PATHOLOGY OF THE ENDOCRINE PANCREAS

DIABETES MELLITUS

- **Definition**
  Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

- **Criteria for the diagnosis of Diabetes Mellitus**

  1. HgbA1C $>6.5$

     OR

  2. Fasting Plasma Glucose $\geq 126 \text{ mg/dl}$ (Fasting is defined as no caloric intake for at least 8 h.)*

     OR

  3. Two-hour plasma glucose $\geq 200 \text{ mg/dl}$ during an oral glucose tolerance test
     The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

     OR

  4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose $\geq 200 \text{ mg/dl}$

*Criteria 1–3 should be confirmed by repeat testing

- **Acute problems with diabetes** usually result from hyperglycemia as seen in either diabetic ketoacidosis or non-ketotic hyperosmolar state.

- **Long term complications** can be devastating and include:
  - Retinopathy
  - Nephropathy
  - Neuropathy
  - Vasculopathy with cardiovascular disease
  - peripheral vascular (arterial) disease
  - cerebrovascular disease
Classification of diabetes mellitus

The classification of diabetes includes four clinical classes:

Type 1 diabetes (results from β-cell destruction, usually leading to absolute insulin deficiency)

Type 2 diabetes (results from a progressive insulin secretory defect on the background of insulin resistance)

Other specific types of diabetes due to other causes, e.g., genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of HIV/AIDS or after organ transplantation)

Gestational diabetes mellitus - women develop glucose intolerance, diabetes mellitus during pregnancy (previously euglycemic); typically resolves after delivery however increased risk of DM in 10-20 years

How do you manage individuals who have a fasting glucose that is too high or Hemoglobin A1C 5.7 to 6.4 percent?

These patients are at increased risk of development of diabetes mellitus.

- A normal fasting plasma glucose is <100 mg/dl
  - A fasting glucose between 100 and 125 is defined as impaired fasting glucose.

Would be aggressive with diet and exercise in these individuals and make sure they are sent to an ophthalmologist, check lipids, BP, and consider cardiovascular risks. Would also follow for development of overt diabetes.

DIABETES MELLITUS, TYPE 1

Basics

- An absolute deficiency of insulin caused by, usually, a cell-mediated, autoimmune destruction of the pancreas.

- Normally presents before age 20 but can occur at any age.

- Classically presents with polyuria, polyphagia, polydipsia. May present with diabetic ketoacidosis as first manifestation (confusion or lethargy, dehydration, tachypnea, Kussmaul respirations, “fruity” breath).
Sometimes presents less dramatically with enuresis, growth retardation, or fasting hyperglycemia discovered incidentally.

- Although discovery/diagnosis of diabetes mellitus, type 1 may occur suddenly, the autoimmune process begins years to months before overt diabetes is recognized. After overt diabetes mellitus appears, there often still remain a few Beta cells and a “honeymoon period” is possible in which, after the newly diagnosed person is treated with exogenous insulin, the remaining Beta cells can secrete enough insulin to avoid hyperglycemia and ketosis for a few months.

- The current understanding of diabetes mellitus, type 1 is that there is a genetic predisposition to developing the disease but a precipitating event (some sort of environmental factor) is required for the beginning of the autoimmune process. Diabetes mellitus, type 1 has strong HLA associations. Best understood that genetics predisposes individuals to the disease but not necessarily the inevitable development of diabetes.

- Review Robbins, Figure 24-30

**Diagnosis of Diabetes Mellitus, Type 1**

- May be obvious. If a child presents sick with classic symptoms and is found to have glucose > 200, very likely to be Type 1 diabetes mellitus.
- Formal criteria – Table 1 (used in the absence of unequivocal hyperglycemia with acute metabolic decompensation)

**Treatment of Type 1 Diabetes Mellitus**

- The fundamental defect is an absolute lack of insulin (contrast with DM, type 2)
  
  Patients must receive exogenous insulin.

