Endocrinology Review

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1. Pituitary disorders:

Anterior pituitary: hormones are **Synthesized and Secreted** from it.
- Hormones: **GH, LH, FSH, TSH, ACTH, PRL**

Posterior pituitary: Hormones synthesized in the hypothalamus and stored in post.pituitary.
- Hormones: **oxytocin and ADH**

- **All hormones coming from hypothalamus** are **stimulatory** except **dopamine** which **inhibits prolactin**, and **Somatostatin** which **inhibits growth hormone**
  - pituitary **stalk lesion** will cause **hyperprolactinemia** **& DECREASE** in all Ant.Pit hormones.

Classification of Pituitary disorders:

1. **Function:**
   - **Hyper**secretion
   - **Hypo**secretion (Hypo**adrenal**ism, Hypo**gonad**ism, Hypo**thyroid**ism, GH deficiency) -PanHypopituitarism

2. **Masses:**
   - **Non functioning:** doesn't release hormones
     - Adenomas, incidentaloma, craniopharyngioma, and metastatic tumors
   - **Functioning:** adenomas
   - **Tumors causing hormone ↑ Excess:**
     - **Prolactinoma**
     - **Somatotropinoma (GH > acromegaly)**
     - **Corticotropinoma (ACTH > cushing's)**
     - **Thyrotropinoma (TSH)**
     - **SIADH**
   - **Tumors causing Inadequate ↓ production:**
     - **Hypopituitarism**
     - **Central diabetes insipidus**
   - **Other:**
     - **Malignant** pituitary tumors: Functional and non-functional pituitary carcinoma.
     - **Metastases** in the pituitary: (breast, lung, stomach, kidney).
     - **Pituitary cysts: Rathke's cleft cyst**, Mucocoeles, Others.
     - Empty sella syndrome.
     - **Pituitary abscess**, in TB patients.
     - **Lymphocytic hypophysitis**, antibodies attacking the pituitary.
     - Carotid aneurysm

- Epidemiology:
  Functional: genetic (MEN 1, Gs alpha mutation) PTTG gene, FGF receptor -4)
- Principles of endocrine investigations:
  - Timing: release has a rhythm (circadian, pulsatile, or monthly)
    - Random measurements are invalid
    - Sequential or dynamic tests may be required
  - Choice of dynamic test:
    - **Hormone Deficiency:** choose stimulation test
    - **Hormone Excess:** choose suppression test
    - Avoid interpreting 1 test in isolation
  - Imaging:
    - Secretory cells take up substrates which can be labelled
    - high prevalence of incidentaloma
  - Biopsy: difficult to classify histologically
    - Only done as part of therapeutic operation
  - Majority of pituitary tumors are benign
- **Symptoms may arise from:**
  - **Hormones (excess or deficiency)**
  - **Local mass effect:**
    Optic chiasm: visual field defect (bitemporal hemianopia)
    Cavernous sinus with III, IV, V, VI, and V_1 & V_2 cranial nerve lesions
    Bony structures and meninges: headache
    Hypothalamic centers: hypopituitarism, Obesity, altered appetite and thirst, precocious puberty in children
    Ventricles: interruption of CSF flow and hydrocephalus

1. **Non functional pituitary mass**

- **No signs or symptoms** of hormone excess or deficiency
- 25% of pituitary tumor

- could be micro or macro
- **asymptomatic (incidental by MRI)**
- **Macro**adenoma > **mass effect:** mechanical pressure or infiltration of surrounding structures
- Hormonal findings: normal, PRL may be low, high, or normal.

  Low if it invades hypothalamus
- Treatment:
  - Observation
    - Annual follow up for 5 years and then as needed
    - Visual field exam Q6-12 months (optic chiasm)
    - Observe for a slow growing tumor
  - Surgery: if symptomatic
  - Adjunctive therapy: radiation to prevent growth

Functional pituitary mass:

❖ **Prolactinoma:**

- **Most common** functional adenoma
- Some GH producing tumors also secrete PRL
- 90% in women > micro
- 60% in men > macro
- PRL inhibited by hypothalamus (dopamine)

Diagnosis:

Clinical features:

- in women: **galactorrhea**, nipple discharge, **amenorrhea, and infertility**
- men: **decreased libido, subfertility, and ED**
- there may be **mass effect**

no clinical significance if there is no mass invading the hypothalamus

Biochemical (hormonal):

- **PRL levels are high**
- TSH to **rule out hypothyroidism**
- IGF-1 to **rule out GH co secretion**
- Other hormones normal or low

Anatomical: CT or MRI

- < 1 cm: micro
- > 1 cm: macro

Treatment:

Medical first line: dopamine agonist (bromocriptine)

- not recommended for breastfeeding mothers

Surgical: pressure symptoms

Ddx:

- Adenoma
- Hypothyroidism (primary)
- **Drugs** that interfere with dopamine secretion or action: **phenothiazines**, **metoclopraminde**, **methyl dopa**, **verampil**, **H2 blocker**, **estrogen**, opiates
- Lack of sleep, stress, pregnancy, lactation, chest wall stimulation

❖ **Growth hormone secreting adenoma**

Acromegaly in adults and **gigantism** in children

It Causes:

- Isolated: panhypopituitarism
- Pituitary tumor as mass effect > GH def

Clinical features:

Compression of surrounding structures: **mass effect**

lack of secretion of other hormones: due to **destruction and invasion of pituitary**

Excessive GH secretion:

- Acral enlargement > **large hands and feet**
- **Soft tissue enlargement** > visceromegaly, thick skin, oily, **sweaty**, and **carpal tunnel**
- **Neuropathy,** fatigue, lethargy, and sleepiness
- **Galactorrhea**
- **Arthropathy:** arthralgia and degenerative arthritis
- **Impaired glucose tolerance** and DM
- **CVS: cardiomegaly**, CHF, diastolic dysfunction (early sign of cardiomyopathy), **HTN**, LVH, and obstructive sleep apnea
- **Enlarged kidney** > absorb Na and water > hypertension

Biochemistry:

- Random GH levels is not useful
- **Screening (initial): IGF-I**
  - If normal, strong indication that the patient does not have acromegaly
- **Confirmatory test**: **oral glucose tolerance test** (diagnostic)
- Pituitary Hormone levels, fasting/random blood sugar, HbA1C, and lipid profile

Imaging:

MRI and CT of the pituitary

Echo: diastolic dysfunction (early sign of cardiomyopathy)

Skull x ray: thick heel pad >/= 22m

Treatment:

1st line: surgical (trans-sphenoidal adenoectomy)

2nd line: **somatostatin analogs** (octreodtide) or dopamine agonist

3rd line**: somatostatin receptor antagonist** (pegvisomant)

last resort: radiotherapy

❖ **Corticotropinoma:** ACTH releasing adenoma

- HPA axis: circadian rhythm, altered by stress, liver and renal failure
- ACTH releasing hormone **Results in Cushing's disease**

Clinical features:

- **Moon face, acne, hirsutism**
- **Supraclavicular fat pad, central obesity, stria (purple)**, difficult IV cannulation (**easily bruised and poor wound healing**), **Ecchymoses**
- Depression, **recurrent infections, irregular menses**
- **Diabetes, proximal muscle wasting and weakness, osteoporosis**
- **HTN**, **LVH, diastolic dysfunction,** IVS hypertrophy
- **Obstructive sleep apnea**

Biochemistry:

- High cortisol and ACTH
- **24 hour urinary free cortisol**
- **1 mg dexamethasone suppression test >** cortisol levels don't decline as they should
- Midnight salivary cortisol

Imaging:

- MRI
- ECG: high QRS and inverted T wave, Echo: pre-op

Treatment:

1st line: **Surgical (Transsphenoidal surgery)**

- If persistent > **Radiation to prevent regrowth**
- If persistent > **Adrenalectomy**:
  - nelson's syndrome: expanding intracellular tumor and hyperpigmentation

Medical (Mitotane)

