# Diabetes Mellitus

Pathophysiology

## Diabetes Mellitus

- 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 gluceoneogenesis 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 (pancreastitis, 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 D**iuresis**.
- 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 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

## 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

## 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 tryglycerides, polcystic 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 aborption 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

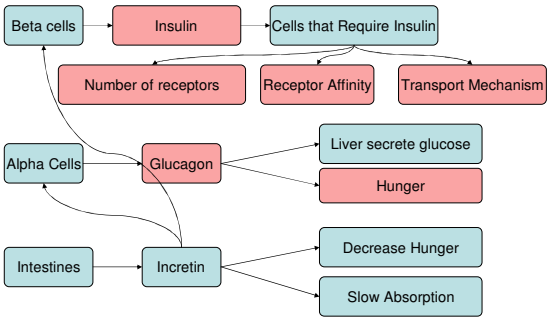
## Complications of DM

- 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




## Treatment: Traditional Oral Meds

- Insulins
- Secretagogues (Hypoglycemia)
  - Sulfonylurea
  - Metiglinides
- Metformin
- -glitazones
- 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 empying
  - Descreases glucagon emptying