Diabetes Mellitus

- Pancreatic Cells
  - Beta cells : produce insulin and amylin
  - Alpha cells : produce glucagon
- normal insulin actions
  - decrease gluconeogenesis
  - increase glucose uptake by skeletal muscles
  - inhibition of glucagon secretion and it's gene
  - inhibits lipolysis
- Incretins
  - gastrointestinal hormones that increase glucose dependent insulin secretion
  - Glucose in the small intestine stimulates incretin release
  - Incretins are carried through the circulation to the pancreatic beta cells
  - Incretin stimulation of beta cells causes them to secrete *more insulin* in response to the same amount of blood glucose (more insulin release)
  - 2 main incretin hormones in humans, GIP (glucose dependent insulinotropic peptide aka gastric inhibitory peptide) and GLP-1 (glucagon-like peptide 1)
  - they also inhibit glucagon release
  - the end result is lowering glucose levels
  - DPP-4 enzyme deactivates incretins
- A group of disorders not a single disease that develop as a result of absolute or relative deficiency of insulin
- Other metabolic disturbances in addition to hyperglycemia occur in uncontrolled diabetes include altered lipoprotein dynamics and elevated free fatty acid levels
- Diagnosis is based on 3 measurements
  - fasting plasma glucose (more than 8 hours)
  - 2 hour post load plasma glucose
  - HbA1c
- fasting plasma glucose (mg/dl)
  - normal : < 100
  - prediabetic : 100-125
  - DM : > 126
- 2 hour post load plasma glucose (glucose tolerance test)
  - normal : < 140
  - prediabetic : 140-199
  - DM : > 200
- HbA1c : % of Hb in circulating erythrocytes thats glycosylated

    - normal : < 5.6
    - prediabetic : 5.7-6.4
    - DM : > 6.5
- a random serum glucose level >200 indicates DM
- Gestational diabetes mellitus
    - recognized during pregnancy week 24
    - plasma glucose level of 92 mg/dl or higher
    - associated with fetal malformation and delivery issues
    - can cause T2DM post delivery
- two types of DM : type 1 and type 2 (type 2 represent 85%)
- C peptide
    - a fragment of the insulin precursor proinsulin which is cleaved during the synthesis of insulin
    - It is secreted and circulates in proportion to endogenous insulin production but is absent from injected exogenous insulin preparations
    - A fasting C peptide level can be measured in T1DM to confirm marked deficiency in insulin secretion (low C peptide) but it is normal in T2DM
- there are other types of DM that are inherited monogenic autosomal dominant disorders that are designated maturity onset diabetes of the young MODY with clinical features similar to T2DM but onset typically before 25 years of age
- other etiologies
    - Diseases of the exocrine pancreas : pancreatitis / trauma / neoplasia / cystic fibrosis / hemochromatosis
    - Endocrinopathies : Cushing syndrome / acromegaly / pheochromocytoma / glucagonoma / hyperthyroidism / somatostatinoma / aldosteronoma
    - Drug or chemical induced : Glucocorticoids and thiazides (most common) / phenytoin / thyroids
    - Infections : congenital rubella / CMV
- family history is a major risk factor for both types

Type 1 DM T1DM

- age of onset < 30 (peak between 6-14)
- T1DM can present in adulthood and is then referred to as latent autoimmune diabetes of adulthood LADA
- extensive destruction of the insulin producing beta cells within the islets of Langerhans in the pancreas precipitated by environmental insult like microbial, chemical or dietary