In pregnant women

- 1st trimester: surgery
- 2nd trimester: adrenal enzyme inhibitors or surgery
- 3rd trimester: early delivery, enzyme inhibitors until lung maturity

❖ **Thyrotropinoma:**

- Signs of **hyperthyroidism**
- **High TSH, free T4 and T3**
- Treatment:
  - Pre-op: **anti-thyroid meds**
  - **Surgical resection of adenoma**
  - **Medical therapy: somatostatin analogue**

Hypopituitarism

- panhypopituitarism: **deficiency in all anterior pituitary hormones**
- **Caused by: 7 I's**

infarction: Sheehan's syndrome (pituitary infarction following severe postpartum hemorrhage)

iatrogenic: radiation and surgery

invasive: large pit tumors (most common) and craniopharyngioma

infiltration: sarcoidosis, hemochromatosis

injury: head trauma

infection: TB

idiopathic

- Clinical picture:

Lack of FSH & LH → **Hypogonadism: amenorrhea**

Lack of TSH → **hypothyroidism**

Lack of **ACTH → adrenocortical insufficiency**

Prolactin deficiency → **failure** of postpartum **lactation**

Deficiency of GH → produces **short stature in children**

All the above → PanHypopituitarism

- Investigations:

Baseline studies: TSH, ACTH, FSH, LH, PRL, GH, and blood levels of IGF-1 (GH undersecretion)

Stimulation: TRH stimulation, GnRH (LHRH) stimulation, insulin tolerance test

Imaging: **CT and MRI**

- Treatment:

Remove the cause

Replacement therapy:

In secondary hypothyroidism give → Thyroxine

In secondary hypoadrenalism give → Hydrocortisone

GH deficiency give → GH analogues

Gonadotroph deficiency give → Testosterone monthly injections in men and Estrogen + progesterone in women.

- BUT If fertility is desired, give → LH and FSH analogues (For induction of ovulation in women, spermatogenesis in men)

❖ **GH deficiency:**

- Decreased GH > short stature
- Screening: IGF-I
- Dynamic testing:
  - **Insulin tolerance test**
  - **Clonidine stimulation test**
  - **Glucagon stimulation**
  - Exercise testing
  - Arginine GHRH
- X ray: delayed bone age
- MRI
- **Treatment: GH replacement**

❖ **Central hypothyroidism:**

Low T4 and TSH, Symptoms of **hypothyroidism**
Imaging: **MRI**
Tx: thyrozine replacement and surgical removal of pit adenoma

Hypothalamus and posterior pituitary

❖ **Diabetes insipidus:**

Central DI: **decreased ADH**

- Neurosurgery, head trauma, primary or secondary tumors, infiltrative disease, vascular disease, or idiopathic
- Rare w/ Sheehan's

Other types not related to hypothalamus:

- **Nephrogenic DI**: renal resistance to ADH secretion
- Psychogenic

Symptoms:

- **Abrupt polydipsia and polyuria**

Investigations:

- Increased urine volume, decrease osmolality and specific gravity
- **Serum Na: elevated**
- **Water deprivation test: central vs nephrogenic**
  - Restrict fluids or admin hypertonic saline to increase serum osmolality (295-300)
    > **In central:** urine osmolality still low and **returns to normal after vasopressin**
    > **Nephro:** exogenous **vasopressin does not alter urine osmolality**

Treatment:

Central DI: **DDAVP (Desmopressin Acetate): Synthetic analog of ADH**

- Not catabolized by vasopressinase → No vasopressor action
- Administered intranasally or p.o
- Safe in pregnancy and breastfeeding

Nephrogenic: correct underlying cause and hydrochlorothiazide

❖ **SIADH:**

Continued ADH secretion in spite of plasma hypotonicity and a normal or expanded plasma volume.

Causes:

- meningitis, head trauma, tumors.
- Pulmonary: Pneumonia,TB, small cell Ca (ectopic production of ADH)
- Drugs: Chlorpropamide, Carbamazepine, Cyclophosphamide ,Vincristin.

Symptoms:

Nausea, irritability, headache

Mild dilutional hyponatremia

Fits and coma may occur with severe hyponatremia

Finding:

Low serum Na and increase urinary Na

Low serum osmolality and increase inappropriate urine osmolality

Treatment:

Removal of underlying cause

Restrict fluid intake (0.5-1)

Demeclocycline

Severe: hypertonic saline (IV) or NS + furosemide

2. Obesity:

❖ **Definition:** excess accumulation of fat in the body 20% or more over an individual's ideal body weight.

❖ **Surrogate measures of adiposity →** Body mass index(BMI): (Most accurate, Most Reliable, Easiest).

Classification	BMI (kg/m2)	Risk of comorbidities
Underweight	<18.5	Low (but risk of other clinical problems increases)
Normal Range	18.5-24.9	Average
Overweight Pre-Obese	>25.0 25-29.9	Mildly increase
Obese Class I Class II Class III	>30 30-34.9 35-39.9 >40.0	 Moderate Severe Very Sever

❖ **Classification of obesity as per fat distribution:**

➢ **Android (or abdominal or central, males)**

- Collection of fat mostly in the abdomen (above the waist)
- Apple-shaped
- Associated with insulin resistance and heart disease
  - DM_2
  - Hypertension
  - Dyslipidemia
- Assessed by:
  - MRI
  - Dual X-ray absorptiometry(DEXA)
  - Single CT slice L4/L5
  - Waist: hip ratio

- Waist circumference: The narrowest circumference midway between the lower border of the ribs and the upper border of the iliac crest, taken from the side. waist circumference and BMI are the most used. waist circumference is the vital sign for obesity.

Population	Risk of Metabolic Complications of Obesity	
	Increased	**Substantially Increased**
Caucasian (WHO)		
Mem	>94 cm	>102 cm
Women	>80 cm	>88 cm
Asia (IASO/OTF/WHO)		
Men		>90 cm
Women		>80 cm
China (WGOC)		
Men		>85 cm
Women		>80 cm

➢ **Gynoid(below the waist, females)**
- Collection of fat on hips and buttocks
- Pear-shaped
- Associated with mechanical problems

❖ **Obesity in Children:** In assessing obesity in children, we need to take into account weight, height AND growth

❖ **Etiology & Pathogenesis:** Body weight is ultimately determined by the interaction of: Genetic (polygenic), Environmental, and Psychosocial factors Acting through several physiological mediators of food intake and energy expenditure.

❖ **Factors predispose to obesity:**

➢ Lifestyle:
- Sedentary lifestyle lowers energy expenditure
- 52 % of Saudi women are inactive, < 19 % doing regular physical activity
- Prolonged TV watching

➢ Sleep deprivation:
- < 7 hours of sleep → obesity
- sleep → ↓ leptin, ↑↑ Ghrelin → ↑ appetite and CHO eating at night

➢ Cessation of smoking: Because the nicotine suppress the appetite. So they don't eat and maintain their weight, when they were smoking.
- Average weight gain is 4 kg
- Due to nicotine withdrawal
- Can be prevented by calories restriction and exercise program

➢ Social influences:
- Obese parents most likely to have obese children
- Obese individuals are surrounded by obese friends

➢ Diet:
- Overeating, frequency of eating, high fat meal, fast food(> 2 fast food/wk)
- Night eating syndrome: if > 25 % of intake in the evening

❖ **Etiological classification of obesity:**

- ➢ Neuroendocrine disease: Ventromedial hypothalamus damage (Tumors, Inflammatory lesions, Other hypothalamic disease) (Hypothyroidism, Cushing). Cushing syndrome and using steroid therapy is the most common metabolic and endocrine causing obesity.
- ➢ Drug-induced (insulin, sulfonylureas, antipsychotic and antiepileptic, steroids)
- ➢ Dietary (High carbohydrate diet, High fat diet)
- ➢ Reduced energy expenditure
- ➢ Genetic factors

