Diabetes Mellitus

Pathophysiology

• Literally “sweet urine”
• Defined by excess blood serum glucose
  – Normally all glucose in the PCT is reabsorbed by active transport
  – When blood glucose is elevated, transporters become saturated and glucose “leaks” into urine
• Like hypertension, diabetes is a disease of degree. “Normal” blood glucose is relative

Glucose

• Six carbon simple sugar
• Used as an energy source by most cells
• Used exclusively by some cells, esp. brain
• Absorbed in the GI tract
• Transported in the blood
• Stored in the liver and skeletal muscle as glycogen

Insulin

• Hormone released by beta cells in Islets of Langerhans in the pancreas
• Is required by body cells to initiate active transport of glucose into the cell
  – Skeletal muscle – stores glucose as glycogen
  – Adipose tissue – stops release of fatty acids
  – Liver – stops gluconeogenesis, start producing glycogen and fat
  – Brain does not require insulin for glucose uptake

Other glucose regulating Hormones

• Glucagon – produced by alpha cells
  – Motivates adipose cell release of fatty acids
  – Signals liver to being gluconeogenesis and release glucose stored as glycogen
  – Signals hunger
• Epinephrine – causes release of glycogen
• Cortisol – glucose secretion, hunger
• Growth hormone – glucose secretion

Classifications of DM

• Type I – beta cell destruction
  – Immune mediated
  – Idiopathic
• Type II
• Other
  – Various genetic causes
  – Disease of exocrine pancreas (pancreatitis, cystic fibrosis)
  – Endocrinopathies (e.g. Cushing’s Syndrome)
  – Iatrogenic (steroids, methotrexate, surgery)
  – Infections (CMV)
• Gestational diabetes
Common Symptoms

- Classic triad (the Polys)
  - Polyuria
  - Polydipsia
  - Polyphagia
- Blurred vision
- Life threatening
  - Ketoacidosis
  - Nonketotic Hyperosmolar syndrome
- Chronic
  - Impairment of growth and healing
  - Susceptibility to infections

Long Term Complications

- Macrovascular
  - MI
  - Stroke
  - PAD
- Microvascular
  - Nephropathy
  - Retinopathy - blindness
  - Neuropathy - amputations, gastroparesis,
    - Impotence

Measuring DM

- Fasting plasma glucose (FPG)
- Oral glucose tolerance test (OGTT)
- Casual plasma glucose
- Post prandial plasma glucose
- Glycosuria: Serum glucose > 180
- Glycosylated hemoglobin (HgbA1c)
- Somogyi effect
- Dawn phenomenon

Normal and High Glucose

- Fasting Plasma Glucose (mg/dl)
  - 70 – 99 Normal
  - 100 – 125 Prediabetes (previous impaired glucose tolerance or impaired fasting glucose)
  - >126 Diabetes
- Hgb AIC
  - 3.5 – 5.5% normal
  - 5.6 – 7% controlled diabetes
  - >7% uncontrolled diabetes

General Pathophysiology

- Insulin is not present in adequate amounts or if it does not function adequately
- Insulin dependent cells cannot uptake glucose
  - Glucose levels rise
  - Cells begin to use alternate energy sources: glycogen, fatty acids
  - Cells begin to starve signalling need for more glucose
  - Glucagon and other glucose raising hormones are released

General Pathophysiology

- **Hunger** is stimulated
- **Thirst** is stimulated as osmolarity increases d/t high glucose
- Once serum glucose > 180 glucose spills into urine causing osmolar **Diuresis**.
- Eventually, cells will exhaust glycogen stores and begin
  - Fat becomes primary energy source
  - Protein breakdown
General pathophysiology

- Weight loss 2° polyuria & starving cells
- Ketoacidosis: Ketones, fat metabolism byproducts, begin to accumulate
  - Lowers blood pH: Kussmaul breathing
  - Buffered to acetone and exhaled: fruity breath
- Diabetic coma: If ketoacidosis not reversed
- Glucagon is an exacerbating factor; if glucagon secretion is impaired, the whole process is slowed

Type I DM

- 10% of all DM cases
- Obsolete: Juvenile onset or Insulin Dependent Diabetes Mellitus (IDDM)
- Characterized by destruction of beta cells and subsequent loss of insulin production
- Alpha cells may also be affected (glucagon)
- Destruction usually caused by autoimmune reaction

Type I DM

- Genetic:
  - 10 – 13% of DM-1 patients have first degree relative with disease;
  - HLA-DR and HLA-DQ alleles
- Environmental: seasonal onset; viruses
- Usual onset is childhood or adolescence
  - Peaks at age 12; may delay into 20’s
- Natural Hx: previously thought precipitous
  - Genetic susceptibility: long preclinical period
  - Immune destruction

Type 2 DM

- Most common form of DM in U.S.
- Obsolete: Adult onset or Non-Insulin Dependent Diabetes Mellitus (NIDDM)
- Usually begins in middle age*
- Obesity almost always present (BMI > 30)
- Little risk of ketoacidosis
- Combination
  - Insulin resistance
  - Decreased insulin secretion

