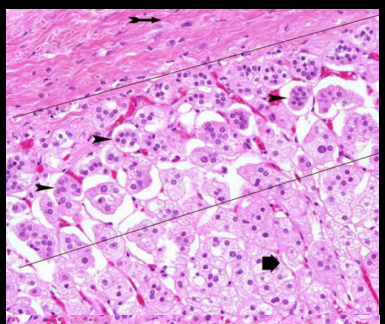
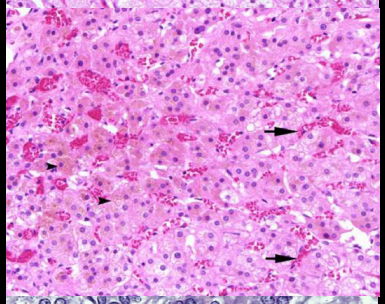
LO1 Path of Adrenal Gland

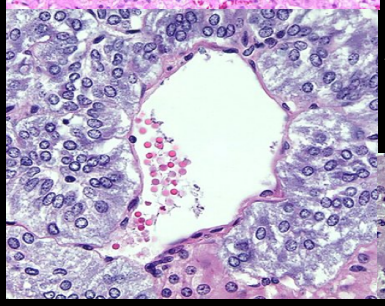


→ zona glomerulosa

→ zona fasciculata

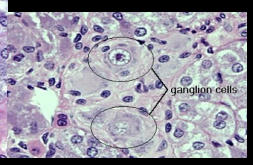


→ zona reticularis



→ medullary chromaffin cells

basophilic cytoplasm



HYPERADRENAL SYNDROMES

*Cushing syndrome (excess glucocorticoids)

TOO MUCH CORTISOL

→ truncal obesity, HTN, muscle weakness (prox. fast-twitch fibers), 2° DM, easy bruising, striae, osteopenia

→ IN CHILDREN: decreased linear bone growth

→ EXOGENOUS = (MC) due to admin of corticosteroids

→ ENDOGENOUS

→ ACTH-dependent

↑ACTH
*HYPERPLASIA

① Cushing Disease:
- ACTH secreting pituitary adenoma

② Ectopic production of ACTH
TO
- small cell carcinoma of lung
- other paraneoplastic conditions

→ ACTH INdependent

= primary cortical hyperplasia: ↑cortisol w/ ↓ACTH

* macronodular hyperplasia → unilateral ↓ACTH

* Primary adrenal neoplasms
- adrenal adenoma

* Bilateral macronodular hyperplasia (rare)
- produce cortisol by non-ACTH hormones due to expression of their receptors on cortex

* McCune Albright syndrome: macronodular hyperplasia
- gain of function GNAS mutation

★ TRIAD:
- polyostotic fibrosis
- café au lait spots
- autonomous endocrine hyperfunction

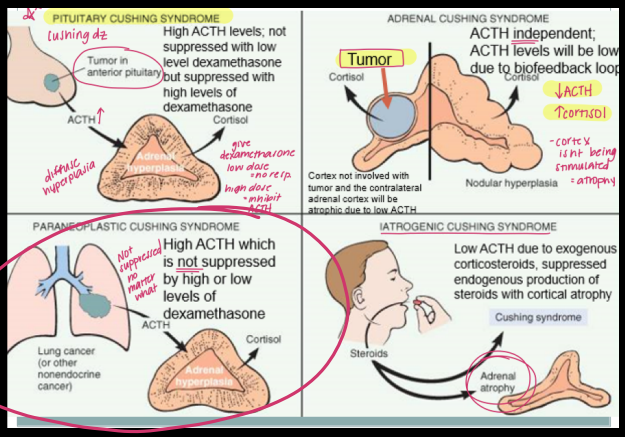
★ Primary Pigmented Nodular Adrenal Dz (PPNAD)
★ auto dominant PRKAR1A mutation
→ Carney syndrome → tumors & endocrine dysfcx)
- myxomas

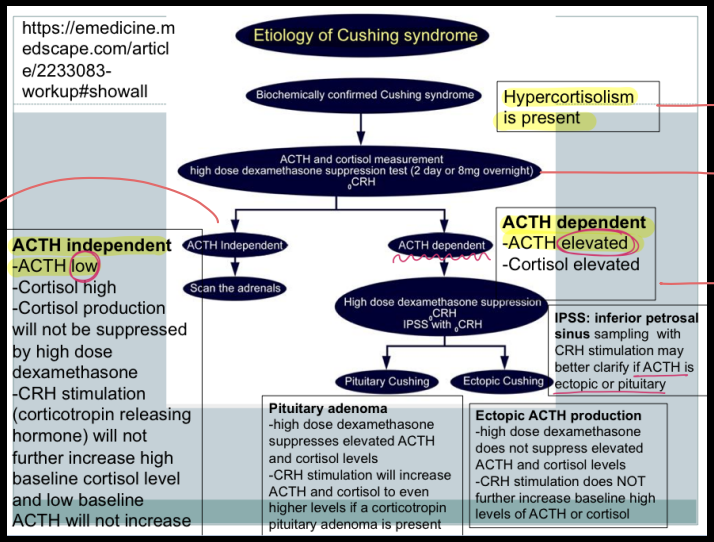
★ ADRENAL MORPHOLOGY:

TQ
★ cortical atrophy
w/ ↓ACTH (exogenous steroids)

★ diffuse hyperplasia
w/ ACTH ↑ (ACTH dependent Cushings)
→ thick & yellow cortex

★ ACTH independent ★
- ★ Macronodular hyperplasia
- ★ Micronodular hyperplasia





identify hypercortisol state

give high dose dexamethasone

if ACTH is low & cortisol is high:
★ ACTH independent (MC adrenal adenoma)

if ↓ACTH = pituitary adenoma
if ACTH is NOT suppressed: ectopic

★ Pituitary adenoma: ↑ACTH & cortisol
Ø suppressed w/ low dose, but suppressed by high dose