❖ **Hypothalamic modulators of food intake:**

Orexigenic (Increase Appetite)	**Anorexigenic** (Decrease Appetite)
NPY	CART
AGRP	CCK
MCH	CRH
Galanin	*a*-MSH
Orexin	Insulin
Ghrelin The hormone of hunger Secreted in the stomach, acts on hypothalamus to stimulate appetite, peak before meal and decrease after.	GLP-1
Noradrenaline	PYY 3-36
Endocannabinoids	**Leptin**, Suppress our appetite from adipocytes and acts on hypothalamus to decrease food intake and stimulate energy expenditure.
m, κ Opioids	Urocortin
Neurotransmitters	Bombesin

❖ **Health consequences of obesity: increased rates of mortality and morbidity** → Each 5 kg/m2 increase in BMI was associated with significant increase in mortality related to:

- ➢ IHD and stroke
- ➢ Diabetes and non-neoplastic kidney disease Diabetes is the most common metabolic complications of obesity
- ➢ Different types of cancer (Colon, Liver, NHL)
- ➢ Respiratory disease (obstructive sleep apnea)
- ➢ Acanthosis nigricans → insulin resistance

❖ **Energy expenditure:**

- ➢ Resting metabolism:
  - ■ 800 to 900 kcal/m^2/24hr → Females <Males → Declines with age
- ➢ Physical exercise:

        - ~ 1/3 of daily energy expenditure → Most easily manipulated
    - Dietary thermogenesis:
        - Energy expenditure which follow the ingestion of meal May dissipate ~ 10% of the ingested calories, In the obese, the thermic effects of food are reduced (especially in patients with diabetes).
    - Adaptive thermogenesis:
        - With acute over – or underfeeding Shift in overall metabolism as large as20%

- **Genetic factors in obesity:**
    - Dysmorphic or syndromic: syndromes at which change in one gene or two are detected and obesity is a sign.
    - Single-gene cause of obesity:
        - Leptin and leptin gene deficiency, POMC deficiency
    - Genetic defects with non syndromic obesity:
        - Melanocortin receptor system abnormalities
    - Genetic susceptibility to obesity:
        - If both parents are obese~80% of the offspring will be obese
        - If only one parent ~ 10% of the offspring will be obese

- **Metabolic Consequences Of Deleting The Mitochondrial Glycerol 3-Phosphate Dehydrogenase:** G3PD is a gene that causes obesity when it was knocked down we had more glycerides and less thermogenesis.

- **Management of obesity:**
    - lifestyle modification:
        - Selection of lower fat, lower carb foods Modified food guide pyramid Increase fruits & vegetables, Lower fat preparation techniques, Estimation of portion size.
        - Exercise is good for weight maintenance and good for fitness. Diet is good for weight reduction Ideally 30 min 5 times a week moderate intensity exercise is considered as regular exercise. Initial goal: 10% weight loss Within 6 months
    - pharmacotherapy:
        - Indicated in:
            - BMI > 30, BMI 27-30 with comorbidities → Should not be used for cosmetic weight loss, Used only when 6 months trial of weight and exercise fail to achieve weight loss.
        - Sympathomimetics: no longer used.
        - Pancreatic lipase inhibitor:
            - Orlistat: inhibits fat absorption → steatorrhea and bloating.
            - Major C/I:
                - Chronic malabsorption syndrome
                - Cholestasis
                - Pregnancy and breastfeeding
        - Antidepressant
        - Antiepileptic
        - Diabetic drugs: metformin
    - Surgery
        - three questions must be asked before proceeding to surgery:
            - is the patient prepared? (will he stick to a healthy lifestyle after? or will he get depressed by the complications?).

- well motivated patients? Because if he is not , he will gain weight again and not interested to maintain his weight.
- what is the cause of obesity? (secondary causes can't be treated by surgery like cushing's)

- Restrictive techniques are technically easier, have lower complication rates, but result in less weight loss than malabsorptive techniques.
- Gastric banding With high failure rate, Because the band may distend with heavy meal, and the patient themselves may come to us and ask to deinflate the band when he want to have heavy meal that day.
- Now the sleeve is the most common.
- Follow up is crutial If there is no lifestyle modification, they will gain weight again and stomach get expanded.

3. Hyperlipidemia:

- Exogenous: Chylomicrons come **from the gut** > metabolized by **lipoprotein lipase** > **releases FA**
- Endogenous: **to the liver > break down of IDL to LDL by hepatic lipase** > LDL binds with **LDL receptors** > back to the liver
- High oxidized LDL cholesterol atheroma > in the walls of arteries occur > atherosclerosis
- **HDL** cholesterol is able to go and **remove cholesterol from atheroma**
- Atherogenic cholesterol: LDL, VLDL, and IDL
  - **LDL particles > LDL, most atherogenic**
- **High TGs > pancreatitis**
  - We use premature HDL to treat pancreatitis, because it will take up cholesterol
- **LDL vs LDL particles: the smaller the particles the more dangerous** and higher risk of CV disease
- TGs in lipoprotein:
  - Chylomicrons more than > VLDL more than > IDL
- Plasma lipoprotein:
  - Chylomicrons: source > gut major lipid> dietary TGs atherogenicity> pancreatitis
  - VLDL: source > liver major lipid > endogenous TGs
  - IDL: source> VLDL remnant major lipid > chylomicrons esters and TGs
  - LDL: source > VLDL and IDL major lipid > chylomicron esters
  - **HDL**: source > gut and liver major lipid > chylomicron esters and PLs
    - ✓ **Antiatherogenic and cardioprotective**
- General **causes of hyperlipidemia:**
  - **Diet and obesity**
  - **Pregnancy**
  - **Hypothyroidism and DM**
  - **Nephrotic syndrome, obstructive liver disease, and SLE**
  - **Acute hepatitis and AIDs**
- **Hereditary causes:**
  - **Familial hypercholesterolemia:**
    - **Codominant genetic disorder in heterozygous form**
    - **Mutation in LDL receptor**
      - **LDL not taken up by the liver**

        - **LPL deficiency will lead to elevated chylomicrons + VLDL that has TGs > elevated TGs**
    - high risk of **atherosclerosis and tendon xanathoma, tuberous xanthomas, corneal arcus and xanthelasmas of eyes**
- Dietary sources of cholesterol:
    - monosaturated: low LDL high HDL
    - polysaturated: low LDL high HDL
    - Saturated: increase LDL and HDL
    - Trans: high LDL
- **Primary hypercholesterolemia:**
    - **Familial: LDL >190**
        - Genetic defect: **LDL receptor**
        - Clinical features:
            - **Hetero: CAD (30-50 years of age)** and TC: 7-13
            - **Homo: CAD before 18** and TC > 13
    - **Familial defective apo-B100**
        - **Apo B-100**
        - CF: premature CAD and TC: 7-13
    - **Polygenic:**
        - CF: premature CAD and TC: 6.5-9
    - **Familial hyperalphalipoproteinemia**
- **Primary hypertriglyceridemia:**
    - **LPL deficiency:**
        - Genetic defect: **endothelial LPL**
        - CF: hepatosplenomegaly, abdominal cramps, and **pancreatitis**
        - TG > 8.5
    - **Apo C-II deficiency:**
        - Genetic defect: **apo C II**
        - Abdominal cramps and **pancreatitis**
        - TG > 8.5
    - Familial hypertriglyceridemia:
        - Unknown enhanced hepatic TG production
        - Dominant
        - CF: abdominal cramps, pancreatitis
- **Primary mixed hyperlipidemia:**
    - Familial dysbeta-lipoproteinemia:
        - Genetic defect: apo E, high VLDL, and chylo
    - Familial combined:
        - genetic defect: high apo B-100
        - dominant
- **Secondary hyperlipidemia: imp**
    - **DM: VLDL**
        - Increased VLDL production
        - Decreased LDL and altered LDL
    - **Hypothyroidism: LDL**
        - Decrease LDL-rec. and LPL
    - **Obesity: VLDL**
        - Increased production
    - **Anorexia: LDL**

