* Normal plasma osmolality: 285-295 mOsm/Kg (285-295 mmol/Kg)
* Osmolality = (2x[Na+]) + (glucose/18) + (BUN/2.8)
* Plasma osmolality is most important determinant of ADH secretion → Main effect is ↓ water excretion in late distal tubules.

* Posterior pituitary hormones: - oxytocin - ADH
* Anterior pituitary hormones: - TSH - ACTH - Prolactin - Growth hormone
(FLAT-PiG) - LH - FSH

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* Pituitary tumors:
  * Presents with hyper secretion, hypopituitrasim or, mass effect.
  * Often incidental finding.
  * Evaluation: ① 1st step: Determine if functional or not
    ② 2nd step: Determine if ⊕ Mass effect or not
    → Depending on size: >1 cm adenoma (Macroadenoma) → Evaluate for hyper+ hypo secretion + vision loss.
    <1 cm adenoma (Microadenoma) → Evaluate for hyper secretion only, their size does not cause mass effect (hypo secretion + vision loss).
  * clinical presentation depends on hormone affected.
    * Prolactinomas are most common functioning adenomas.
    * Gonadotrophs are most common non functioning adenomas → become Macroadenomas.
    * Somatotrophs cause Acromegaly (screen by IGF-1 levels)
  * typical mass effect: Headache, diplopia, visiual fields defects (Bitemporal hemianopsia)

* Pituitary apoplexy: * Acute hemorrhage into an adenoma.
  * Severe ① headache, ② nausea, ③ vomiting, ④ altered mental status, ⑤ vision loss.
  * ttt immediately with glucocorticoids.
  Endocrine emergency ←

* Diagnosis: * MRI is the imaging of choice
  * If size <1cm → check; Prolactin, IGF-1, TSH + FT4, LH + FSH, and screen for cortisol;
    ① or ② or ③ → ① Low dose (1 mg) Over night dexamethasone suppression test. or
    ② 24-hour urine cortisol.
    ③ Mid night salivary cortisol.
  * In >1cm;
    * check ACTH stimulation test (cortisol deficiency screening)
    * check FSH, LH in postmenopausal women, testosterone in men
    * Premenopausal women: ask about menstrual changes.

* Hyperprolactinemia and prolactinoma:-
  * serum PRL: >20 ng/ml (>20 µg/L)
  * Most common functional adenoma.
  * Mostly microadenomas, but can also be macroadenomas; PRL levels correlate with tumor size (>100 ng/ml for macroadenomas)
  * ↑PRL → ↓ LH, FSH → causing erectile dysfunction and hypogonadism in men, Amenorrhea and galactorrhea in females. That's why it is dx in women earlier than men.
  * ttt:
    * Surgical → (tumor size >1 cm, Hypogonadal symptoms, galactorrhea, women ⊕ impaired fertility) transphenoidal (for pts who fail medical ttt).
    * Medical → Dopamine agonists (Cabergoline: 1st line) Bromocriptine (2nd line).
    * Radiotherapy → Post surgery to remove any remnants of the tumor.

always check TSH level and pregnancy test before ttt.

* Acromegaly.
  * Due to ↑GH, 99% of cases due to benign adenoma seen on CT or MRI.
  * ↑↑ IGF-1 (produced in the liver, and mediates growth promoting effect of GH).
  * if IGF-1 levels are elevated → confirm acromegaly dx by OGTT (75g oral glucose then test after 1 hour); if GH > 1ng/ml → This is Acromegaly.
  * ttt all patients with transsphenoidal surgery; whether they are symptomatic or not.
  * Medical therapy: for pts with residual tumor.
    * Octreotide (somatostatin analogue) +/- dopamine agonist (cabergoline or Bromocriptine) or GH receptor antagonists (pegvisomant)

* Diabetes insipidus:
  * Kidneys are unable to retain free water → dilute urine despite ↑ plasma osmolality
  * characterized by thirst (with polydipsia) and the production of large amounts of dilute urine urine (>=3L/day).
  * Patients are normonatremic if they have access to water, but are hypernatremic if water access is limited.
  * The first symptoms is nocturia.
  * Can be central (↓ADH production) or nephrogenic (renal resistance to ADH effect)

  → * Neurogenic DI (central): either acquired or congenital.
    * Acquired occurs when damage of disease of posterior hypothalamus.
    * Causes: ① Trauma ② Bran Ca or mets ③ Neurosurgery ④ systemic infiltrative disease (Sarcoidosis)

  → * (ADH-resistant DI):
    * Acquired or due gene mutations in ADH receptor or the aquaporin (transmembrane protein that ↑ water permeability of renal collecting tubules in response to ADH)
    * Acquired causes:
      ① Drugs (specially lithium.)
      ② Hypercalcemia (serum >11 mg/dL)
      ③ chronic hypokalemia (serum k^+ < 3mEq/dL)
      ④ Intrinsic renal disease (specially Sjögren syndrome)

  * Both types can be complete or partial.
  * Differentiate between the 2 by water deprivation test
  * If Na^+ is not high, restrict water intake, then measure urine osmolality, plasma osmolality and serum Na^+ every 2 hours.
  * If urine osmolality becomes >600 → no DI (Do not use desmopressin).
    If urine osmolality <600, wait until serum Na^+ rises to 144-145 then give desmopressin
    → Asses urine osmolality every 30 mins for 2 hours.