TQ

★ Ectopic ACTH secretion ↑ACTH & cortisol
Ø suppressed by any dose

★ Adrenal tumor: ↓ACTH, ↑cortisol
Ø suppressed by any dose

HYPERALDOSTERONISM → causes HTN & Hypokalemia

Primary: autonomous overproduction; ↓RAAS
★ bilateral idiopathic hyperaldosteronism (MC)
- bilateral nodular hyperplasia

TQ
★ aldosterone secreting adenoma
= Ø atrophy adjacent bc Ø ↑ACTH

pt w/ resistant HTN or young pt w/ HTN dx: aldosterone suppression test

- older pts, less severe HTN; mutation in KCNJ5 (potassium channel)

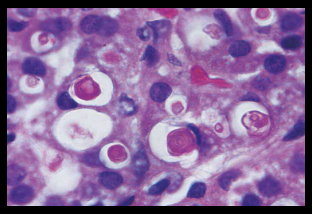
★ aldosterone-producing cortical adenoma = CONN SYNDROME

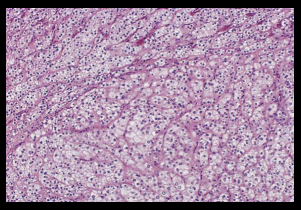
- KCNJ5 mutation → potassium channel = GIRK4 in zona glom cells (↑Na; depolarize)

★ spironolactone bodies

unilateral

★ adenoma = well circumscribed, yellow, adjacent cortex is NOT ★★ atrophic (as seen in cortisol producing adenoma)





★ familial hyperaldosteronism type I

bilateral

TQ

- rearranged csome 8 puts CYP11B2 (aldosynthase) under control of CYP11B1 (ACTH responsive)

→ now aldo Ø responsive to Ang II, it responds to ACTH & can be suppressed by dexamethasone challenge ★

Secondary: extra-adrenal activation of RAAS ↑

ADRENOGENITAL SYNDROMES → virilizing syndromes = ↑↑androgen production by adrenal cortex

- Excess ACTH = ↑androgens
  - cushings → hirsutism
- Adrenocortical neoplasms
  - more likely androgen-secreting adrenal carcinomas → VIRILIZING SYNDROMES

★ Congenital Adrenal Hyperplasia (CAH)

- auto. RECESSIVE
- MC 21α hydroxylase deficiency

↓ glucocorticoids
↓ mineralocorticoids] ↑ACTH
↑ androgens

↑ACTH → bilaterally hyperplastic adrenal cortex (TQ)

CLASSIC adrenogenitalism
→ salt wasting, virilization, HYPOtension → CV collapse

SIMPLE adrenogenitalism
→ NO SALT WASTING
- ambiguous genitalia w/ progressive virilization (females)

NONCLASSIC / LATE ONSET
→ partial 21α deficiency
Ø dx @ newborn screening
hirsutism, menstrual irreg. in females // precocious puberty & oligospermia in males

ADRENOCORTICAL INSUFFICIENCY can also be caused by infection (TB, AIDS, fungal)

★ acute: adrenal crisis → intractable vomiting, abdominal pain, hypotension, coma, CV collapse
- chronic + acute stress
- steroid withdrawal
- hemorrhage → DIC, Waterhouse-Friderichsen → N. meningitidis

★ chronic: addison's dz; 90% destruction +
→ HYPERPIGMENTATION

- Autoimmune adrenalitis: shrunken glands

★ APS1 (rare) → chronic candidiasis, ectodermal dystrophy, autoimmune disorders
→ AIRE gene mutation (absence)

★ APS 2 (common) → 4th decade of life: adrenal insuff + autoimmune thyroiditis w/ or w/o T1D

Clinical manifestations of Addison Disease (primary chronic adrenocortical insufficiency)

- Insidious course sneaky
- Progressive weakness, easy fatigability *
- Gastrointestinal disturbances – nausea, vomiting, anorexia, weight loss, diarrhea → common px sxs
- Hyperpigmentation of skin at sun exposed areas and pressure points – caused by elevated levels of pro-opiomelanocortin (POMC), precursor to ACTH and MSH ↑ACTH & MSH → Hyperpigmentation (1° insuff)
- With mineralocorticoid (aldosterone) deficiency – hyponatremia, hyperkalemia, volume depletion, hypotension
- Hypoglycemia may occur in glucocorticoid deficiency

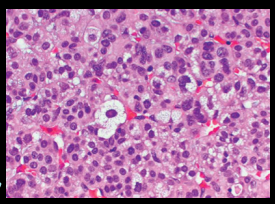
Secondary Adrenocortical Insufficiency

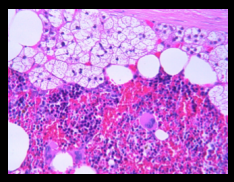
- **Decreased ACTH causes secondary hypoadrenalism due to:**
  - Pituitary or hypothalamic disease resulting in decreased ACTH ↓
  - Prolonged administration of exogenous steroids
  - → Suppresses ACTH and adrenal production of glucocorticoids
- Clinical manifestations similar to Addison disease EXCEPT:
  - **NO HYPERPIGMENTATON** since ACTH and its precursor POMC is not elevated
  - **No symptoms of salt wasting** since ALDOSTERONE is normal or near normal ACTH doesn't control aldosterone
- Gross Morphology – Small flattened glands with thin cortex with slight residual lipid and unaffected medulla can't find cortex

LO2 Adrenal Path II

* Adrenocortical Adenoma (functional or nonfunctional)

- Functional
  - hyperaldosteronism / Cushing Syndrome (cortisol)
    - ↓ Ø atrophy bc ACTH is NOT suppressed
    - ↓ atrophy!
  - well circumscribed nodule, yellow
  - may have some degree of atypia
  - eosinophilic or lipid-like cytoplasm





* Adrenal myelolipoma

- mature fat & hematopoietic cells from all 3 lineages

In the cortex...

