Unexplained fatigue
- Sexual dysfunction
- Frequent infections – esp. UTI, skin
- Numbness/tingling – esp. in feet
- Delayed or lack of wound healing

Signs of Hyperglycemia

- Elevated blood glucose
- Glucose in the urine
- Acanthosis nigricans
  - Darker, thick velvety skin in body folds and creases
  - Associated with hyperinsulinemia
  - Insulin deposition in skin leads to hyperplasia

Diagnosis

**Pre-diabetes**
- Impaired Fasting Glucose (IFG)
  - FBG = 100-125 mg/dL
- Impaired Glucose Tolerance (IGT)
  - 2-hr OGTT = 140-199 mg/dL
- Hemoglobin A1C = 5.7-6.4%

**Diabetes** – Non-pregnant adults and children
- Fasting blood glucose ≥ 126 mg/dL OR
- Symptoms of diabetes with random BG ≥ 200 mg/dL OR
- 75 gm OGTT with a 2 hr glucose ≥ 200 mg/dL
- Hemoglobin A1C ≥ 6.5%
- All positive values should be confirmed.
Societal Importance of Diabetes

- Population – 26.5 million with diabetes, 75% are diagnosed
- 8.2% of total US population, 25% of people age 60 or older
- 1.6 million new cases diagnosed in people age 20 or older in 2006
- Direct and indirect costs of care and treatment of diabetes in 2007: – 174 BILLION dollars

Main Classifications

- Type 1
  - Also called IDDM, Type I, or juvenile onset
- Type 2
  - Also called NIDDM, Type II, or adult onset
- Gestational diabetes
  - Also called GDM

Other Causes of Diabetes

- Genetic defects
  - Beta cell function
  - Insulin action
- Secondary Causes
  - Endocrine disorders
  - Pancreatic disorders
- Medications
  - Glucocorticoids (including inhaled), niacin, phenytoin, pentamidine, thyroid hormones, sympathomimetics, protease inhibitors, diazoxide, α-interferon, atypical antipsychotics, GnRH agonists, thiazide diuretics (?)
Physiology Review

- Pancreas
  - Beta cells (Islets of Langerhans)
    - Produce insulin and amylin
    - Insulin stored with C-peptide and co-secreted
  - Alpha cells
    - Regulate glucagon secretion (hepatic glucose output)

Physiology – Insulin Secretion

- Stimulated by glucose > 70 mg/dL
  - In fasting state
    - Small bursts of insulin every 10 minutes
    - Greater bursts every 80-150 minutes
  - Meals/Major stimuli
    - Incretin release leads to large (4-5x baseline) burst that lasts for 2-3 hours
      - First Phase Insulin Release – suppresses glucagon, regulates gastric emptying
      - Second phase insulin release

Physiology – Glucose Homeostasis

- Fasting State – low insulin
  - 75% glucose disposal - NON-insulin dependent tissues
  - Glucose levels maintained by:
    - Counter-regulatory hormones – glucagon, GH, epi
      - Glucagon – prevents hypoglycemia, restores normoglycemia
      - Promote
        - Hepatic gluconeogenesis and glycogenolysis (85% of glucose)
        - glucose transporters on cell surfaces
        - Lipolysis – FFA release
          - Stimulates hepatic glucose output
          - Suppresses glucose uptake

- Non-fasting or Post-meal – high insulin
  - CHO intake
    - glucose
    - β-cell insulin
  - Increased insulin leads to:
    - Suppression of hepatic glucose production
    - Glucagon release from alpha cells inhibited
    - Stimulation of peripheral tissue glucose uptake
      - Binds receptor target sites:
        - glucose transporters on cell surfaces
        - Inhibition of lipolysis in adipocytes
        - Lowers hepatic glucose
        - Increases glucose uptake
        - Anabolic processes – glycogen, protein, lipid synthesis
    - Gene regulation
**Physiology – Glucose Homeostasis**