* Note: Do not restrict water if Na >145 mEq/L, these are already self restricted. Proceed to desmopressin administration.

① * In central DI; no ↑ADH in response to ↑serum osmolality, low urine osmolality
  - Desmopressin ↑ urine osmolality (normal kidney response)
  * Therefore, Central: Doesn't respond to water deprivation test, but does to desmopressin
    (no ↑ urine osmolality) (↑urine osmolality.)
  * ttt:
    - subcutaneous or intranasal Desmopressin. (counsil pts not overuse it. → may cause drug induced SIADH.

* Note: Primary polydipsia (Psychogenic polyuria): presents with polyuria + polydipsia.
  * Mimics DI, but is differentiated from DI by water restriction test
  → they improve immediately bcz they can concentrate urine with urine restriction.

② * In nephrogenic DI;
  * Urine is dilute despite High ADH levels. / giving desmopressin does not ↑ urine osmolality.
  * ttt: Low Na^+ diet / thiazide diuretic or amiloride added.

* Notes

DI presents : (with or without hypernatremia) + polyuria/polydipsia ; SIADH presents with hypo natremia + normal volume.

---

* Thyroid gland :-
* Hypothyroidism :-

* Symptoms :
1. Fatigue.
2. weight gain.
3. Cold intolerance.
4. Menstrual irregularities.
5. Mental slowness.
6. Depressed mood.
7. Constipation
8. Brittle nails
9. Puffiness in face
10. Extremity swelling
11. Hoarseness
12. Alopecia.
13. Dry skin
14. ↓ tolerance to exercise
15. Carpal tunnel syndrome.

* Signs :
1. Goiter.
2. cool/pale skin.
3. Coarse hair.
4. Periorbital edema.
5. Tongue enlargement. (severe cases)
6. Delayed reflexes.
7. Bradycardia.

* Labs : showing :-
1. Hyponatremia (euvolemic)
2. Macrocytic anemia.
3. Hyperlipidemia
4. ↑ prolactin level → so check thyroid function in women with ↑PRL after confirming that she is not pregnant.
5. pericardial effusion on echo (rare).

* Diagnosis :-
* check TSH level (and T_4 if 2ry (Pituitary) or tertiary (Hypothalamic) causes are suspected)
  * ↑TSH + ↓FT4 = Primary hypothyroidism.
  * ↑TSH + Normal = Subclinical hypothyroidism. (Rx only if TSH is >10 μU/mL)
  * Low or inappropriate normal TSH + Low FT4 = secondary or tertiary hypothyroidism or sick euthyroid.

* ttt :
* Replace Levothyroxine (no benefit of combining T_4+T_3 is achieved beyond T_4 monotherapy)
  → goal is to keep TSH within lower half of normal.
* Always ttt pregnancy hypothyroid, follow up every 4 weeks.

* Myxedema comas
* Thyroid emergency. (Mortality 30-40%)
* More in elderly + Heart diseased pts.
* Clinical diagnosis (not biochemical)
* Any thing causing hypothyroidism can cause it (non-ttt long standing hypothyroidism) → precipitated by infection, heart disease, cold temperatures.
* presentations
  * Progressive hypothyroid symptoms; ① ↓ mentation ② Bradycardia ③ Hypothermia
    also ; hypoventilation, hypoglycemia, hypotension
  * Rarely ; patient may present with psychosis.
  * Pt may have pericardial effusion. seizures in 25% of patients.
* Labs :
Hypoglycemia, hyponatremia, anemia, hyperlipidemia.

* Diagnosis : Hx, PE and draw (TSH, T_4, baseline cortisol and ACTH levels) → To rule out coincidental adrenal insufficiency.
→ if stable.

* Before initiating therapy ; give high dose of cosyntropin (synthetic ACTH) ; obtain follow up cortisol at 30 and 60 mins → (to asses if the pt has normal response to ACTH).

* If unstable; start glucocorticoids w/o doing ACTH stimulation test

* ~~Hb~~ * T_3 (advantages: rapid onset), or IV T_4, or combined $T_4 + T_3$ (preferred option)
  * Glucocorticoids (empiric stress dose) until adrenal insufficiency is ruled out by ACTH stimulation test
  * Empiric Abx, until infection is ruled out
  * Give IV fluids and warm the body (Avoid hypovolemia).