- Adenomas = Nonmalignant nodules
  - Functional → most likely Cushing syndrome or hyperaldosteronism
  - PRKAR1A mutation → PPNAD
  - Usually yellow, other adrenal gland will atrophy if functioning
- Myelolipomas
  - Benign
- Carcinoma = MALIGNANT
  - Usually functional with CTNNB1 (β-catenin) mutations / MEN1, P53
  - THINK LI FRAUMENI OR BECKWITH-WIEDEMANN SYNDROME
    - Li fraumeni → P53 mutation → sarcomas, breast cancer, leukemia, brain, ADRENALS
    - Beckwith-wiedemann → big tongue, omphalocele at birth, organomegaly, wilms tumors, issues w/ IGF-1 like GH
  - Unencapsulated, poorly circumscribed, invasive, can invade into the adrenal vein, vena cava, lymph
- Metastatic cancer
  - Usually from LUNG, liver, bone, breast, melanoma metastasis

* Adrenocortical carcinoma → more likely to be functional

TQ

- often cause virilizing syndromes (androgen production)

→ Familial syndromes:

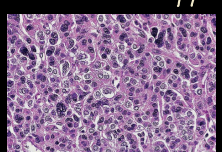
female pt w/ Hx of tumors px w/ hair growth, mass on adrenal, MC mutation = TP53

1. Li Fraumeni = TP53 germline mutation; super prone to malignancies
2. Beckwith-wiedmann syndrome = organomegaly, hx Wilm's tumor, mutation in IGF 2

- necrosis, hemorrhage, & cystic Δ
- adjacent cortex may be atrophic in functioning tumors if ACTH is suppressed

GROSS:

- can be well diff. or anaplastic w/ bizarre giant cells
- hyperchromic mitosis & multinucleated = malignant



* Pheochromocytoma:

- tumor of chromaffin cells that secrete catecholamines
- intermittent HA, palpitations, sweating, HTN

Rule of 10:

- 10% extra adrenal (like paragangliomas)
- 10% bilateral
- 10% malignant
- 10% Ø HTN

Familial: 25%

TQ

- RET, NF1 → enhance growth factor receptor pathway → thyroid tumor
- VHL → increase activity of HIF (same w/ EPAS1) → CNS tumor
- ** SDHB → HIGHEST MALIGNANCY POTENTIAL → GI/stromal tumor

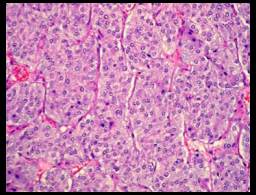
Syndrome	Gene	Associated Lesion	Other Features
Multiple endocrine neoplasia, type 2A (MEN-2A)	RET	Pheochromocytoma/paraganglioma	Medullary thyroid carcinoma * Parathyroid hyperplasia
Multiple endocrine neoplasia, type 2B (MEN-2B)	RET	Pheochromocytoma/paraganglioma	Medullary thyroid carcinoma Marfanoid habitus Mucocutaneous GNs
Neurofibromatosis, type 1 (NF1)	NF1	Pheochromocytoma	Neurofibromatosis Café-au-lait spots Optic nerve glio
Von Hippel-Lindau (VHL)	VHL	Pheochromocytoma/paraganglioma	Renal cell carcinoma Hemangioblast Pancreatic endocrine

+CNS tumor

WBOT

TQ

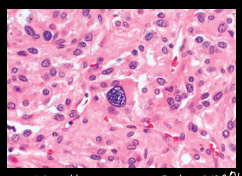
young person w/ hx of thyroidectomy w/ sxs of HA, sweating & palpitations → RET * → Pheochromocytoma



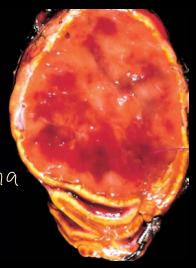
GROSS: look like adenoma

HISTO: Zellballen = nest of chromaffin or cheif cells (+S100)

★ HISTO DOES NOT PREDICT MALIGNANCY FOR PHEOs! ONLY METASTATIC DZ CAN INDICATE MALIGNANCY



Zellballen = pheochromocytoma



well circumscribed, looks ~ adenoma

Diagnosis ★ How we make the dx

- urinary & plasma fractional metanephrines & catecholamines

Tx: surgery & adrenergic blockers (pre & post)

★ Neuroblastoma: tumor of sympathetic ganglia & adrenal medulla derived from primordial neural crest cells (40%) ★ BOARDS

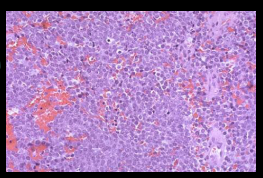
- MC extracranial solid tumor of childhood
- sporadic but germline mutation in anaplastic lymphoma kinase (ALK)

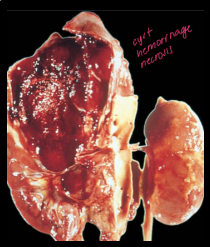
can also occur in brain, pelvis, or neck OR anywhere in paravertebral abdomen

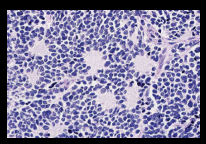
Histo: sheets of small round blue cells

homer-wright pseudorosettes around neuropil

[eosinophilic fibrillary material corresponding to neuritic processes of primitive neuroblasts]



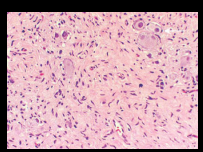




Maturing Neuroblastoma = Ganglioneuroblastoma → Ganglioneuroma

↑VMA

★ Schwannian stroma must be present



Clinical: young pt; blue nodules, proptosis & ecchymosis

90% make catecholamines but HTN is less common

TQ PROGNOSIS: age & stage = most important (UNLESS MYCN oncogene amplification) = WORST PROGNOSIS → age/stage DO NOT MATTER

★ Which of the following has the worst prognostic significance?