        - Decreased bile secretion and LDL catabolism.
    - **Nephrotic syndrome: LDL**
        - Increase Apo B-100
        - Decrease LPL and LDL-rec.
    - **uremia and dialysis: VLDL**
        - Decrease LPL and HTGL
    - **Pregnancy: VLDL and LDL and HDL (all increased)**
        - Increase estrogen and VLDL production.
        - Decrease LPL
    - **Biliary obstruction: low HDL**
        - No CAD
    - Alcohol: increased VLDL and HDL
        - Depends on dose, diet, and genetics
- Investigations:
    - Non fasting: HDL and total cholesterol
    - Fasting: HDL, cholesterol, and TGs
        - LDL= cholesterol –(HDL + TGs /5)
- When to check:
    - NCEP:
        - Begin at 20 with fasting panel and repeat every 5 years
    - US preventive services task force:
        - Women > 45 and men > 35
        - Check HDL and cholesterol every 5 years
        - If total cholesterol >200 or HDL < 40: fasting panel
        - Cholesterol screening begins at 20 in case of:
            - ✓ CV risks, diabetes, or family history
- Goal of treatment:
    - LDL and non LDL like cholesterol and HDL (elevate): prevent coronary heart disease outcomes like MI
    - **TG: to prevent pancreatitis** and coronary heart disease outcomes
        - **TG > 10 high risk for pancreatitis**
- Estimating 10-year risk for ASCVD:
    - Age, BP, cholesterol, HDL, LDL, DM, smoking, on anti HTN, statin, or aspirin
    - If the patient has established **coronary artery disease > high intensity statin**
        - **Except if the patient is > 75 years' old**
    - **If LDL > 190 > high intensity statin**
    - **Diabetic and > 40 years old > high intensity statin**
    - **Overall:**
        - **< 5% no need for medication**
        - **5-7.5% mod intensity statin**
        - **> 7.5% high intensity statin**
- Statins:
    - high intensity:
        - Daily dose lowers LDL by 50%
        - atorvastatin **(40+) 80 mg,** rosuvastatin **(20-40) mg**
    - mod intensity:
        - daily dose lowers LDL by 30-50%
        - low intensity:
            - lowers < 30%
- Treatment of hyperlipidemia:

- lifestyle modification: **low cholesterol diet, exercise, quit smoking and drinking alcohol**
- **Meds:**
  - **Statins: HMG CoA reductase inhibitors**
    - decrease LDL (18-55) and TGs (7-30)
    - increase HDL (5-15)
    - SE: myopathy and increased liver enzymes
  - **Ezetimibe: cholesterol absorption inhibitor**
    - Decrease LDL (14-18) and TGs (2)
    - Increase HDL (1-3)
  - **Nicotinic acid:**
    - Decrease LDL (15-30) and TGs (20-50)
    - Increase HDL (15-35)
    - SE: flushing, hyperglycemia, hyperuricemia, GI distress, and hepatotoxicity
  - **Fibric acids: Gemfibrozil and Fenofibrate**
    - Decrease LDL (5-20) and **TGs (20-50)**
    - Increase HDL (10-20)
    - **Best treatment to prevent pancreatitis (fenofibrate)**
    - SE: dyspepsia, gallstones, and myopathy
  - **Bile acid sequestrants: cholestyramine**
    - Decrease LDL and increase HDL
    - No change in TGs
    - GI distress, constipation, decreased absorption of other drugs
  - **PCSK9: Evolocumab and alirocumab**
    - Decrease LDL (50-60)
    - SE: Injection-site reactions, muscle pain, neurocognitive adverse events. These included memory impairment and confusion

4. DM type 1:

- Increase in plasma glucose and deficiency of insulin
- Genetic disease
  - Type II is familial
- Two peaks in incidence: 9 and 13
- Associated with other autoimmune diseases like celiac, thyroid, vitiligo

❖ **Pathogenesis:**

- autoimmune
  - Chromosome 6, short arm, segment DR3 and 4 > drive mRNA to make something called islet cell antibodies > go through circulation to reach the pancreas > attack and cause inflammation (insulitis) and destruction of beta cells > insulin deficiency
- Environmental: **mumps, coxsackie B, and EBV** > trigger T lymphocytes > mRNA transcribes antibodies against the virus > activate segment DR3 and 4 > islet cell antibodies

❖ **Clinical presentation:**

- **Polyphagia, polydipsia, polyuria, and weight loss**
- Onset acute and in youth
  - Symptoms develop quickly

- DKA (most common presentation)
  - Polyuria and polydipsia
  - Abdominal pain (nausea and vomiting)
  - Dehydration
  - Fruity breath
  - Kussmaul breathing
  - Mental changes (confusion or coma)

❖ **Diagnosis:**

- Random blood sugar: > 200 mg/dL
  - Good for screening (sensitive)
- Fasting blood sugar: >/= 126 mg/dL
  - Good for diagnosis (specific)
- OGTT: best confirmatory test
- HbA1c: >/= 6.5

❖ **Management:**

◆ insulin is the main treatment (commonly causes hypoglycemia)

- Disease isn't evident until 90% is lost > start treatment immediately
- Administration:
  - · SC self injections in abdomen, buttocks, arm, and legs
  - · IV or IM in DKA
- Not given orally because stomach acid will break it down and inactivate it
- Preparations:
  - Ultra short: lispro and aspart
  - Short: regular and humulin
  - Intermediate: NPH and lente
  - Long acting: **glargine** and detemir

◆ Diet and lifestyle modifications: improve chances against complications

◆ Beta cell transplant: can cure the patient but

- 2 brain dead donors
  - transplant starts to dysfunction after 5 years
  - patient needs to be on immunosuppressants

◆ whole organ transplant, or with other organ like kidney

- Note that long term immunosuppression is needed

5. DM type 2:

- Resistance to the action of insulin and inability to produce insulin to overcome the resistance
- Often associated with other disorders > metabolic syndrome or insulin resistance syndrome
  - Hypertension, dyslipidemia, NASH, and PCOS in women
  - Common in obese people

❖ **Risk factors:**

- Genetic: largest effects is seen with variation in TCF7L2
  - Involved in beta cell function of regulation of cell cycling and turnover suggesting that altered regulation of beta cell mass is a key factor
- Environmental:
  - Diet and obesity: 10x more in people with a BMI > 30
  - Age: middle aged and elderly

❖ **Pathophysiology:**

- Normal blood glucose levels are maintained by:

        - Suppression of hepatic glucose production
        - Stimulation of hepatic glucose uptake
        - Stimulation of glucose uptake by peripheral tissues.
    - Incretin effect:
        - Insulin: primary regulator of glucose metabolism and storage
        - Glucagon-like peptide 1 (GLP-1) and gastrointestinal peptide (GIP) can increase secretion of glucose metabolism
        - as a result, insulin release is greater when glucose is administered by mouth
    - Insulin resistance:
        - Initially: elevation of insulin secretion > to maintain normal blood glucose level
        - With time in susceptible individuals > beta cells are unable to sustain the increased demand > insulin deficiency
        - First theory: intra-abdominal adipose tissue
            - FFA, adipokines, TNF-a (imp), IL-6, RBP4 > modify or contribute to insulin resistance
            - GLP1 and GIP resistance also plays a role
        - Second theory: physical activity
            - Inactivity > down regulation of insulin-sensitive kinases > promote accumulation of FFAs within skeletal muscle.
            - Physical activity allows non-insulin-dependent glucose uptake into muscle, reducing the 'demand' on the pancreatic β cells to produce insulin.
    - Pancreatic beta cell failure:
        - deposition of amyloid in the islets
        - elevated plasma glucose and FFAs also exert toxic effects on pancreatic β cells > impaired insulin secretion.
        - numbers are reduced, but mass is unchanged and glucagon secretion is increased
        - At the time of diagnosis, around 50% of β-cell function has been lost and that leads to a progressive decline

❖ **Signs and symptoms:**
- Polydipsia, polyphagia, and polyuria
- Change in weight (loss)
- Nocturia, mood changes, difficulty concentrating
- Fatigue and lethargy
- Blurred vision
- Pruritus vulvae, balanitis
- Nausea, headache, and neuropathy