  ► The norm increasingly is for intensive treatment with multiple checks of whole blood glucose by finger stick and multiple injections during the day.
  ► The short term goal is to maintain a normal blood glucose and avoid ketoacidosis. The long term goal is to have good measures of glucose control (HgbA1c or glycosylated hgb, usually check every 3-4 months) as well as careful attention to other risks.
  ► The key to success in managing diabetes mellitus is involvement of the patient in his/her own care, careful education, and close follow-up.
  
  ► Hypoglycemia is a serious and common complication of treatment. Low blood glucose can cause altered mental status and progress to seizures and coma. The more aggressive and intensive the insulin therapy, the greater the risk for hypoglycemia. Symptoms include anxiety, sweating,
difficulty with vision, but are unpredictable. With prolonged diabetes and extensive neuropathy, some of these warning symptoms can disappear! Treatment, if person is awake consists of concentrated sweets, juice, cola…if person is confused or obtunded then oral route is dangerous…give glucagon or IV D50W.

➢ DIABETES MELLITUS, TYPE 2

Basics
- Insulin production is inadequate to maintain euglycemia but insulin secretion usually remains until late in disease.
- A very strong genetic component, multiple genes involved, no HLA association. The presence of first-degree relatives with diabetes mellitus, type 2 is a much stronger risk factor for development of the disease than with Type 1.
- A strong association with obesity.
- Insulin resistance is a major factor along with insulin deficiency. Resistance to the effects of endogenous insulin can occur for a variety of reasons, and thus it is likely that diabetes type 2 is a heterogeneous disorder. There is beta cell hypertrophy in diabetes type 2 (early in course of disease) to compensate for diminished effectiveness of insulin, but proves inadequate to prevent an elevated glucose as well as other effects of insulin resistance syndrome. (See below)
- Usually enough insulin to restrain ketone production and prevent diabetic ketoacidosis.
- In severe stress secondary to a serious illness, ketoacidosis may occur in a Type 2 diabetic.

Insulin resistance syndrome
Impaired glucose tolerance and impaired fasting glucose can be precursors of diabetes mellitus, type 2 with a series of other metabolic derangements that increase risks of morbidity and mortality. These include:
- Hyperlipidemia: ↑ triglycerides, ↓ HDL, ↑LDL
- Hypertension
- ↑Plasminogen activator inhibitor 1 with ↓fibrinolysis
- Increased risk of cardiovascular morbidity and mortality
- Obesity
- Associated with hyperandrogenism in women and polycystic ovaries.

Treatment of Diabetes Mellitus, type 2
- Diet and exercise are cornerstones and a motivated, educated patient is crucial for success.
Weight loss can reverse hyperglycemia, especially with impaired fasting glucose and impaired glucose tolerance.

Pharmacotherapy now has a number of options including monotherapy with oral agents, the use of insulin, combination of oral agents, or combination of oral agents and insulin.

Pharmacotherapy should not be a substitute for diet and exercise.

- **Maturity Onset Diabetes of the Young (MODY)**
  - A series of different disorders with genetic specificity involving a chromosomal mutation - genetic defect in β-cell
  - Frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years).
  - Characterized by impaired insulin secretion with minimal or no defects in insulin action.
  - Inherited in autosomal dominant pattern

- **Diabetic emergencies: Diabetic ketoacidosis (DKA) and Non-Ketotic Hyperosmolar State (NKHS)**