* Mortality of myxedema coma: related to hypothermia degree.

* Hyperthyroidism:
  * M.C.C is autoimmune graves disease, other causes:
    - Multi Nodular goiter
    - ① MNG
    - ② Thyroiditis
    - ③ Toxic adenoma
    - ④ Due to autoimmune thyroiditis (Hashitoxicosis)
    - ⑤ factitious thyrotoxicosis (exogenous thyroid hormone.)
    - ⑥ Subacute thyroiditis
    - ⑦ Iodine induced
    - ⑧ TSH prodeing tumors
    - ⑨ Postpartum thyroiditis.

* Signs + symptoms:

* Symptoms:
  - ① Anxiety and restlessness
  - ② Irritability
  - ③ Insomnia
  - ④ Diarrhea / Hyperdefecation
  - ⑤ Poor concentrations
  - ⑥ weight loss.
  - ⑦ Heat intolerance.
  - ⑧ Alopecia
  - ⑨ Onycholysis.
  - ⑩ Dyspneen
  - ⑪ Menustrual irregularities (women)
  - ⑫ Gynecomastia, ↓libido (Men)

* Signs:
  - ① Goiter
  - ② Lid lag
  - ③ Warm skin
  - ④ Exophthalmos
  - ⑤ Tremor
  - ⑥ Tachycardia
  - ⑦ Atrial Fibrillation (certain hyperthyroidism in new onset A Fib elderly pt).

* Abnormal general labs / studies:
① Low cholesterol + LDL / ② Normocytic, Normochromic anemia / ③ Hypercalcemia / ④ Osteopenia / ⑤ Dilated Cardiomyopathy

* Graves disease:
  * Thyroid stimulating immunoglobulins, IgG that binds to and ④ TSH receptors in the thyroid gland.

* characteristic Findings:
  - ① Diffuse, soft symmetrical goiter.
  - ② Presence of bruit on thyroid auscultation
  - ③ Opthalmopathy: Proptosis + periorbital edema + extra ocular movement Problem → Diplopia. Corneal ulceration.
    - ↑ in smokers and post RAI therapy
    - Mild-Moderate GO: tx with steroids
    - severe: RAI is CI.
  - ④ Dermatopathy: Pretibial Myxedema due to lymphocyte infiltrate → Peau d'orange appearance (red, thickened dermis).
  - ⑤ Immune mediated hematologic abnormalities:
    - → Pernicious anemia + idiopathic thrombotic purpura.

* Diagnosis:
  - Hx + PE + Labs (TFTs + thyroid uptake + scan.)
    - TFTs: TSH low, ↑FT_4
    - uptake + scan: Diffuse ↑ uptake.
  - * Thyroid stimulating immunoglobulins (TSI) are ④ in 90% of graves disease.
    - Also known as thyroid

* ttt: * Medical: Methimazole (MMI) and propylthiouracil (PTU) → Hepatic toxicity and agranulocytosis.
  * β blockers.
  → preferred in non pregnant patients.
* Surgical: Optimal for pregnant pts (2nd trimester)
* Radioactive iodine

*Thyroid storm:

* 2nd thyroid emergency (the other is myxedema coma)
* High mortality rate.
* In untreated or undiagnosed hyperthyroid patients, that is precipitated by surgery, infections, an iodine load (such as amiodarone, or contrast dye).

* Symptoms:
  * Similar to symptoms of hyperthyroidism (more severe):
    ① HTN. ② Tachycardia. ③ HF.
    ④ Fever. ⑤ Psychosis or delerium. ⑥ Nausea + Vomiting
    ⑦ Vomiting

* Clinical Dx rather than biochemical diagnosis.
* suspect it in hyperthyroid pt + fever, altered mental status, and tachycardia
  → ↓↓↓TSH, ↑↑↑ Free T4. (All 3 things)
* They die from Cardiovascular collapse → ttt with supraphysiologic glucocorticoids dose.

ttt: ① Glucocorticoids
② β Blockers (IV propanolol or esmolol)
③ PTU - High dose: to prevent formation
④ stable Iodide: to prevent Thyroxine release
⑤ Abx to ttt infection. (or until it's excluded.)
⑥ Supportive care; IV fluids, cooling blankets, etc...