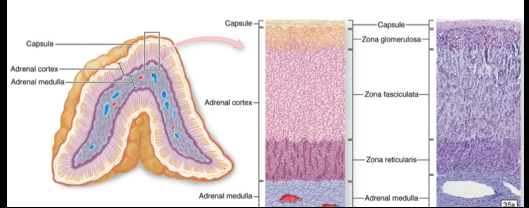
L03 Adrenal Gland Physio:

	1° regulator	secretory products
L01 ZG	RAAS	aldosterone
ZF	ACTH, CRH	cortisol
ZR	ACTH, CRH	sex hormones

L01:

The adrenal gland

- Adrenal cortex has 3 layers:
  1. Zona glomerulosa → mineralocorticoids → aldosterone **(SALT)**
  2. Zona fasciculata → glucocorticoids → cortisol **(STEROID)** /sugar
  3. Zona reticularis → androgens → dehydroepiandostendione (DHEA), DHEA-sulfate, androstendione **(SEX)**



L02 "synthesis & action of hormones" & "role of adrenal medulla in response to stress"

★ Adrenal Medulla = Fight or Flight; release of catecholamines

Tyrosine —RLS (tyrosine hydroxylase)→ L-Dopa → Dopamine → Norepi (20%) → Epi (80%) (PNMT)

Nuts, bananas & cheese

PHEO

TQ Phentolamine n-methyltransferase
- in adrenal medulla
- induced by glucocorticoids

PHEOCHROMOCYTOMA: [HA, palpitations, sweating] classic triad (Ø HTN in triad...)

dx: 24hr urine catecholamines

★ pheos usually (90%) happen in adrenals due to PNMT

- Heart rate ↑
- Cardiac output ↑
- Blood pressure ↑
- Redistribution of blood flow from skin and viscera to skeletal muscle
- Ventilation ↑ (airway dilation)
- GI motility and secretions ↓
- Blood glucose ↑

L03 "synthesis, actions, regulation"

★ ZG → aldosterone mineralocorticoids

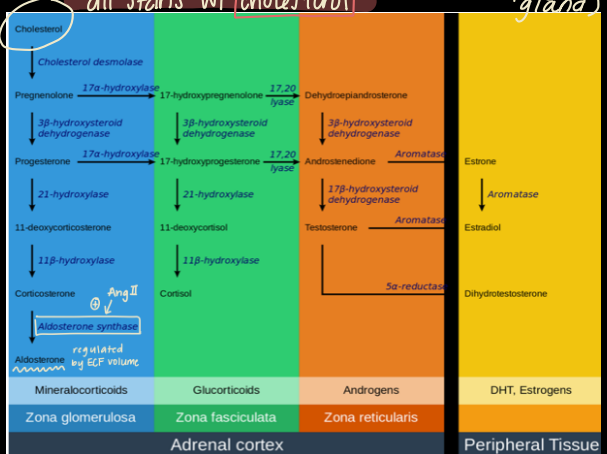
TQ 1° control = ECF volume → [↑Na resorption, ↑K+ secretion, ↑H+ secretion] @DCT & CD principle & intercalated cells

★ Regulated by Δ ECF volume via RAAS system (Ang II)

ØACTH!

TQ ACTIVATED BY ACTH (Ø ACTH = atrophy of gland)

all starts w/ cholesterol



- serum K+ also affects aldo synthesis:
  - [↑K+ → ↑aldosterone, ↓K+ = ↓aldosterone] → always make sure potassium is normal before checking aldosterone

★ MR specificity guaranteed by 11β-HSD
- DCT have MR

→ MR has equal affinity for cortisol & aldosterone so 11βHSD converts cortisol to cortisone allowing aldosterone to bind to its receptor

→ licorice blocks 11βHSD
→ looks like mineralocorticoid excess bc cortisol sits on receptor
→ HTN, Hypokalemia, alkalosis

TQ ★↑↑cortisol (cushing's) can also overshadow aldosterone & compete for MR

★ZF → cortisol

★ACTH family: POMC → ACTH, β-endorphin, MSH

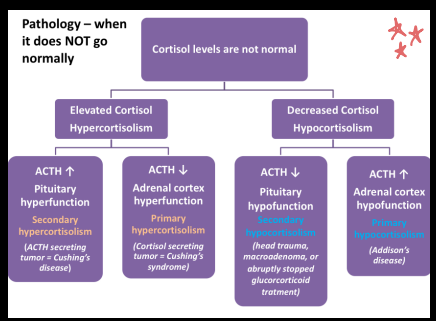
★ Actions: gluconeogenesis, antiinflammatory, suppress immune response,

TRANSPORT: mostly protein bound on transcortin (corticosteroid binding globulin (CBG)

TQ ↓CBG in obesity ∴ total cortisol looks LOW
↑CBG in pregnancy ∴ total cortisol looks HIGH

break things down!

Actions of Glucocorticoids
Increase gluconeogenesis
Increase proteolysis (catabolic)
Increase lipolysis
Decrease glucose utilization
Decrease insulin sensitivity
Inhibit inflammatory response
Suppress immune response
Enhance vascular responsiveness to catecholamines
Inhibit bone formation
Increase GFR
Decrease REM sleep



★ZR → Androgens

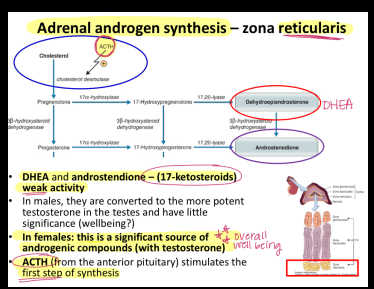
[females: pubic & axillary hair, libido
males: same as testosterone]