alongside genetic factors

- immune mediated form has anti islet cell antibodies & anti insulin antibodies like Glutamic acid decarboxylase GAD antibodies (zinc transporter antibodies is specific for T1DM)
- dependence on insulin therapy for survival
- can have adulthood onset
- can be autoimmune (type 1A) or idiopathic (type 1B)
- associated with other autoimmune diseases like vitiligo or hashimoto thyroiditis
- associated with hyperglycemia with ketoacidosis
- environmental factors that may lead to T1DM
    - viral infections
    - immunization
    - cow milk at early age
    - vitamin D deficiency
    - maternal age / preeclampsia / neonatal jaundice
    - high birth weight
- clinical features
    - polyuria : bed wetting for children and nocturia
    - weight loss
    - polydipsia and polyphagia
    - energy loss and lethargy
- treatment is with exogenous insulin
- exogenous insulin preparations differ in
    - rapidity of absorption
    - degree of peaking of blood levels
    - duration of action after subcutaneous injection
- Insulins and their duration of action in hours
    - ultra short acting : aspart / Lispro / glulisine (3-5)
    - short acting : regular insulin (6-8) : basal (given before meals)
    - intermediate acting : Neutral protamine Hagedorn NPH (12-16)
    - Long acting : Glargine / Detemir (24)

Type 2 DM T2DM

- age of onset > 40
- has a gradual onset with progression over multiple years or even decades manifested as gradual insulin resistance
- the gradual insulin resistance is accompanied by increased serum insulin to a certain point

to match the resistance

- other mechanisms : beta cell dysfunction / Impaired insulin processing
- associated with obesity
- absence of ketoacidosis complication except in extreme cases
- there is compromised function as well as a reduced number of beta cells
- have low levels of HDL but high levels of LDL and high triglycerides (diabetic dyslipidemia)
- Clinical features
    - polyphagia, polydipsia, and polyuria
    - Skin manifestations
        - Acanthosis nigricans
            - associated with insulin resistance and obesity
            - can also be related to underlying malignancy (gastrointestinal and lung)
            - treated by weight reduction or antibacterial
        - Necrobiosis lipoidica

Complications

- Diabetic nephropathy (microvascular)
    - can develop in T1DM and T2DM
    - May end in end stage renal disease ESRD
    - Patients are usually asymptomatic until late in course
    - Characterized by proteinuria and rising creatinine
    - Urine albumin measurement should be performed annually to screen for diabetic nephropathy after 5 years of diagnosis
    - in T1DM : increase in rate of urinary albumin by 10-20% per year (mainly present as Macroalbuminuria (> 300)
    - in T2DM : starts as Microalbuminuria (< 30)
    - in T2DM screening starts at time of diagnosis but T1DM screening starts 5 years earlier
    - Factors that may increase urinary albumin excretion over baseline values include
        - exercise within 24 hours
        - fever
        - infection
        - congestive heart failure
        - marked hyperglycemia

        - marked hypertension
        - pyuria or hematuria
    - treated by ACEi in T1DM and ARBs in T2DM
- Diabetic Retinopathy (microvascular)
    - leading cause of blindness in adults aged 20-74
    - affects early all patients with T1DM
    - Factors that increase the risk of retinopathy
        - Hyperglycemia
        - Presence of nephropathy
        - High blood pressure
        - Pregnancy in patients with T1DM
    - Usually asymptomatic unless vitreous hemorrhage occurs (causing visual loss)
    - treated by Laser photocoagulation therapy
- Diabetic Neuropathy (microvascular)
    - can be classified into
        - Generalized symmetrical polyneuropathy : acute sensory or chronic sensorimotor
        - Focal and multifocal neuropathies : cranial, truncal, focal limb or proximal motor (amyotrophy)
        - Autonomic : cardiac, gastrointestinal, genitourinary
    - Chronic sensorimotor distal symmetrical polyneuropathy DPN and diabetic autonomic neuropathy DAN are the two most common neuropathies
    - loss of vibration & proprioception reflect large fiber loss
    - loss of pain, light touch and temperature reflect small fiber loss
    - chronic metatarsal phalanges flexion causes claw toe deformity
    - Distal symmetrical polyneuropathy DPN
        - Up to 50% of DPN cases may be asymptomatic, increasing the patient risk of insensate foot injuries, which can ultimately lead to ulcers and amputations
        - patients with symptoms have Burning, electrical or stabbing sensations or paresthesias
        - manifesting as a bilaterally symmetrical, distal, primarily sensory polyneuropathy with or without motor involvement in a glove and stocking distribution
        - symptoms worse at night
        - motor symptoms are at late stage and rare
        - leads to ulcers, ischemia and diabetic foot
        - Examination in DPN shows loss of vibration, pressure, pain and temperature