*Thyroiditis:

* Acute: painful; Due to bacterial infection or trauma (physical or radiation).

self limited ↓
* Subacute: painful; Due to viruses (aka: granulomatous or De quervain's)
  * 30-50 yrs females > Males
* Chronic: painless; Autoimmune mediated (Hashimoto thyroiditis) + post partum thyroiditis.
  → M.C.C of primary hypothyroidism
  ~95% are anti TPO Abs ⊕

* These patients (of thyroiditis) initially present as hyperthyroid phase due to inflammation
  → followed by hypothyroid phase

Adrenal Gland

* Congenital Adrenal Hyperplasia:

* Congenital, AR, cause ↓ cortisol production due to defect in 1 enzyme:-
  ① 17α hydroxylase / ② 11β hydroxylase / ③ 21β hydroxylase.
* CYP 21A2 mutation - 95%. (21β hydroxylase deficiency).
  → Blocks cortisol production → ↑ androgens.
* Symptoms can be severe, moderate, or mild symptoms. / ↑ACTH (due to ↓ cortisol) → causing adrenal hyperplasia.
* Severe form 21-hydroxylase deficiency → causing "salt loosing" form of CAH.
* Newborns may present with adrenal "crisis (Hyponatremia, hyperkalemia).

* Females with salt losing type are born with ambiguous genitalia.
* Virilization occurs in both males and females.
* Moderate form (21-Hydroxylase deficiency) present with simple virilization
  - Females: Prepubertal virilization.
  - Males: Precocious puberty.
* Mild cases:
  * late onset, Females: Post pubertal virilization.
  * Labs: early morning ↑ blood levels of 17-Hydroxyprogesterone.
* CAH is also caused by 11B-Hydroxylase → ↑ 11 deoxy cortisol + 11 deoxycorticosterone (DOC)
  * DOC has mineralocorticoid activity
  * As with 21 hydroxylase deficiency; ↓ cortisol → shifting synthesis to ↑ testosterone
  * Aldosterone is low, but DOC cause Mineralocorticoid excess presentation (Hypertension, hypokalemia, Metabolic alkalosis)

* Cushing syndrome:
  * Excess glucocorticoids in circulation.
  * Symptoms: ① Easy fatigability, ② Proximal muscle weakness, ③ Easy bruising, ④ Emotional lability (psychosis)
    * In women:
      also Amenorrhea, Hirsutism, and acne
  * Physical exams.
    * Facial plethora (moon facies; round red face)
    * Thin skin
    * Thick purple bright striae (wide striae)
    * Cervicodorsal fat pad (buffalo hump) and truncal obesity
    * Cortisol in high concentrations → ⊕ Mineralocorticoid activity → (HTN, Hypokalemia, Metabolic alkalosis)
    * Comorbidities: Osteoporosis, insulin resistance (20% of Pts have type 2 DM).

  * Causes: Most-to-least frequent:-
    ① Iatrogenic glucocorticoids administration
    ② ACTH secreting pituitary adenoma (cushing disease)
    ③ Ectopic ACTH producing tumor. Bronchogenic, pancreatic or thymic ca.
      (small cell lung Ca is M.C.C of ectopic cushing's syndrome in >60 yrs)
    ④ Bilateral adrenal hyperplasia.
    ⑤ Adrenal adenomas or Carcinomas.

---

* Cushing syndrome caused by pituitary adenoma is called cushing disease

* Cushing syndrome; * urine cortisol is ↑↑↑. (slightly)
  * ACTH ⊕ Cortisol, Mineralocorticoids, and androgens.
  → so in cushing disease; ↑ACTH causes virlization, hirsutism, and acne in females.

* Work up:-

Step 1
* 1st thing; exclude exogenous glucocorticoids administration
* Then check for cortisol excess:-
  ① 24 hr-urine cortisol / ② Late night salivary cortisol
  ③ Low dose (1mg) dexamethasone suppression test.
  → Confirm an abnormal test by repeating it or with another test.

Step 2

* Determine if the cushing disease is ACTH dependent or ACTH non-dependent.
  → measure ACTH level (normally it should be ↓↓↓).
  * if ACTH is measurable → ACTH dependent Cushing syndrome (either cushing's disease or ectopic ACTH producing tumor).
    → go to step 3a.
  * if ACTH is Low → ACTH independent cushing syndrome (adrenal hyperplasia, adrenal nodule or adrenal carcinoma)
    → go to step 3b.

* Step 3a: ACTH dependent cushing syndrome :-
  → Do Pituitary imaging with gadalonium contrasted MRI.
  * if not seen → Do Inferior petrosal sinus venous sampling (IPSS ; detects local ACTH production)
  * if MRI is free, and IPSS are both ⊖, get CT chest and abdomen
    ↳ looking for ectopic ACTH producing tumor. (Lung or carcinoid)

* Step 3b: ACTH independent cushing syndrome :-
  * Mostly caused by adrenal tumor → CT scan of adrenals and look for any tumor

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* Adrenal insufficiency :- (AI)
  * Either primary (Addison disease; Disease of Adrenal gland) or secondary (pituitary disease).
  * when AI presents acutely → called addison crisis.
  * Primary AI is mostly due to adrenalitis, but can be caused by infiltrative or granulomatous diseases (HIV/AIDs, CMV, TB, amyloidosis, sarcoidosis)
  * Secondary AI ; M.C.C is rapid withdrawl from exogenous glucocorticoids.