❖ **Investigations:** diagnosis of exclusion

✓ Gold standard for diagnosing diabetes: OGTT

- Blood testing:
    - Glucose: capillary > monitor treatment
    - Ketones: detects B hydroxybutyrate, useful in insulin adjustment during intercurrent illness or sustained hyperglycemia to prevent or detect DKA.
    - HbA1c: more sensitive to glycemic control of the last 3 months
- Urine:
    - Glucose: 1-2 hours after a meal
        - Could be due to low renal threshold

- Ketones: not pathogenomic, common in people who are fasting, vomiting, excirsing, following keto diet. But when associated with glycosuria > diabetes is highly likely
- Protein: Standard dipstick testing will detect urinary albumin > 300 mg/L but smaller amounts (micro) require specific sticks or laboratory urinalysis. (diabetic nephropathy → proteinuria)

- The glucose cut-off that defines diabetes is the level above which there is a significant risk of microvascular complications
- Pre diabetes: high risk of developing diabetes but low risk for miscrovascular complications
- Diagnostic Criteria of Diabetes:
  - Plasma glucose in random sample or oral glucose tolerance test ≥ 11.1
  - Fasting plasma glucose= ≥ 7.0 mmol/L
  - HbA1c >/= 6.5%
- Asymptomatic patients > second confirmatory test (separate occasion)
- Symptomatic + positive test > type 2 DM

❖ **Complications:**

◆ Macrovascular:
- Coronary artery disease.
- Peripheral artery disease.
- Cerebrovascular disease.
- Overall lifespan is decreased by 6 years.

◆ Microvascular:
- Diabetic nephropathy.
- Diabetic retinopathy.
- Diabetic neuropathy
  - ➢ diabetic foot

- Complications may be present at diagnosis, progress with time, and control limits complications

❖ **Management:**

✓ Goals:
- Education: multidisciplinary team
- Self assessment of glycemic control: to use the results to guide insulin dosing and to manage exercise and illness
- Therapeutic goal:
  - ◆ Early (lifestyle changes or OHG) HbA1c 6.5% or less
  - ◆ Older patients w/ CVD or on insulin HbA1c 7.5% or less
- In new cases of diabetes, adequate glycemic control can be obtained by diet and lifestyle advice alone in approximately

- Diet and lifestyle: first line
  - Healthy food, weight reduction, exercise, smoking cessation and reduce alcohol consumption
- Metformin: first line
  - Increases insulin sensitivity and helps with weight loss
  - CI: CKD > lactic acidosis
- Sulfonylurea: increase insulin release from the pancreas > driving glucose intracellular and increasing weight
- Thiazolidinediones (glitazones): CI in CHF
- Nateglinide and repaglinide: same MOA as sulfonylurea w/o sulfa
- Alpha glucosidase inhibitors (acarbose, miglitol) are agents that block glucose absorption in the bowel.

- Decrease by ½ point in HbA1c
- SE: diarrhea, flatulence, abdominal pain
- Can be used in RF

○ Incretins (exenatide, sitagliptin, saxagliptin, linagliptin)
- Decrease gastric motility > weight loss
- Exenatide > pancreatitis

○ Pramlintide
- Decreases gastric motility, glucagon levels, and appetite

○ Insulin: when OHG fail
- Glargine: much more steady blood levels than NPH
- NPH insulin: twice a day.
- Long-acting insulin is combined with a short-acting insulin such as lispro, aspart, or glulisine.
- Regular insulin is sometimes used as the short-acting insulin.
- The goal of therapy is HgA1c <7%.
- can be used in pregnancy
- patient came with HBA1c >10%: premixed insulin.

6. DM complications:

- Diabetes is the **leading cause** of: **blindness, renal failure, and non-traumatic lower extremity amputation**
- Usually present after long period of hyperglycemia
- Complications classification: Acute (**DKA, HHS**), or Chronic (**Microvascular, Macrovascular**)
- DKA is the most common cause of death in children and adolescents w/ DM1

❖ **DKA:**

When there is no insulin (type 1) and the body needs energy, the body will use fat (lipolysis) > lead to production of ketones > DKA

○ Omission of insulin > DKA, causes:
- Pt stop taking insulin when they have **Gastroenteritis** with **false** belief: (no food =No insulin)
- **Insulin pump failure**
- **Acting out or eating disorder to reduce weight**

○ Clinical features of DKA:
- **Thirst, polyuria,** Weakness
- **Abdominal pain, nausea, and vomiting**
- Physical exam:
  - ★ **Kussumal breathing**
  - ★ **Fruity breath**
  - ★ Hypothermia, tachycardia, and orthostatic hypotension (supine)
  - ★ Dry mucous membrane and poor skin turgor
  - ★ **BG > 250 + high anion gap + ↑ blood & urine ketones + ↓intracellular K**

❖ **HHS**

○ Clinical features of HHS:
- More **insidious** and has **greater osmolality** and mental status changes
- **Dehydration with shock like state**
- Usually patient is **older, + comorbidities, type 2, BG > 600,** and severe dehydration

- Diagnostic criteria:
  - Lab findings:
    - **Hyperglycemia, ketones** (serum and urine)
    - Low bicarb and **high anion gap**
    - **Low arterial PH (metabolic acidosis)**
    - Low PCO2
    - **High K <u>BLOOD</u> level**
  - K in DKA:
    - Urinary loss and **K stores are reduced**
    - Intracellular > extracellular:
      - Insulin def, high blood glucose, and cells buffer hydrogen ions
      - Levels high before treatment but may drop during therapy
  - Ketones:
    - **Nitropusside reaction** in the lab > measures acetones and acetoacetate
- Treatment:
  - **Correction of dehydration, hyperglycemia, and electrolyte**
  - Identification of comorbid precipitating events
  - Frequent patient monitoring
  - **Fluids:**
    - **1-2 L as a bolus then cont rate**
    - **Normal saline**
  - **K:**
    - **K is high (>4.2): insulin, and check K serum within 1-2 hours**
    - **K is low (< 3.3): K before insulin**
    - **K level in between: both K and insulin at the same time**
  - **Insulin:**
    - **0.1 U/Kg bolus** then **0.1 U/kg effusion** until **blood sugar reaches 200**, we **add D5**
    - bring blood sugar level down to an acceptable range slowly
  - **When to Transition from IV Insulin Infusion > SC:**
    - **BG6 < 200 mg/dL and 2 of the following:**
    - HCO3 ≥ 18 mEq/L
    - Venous pH>7.3
    - **Anion gap ≤ 12 mEq/L.**
    - **Good oral intake.**

❖ **Vascular:**

- **Micro** (specific): **retinopathy**, **neuropathy**, and **nephropathy**
- **Macro: CAD, PAD, CVA**
- Pathology:
  - **Protein glycation**
  - **↑ free radical generation formation.**
  - **Activation of protein kinase C**
  - **↑ d-dimers**
  - All this leads to **inflammation of blood vessels** + **hypercoagulable state**

- **Retinopathy:**
  - **Non-proliferative:** late **first decade** or early second decade of disease
    - retinal vascular **microa-neurysms**, **blot hemorrhage**, and **cotton wool spots.**
  - **Proliferative: hypoxemia** > **neovascularization** leading to vitreous hemorrhage, fibrosis, and **retinal detachment.**

- **Macular edema: both stages**
- Treatment:
  - **Prevention (most effective)**
  - Glycemic and BP control (slow progression)
  - Laser Photocoagulation.
  - Ocular injection (Anti-VEGF10 therapy for macular edema)
  - Screening: **annual dilated eye exam**

- **Nephropathy:**
  - **Micro and macro albuminuria**
  - Other important risk factors like HTN
  - Treatment:
    - Prevention, **control BP and DM**
    - **ACEI or ARBs**
  - Screening: **albumin creatinine ratio in spot urine (annual)**
- **Neuropathy: most common**
  - Polyneuropathy:
    - Distal and symmetric
    - Sensory loss and loss deep reflex (ankle)
    - **Axonal degeneration, irreversible damage related to DM**
  - Mononeuropathy:
    - Cranial or peripheral (**3rd CN:** eyes look down and out)
    - **Autonomic**, **CVS**, **GI**, or **GU**
  - Treatment:
    - Prevention and glycemic control
    - Treat risk factors like dyslipidemia, HTN, smoking, B12 or folate
    - Symptomatic treatment: amitriptyline or pregabalin
    - Precaution
  - Screening: Monofilament examination and ask patient about symptoms.