sensation and absent reflexes
        - Signs of peripheral autonomic sympathetic dysfunction : Warm or cold feet, distended dorsal foot veins, dry skin, calluses in pressure bearing areas
    - mononeuropathy multiplex might happen or thoracic and lumbar nerve root polyradiculopathies
    - Diabetic amyotrophy causing muscle atrophy and weakness most often involving the anterior thigh muscles and pelvic girdle is an uncommon form of diabetic neuropathy that often resolves after several months
    - Patients at increased risk for ulcers and amputations
        - Duration of diabetes 10 years or more
        - Male
        - Poor glucose control
        - Cardiovascular, retinal, or renal complications
        - Peripheral neuropathy with loss of protective
        - Altered foot biomechanics, bony deformity
        - Presence of peripheral vascular disease
        - History of ulcers or amputation
    - Cardiovascular autonomic neuropathy CAN
        - Associated with morbidity and increased mortality
        - Limits exercise capacity
        - May lead to sudden death or silent cardiac ischemia
        - Presentation : Resting tachycardia (> 100) with exercise intolerance and orthostatic hypotension
        - Atherosclerotic MI accounts for approximately 80% of all diabetic mortality
    - Genitourinary autonomic neuropathy
        - erectile dysfunction, retrograde ejaculation, bladder dysfunction causing recurrent urinary tract infections, pyelonephritis, incontinence and palpable bladder
    - GI neuropathy : gastroparesis, enteropathy with constipation or diarrhea
    - strokes and TIAs are common
    - the most important treatment and prevention of diabetic neuropathy is glucose control
    - pain control for diabetic neuropathy : tricyclics / carbamazepine / oxycodones
- Diabetic Ketoacidosis DKA
    - develops mainly in T1DM but can occur in T2DM especially during acute illness like severe infection, MI, appendicitis, pancreatitis, glucocorticoids or trauma
    - infections : pneumonia / gastroenteritis / UTI

- most often develops when patients with known T1DM stop taking prescribed insulin
- more in younger patients and females
- life threatening condition : high mortality if associated with coma and hypotension
- pathophysiology of DKA results from the combined effects of insulin deficiency and increased levels of insulin counter regulatory stress hormones (cortisol / catecholamines / glucagon / growth hormone)
- insulin deficiency - high glucose - increased glycogenolysis and gluconeogenesis - muscle breakdown - releasing aminoacids- more gluconeogenesis - extremely high glucose levels - glycosuria - coexcretion of large amounts of water, Na+ and K+ - polyuria and fluid depletion - hyperosmolality
- Because of insulin deficiency there is decreased lipogenesis and accelerated lipolysis leading to increased levels of circulating free fatty acids, which serve as a substrate for the hepatic synthesis of ketone bodies which are acids leading to metabolic acidosis
- ketone bodies synthesis requires acyl CoA to enter the mitochondria by CPT1 enzyme which is inhibited by malonyl CoA and since we have excess glucagon and glucagon decreases malonyl CoA - more CPT1 - more ketones
- symptoms : polyuria / polydipsia / blurred vision / weakness / anorexia / nausea and vomiting / abdominal pain / altered mental state / dehydration / hypotension / tachycardia / dry skin / Kussmaul breathing
- symptoms develop within 24 hours
- patients have fruity odor
- no fever associated
- neurological signs like hemiparesis and coma are rarely seen in DKA (patients are alert)
- associated with hyperventilation to compensate for acidosis : Kussmaul deep respirations
- abdominal pain
    - more in children
    - not seen in HHS
    - seen if HCO3 is < 5
    - not related to severity
- serum glucose is 250-800 mg/dl
- arterial pH is 7.25-7.3 with anion gap > 10
- Measurements of urine ketones may be misleading because urinary ketones can be positive during fasting in the absence of DKA
- main complication is cerebral edema