- **Non-fasting**
  - Glucose utilization
    - 80-85% of glucose taken up by muscles
    - 4-5% of glucose taken up by adipocytes
  - Amylin – co-secreted with insulin in response to food intake
    - Regulates rate of systemic glucose appearance
      - Slows gastric emptying
      - Suppresses glucagon
      - Induces satiety/Reduces food intake

- **Incretins (GLP-1, GIP)**
  - GLP = glucagon-like peptide
  - GIP = glucose-dependent insulinotropic polypeptide
    - Secreted by gut with food intake and glucose > 90 mg/dL
    - Provide incretin effect
      - Signal β-cells to release insulin
      - Suppress glucagon release
      - Slow gastric emptying
      - Increase satiety/Reduce food intake
      - Rapidly inactivated by DPP-4 (dipeptidyl-peptidase)

**Pathophysiology of Diabetes**

- **What goes wrong?**
  - Genetic predisposition
  - External environmental stimuli
    - Trigger autoimmunity to β-cells
    - Leads to β-cell destruction
  - Timeline
    - Protracted preclinical period with (+) immune markers and β-cell destruction
    - Hyperglycemia when 80-90% of β-cells destroyed (Lose insulin and amylin)
    - Transient remission “honeymoon phase”
    - Type 1 diabetes
Pathophysiology – Type 1

- Clinical Course
  - Younger patients – rapid β-cell destruction and presentation with ketoacidosis
  - Young adults – can maintain insulin secretion to prevent ketoacidosis for years
- Latent Autoimmune Diabetes in Adults (LADA)
  - Type 1, but diagnosed at a later age (>30 yo)
  - 14-33% of patients originally diagnosed with Type 2
  - Have immune markers for Type 1
  - Characterized by early failure of oral agents and insulin dependence
- Idiopathic diabetes – No known etiology, No evidence of autoimmunity

Pathophysiology – Type 2

- Usually no identifiable cause
- Risk Factors
  - Family History
  - Overweight/Obesity (BMI ≥ 25)
  - Physical Inactivity
  - Race (Native Americans, Latinos, Asian Americans, African Americans, Pacific Islanders)
  - IGT or IFG
  - Hypertension (>140/90)
  - HDL ≤ 35 mg/dL
  - TG ≥ 250 mg/dL
  - Hx of GDM or baby ≥ 9 lbs.
  - Hx of vascular disease
  - Polycystic ovary disease
  - Acanthosis nigricans

- Insulin resistance with inadequate compensatory increase insulin secretion
- Insulin resistance
  - Dysfunctional glucose utilization at muscle
  - Glucose output from liver not properly inhibited
  - FFA release from adipocytes not properly inhibited
- Defects in insulin secretion
  - At diagnosis
    - 50% reduction in β-cell function, decline continues
    - Abnormal insulin response to hyperglycemia
    - Insufficient amylin secretion
    - Blunted incretin response (GLP-1)
    - Loss of first-phase insulin secretion (no glucagon inhibition)
Pathophysiology – Type 2

- Sites of insulin resistance
  - Peripheral skeletal muscle – PRIMARY
    - Onset of insulin action is delayed
    - Decreased ability to stimulate glucose uptake
      - Leads to ↑ postprandial BG
    - Insufficient glycogen storage
  - Liver
    - More insulin needed to suppress glucose output from glucagon action ➔ increased hepatic output during the fed state
    - Increased glucose production during fasting state leads to ↑ fasting BG

- Adipocyte
  - Need more insulin to inhibit lipolysis in the fed state ➔ increased FFAs
  - Sustained, increased FFAs worsen insulin resistance AND impair insulin secretion
  - FFAs stored as TGs in adipocytes, muscle, and liver
    - Increased fat stores
    - Visceral adipose tissue (VAT) vs. subcutaneous adipose tissue
      - VAT correlated with IR and ↓ rate of lipolysis and FFAs