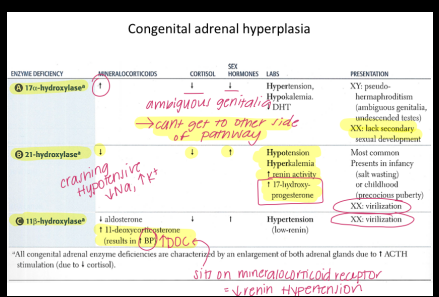
MC CAH: 21ahydroxylase deficiency

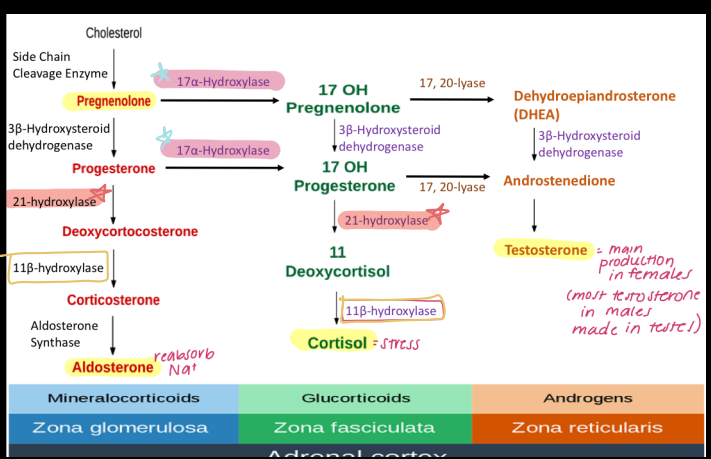
Ø aldosterone
Ø cortisol

what you test for → ↑↑17 hydroxyprogesterone

TQ → salt wasting, hypotension, virilization in females



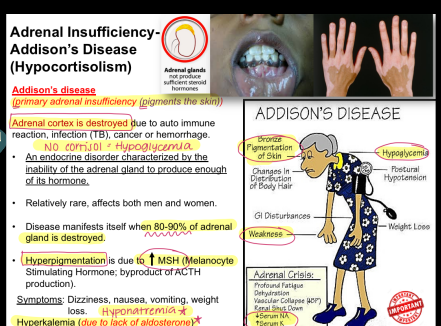




L04 Pharm of HPG axis:

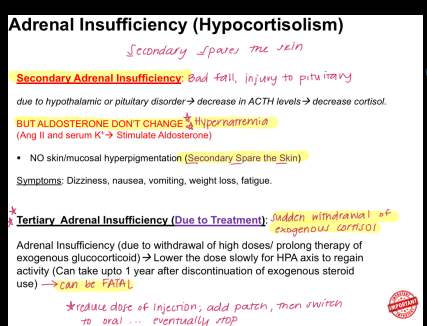
★ [Primary vs Secondary Adrenal insufficiency:]

1°



hyperpigment salt wasting, hypoglycemia

2°



↓cortisol due to pituitary problem
∴ ↓ACTH
∴ Ø hyperpigment
& aldosterone stimulated by Ang II ∴ Ø salt wasting

ADDISON'S DISEASE

: replacement therapy for LIFE; start LOW, go SLOW

→ oral hydrocortisone = drug of choice → corrects glucocorticoid deficiency

or

→ Prednisone = Pregnancy drug of choice bc activated to prednisolone in liver & fetus Ø liver :)

and

→ Fludrocortisone = ONLY IF MINERALOCORTICOID DEFICIENCY!!

- ang II may be maintaining aldosterone (esp if 2° adrenal insufficiency)

★ Glucocorticoid ADE:

- obesity, diabetes, & osteoporosis
- acute cessation → acute adrenal insufficiency (fatal)

HYPERALDOSTERONISM

1° : ↓RAAS + ↓K+

2° : ↑RAAS + ↓K+

tx: mineralocorticoid receptor antagonist (competitively inhibit)

→ spironolactone ADE: Hyperkalemia + gynecomastia

→ eplerenone ADE: Hyperkalemia

CUSHING SYNDROME:

tx:

① surgery in pituitary/adrenal tumors → replacement steroids for life

② radiation

③ medication to control cortisol when 1 & 2 don't work

★★★ TQ → Ketoconazole: inhibits 17,20 lyase @ low dose (decrease androgens); inhibits side chain cleavage @ high dose (cholesterol desmolase ∴ ↓all hormones)

Mitotane: affects adrenocortical mitochondria → decreases all hormones

Metyrapone: inhibits 11β hydroxylase → decrease cortisol & aldosterone, should ↑ACTH
diagnostic drug to test hypothalamic & pituitary response

Mifepristone: blocks glucocorticoid receptor → treats hyperglycemia in Cushing's

HPG Axis Drugs

★ Leuprolide / Gonadorelin: GnRH analogs; sustained release is inhibitory

→ evaluating HPG function

TQ → tx endometriosis, precocious puberty, Breast CA, & palliative tx of prostate CA

★ ADE: DVT, hot flashes; CI in pregnancy & lactation

★ TESTOSTERONE FLARE!

TQ → pt begins palliative care for advanced prostate CA & experiences bone pain & arrhythmias. MOA of tx you should administer?

Testosterone Flare

- May drive rapid growth of small tumors during metastasis
- Drives bone pain
- Spinal compression
- Renal ureteral obstruction ★
- Cardiovascular crisis ★ arrhythmias
- Leuprolide – induced may surface in 3 days to 3 weeks.

→ tx testosterone flare w/ Flutamide (androgen antagonist)

★ Degarelix: GnRH antagonist

tx for advanced prostate CA

CI preg., lactation, & unknown cause vag. bleeding

Ø FLARE

can promote osteoporosis

★ Flutamide: androgen antagonist

tx metastatic prostate CA & testost. flare

L07 Glucose Metabolism

1. Explain the synthesis, dissect the regulation of secretion, and predict the actions of:
   a. insulin
   b. glucagon
2. Apply above knowledge to integrated hormonal regulation of glucose homeostasis and intermediary metabolism.