❖ **Non vascular complications:**

- Gastroparesis, infections, skin changes, and hearing loss
  - ✓ CVS: important factor for ischemic heart disease
- Treatment:
  - Aggressive cardiovascular risk modification and early glycemic control
- Screening: symptoms & signs, not recommended in asymptomatic patients

- Lower extremity complications:
  - Interaction of several pathogenic factors:
    - **Neuropath**y (interfere with normal protective mechanism)
    - Abnormal foot biomechanics (Hammer toe, charcot foot) leading to **abnormal weight bearing.**
    - Autonomic neuropathy (anhidrosis promoting **dry skin** and fissure formation)
    - **PAD and poor wound healing** (impaired resolution of minor breaks in skin)
  - Risk factors for foot ulcer or amputation:
    - Male
    - **Hx of previous ulcer or amputation (most important)**
    - Duration of DM > 10 years
    - Peripheral neuropathy and Visual impairment
    - Abnormal structure of the foot
    - PAD and smoking
    - Poor glycemic control
  - Treatment:

- Prevention.
- Identification of high risk individuals.
- Education.
- Institution of measures to prevent ulceration.
- Attention to other risk factors for vascular disease.
- For developed ulcer, multidisciplinary team.

7. Thyroid disorders:

Hyperthyroidism

- Thyrotoxicosis: clinical syndrome that results when tissue is exposed to high levels of circulating thyroid hormone
- Conditions associated with thyrotoxicosis:
    - o Diffuse toxic goiter (Grave's) (most common)
    - o Toxic adenoma
    - o Toxic multinodular goiter
    - o Subacute thyroiditis
    - o Hyperthyroid phase of hashimotos
    - o Thyrotoxicosis factitia
- Diffuse toxic goiter: most common
    - o More common in females
    - o Clinical features:
        - Thyrotoxicosis + exophthalmos (orbitopathy)
        - Goiter
        - Dermopathy (peritibial myxedema)
- Etiology: autoimmune, peak incidence 20-40 years of age
- Pathophysiology:
    - o IgG Abs directed against TSH receptors (TSH-R Abs and TSH Stimulating Abs)
    - o Stimulation of TSH receptor on thyroid follicular cells increase thyroid hormone production and cell proliferation (diffuse goiter)
- Pathogenesis: local viral infection > inflamm reaction > IFN-g and cytokines > HLA class II expression induced on thyroid follicule cells > thyroid specific T cells will recognize the antigen present on HLA II and activated > activated thyroid specific T cells stimulate B cells to produce TSH receptor stimulating Abs > hyperthyroidism
- Function tests:
    - o High T4
    - o Low TSH
    - o Eye signs:
        - +ve: no further tests
        - -ve: thyroid scan
    - o thyroid scan: when patient does not show typical clinical manifestations:
        - hot: overproduction
            - ★ low risk of malignancy
            - ★ graves and TMN
        - warm: low risk of malignancy
        - cold: higher risk of malignancy (but most are benign)
            - ◆ spon resolving hyperthyroidism

- subacute thyroiditis
- thyrotoxic phase of hashimotos
- iodine loaded patients
- on T4 therapy
- struma ovarii

❖ **Symptoms**:
- o sweating, thin hair, heat intolerance
- o increased appetite, anxiety, tremor
- o diarrhea, palpitations, Afib
- o lid lag and retraction, hypercalcemia, and weight loss

- Atypical presentations
  - o clinical:
    - thyrotoxic periodic paralysis (electrolyte imbalance and hypokalemia)
    - thyrocardiac disease
    - apathetic hyperthyroidism (common presentation in elderly)
      - weight loss, depression, …
    - familial dysalbuminemic hyperthyroxemia
  - o biochem: TSH-R Ab and free T3

❖ **Complications:**
- o thyroid storm (thyrotoxic crisis): predisposing conditions
  - fever, agitation, altered mental status
  - Afib and heart failure

❖ **Treatment:**
- o Antithyroid drug therapy: propylthiouracil (safe in pregnancy) and methomazole
- o BB for symptomatic relief
- o Super saturated potassium iodine: decreases synthesis of thyroid hormones
- o Radioactive iodine therapy: most common
  - CI in exophthalmos
  - I131 is most commonly used
- o Surgical: if meds and radioactive iodine failed
  - Subtotal thyroidectomy
  - Prep for surgery: control HR, BP, thyroxine levels
  - Complications:
    - Hypothyroidism and hypoparathyroidism (hypocalcemia)
    - Recurrent laryngeal nerve injury

- Complications of graves treatment:
  - o Thyrotoxic crisis: with high dose you need to prevent the conversion of T4 > T3 w/ steroids then propylthiouracil then IV BB and iodine
  - o Orbitopathy
  - o Thyrotoxicosis and pregnancy
- Treatment of other forms of thyrotoxicosis:
  - o Toxic adenoma and toxic multinodular goiter: meds, radio-iodine, surgery
  - o Amiodrane: graves type > antithyroid.. thyroiditis type > symptomatic
  - o subacute thyroiditis: treat symptoms

Hypothyroidism

- Etiology:
  - o primary:
    - Hashimoto (most common)

        - With goiter, idiopathic thyroid atrophy (end stage, autoimmune, graves or hashi)
    - Neonatal (mom taking TSH R blockers)
    - Radioactive iodine therapy for graves
    - Subtotal thyroidectomy for graves or nodular goiter
    - Excessive iodine intake
    - Subacute thyroiditis
    - Iodine deficiency
    - Goitrogens (Li, amiodarone, antithyroid therapy)
    - Inborn errors
  - Secondary: hypopituitarism (primary adenoma, ablative therapy, destruction)
  - Tertiary: hypothalamic dysfunction
  - Other causes: peripheral resistance to the action of thyroid hormones (high hormones in blood but symptoms of hypothyroidism
- Pathogenesis:
  - Accumulation of glycosaminoglycans (hyaluronic acid) in interstitial tissue
    - Face, heart, hand
  - Increase capillary permeability to albumin
  - Interstitial edema
- **Clinical features:**
  - Common: fatigue, coldness, weight gain, constipation, menses irregularity, and muscle cramps
  - Physical: cool, dry skin, puffy face and eyes, hoarse voice, slow reflexes, and yellowish skin discoloration
  - Clinical manifestations:
    - Anemia: impaired Hb synthesis, iron def, folate, def, pernicious (B12)
      - Due to absorption problems
    - Pulmonary: shallow slow respiration > respa failure
    - GIT: ileus
    - Renal: impaired GFR and water intoxication
    - CNS: lethargy, decreased concentration, anovulotary cycles, depression and agitation
    - Heart: bradycardia, decreased CO (low voltage ECG, due to pericardial effusion), cardiomegaly, and pericardial effusion
    - NM: paresthesia, muscle weakness, and carpal tunnel
- **Complications:**
  - Myxedema: end stage
    - Weakness, stupor, hypothermia, hypoventilation, hypoglycemia, hyponatremia, water intoxication, shock, and death
    - Associate illness (precipitating factors): pneumonia, MI, cerebral thrombosis, GI bleed, ileus, excessive fluid and sedatives admin
    - Three main issues: CO2 retention (hypoxia), fluid and electrolyte imbalance, and hypothermia
  - Myxedema and heart disease: sudden increase in metabolism > overload > ischemia
  - Hypothyroidism and neuropsychiatric disease
- **Diagnosis:**
  - Biochem:
    - primary hypothyroidism: high TSH and low T4
    - secondary: low TSH and T4
      - free T4 only ordered after TSH is normal