* Polyglandular autoimmune syndrome 1 : (3)
  ① chronic mucocutaneous candidiasis ② Hypoparathyroidism ③ Adrenal insufficiency.
  * Malabsorption, pernicious anemia, hepatitis, alopecia.

* Polyglandular auto immune syndrome 2: (4)
  - ① Addison disease
  - ② Chronic autoimmune thyroiditis.
  - ③ POF (Premature ovarian failure)
  - ④ Type 1 DM.
  * Associated: Pernicious anemia, alopecia, vitiligo.

* Schmidt syndrome : Type 2 polyglandular autoimmune syndrome + Hypothyroidism + Adrenal insufficiency + Type 1 DM.
  → Replace cortisol first before thyroid hormone ; bcz replacing thyroid first will lead to worsening of the condition leading to death

* The preeminant symptom is weakness.
  * other symptoms; N/V, abdominal pain (vague), hypoglycemia
  * Hyperkalemia in 20%-
  * Primary AI (↑ ACTH) : Hyperpigmentation + Hypotension + Hyponatremia + Hyperkalemia (Low aldosterone)
  * Secondary AI (↓ ACTH) : No Hyperpigmentation or hyperkalemia (normal aldosterone)

* Diagnosis and tt:
  * Stable pt: Perform ACTH stimulation test: ① Draw baseline cortisol. ② Give cosyntropin (ACTH analouge). ③ Recheck cortisol levels at 30 and 60 mins
    * If cortisol is < 18-20 µg/dL → pt. has AI.
    * ACTH level determine if primary (High ACTH) or secondary (Low ACTH)
  * Shocked pt:
    * Give IV fluids + dexamethasone immediately.
    * Then perform ACTH stimulation test when the pt is stable.
    * Acute adrenal insufficiency needs to be treated immediately.

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* Hyperaldosteronism:
  * Primary hyperaldosteronism: (Disease in adrenals): Low renin, HTN, Hypokalemia, Metabolic alkalosis.
  * Secondary hyperaldosteronism: (Disease in Kidneys): High renin ↓ renal blood flow due to stenosis of fibromuscular dysplasia → ↑ renin → ↑ angiotensin II → ↑ aldosterone

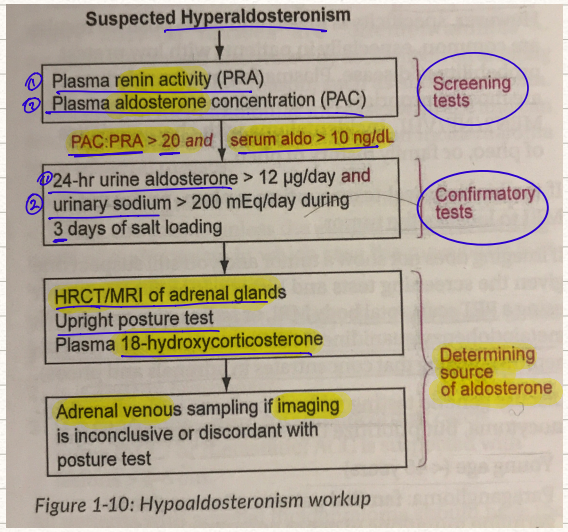

Figure 1-10: Hypoaldosteronism workup

* Diagnosis:
  ① Screening:
    ① Plasma renin Activity (PRA) and plasma aldosterone concentration (PAC)
    * Primary hyperaldosteronism:
      → ↑ PAC : PRA ratio.
      (↑PAC, ↓PRA)
    * Secondary:
      Both PAC & PRA are ↑ and PAC/PRA ratio < 10.

  ② Confirmatory tests:
    ① * By trying to suppress the cortisol (give 2L normal saline over 3-4 hours)
    or ② test 24h urine aldosterone

→ once confirmed Primary hyperaldosterone → Do CT abdomen looking for adrenal adenomas.
→ if unilateral nodule is seen:-
  < 40 yrs → Go straight to surgery; Rare to have non functioning adenoma at this age.
  > 40 yrs → Perform adrenal vein sampling (PAS) → to prove that adenoma is functional

Hypoaldosteronism

The most common cause of hypoaldosteronism is decreased production of renin in diabetic patients with mild renal failure (hyporeninemic hypoaldosteronism, a.k.a. Type 4 renal tubular acidosis [RTA]). It is also seen in patients with chronic interstitial nephritis, chronic NSAID use, and heparin therapy.