INSULIN: promotes storage of ingested nutrients

glucose & K^+ into cell

- peptide hormone A&B chains connected by C-peptide
- synthesized in ER of β cells → cleaved @ golgi
- → C-peptide released in equal amount w/ insulin

how you tell the diff between endogenous & exogenous insulin OD

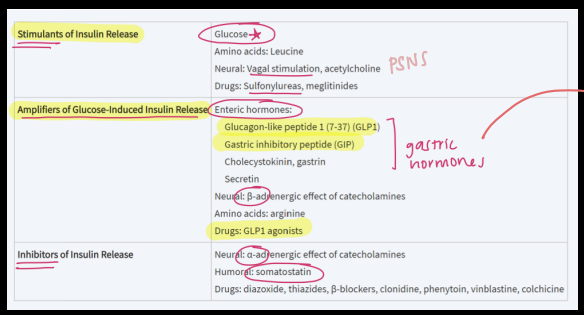
- Glucose-mediated insulin release:

@ β-cell of pancreas:

1. glucose taken up into cell via GLUT2 (Ø need insulin)
2. glucose forms ATP↑ (↑ATP:ADP ratio)
3. ATP closes K^+ channels
4. Depolarize
5. ↑intracellular Ca^{2+}
6. insulin release via exocytosis

TQ

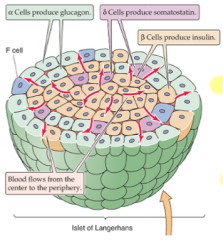
catecholamines inhibit insulin secretion by ↓cAMP



Stimulants of Insulin Release	**Glucose** ★
	Amino acids: Leucine
	Neural: Vagal stimulation, acetylcholine (PSNS)
	Drugs: Sulfonylureas, meglitinides
Amplifiers of Glucose-Induced Insulin Release	Enteric hormones: (gastric hormones)
	Glucagon-like peptide 1 (7-37) (GLP1)
	Gastric inhibitory peptide (GIP)
	Cholecystokinin, gastrin
	Secretin
	Neural: β-adrenergic effect of catecholamines
	Amino acids: arginine
	Drugs: GLP1 agonists
Inhibitors of Insulin Release	Neural: α-adrenergic effect of catecholamines
	Humoral: somatostatin
	Drugs: diazoxide, thiazides, β-blockers, clonidine, phenytoin, vinblastine, colchicine

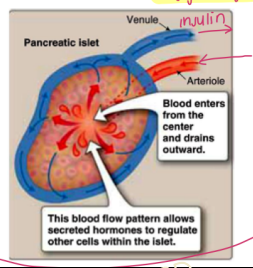
incretins increase insulin amplifiers: → potentiate response of β cell to glucose

ISLET FUNCTIONAL STRUCTURE



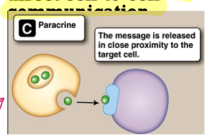
insulin = central
glucagon = peripheral
↓
blood flow in pancreas = central towards periphery
∴ insulin can inhibit glucagon secretion (paracrine signaling)

- **Insulin** secreting **β cells** are the majority → they are located **centrally**
- **Glucagon** secreting **α cells** are located more **peripherally**
- Blood enters in the center of the pancreatic islet and flows towards the periphery → optimal for paracrine signaling → **pancreatic hormones alter each-others secretion – insulin inhibits glucagon secretion**
- Adjacent cells are connected via **gap junctions** → allow for **direct cell-to-cell communication**



paracrine & endocrine

insulin inhibits glucagon via paracrin



FEED FORWARD

↑GLP1 & GIP

Why oral glucose evokes greater insulin response than IV

INCRETINS INCREASE INSULIN

GI REGULATORY HORMONES ((FEED FORWARD) – PREPARE THE BODY FOR NUTRIENT METABOLISM → ORAL GLUCOSE ADMINISTRATION EVOKES GREATER INSULIN RESPONSE THAN IV ADMINISTRATION (INCRETIN EFFECT)

two peaks:

food → 8-10min peak (spike) → 30-45min peak (slow & steady rise) → baseline @ 90-120min

Glucose Transport:

facilitated diffusion along concentration gradient:

- GLUT1: brain & RBCs, unidirectional, Ø require insulin
- GLUT2: β-cells/liver, bidirectional; Ø require insulin
- GLUT4: adipocytes, skel m.; REQUIRES INSULIN

against concentration gradient: 1:1 w/ Na^+

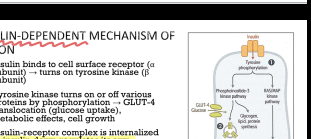
- SGLT1: small intestine
- SGLT2: kidney PCT

(2° active transport)

INSULIN-INDEPENDENT GLUCOSE UPTAKE - LIVER

- FED state → ↑Hexokinase
  - Insulin binds to its receptor and facilitates glucose 6-phosphorylation (by hexokinase) that traps glucose and keeps intracellular glucose concentrations low
  - Trapped glucose is stored as glycogen or converted to fat for storage
- FASTED state
  - Glucose levels increase in the hepatocytes (from glycogen breakdown and gluconeogenesis) → glucose leaves the liver and enters the circulation to maintain blood glucose levels for critically glucose-dependent organs (brain, RBCs) have glucose for brain ∴ Ø trapping

liver makes glucose for brain & RBC when energy is low

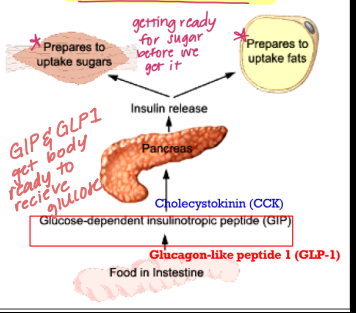


C. Hepatocyte. In the fed state, the liver cell takes up glucose and forms glycogen and fatty acids. D. Hepatocyte. In the fasted state, the liver cell makes glucose from glycogen or amino acids and transports it to the blood.