Type 1 DM

- Presentation
  - Three polys, Blurred vision, weight loss
  - Often ketoacidosis is first clinical manifestation
  - Spontaneous remission: Honeymoon period
- Treatment
  - Diet
  - Self Blood Glucose Monitoring
  - Exercise
  - Insulin
  - Pancreas transplant

Insulin Resistance

- Receptors:
  - Insulin Receptor
  - Insulin-like Growth Factor receptor (IGF-1)
- Factors
  - Receptor concentration
  - Receptor affinity & function
- Mechanisms
  - Genetic defects
  - Insulin receptor Antibodies
  - Accelerated insulin destruction
Insulin Resistance

- Obesity is most common
  - Decreased number of receptors
  - Failure of receptor to activate
- Skeletal muscle: failure of glut-4 transport
- Compensatory mechanism: secrete more insulin → **hyperinsulinemia**
- Insulin resistance syndromes
  - Metabolic syndrome
  - Type 2 DM, Gestational Diabetes
  - Hyperandrogenism in Polycystic ovary dz

Metabolic Syndrome

- Identifying insulin resistance early: any 3 of the following five symptoms:
  - Waist > 40 inches men; >35 inches women
  - Triglycerides > 150
  - HDL < 40 men; < 50 women
  - BP > 130/85
  - FPG > 100 (prediabetes)

Role of Glucagon

- Increased evidence of importance
- Insulin and Glucagon usually reciprocal
- In DM2 both may be high; amylin is low
- Amylin: hormone secreted by beta cells; inhibits glucagon

Natural History of DM 2

- At risk person: genetics plus age, obesity, sedentary lifestyle, ↑WHR, Gestational DM, Polycystic ovary disease
- Compensatory Hyperinsulinemia develops
- Glucose levels remain normal for years
- Eventually pancreas begins to fail
- Blood glucose levels begin to rise
- **Foot stomp:** patient has the disease process long before clinical DM2 dx

Presentation of DM 2

- Gradual subtle onset, look for risk factors
  - Fam Hx, Obesity, Sedentary, HTN, WHR, low HDL, high triglycerides, polycystic ovary, prediabetes
  - Vascular complications: PAD, MI, Stroke, Endothelial Dysfunction, Impotence
  - Hypercoagulopathy: ↑plasminogen activator
- Later
  - Classic: polys, blurred vision
  - Neuropathy, nephropathy, retinopathy

Treatment of DM 2

- Behavioral modifications
  - Calorie restriction → insulin levels drop before weightloss begins
  - Weightloss
  - Exercise: improves insulin use in muscle cells
  - Increased fiber: reduces glycemic effect
  - Pharmacotherapy
Pharmacotherapeutic strategies
- Stimulate pancreas to secrete more insulin
- Give exogenous insulin
- Increase insulin sensitivity
- Suppress liver gluconeogenesis (inhibits effects of glucagon)
- Delay absorption of carbohydrates

Treatment Approach
- Old thinking
  - Start with secretagogue
  - Then add biguanide (inhibit glucagon activity)
  - Then add thiazolidinediones (TZDs) (reduce insulin resistance)
  - When everything fails, use insulin

Gestational Diabetes
- Any diabetes acquired during pregnancy
- Mechanism is similar to DM 2
- After pregnancy
  - May resolve and never come back
  - May resolve, but patient may develop DM 2 later in life
  - May continue (becomes DM 2)

Other DM Diseases
- Reduce or eliminate secondary causes is possible
- If absolute absence of insulin, Treat like DM1
- If insulin is still being secreted, treat like DM2
- Gestational – special case because of unborn child must be taken into consideration

Complications of DM
- Most likely to kill you: MI, Stroke
- Most likely to make your life living hell
  - PAD: poor wound healing, claudication
  - Neuropathy: see next slide
  - Retinopathy: blindness
  - Nephropathy: proteinuria → CRF → dialysis
  - Impotence

Neuropathy
- Autonomic
  - Gastroparesis: heartburn & constipation
  - Urinary retention
- Peripheral
  - Ulcers, amputations
  - Charcot joints
  - Neuralgia
Pathophysiology

- Beta cells → Insulin → Cells that Require Insulin
  - Number of receptors
  - Receptor Affinity
  - Transport Mechanism

- Alpha Cells → Glucagon → Liver secretes glucose
  - Hunger

- Intestines → Incretin → Decrease Hunger
  - Slow Absorption

Treatment: Traditional Oral Meds
- Insulins
- Secretagogues (Hypoglycemia)
  - Sulfonylurea
  - Metiglinides
- Metformin
- -gltazones
- Glucosidase inhibitors (rarer)

Treatment: New Drugs
- Incretin mimetics (GLP-1): SQ injection
  - Weightloss
- Dipeptidyl peptidase-4 inhibitors
  - Reduces destruction of GLP
- Amylin analog: glucagon antagonist
  - Slows gastric emptying
  - Decreases glucagon emptying