Suspect hypoaldosteronism in patients with hyperkalemia and normal anion gap metabolic acidosis out of proportion to the renal disease (low aldosterone leads to failure to excrete H^+/K^+ in the distal tubule). Patients are unable to retain Na^+ in states of volume contraction, and they develop postural hypotension. *

Start the workup by excluding AI as a cause of the hyperkalemia and hypotension because, clinically, they can look similar; perform an ACTH stimulation test. Next, measure renin and aldosterone levels during upright posture and salt restriction (renin is low in this diagnosis but high in AI). Treat with a mineralocorticoid (fludrocortisone). If hypertension and edema are present, do not use fludrocortisone; treat with a low-potassium diet and a loop diuretic.

* Diabetes Mellitus

* classification of DM is based on the mechanism of dysfunction (type 1+2)
  1. Pre diabetes : Impaired glucose tolerance (IGF) and impaired fasting glucose (IFG)
  2. Type 1 DM (IDDM). (<10%, mostly autoimmune mediated (most common), but can be idiopathic.
  3. Type 2 DM (NIDDM). (>90%).
  4. Gestational DM. (Diabetes or glucose intolerance with pregnancy).

DM due to other types:

* Drug induced or chemicals: BBs, statins, steroids, OCPi, thiazides
* Endocrinopathies: Cushing's syndrome, Acromegaly, pheochromocytoma.
* Exocrine pancreas induced: Trauma, surgery, pancreatitis, Cystic fibrosis
* Genetic defects of beta cells: MODY, LADA (Latent autoimmune Diabetes in adults) → Type 1.5 DM
  - MODY: * A.D. * Defects in production or release of insulins

* Diagnosis and screening:

* Normal fasting plasma glucose (FBS) is <100 mg/dL
* Diagnosis of pre-diabetes (1 of these)
  1. Impaired FBS ; 100-125 mg/dL
  2. Oral glucose tolerance test ; 2 hrs post prandial 75g glucose → 140-199 mg/dL
     2 hrs post plasma glucose.
  3. HbA1C : 5.7-6.4%

* Most accurate method to dx prediabetes is OGTT.
* Diagnosis of Diabetes

confirm by retesting (unless pt has DKA or hyperosmolar coma).

1. FBG: > 126 mg/dL → Most accurate method to dx DM
2. OGTT: >200 mg/dL
3. HbA1C : >6.5%
4. Random glucose >200 mg/dL.

* We dx using plasma glucose level. The capillaries whole blood (finger stick) is not used for diagnosis, but for self monitoring of DM pts.

* Start screening for DM at 45 yrs with 3 years interval. (younger if obese: ≥25 BMI).
  and have:
  1. CVD
  2. 1st degree relative with DM.
  3. Acanthosis nigricans, PCOS, nonalcoholic liver disease.
  4. Sedentary
  5. Non Caucassian
  6. HTN
  7. Dyslipidemia (HDL < 35 mg/dL, TG >250 mg/dL)
  8. Hx gestational DM.

* Prediabetes

* 6 folds ↑ in developing DM
* wt loss (5-10%) → ↓ risk by 50% (also: regular exercise 30-60 mins + low Na+ diet / high fiber diet)
* No drugs are used for prediabetes.
  - Metformin may be given to high risk pts (↓ risk of type 2 DM by 30%.

* Type 1 DM:

* cell Mediated B cell destruction → Absolute insulin deficiency.
* 90% have auto antibodies against
  1. islets cells
  2. Insulin
  3. Glutamic acid decarboxylase (GAD) ← most useful
  4. tyrosine phosphatase IA2

*triggered by genetic, immunologic and environmental factors.
*95% are HLA-DR 3, DR 4 ⊕

* Type 1 Patients → Prone to Ketosis.
*Autoimmune associations :-
① Hashimoto's thyroiditis
② Primary adrenal insufficiency.
③ celiac
④ Vitiligo
⑤ Pernicous anemia.
⑥ Myasthenia gravis

*tt:
Insulin.
*Multiple daily injections:
Long acting ← 1) Basal insulin :- ① Galgrine ② Detemir
Short acting ← 2) Post prandial insulin ("Bolus") :- ① Regular ② Aspart ③ Lispro ④ Glulisine

3) Intermediate acting insulin:
- Used to cover fasting + meals. (not as much as long acting)
*NPH
*Premixed insulin (70/30 ; NPH/R) is not recommended anymore in treating type 1 DM

* Best way is to council pt into carbohydrate count method → then Insulin: Carbohydrate ratio → how much insulin they should get preprandial short acting insulin.
*Use of mobile apps have ↑ Patient ability to calculate carbohydrates
* Insulin pumps carries risk of hypoglycemia.

* Honey moon.
* somogyi effect. (Nowdays; do not reduce the insulin.)
* Dawn phenomenon (4:00 - 7:00 am) → tt delay the long acting insulin.