INSULIN-DEPENDENT MECHANISM OF ACTION

1. Insulin binds to cell surface receptor (α subunit) → turns on tyrosine kinase (β subunit)
2. Tyrosine kinase turns on or off various proteins by phosphorylation → GLUT-4 translocation (glucose uptake), metabolic effects, cell growth
3. Insulin-receptor complex is internalized → insulin down-regulates its own receptor on target cells
   - Hyperinsulinemia = excess down regulation = insulin "resistance" causes peripheral resistance

Feedforward Mechanism



AMP kinase effect: energy sensor in brain, liver, muscle

↓intracellular glucose = ↓ATP & ↑AMP = ↑AMPK

TQ

→ activates catabolic pathway → want to utilize energy stores in body bc ↓ATP

exercise:

- ↑FA oxidation
- ↑insulin-dependent glucose uptake
- ↓mtor & protein synth pathway (mtor = mitogenic)
- ↑sensitivity to insulin

Metformin activates AMPK pathway

GLUCAGON: synthesized as 1 protein (proglucagon) by α cells in pancreas & intestinal L cells (make GLP1, GLP2 only)

★ The most important stimulus for glucagon secretion is BG <100 mg/dL

TQ

Most important stimulus for glucagon release

DING DING DING

BG<100 = glucagon release

Table 9-15 Factors Affecting Glucagon Secretion

Stimulatory Factors	Inhibitory Factors
Fasting	Insulin
Decreased glucose concentration	Somatostatin
Increased amino acid concentration (especially arginine)	Increased fatty acid and ketoacid concentration
Cholecystokinin (CCK)	
β-Adrenergic agonists	
Acetylcholine	

Coordinated inhibitory effect of insulin on glucagon release

somatostatin inhibits both glucagon & insulin for steady state

glucagon stimulates insulin secretion

makes sense so you can use the glucose you're making

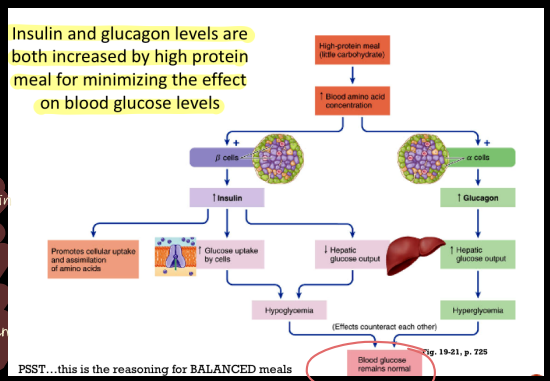
GLUCAGON MOA:

1. glucagon binds G_s → adenylyl cyclase
2. adenylyl cyclase → cAMP↑
3. cAMP phosphorylates things for metab. effects of glucagon

@LIVER: glycogenolysis // inhibit glucokinase
gluconeogenesis // inhibit glycolysis by inhibiting glucokinase, PFK, PK
fat oxidation // inhibit acyl coA carboxylase ∴ breaking down fat!!

(in glucagon world) we want to make glucose for energy for when we are starving

SOMATOSTATIN polypeptide synth. by hypothalamus & δ cells & GI mucosa
→ inhibits secretion of insulin & glucagon in paracrine fashion @ islets
prolongs gastric emptying, decreases gastric acid → slows things down
stimulated by: all nutrients & β adrenergic agonists



TQ: just high protein = Ø Δ in BG ∴ ppl w/ hypoglycemia need to add fat & protein to a carb rich meal to flatten insulin curve

same as low glycemic index → Ø spike

LOB T1D:

- Understand pathogenesis of T1D ✓
- Recognize symptoms of T1D ✓
- Utilize current recommendations to guide treatment of T1D ✓
- Recognize presentation of acute complications of T1D ✓
- Apply biochemical and physiologic principles of glucose metabolism to manage acute complications of T1D ✓
- Understand implications of T1D in a pediatric patient ✓

★ Pathogenesis: islet autoantibodies destroy pancreatic β cells (T-cell mediated)
★ Ø insulin; β cells do NOT respond to insulinogenic stimuli
★ ↑ glucagon (body thinks it's starving)
★ @ liver, muscle & fat = BREAKDOWN
→ ketone build up
→ reversible w/ exogenous insulin (oral medications Ø work)
★ HLA DR3 & DR4 ↑ risk; super high genetic link
- protective = DQB1*0602, DQA1*0201, DRB1*1401
★ Environmental factors:
↑ RISK [- viruses: COXB, rubella - aseptic living
↓ RISK [- breastfeeding >6mos - intro of cereals between 3-7mos

TQ

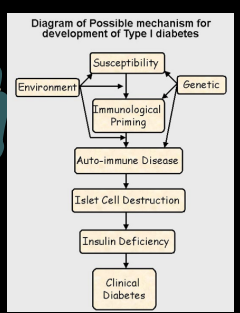
★ Staging:
① autoimmunity
② IFG and or IGT; Ø sxs
③ symptomatic

Autoimmunity in T1D:

- Antibodies against Beta cell proteins
  - Glutamic acid decarboxylase (GAD) – most sensitive
  - Islet cell antibodies (ICA)
  - Tyrosine phosphatase IA-2 autoantibodies (IA2)
  - Insulin autoantibodies (IAA)
- Detectable prior to onset of hyperglycemia – Stage 1 (show up early) — WHO do we test? family Hx
  - Occasionally decades earlier in LADA
- Risk increased with increased # of autoantibodies – nearly 100% risk with two or more followed over 10 years → super sensitive

TQ
★★ pt w/ family hx of T1D (born parents) presents w/o sxs
★ you can get glutamic acid decarboxylase (GAD) levels