  - **Diabetic Ketoacidosis (DKA)**
    - Pathogenesis is lack of insulin resulting in accelerated lipolysis in setting of increased counter regulatory hormones (epinephrine, norepinephrine, cortisol, growth hormone) leading to increased ketogenesis with resultant ketoacidosis.
    - Essentially a disease of diabetes mellitus, type 1 or other diabetic conditions with an absolute lack of insulin.
    - Precipitating causes include sepsis, MI, another major illness, or non-compliance with insulin.
    - Acidosis, dehydration, and derangements in potassium can be life-threatening.
    - Management requires intravenous insulin to shut off ketogenesis and lipolysis, stop hyperglycemia; volume and fluid replacement to counter fluid losses; very careful repletion of potassium and other electrolytes.
    - Potassium may be initially very high in setting of acidosis. With insulin, potassium can drop to dangerously low levels and danger of cardiac arrest.
Non-Ketotic Hyperosmolar State
- Marked hyperglycemia and hyperosmolarity; (blood glucose often much higher than in DKA).
- Little or no ketosis, although may have a metabolic acidosis secondary to lactate formation in the setting of hypoperfusion. Essentially a complication of diabetes mellitus, type 2
- Extreme dehydration is a consequence of massive osmotic diuresis with resultant mental status changes, seizures, diminished consciousness and coma.
- Elderly at special risk because of decreased thirst…not uncommon in hot summer, mild diabetes, no air conditioning.
- Fluid replacement is the key to management.

How does the presence of hyperglycemia translate into the complications of diabetes mellitus?
- The pathogenesis of long-term complications of diabetes is multifactorial, although persistent hyperglycemia (“glucotoxicity”) seems to be a key mediator.
- Multiple pathways have been described that may link high blood glucose levels to associated DM complications.
- Four of the better understood pathways are a) formation of advanced glycation end products, b) activation of protein kinase C and c) intracellular hyperglycemia with disturbances in polyol pathways d)generation of fructose-6-phosphate

a) Formation of Advanced Glycation End Products (AGEs)
- AGEs form from glucose-derived dicarbonyl precursors generated intracellularly in proportion to intracellular hyperglycemia and react with free amino groups in N-terminal amino acids and lysine residues of proteins. (HgbA1c is one such molecule).
- Proteins modified by AGEs have altered function.
  - AGEs bind to a specific receptor (RAGE) which is expressed on inflammatory cells, endothelial cells and vascular smooth muscle. The AGE-RAGE signaling axis leads to detrimental effects in the vascular compartment, including endothelial dysfunction by reducing nitric oxide (NO), producing inflammatory reactions, and leading to oxidative stress.
    Clinical implications: This has shown to result in acceleration of large vessel injury and microangiopathy in animal models.
○ AGEs can directly cross-link extracellular matrix proteins which are resistant to proteolytic digestion. AGE-modified matrix components may trap plasma or interstitial proteins
Clinical implications: In capillaries, including those of renal glomeruli, plasma proteins such as albumin bind to the glycated basement membrane, accounting in part for the basement membrane thickening that is characteristic of diabetic microangiopathy.
In large vessels, trapping of LDL retards its efflux from the vessel wall and enhances deposition of cholesterol in the intima. Leads to acceleration of atherogenesis.

b) Activation of Protein Kinase C
○ Elevated levels of glucose increase levels of protein kinase.
○ Downstream effects of activation of this protein kinase C include
  ► Production of proangiogenic vascular endothelial growth factor (VEGF)
  Clinical implications: VEGF is implicated in the neovascularization of diabetic retinopathy. VEGF inhibitors are now being used in the tx of diabetic retinopathy
  ► Decreased expression of endothelial nitric oxide synthase resulting in elevated endothelin-a (vasoconstrictor) and decreased NO (vasodilator)
  ► Production of profibrinogenic factors (TGF-β) leading to increased deposition of extracellular matrix and basement membrane material
  ► Increased PAI leading to reduced fibrinolysis and possible vascular occlusive episodes
  ► Production of proinflammatory cytokines by vascular endothelium

Clinical implications: Lead to changes in retinal and renal blood flow, contractility, permeability which contribute to the development of Retinopathy, Nephropathy
Promote hypertension and atherogenesis

c) Intracellular Hyperglycemia and Disturbances in Polyol Pathways:
○ When glucose is insufficiently metabolized by insulin-stimulated routes, it can overflow into the sorbitol (polyol) dehydrogenase pathway via the enzymes aldose reductase and sorbitol dehydrogenase.