- TRH stimulation: not used anymore
- Serology: thyroid Ab (in autoimmune)
  - Mildly elevated TSH with normal T4

❖ **Treatment:**

o Levothyroxine:
- Take in the morning
- Do blood fasting before taking daily dose
- Increase dose in malabsorption, pregnancy and lactation, or concurrent admin of aluminum perpetration, cholestyramine, Ca, or Fe compounds
- If the patient is on meds that affects thyroxine absorption > separate them by 4 hours

o Myxedema: emergency
- Monitor blood gasses
- Intubate and mechanical ventilation
- Treat associated medical problems
- Avoid excessive hydration
- Assess adrenal function and treat if needed
- Pit myxedema: glucocorticoid replacement is essential
- IV levothyroxine
- Be cautious with coronary artery disease
- Active rewarming is CI

o Myxedema and heart disease: start treatment slowly in long standing hypothyroidism and in elderly patients

- Toxic effects of levothyroxine therapy
  - o No allergies, adjust dose and no side ffects
  - o Hypothyroidism could happen if dose not adjusted
    - Cardiac, osteopenia, and osteoporosis

8. Parathyroid disorders:

- Calcium is maintained by 3 hormones:
  - o PTH:
    - Secreted by parathyroid gland
    - Response to hypocalcemia and regulated by conc of serum ionized calcium
    - Effect: increases Ca and decreases PO4
    - Physiology: directly on bones and kidneys and indirectly on the intestines
  - o Calcitonin: PTH antagonist
    - Secreted by: parafollicular cells of thyroid gland
    - Released in response to high plasma ionic calcium
    - Effect: decreases Ca and increases PO4
    - Physiology: inhibits osteoclasts from breaking down bone and inhibit Ca reabsorption in renal tubular cells
  - o Vitamin D:
    - Absorption starts at the skin from direct sunshine > liver > kidney (active form) under the influence of PTH
    - Increases renal and intestinal Ca and PO$ absorption
    - We measure 25-hydroxyvitamin D

- While most potent is 1,25 dihyroxyvitamin D3

Hyperparathyroidism

- Over production of PTH by one or more hyper functioning parathyroid gland
  - Autonomously hyperactive
- Leads to hypercalcemia which fails to inhibit the gland activity in the normal manner
- Common after 50 and in women

❖ **Causes:**
- Most common: a single adenoma (80%)
- Four gland hyperplasia
- Parathyroid carcinoma (rare)

❖ **Clinical features:**
- Most common is asymptomatic hypercalcemia
- Kidneys: nephrolithiasis (stones) and nephrocalcinosis
- Bones: osteoporosis, fractures, osteitis fibrosa cystica, salt & pepper appearance of the skull
- Muscle pain and weakness
- PUD and pancreatitis
- Gout and pseudogout
- Fatigue and lethargy
- depression, psychosis, and anxiety
- hypertension > ventricular hypertrophy
- short QT interval
- anemia

- Complications commonly relate to bones and kidneys
- Diagnosis: picked up routinely
  - lab tests:
    - elevated Ca
    - elevated immunoreactive PTH (characteristic)
    - serum phosphate is low (primary)
  - radiology:
    - plain X ray of hands: can be diagnostic
    - preoperative localization of parathyroid glands:
      - US, MRI, CT, and thallium, tehcnichum, and scan

❖ **Treatment:**
- Medical: before surgery to lower Ca because its not safe and acute severe forms
  - Hydration with saline and forced diuresis
    - Prevent reabsorption by renal tubules
  - Calcitonin: prevent bone resorption
  - Bisphosphonates: prevent bone resorption
  - Phosphate: commonly used as a temporary measure during diagnostic work up
  - Estrogen: postmenopausal women
  - Steroids
  - Mythramycin: hematological and solid neoplasms causing hypercalcemia
  - Cinacalcet: unwilling to undergo surgery or not fit
- Surgical: curative!
  - Recurrence observed in multiple glandular disease
  - Indications: symptomatic, under 50, and asymptomatic but with significant hypercalcemia

- Ddx of hypercalcemia: when Ca is elevated and PTH is normal think about other reasons
    - Parathyroid related: Li therapy, thyrotoxicosis, and familial hypocalciuric hyperkalemia (PTH is normal)
    - Vit D related: intoxication, increased production 1,25 (OH)2D, sarcoidosis, other granulomatous diseases, idiopathic hypercalcemia
    - Malignancy: solid tumor with metastasis or humoral mediation of hypercalcemia, and hematologic malignancy
    - High bone turnover: hyperthyroidism, immobilization, thiazides, and Vit A intoxication
    - Renal failure: secondary hypoparathyroidism, Al intoxication, milk alkali syndrome, adrenal insufficiency
- Secondary hyperparathyroidism:
    - Increase in PTH that is adaptive and unrelated to intrinsic disease of the parathyroid
    - Due to chronic Ca deficiency > stimulation of parathyroid gland
    - Happens in:
        - CKD: Ca might be normal or low but PO4 will be high
        - Vit D def: both Ca and PO4 will be low

Hypoparathyroidism:

- Low Ca and elevated PO4 with diminished or absent circulating iPTH
- Causes:
    - Surgical resection (most common)
    - Idiopathic: autoimmune
        - Young, genetic, autosomal recessive (MEDAC syndrome)
        - Juvenile familial endocrinopathy
        - Hypoparathyroidism – Addison's disease – mucocutaneous candidiasis (HAM) syndrome
        - Pernicious anemia
        - Ovarian failure
        - Autoimmune thyroiditis
        - Diabetes mellitus
    - Functional: due to low magnesium levels
        - Important for release and peripheral action of PTH
        - Only correct the Mg
- **Clinical features:**
    - Neuromuscular: decreases the thresthold of excitation
        - Paresthesia, numbness, and tetany
        - Hyperventilation
        - Convulsions
        - Adrenergic symptoms
    - Signs of latent tetany: chevostek sign, trousseau, and extrapyramidal manifestations
    - Cataract (posteriolenticular)
    - Prolonged QT interval, hypotension, refractory HF w/ cardiomegaly
    - Abnormal enamel formation with delayed or absent dental eruption and defective dental root formation
    - Malabsorption like in celiac
- **Diagnosis:**
    - Make sure the patient is not in renal failure
    - Hypocalcemia, hyperphosphatemia, and low iPTH (confirms)
- **Treatment:**

    - Oral calcium
    - Vitamin D or potent analogues (calcitriol or alfacalcidol)
    - Phosphate restriction in diet
    - Emergency treatment: Ca parenterally and vit D supplement
- Pseudo-hypoparathysoidism
    - Rare familial disorder with target tissue resistant to PTH
    - Short stature
    - Short metacarpal and metatarsal bones
    - low serum calcium level with hyperphosphatemia is associated with increased serum iPTH
- Ddx of hypocalcemia:
    - vit D deficiency or resistance
    - decreased intestinal absorption of vit D or Ca due to primary small bowel disease, short bowel syndrome, or post gastrectomy syndrome
    - drugs that cause rickets or osteomalacia (phenytoin, phenobarbital, cholestyramine, and laxatives)
    - CKD (most common cause)
        - Loss of vitamin D and hyperphosphatemia lowers Ca
    - Acute pancreatitis
    - Citrated blood in massive transfusion (not uncommon).
    - Low plasma albumin, e.g. malnutrition, chronic liver disease.
    - Pseudo-hypoparathyroidism (syndrome of end-organ resistance to PTH)
    - Hyper phosphatemia: in phosphate therapy.