        - mainly in children
        - happens due to treatment
        - headache with reduced level of consciousness
            - seizures might happen, bradycardia, respiratory arrest, pupillary dilation, incontinence
        - high morality rate
        - treatment : mannitol / hypertonic saline 3%
    - serum anion gap is usually greater than 12 mEq/L
    - treatment : insulin IV / fluid replacement / potassium repletion / phosphate PO4
    - we also give bicarbonate to help with acidosis
    - resolution happens when
        - anion gap < 12
        - serum glucose < 200
        - serum HCO3 > 18
        - pH > 7.3
- Hyperglycemic Hyperosmolar State HHS
    - occurs almost exclusively in patients with T2DM
    - Patients often are elderly and frequently have compromised renal function
    - insulin deficiency - insulin resistance - hyperglycemia, glucosuria, and osmotic diuresis
    - the presence of some endogenous insulin secretion suppresses lipolysis and ketogenesis enough to prevent ketoacidosis
    - Patients with HHS typically develop more marked hyperglycemia, fluid and electrolyte deficits, and hyperosmolality compared to those with DKA
    - symptoms of lethargy, polyuria, polydipsia, weight loss or even focal deficits like a stroke
        - neurological signs develop when osmolality is > 320-330 mosmol/kg
    - symptoms develop over days not within 24 hours
    - serum glucose is > 1000 mg/dl
    - HHS is associated with infections, diuretic use, residency in nursing homes and vascular events
    - MI is a the main cause of death
    - same treatment plan
    - Insulin therapy should be started only after rehydration is in progress (after K+ repletion cause it causes arrhythmias)
    - PO4 is given when
        - cardiac arrhythmias

        - hemolytic anemia
        - respiratory depression
        - serum phosphate < 1 mg/dl
    - resolution happens when
        - serum glucose < 250-300 mg/dl
        - osmolality < 315 mosmol/kg
        - patient alert and able to eat

Prevention and Treatment

- exercise (walking 45 mins aday) and weight loss is The most effective way for prevention
- diet : 1/2 fibers 1/4 protein 1/4 starch
- insulin therapy is used in T2DM when HbA1c is > 10%, FPG > 250, 2h > 300
- Biguanides : metformin
    - given for prevention
    - given orally 500 mg each pill
    - Suppresses hepatic glucose output
    - No weight gain or hypoglycemia when used as monotherapy
    - causes nausea and diarrhea and lactic acidosis
    - contraindicated in renal and liver compromise / heart failure / sepsis / DKA / hypotension
    - can cause vitamin B12 deficiency
- Sulfonylureas and Meglitinides
    - Sulfonylureas : Glimepiride and Glibenclamide
    - Meglitinides : Repagnilide
    - both stimulate insulin secretion
    - contraindicated in pregnancy
    - Both cause hypoglycemia
    - Sulfonylureas cause weight gain
- Acarbose
    - Delays glucose absorption by inhibition of pancreatic alpha amylase and intestinal alpha glucosidase
    - causes GI cramps and diarrhea
- Thiazolidinediones
    - Rosiglitazone (-itazone)
    - enhance peripheral tissues sensitivity to insulin (insulin sensitizer on adipose tissues, liver and muscles)