○ The major effect of the activation of the polyol pathway is to decrease the amount of intracellular glutathione (an important antioxidant), exacerbating oxidative stress.
  Clinical implications: thought to be contributing pathway to development of diabetic neuropathy (“glucose neurotoxicity”); increased intracellular sorbitol can lead to osmotic changes ie eye lens
**d) Increased production of fructose-6-phosphate**

- Normally, most of the glucose that enters the cell is processed through the Krebs cycle, with a small fraction (≈ 3%) passing through the hexosamine (glucosamine) pathway.
- Fructose-6-phosphate is a product and is subsequently converted to glucosamine-6-phosphate and finally to uridine diphosphate (UDP)-N-acetylglucosamine.
  
  **Clinical Implications:** UDP-N-acetylglucosamine can induce tissue damage through modification of intracellular proteins and alteration of gene expression. Chronic hyperglycemia ensures a constant flux through the hexosamine pathway in susceptible cells, thereby increasing the risk of development of complications.

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**Therapeutic importance of elucidating the above 4 pathways?**

It is a challenge to normalize blood glucose levels consistently in diabetics. Drug therapies that intercept pathogenetic processes after hyperglycemia hold promise for preventing complications.

Candidate drugs that are under investigation include inhibitors of PKC, VEGF, aldose reductase, and AGE formation.

Ranibizumab, a monoclonal antibody that inhibits VEGF in the eye, has been approved by the Food and Drug Administration for the treatment of proliferative diabetic retinopathy. Inhibition of VEGF by ranibizumab, which is injected monthly into the vitreous, is associated with improvements in diabetic macular edema and neovascularization.

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**Diabetes Mellitus and Pregnancy**

- **Pre-gestational**” or “Overt DM”
  - Women with pre-existing DM become pregnant
- **Gestational Diabetes**
  - Women previously euglycemic develop impaired glucose tolerance, diabetes first time in pregnancy
    - The milieu of pregnancy favors a state of insulin resistance and can result in gestational diabetes in women with genetic or environmental risks
  - Typically resolves following delivery, however a majority of women develop overt diabetes mellitus in 10-20 years
- **Consequences for neonates, children**
  - With preconception hyperglycemia there is increased risk of low birth weight, congenital malformations
  - Hyperglycemia later in pregnancy has risks for
    - Increased birth weight (macrosomia)
    - Childhood obesity
    - Diabetes later in life

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**PANCREATIC ENDOCRINE NEOPLASMS**

**Basics**

- Also known as pancreatic islet cell tumors
○ Rare compared to neoplasms of the exocrine pancreas
○ They may be functional (elaborate pancreatic hormones) or nonfunctional, single or multiple, benign or malignant
○ Most common islet cell tumor is insulinoma

**Insulinoma**

○ Arise from pancreatic beta cells
○ Usually benign, solitary, small (<2cm)
○ While they secrete insulin, the majority of patients have mild hypoglycemia.
○ Some tumors may produce sufficient insulin to produce clinically significant hypoglycemia
  
  Whipple’s Triad
  a) Hypoglycemic episodes (usually CNS manifestations such as confusion, stupor, loss of consciousness
  b) Blood glucose <50mg/dl
  c) Relieved with food or parenteral glucose
○ Finding and removing the tumor leads to reversal of hypoglycemia

**Zolinger-Ellison Syndrome (Gastrinoma)**

○ Gastrin producing tumor which arises in the pancreas (also can arise in duodenum or peripancretic soft tissues)
○ Hypersecretion of gastric acid leads to severe peptic ulceration – usually multiple and in unusual locations (such as jejunum)
○ 50% of patients have associated diarrhea
○ Therapy = acid suppression; Surgical resection
○ Some tumors are locally invasive or metastatic at time of diagnosis

Other rarer islet cell tumors

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

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
  --can be associated with neural crest tumors (ie neuroblastoma)