Pathophysiology – Type 2

- Timeline
  - Extended preclinical period
    - Insulin resistance, hyperinsulinemia, normoglycemia
    - As fasting BG increases from 80-140 mg/dL, insulin concentrations are 2-2.5X normal
    - When fasting BG exceeds 140 mg/dL, β cells cannot maintain insulin secretion
  - Decreased β cell function and insulin secretory defects lead to drop in insulin concentrations
    - Inability to suppress hepatic glucose output and lipolysis ➔ elevated BG
  - Type 2 Diabetes
Microvascular complications

- Pathologic features similar in:
  - Retina
  - Renal glomerulus
  - Vasa nervorum
- Chronic hyperglycemia is initiating factor
- Complications result from:
  - Excessive protein glycation – proportional to glycemic level
    - Advanced glycosylation end-products (AGEs)
      - Stimulate oxidative reactions, resistant to natural degradation, cause structural damage
  - Activation of oxidative stress
    - Enhanced polyol pathway and protein kinase C activation
      - Osmotic cell injury, decreased antioxidant activity
      - Increased growth factor – thickening of basement membrane
      - Increased cell proliferation and vascular permeability
- Results in:
  - Abnormalities in blood flow and vascular permeability
  - Increased pressure and endothelial dysfunction
  - Microvasculature with thicker walls and narrowed lumens
  - Eventual cell death/apoptosis
  - Leads to further damage

Macrovascular complications

- Rapidly progressive and extensive CV disease with diabetes
  - CV risk present before development of hyperglycemia
- Most likely due to insulin resistance
  - Increased FFAs due to insulin resistance in adipocytes
  - Hyperglycemia – is risk factor; resolving hyperglycemia not shown to prevent CV disease
- Timeline
  - Endothelial dysfunction
  - LDL-C infiltrates subendothelial space
  - Formation of oxidized LDL-C
  - Macrophages take up oxidized LDL-C → foam cells
  - Foam cells accumulate → fatty streak → lesion
- Fasting / Pre-prandial
  - ADA Goal = 70 – 130 mg/dL
- 1-2 hrs. Post-prandial
  - ADA Goal = < 180 mg/dL

Glucose Monitoring

- Urine glucose – Very limited usefulness
  - Variable renal glucose thresholds – usually about 180 mg/dL
  - Poor correlation with blood glucose
  - Results do not indicate severity

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Hemoglobin A1C

- Reflects mean glucose for 2-3 months
- Direct relationship to microvascular complications
- Monitor initially, then every 3-6 months
- Goal < 7%, individual pt. factors considered

Fructosamine

- Measure of glycated serum proteins
- Reflects glucose control over 2-3 weeks
- Useful when unexpected HbA1C
- Not shown to be related to diabetes complications
- Not equivalent to HbA1C
- Fructosamine – HbA1C comparison
  \[ 317 \mu mol = 7\%, 375 = 8, 435 = 9, 494 = 10 \]

Ketones

- Recommended for Type 1 DM and pregnancy with DM
- Measured in urine or special glucose meters
- Results can be negative or small, moderate, or large amounts of ketones present
- Measure at times when at risk for DKA

C-peptide

- Amino acid released with insulin from β cells
- Indirect measure of insulin secretion
- Normal value – 0.17 – 0.83 μmol/L
- Uses
  - Distinguish between Type 1 and 2 DM
  - Determine need for insulin with Type 2 DM
**Glycemic Goals - Summary**

- Primary target = HbA1C
- HbA1C goals individualized based on:
  - Duration of DM
  - Age / Life expectancy
  - Co-morbid conditions
  - Hypoglycemic unawareness
- Self-monitored blood glucose
  - Target meeting fasting goals first
  - Target meeting post-prandial if HbA1C goal not met with fasting goals met

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**American Diabetes Association Goal**

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<thead>
<tr>
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<th>Fasting/pre-prandial BG</th>
<th>Post-prandial BG – 1-2hr</th>
<th>HbA1c</th>
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<tbody>
<tr>
<td></td>
<td>70 – 130</td>
<td>&lt; 180</td>
<td>&lt; 7%</td>
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**QUESTIONS?**

Be sure to join us for the additional parts of this series.