Metabolic bone disease

- Bone types:
    - Cortical: compact > shaft of long bones
    - Trabecular: lattice > vertebrae and ends of long bones
- Types of bone cells:
    - Blasts: bone forming cells, active in the synthesis of the matrix and facilitate the movement of mineral ions between ECF and bone surfaces
    - Osteocytes: permits translocation of mineral in and out of regions of bone removed from surfaces as well as signaling between different bone cells
    - Osteoclasts: bone resorption
- Bone functions:
    - Rigid support to extremities and body cavity which contains vital organs
    - Efficient levers and sites of attachment of muscles > locomotion (important)
    - Large reservoir of ions such as Ca, PO4, Mg, and Na
- Osteomalacia:
    - Failure of organic matrix to mineralize normally
    - Rickets in children and osteomalacia in adults
    - Causes: decrease in the product of concentrations of Ca and PO4 in ECF
        - Vit D deficiency due to:
            - Inadequate exposure w/o dietary supplements
        - GI disease that interrupts normal enterohepatic recycling of vit D and its metabolites > resulting in fecal loss
            - Chronic steatorrhea
            - Malabsorption
            - Surgical resection of large parts of intestine

        - Formation of biliary fistulas
    - Impaired synthesis by the kidney
        - Nephron loss
        - Functional impairment in hypoparathyroidism
        - Congenital absence of hydroxylase (vit D dependent rickets type I)
    - Target cell resistance diminished number of 1,25 (OH)2D3 receptors rickets type II
    - Phosphate def:
        - Dietary: excessive aluminum hydroxide
        - Impaired renal tubular reabsorption
        - Systemic acidosis: CKD, distal renal tubular acidosis, ureterosigmoidoscopy, chronic acetazolamide and ammonium chloride admin.
        - Drug induced osteomalacia: antiepileptic
- o Clinical presentation:
    - Proximal muscle weakness and pain (common)
    - Disease is extensive > deformities: large skill, frontal bossing, bowing of legs.
    - fractures tendency: ribs, vertebral crush fractures, tibia or femur. healing is rapid.
    - waddling gate due to proximal muscle weakness and to the pain and discomfort for during movement of limbs
    - severe muscular hypotonia and paradoxically brisk deep tendon reflexes.
- o diagnosis:
    - Low serum vitamin D
    - Phosphate and calcium: may be normal or low.
    - High serum ALP
    - High PTH
    - Radiology: X ray and bone scan
- o Treatment:
    - Correct underlying cause
    - Dietary deficiency or lack of exposure will respond to small oral doses of vit D, Ca, and sun exposure
    - oral doses of ergocalciferol(D2) or cholecalciferol (D3) for several months will heal the bone disease and restores biochemical and hormonal values to normal
    - administer calcium to provide adequate calcium for bone mineralization
    - ALP and PTH decrease slowly over several weeks but improvement in radiological

- Osteoporosis:
    - Decrease in bone mass and strength > increased fracture tendency
    - Types:
        - I: post menopausal
            - Trabecular
            - Ex. Distal radius > colle's vertebra > crush and wedge
        - II: senile
            - Both cortical of trabecular
            - Ex. Hip > femur neck fracture
    - Causes:
        - Menopause and old age
        - Ca and vit D def

- Estrogen def in women and androgen def in men
- Steroid use
  - For several days > bone loss more on axial bones (40%) and peripheral (20%)
  - Muscle weakness
  - Prednisolone more than 5 mg/day for a long time
- In young people:
  - Hyperparathyroidism, hyperthyroidism, malabsorption,
  - hypercalciuria, chronic lung disease, RA, hepatic disease, and malignancy

○ Clinical features: asymptomatic until a fracture occurs
- wrist or vertebral with a small amount of force
- chronic back pain and kyphosis due to vertebral fractures
- hip fractures > fatal and severe

○ Diagnosis:
- lab: ALP and PTH are normal in patients with sex or age related disease
- radiology:
  - X ray shows bone loss after 30% is lost
  - Single-Photon absorptiometry (SPA)
  - Dual-Photon absorptiometry (DPA)
  - Computed Tomography (CT)
  - Dual-Energy X-ray Absorptiometry (DEXA).

★ Most accurate test in measuring bone mineral density
★ Measure BMD of lumbar and spine and compare that to a healthy woman

○ WHO criteria 94:
- Normal: BMD within 1 SD (T score above -1).
- Osteopenia: BMD which lies between 1 and 2.5 SD “below young normal adult.
- Osteoporosis: more than or equal to 2.5 SD “below young normal adult ”.
- Severe osteoporosis: osteoporosis + with 1 or more fragility fractures

○ Prevention:
- Public awareness
- Adequate calcium and vitamin D supplements
- Physical activity
- Detect and treat early to decrease further progression
- Limit disability and provide rehabilitation

9. Adrenal disorders:

<table>
<tr><th colspan="2">Hypofunction</th></tr>
<tr><th>Primary adrenal insufficiency (Addison disease)</th><th>Secondary adrenal insufficiency</th></tr>
<tr><td>Causes:
Autoimmune (most common), TB
Clinical features:
● hypotension
● Hyperpigmentation (only in primary !!!), due to MSH not ACTH.
weakness, fatigue, N/V, Hypoglycemia…</td><td>Causes:
Panhypopituitarism
withdrawal from glucocorticoid therapy
surgical removal of pituitary glands

Pathophysiology:
ACTH deficiency this leads to:
1- Decreased Cortisol & Androgen secretion.
2- Aldosterone secretion remains normal.</td></tr>
<tr><td colspan="2">Biochemical:
1.Measure Plasma cortisol level:
2.Measure ACTH, renin & aldosterone level
3. ACTH stimulation test (definitive diagnosis!)
· Failure to increase cortisol → Primary adrenal insufficiency.
· Increase in cortisol → Secondary adrenal insufficiency</td></tr>
<tr><td>Treatment: Replace both:
· glucocorticoids (Hydrocortisone)
· Mineralocorticoids (Fludrocortisone)</td><td>Treatment:
· Replace glucocorticoids (Hydrocortisone) Only.</td></tr>
<tr><th colspan="2">Congenital Adrenal Hyperplasia</th></tr>
<tr><td>Caused by: 21-OH deficiency.
Clinical feature:
· Ambiguous genitalia in female
· Dehydration & shock
Management:
· glucocorticoids (Hydrocortisone)
· Mineralocorticoids (Fludrocortisone)
· Surgery (for female)</td><td>Diagnosis
· Electrolytes imbalance (hyponatremia, hyperkalemia, hypoglycemia)
· High 17- OHP
· High androgens</td></tr>
</table>

<table>
<tr><th colspan="2">Hyperfunction</th></tr>
<tr><th>Hypercortisolism (Cushing Syndrome)</th><th>Hyperaldosteronism (Conn's syndrome)</th></tr>
<tr><td>Causes:
· ACTH dependent: pituitary tumor (<u>Cushing's disease</u>) or Ectopic.
· ACTH independent: iatrogenic or Adrenal tumor
Clinical features:
-Moon face - purple striae
-Truncal obesity - osteoporosis</td><td>Causes:
· Adenoma
· hyperplasia
Clinical features:
· Secondary HTN
· High Na, low K, high Cl
· Alkalosis
· Positive chvostek's sign and trousseau sign</td></tr>
<tr><td>Biochemical:
· 24 h urine free cortisol level (high)
· 1 mg DST (no suppression)
· Midnight salivary cortisol (High)
· ACTH measurement to know the cause</td><td>Biochemical:
Initial (screening) test: Aldosterone\ Renin ratio
Confirmatory test:
• Saline infusion test
Imaging tests: CT</td></tr>
<tr><td>Treatment:
· Surgical</td><td>Treatment:
· Adenoma = surgical resection
· hyperplasia = spironolactone</td></tr>
<tr><th colspan="2">Pheochromocytoma</th></tr>
<tr><td>Caused by:
Tumor of adrenal medulla produces catecholamines
Clinical feature:
· Secondary HTN
· Episodic (spells): sweating, palpitation, headache
Diagnosis
· 24 hr urine collection of Metanephrines
· Plasma Metanephrines</td><td>Management:
1. α-blocker then B-Blocker (10-14 days before operation)
2. Oral NaCl: 3 days before surgery
3. Surgical removal (definitive diagnosis)</td></tr>
</table>