*Type 2 DM:
* >90% of diabetes due to Type 2 DM.
* impaired glucose handling.
* Strong genetic component (Multifactorial + polygenic)
* Obesity ↑ insulin resistance (80% of pts are obese
* Pts with Central obesity, HTN, dyslipidemia → Have metabolic syndrome.

* Mechanisms leading to type 2 DM:-
① Insulin resistance in muscle and fat tissue
② Gradual ↓ in insulin secretion by the pancreas.
③ Dysregulated hepatic gluconeogenesis and glucagon secretion
④ ↓ in GI incretins

* Insulin resistance ⊕ with Acanthosis nigricans. (in PCOs, Cushing's, certain medications (niacin, corticosteroids) and acromegaly.

* Treatment of T2 DM:
① Life style modification (If HbA1C > 7.5% → start pharmacologic al therapy).
② Medications:
*Metformin Monotherapy is recommended as initial therapy for most pts unless there are CIs (GFR < 30 ml/minute)

* Medications used to tt T2DM: ① Secretageous (sulfonylurea, Meglitinides (glinides)) ② Sensitizers: - Biguanide (Metformin) → start 500 → max 2000 mg.
- Thiazolindiendiones (glitazones)
③ α-glucosides inhibitors
④ Amyl analogs (Pramlintide)
⑤ Glucagon-like peptide 1 (GLP1; glutides)
⑥ Dipeptidyl-peptidase-4 Inhibitor (DPP-4I) ← (Gliptins)
⑦ SGLT-2 inhibitors. (gliflozin)
⑧ Insulin

* Sulfonylurea (glipizide, glimepride, glyburide)
* Common to cause hypoglycemia + wt gain. → Long acting; ↑ risk of hypoglycemia (mainly elderly.

* Amylin: hormone secreted by pancreatic β cells → regulates influx of glucose by supressing glucagon and Delaying gastric emptying.

* Insulin can be added to oral drugs when there is persistant hyperglycemia; But insulin must be started immediately even before oral hypoglycemics in:-

add oral hypoglycemics later.
① Consistently high random blood glucose (>300 - 350 mg/dL)
② HbA1C: >10 - 12 %
③ HbA1C: >9% with symptoms.
④ Severe symptoms of hyperglycemia or Hx of DKA.

* Approach to drug therapy:
HbA1C <9%: Metformin monotherapy.
HbA1C >9%: Dual therapy (Metformin + (Sulfonylurea or GLP1 agonists or DPP 4I or TZD or SGLT2 inhibitor or basal insulin) — one of these.)
HbA1C >10%, Glucose ≥300 or marked symptoms: Injectable therapy (basal insulin + short acting insulin) + Metformin.

→ Recheck HbA1C after 3 months, then intesify tt more, but do not use >3 drugs

* Glycemic tt goals:- (For Both types 1+2)
* HbA1C <7% (some say 6.5%)
* Avoid hypoglycemia + keep the glucose level as close to normal as possible.
* HbA1C goal is 8% for:-
① Hx of severe hypoglycemia
② Limited life expectancy.
③ Advanced vascular complications
④ Extensive comorbidities.
⑤ Long standing DM + difficulty attaining low HbA1C despite aggressive management.

* Diabetes complications:
(Retinopathy precedes nephropathy) ← * Microvascular (Retinopathy, (neuropathy), nephropathy): start screening once diagnosed immediately. (correlates with duration + Control of DM; CN 3, 6, 7, VS 1 Peroneal, radial; tt with ACEIs/ARBs.)
* Macrovascular (CVD, PAD, stroke, Atherosclerosis).

* All DM pts need annual monitoring for microvascular complications (5 years after dx of type 1, and immediately after dx of type 2).:
- Albumin: creatinine ratio (normal <30 mg albumin: 1g Creatinine)
* Moderate ↑ albuminuria: 30-300 mg/g.
Marked ↑ albuminuria: >300 mg/g.
- check GFR.
- Refer pt to an ophthalmologist for retinal exam.
- Inspect feet and perform a sensory evaluation.

* Hyperglycemic emergencies

① Keto acidosis:

* Sometimes the initial presentation of type 1 DM, but can also occur in type 2 DM.
* Due to partial or complete insulin deficiency → causing lipolysis
* → release fatty acids and ketone bodies (acetone, β hydroxybutyrate and aceto acetate)
→ these have high anion gaps (because ketones are acids), and associated with hyperglycemia causing volume depletion + massive osmotic diuresis.

* Symptoms: N/V, abdominal pain, lethargy and polyuria.