    - side effects : edema / fluid retention / hepatotoxicity / macular edema / bone fractures / MI
    - contraindicated in heart failure and liver disease and IHD
- Incretin based therapy
    - DPP-4 inhibitors
        - given orally
        - can cause pancreatitis / skin reactions / hepatotoxic
        - no effect on weight
    - GLP-1 agonists
        - exenetide (once a week injection)
        - slows gastric emptying
        - suppresses glucagon levels and increase glucose dependent insulin release
        - causes weight loss
        - cause nausea, pancreatitis and renal failure
        - Liraglutide
            - reduce cardiovascular mortality
            - once daily injection
            - significant weight loss
            - causes thyroid c cell hyperplasia
            - expensive
    - causes pharyngitis and UTIs
- Amylin analogues
    - amylin is cosecreted with insulin
    - it is deficient in T1DM and insulin requiring T2DM
    - regulates post meal glucagon
    - given as subcutaneous injection
- sodium glucose cotransporter 2 SGLT2 inhibitors
    - increase using glucose excretion and improve insulin sensitivity
    - causes weight loss and lowers blood pressure with hypovolemia
    - causes genital infections and plasma volume depletion
    - cardiovascular protection : indicated for patients with atherosclerosis, MI, CAD and hypertension
    - reduce progressive of renal disease

Hypoglycemia

- Whipple triad
  - symptoms of hypoglycemia
  - hypoglycemia : blood glucose level < 50 mg/dL
  - relief of symptoms following ingestion of glucose
- autonomic symptoms of hypoglycemia
  - Sweating
  - Palpitations
  - Hunger
  - Pallor
  - Tachycardia
  - Nausea and vomiting
  - Anxiety
  - Hypertension
  - Tremor
  - Irritability
  - Paresthesia
- Neuroglycopenic symptoms
  - Difficulty thinking
  - Dizziness
  - Seizures
  - Fatigue, weakness
  - Visual blurring
  - Loss of consciousness
  - Somnolence
  - Confusion
  - Coma
  - Headache
  - Abnormal behavior
  - Death
- causes
  - Drug Induced
    - Antidiabetic agents (insulin, sulfonylureas, meglitinides)
    - Alcohol
    - beta blockers, ACEi, pentamidine, quinolones
  - Altered Gastrointestinal Function : Alimentary hypoglycemia
  - Insulinoma
  - Insulin-like growth factor IGF2 secreting tumor

    - Autoimmune : Circulating insulin antibodies
    - Endocrine Deficiencies : Glucocorticoids (adrenal insufficiency), growth hormone, catecholamines, glucagon
    - Severe Illness : Sepsis, Hepatic or renal failure
    - Anorexia nervosa
- Patient with diabetes is considered hypoglycemic if blood glucose < 70 mg/dl and it is divided into 3 stages
    - < 70 without symptoms
    - < 55 without symptoms
    - < 70 with symptoms specially cognitive
- Patient with diabetes with blood glucose 90 (> 70) but with symptoms of hypoglycemia : pseudohypoglycemia : happens because patient is used to high glucose levels
- IGF-2 lowers glucose levels, insulin, C peptide and ketone bodies (beta OHB) but increases glucagon
- 72 hour fasting test
    - glucagon is increased in all cases except normal (< 25)
    - ketone bodies only present in normal state (> 2.7)
    - insulin is high in all except normal and IGF-2
    - very high insulin (>>> 3) with very high c peptide (>>> 0.6) with antibodies : autoimmune
    - high insulin low c peptide : exogenous insulin
    - insulinoma : high insulin (not as high as autoimmune or exogenous), c peptide, low BOHB, high glucagon
- Arterial Calcium Stimulation
    - radiological technique used preoperatively to localize or regionalize occult insulinoma with high sensitivity
    - target arteries : splenic / superior mesenteric / gastroduodenal
    - calcium causes abnormal cells to release insulin (double or tripling insulin levels is a positive result)
    - insulinoma : + in one artery
    - islet cell hypertrophy : + in multiple arteries
- insulinoma
    - arise from ductal and acinar cells of pancreas
    - fasting hypoglycemia is the most common symptom
    - weight gain
    - management is surgery or drugs
    - drugs

- diazoxide (drug of choice) : causes edema and hirsutism
- somatostatin analogues