* Precipitating factors: Infection (pneumonia, UTI) and non compliance with DM medications
→ The two most important (most frequent) precipitating conditions for DKA conditions.
* On exam, hypotension can occur due to severe volume depletion.
* Fruity breath and a Kussmaul respirations
* Severe cases are marked by confusion or obtundation (altered level of consciousness)

* Diagnosis:-

① Hyperglycemia (Most of the times).
② Ketosis.
③ High anion gap Metabolic acidosis.

* Also deficits in total K^+ and phosphorus
* Na^+ is usually Low (pseudo hyponatremia); due to osmotic shift of water from inside cells to intravascular space due to hyperglycemia.
→ Correct Na^+ by adding 2 Na^+ for each 100 glucose over 100 mg/dl

* HHS: ① HH precipitating factor
② IV Fluids (aggressive): (2-3 L.) normal saline or switch to 0.45% if the corrected Na^+ is > 135 mEq/L.
③ Start IV insulin at 0.1 ml/kg, when glucose < 200 mg/dl → start 5% dextrose (5D) to IV fluids to avoid hypoglycemia. and keep insulin until ketosis and acidosis is resolved and anion gap returns to normal.
④ If K^+ is < 5.0 mEq/L → start IV KCl immediately
if K^+ < 3.3 mEq/L → start IV KCl and stop IV insulin until K^+ is ≥ 3.3 mEq/L
⑤ HCO_3^- should be given when PH < 7.0, especially if the patient is having respiratory or hemodynamic collapse.

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② Hyperglycemia Hyperosmoler State:

* One of the most serious Acute complications of type 2 DM.
→ Can lead to coma and death.
* Precipitating factors: volume depletion, infections, drug (glucocorticoids), and any serious illness.
* Due to partial insulin deficiency and ↓ fluid intake.
* usually elderly pt, has preceding lethargy, wt loss and polyuria.
* Examination: Coma, confusion, stupor (Due to severe volume depletion).
* CABs: severe hyperglycemia (> 600 mg/dl) + Azotemia, dehydration and volume depletion evidence.

Table 1-4: Diagnostic Criteria for DKA vs. HHS

Parameter	DKA	HHS
Usual glucose at diagnosis	> 250 mg/dL (13.88 mmol/L)	> 600 mg/dL (33.3 mmol/L)
Arterial pH	< 7.3	> 7.3
Serum HCO_3^-	< 18 mEq/L (18 mmol/L)	> 18 mEq/L (18 mmol/L)
Urine ketones	Positive	"Small" or negative
Serum ketones	> 3 mmol/L	< 0.6 mmol/L
Effective serum osmolality	Variable	> 320 mOsm/kg (320 mmol/kg)
Anion gap	> 10 mEq/L (10 mmol/L)	Variable
Mental status	Varies with severity	Stupor/Coma

Adapted from: Kitabchi, A. E., G. E. Umpierrez, J. M. Miles, and J. N. Fisher. 2009. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 32(7):1335–1343.

* if anion gap is present ; it is very mild.

* ~~Tt~~:

① IV fluids + IV insulin
② check corrected Na to see if there is any water deficit → replace gradually over the next 24-48 hrs.
③ K+ replacement.

Hypoglycemia :-

* Whipple triad (for hypoglycemia dx):
① Signs + Symptoms of hypoglycemia ② Low plasma glucose (< 55 mg/dL)
③ Relief of symptoms with supplemental glucose.

Non specific. ← * Symptoms are ① autonomic : palpitations, tremor, sweating, paresthesia
② Neurologic (confusion, impaired consciousness, seizures)

* Hypoglycemia without DM :
Etiology :-
① Drugs (insulin, insulin secretagogues, hypoglycemic agents)
② Hormone deficiency : cortisol, glucagon, epinephrine.
③ Critical illnesses : HF, renal failure, liver failure
④ Islet cells tumor : insulinoma, IGF-1 secreting tumor.
⑤ Non islet cells tumor : Hepatocellular Ca. Fibrosarcoma.
⑥ Functional B cell disorder : Post gastric bypass
⑦ Autoimmune : Endogenous Abs to insulin or insulin receptor

* Diagnosis : Hx + physical exam.
↳ Look for administration of sulfonylurea or insulin.
* check adrenal function (cortisol level ; low cortisol can cause hypoglycemia)
(But low cortisol does not mean adrenal insufficiency ; as recurrent hypoglycemia causes lowers baseline cortisol secretions → low cortisol.)

* 2 classifications :
① Reactive hypoglycemia (post prandial hypoglycemia) :
* Response to a nutrient challenge. (in post gastric bypass pts)

② Non-reactive hypoglycemia (AKA : fasting hypoglycemia)
* M.C.C in hospitalized pts is alcohol abusers, sepsis, Drugs.

* check the following in hypoglycemia :
① Insulin ② C-peptide ③ Pro insulin ④ urine / plasma
SU screen
sulfonylurea ↓