★ can test for autoantibodies before BG increases



SIGNS → polyuria, polydipsia, thirst, blurred vision, nocturia, weakness/fatigue + weight loss due to ↓ muscle mass (catabolism)
→ altered level of consciousness, sweet smelling breath (ketoacidosis), vomiting + impaired growth in children, unequal altered visual acuity, infections

Tx: → insulin replacement therapy; requires frequent BG monitoring
★ Basal Bolus

ACUTE COMPLICATIONS:

★ Hypoglycemia → fatal
★ BG < 30 = LOC / siezure → permanent brain damage / death
★ causes of hypoglycemia:
- Behavioral
- counterregulatory → glucagon response ↓

[★ HYPOGLYCEMIA KILLS YOU NOW]

★ tx: glucose tx 15g carbs → recheck 15min (Ø candy bars)
- juice, glucose tablets, coke
- follow w/ meal

TQ: if emergency (coma/siezure) → "1 amp D50"

ACUTE COMPLICATIONS OF T1D – HYPOGLYCEMIA (kills you NOW)

- Symptoms related to level of hypoglycemia
  - BG < 60 mg/dL
    - Nausea, hunger – parasympathetic
    - Tachycardia, palpitations, sweating, tremors – sympathetic
  - BG < 50 mg/dL
    - Irritability, confusion, blurred vision, headache
    - Neuroglycopenic effect
  - BG < 30 mg/dL (brain never works right again)
    - Loss of consciousness or seizure
- Relative hypoglycemia
  - In patients with persistent hyperglycemia/poorly controlled diabetes
  - Will "sense" or "feel" hypoglycemic at *normal* blood sugar levels
  - Not a risk for neurologic compromise unless d/t drastic change in BG

TQ

MANAGEMENT OF HYPOGLYCEMIA

- Glucose treatment with 15g carbohydrate, recheck in 15min
- Fat will decrease glucose absorption (Ø candy bars)
  - Candy bars are not good for treatment of hypoglycemia
- Examples:
  - 4 oz fruit juice
  - 3-4 glucose tablets
  - 6 oz "pop" or "coke" (tiny CHO)
- Emergency glucagon treatment
  - "1 amp of D50" (Emergency only)
- 10g glucose = 40mg/dL over 30 min
- 20g glucose = 60mg/dL over 30 min
- BG will fall again in 60 min → depends which insulin
- Recommended to follow glucose treatment with a meal

T1D w/ LOC

TQ

★ DKA: rapid mobilization of energy stores ↑BG ↑ketones but Ø insulin
★ ketone = β-hydroxybutyrate
→ dehydration & decreased excretion of H^+ → ACIDOSIS
★ caused by: new onset T1D, Δ dose, stress, noncompliance (skip dose to lose weight)
★ Px: 1-2 days worsening polydip/polyuria, N/V, fatigue, abdominal pain

TQ: osmotic diuresis bc glucose becomes effective osmole

* Labs: ↑BG, HYPERkalemia, HYPOnatremia, dehydration, metab. acidosis (HAGMA)

* Tx:
① Isotonic saline to tx hyperglycemia
② Insulin to tx acidosis (may need to add glucose)
→ switch to subQ once acidosis resolves
warning * >150 mg/dL/hr ΔBG = cerebral edema!!
③ Electrolyte management of Hypernatremia & Hypokalemia that we caused by insulin

TQ

ACUTE COMPLICATIONS OF T1D – DIABETIC KETOACIDOSIS (DKA) - TREATMENT

- FIRST: Hydration treats hyperglycemia
  - 2-3L of isotonic saline dilute osmolles
- SECOND: Insulin replacement treats acidosis TQ
  - Bolus insulin dose after initial hydration
  - Continuous insulin infusion until acidosis resolves !!
  - Dropping BG faster than 150mg/dL/hour shifts fluids and can cause cerebral edema fluid shifts
  - Add 5—10% dextrose to IV fluids when BG <250 mg/dL bc keep giving insulin until acidosis resolves
- THIRD: Electrolyte management
  - Na+ will increase as glucose falls, switch to hypotonic saline following initial rehydration to prevent hypernatremia
  - K+ will fall as glucose normalizes, add to fluids once K+ 5.5 mEq/L or less to prevent hypokalemia
    - add K+ once it normalizes
- Severe acidosis: pH < 7.0
  - One amp bicarb in 0.45% saline solution
    - doesn't really work, only in severe acidosis

Know this slide and keep it handy on rotations!!

LO9 Obesity

1. Identify major components and discuss regulation of energy balance in humans. ✓
2. Identify short- and long-term goals and describe regulation of food intake (appetite). ✓
3. Analyze causes and pathogenesis of obesity; identify pathophysiologic consequences and discuss complications of obesity.
4. Explain the long-term consequences of obesity in both children and adults
5. Identify pathophysiologic consequences and discuss complications of obesity.
6. Describe strategies for weight loss and maintenance
   1. Lifestyle strategies
   2. Pharmacologic therapy
   3. Surgical options

* Energy balance:
→ Energy in food consumed = external work + heat +/- stored energy
* Positive energy balance: energy consumed > external work + heat
* Negative energy balance: energy consumed < external work + heat

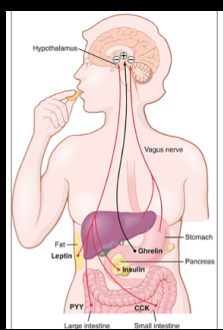
TQ

- Regulatory system for food intake:
  1. Long and short-term afferent signals → sense energy status
  2. Integrating brain centers → hypothalamus
  3. Efferent signals → regulate intensity of hunger, energy expenditure
  - This system *avoids starvation* → the system is more biased toward avoiding energy deficiency than to prevent excess storage

* METABOLIC RATE:
60-70% = basal (BMR)
30-40% = external work

* Feeding Behavior:
- satiation: feeling of fullness; SHORT-TERM SIGNALS
→ ghrelin, CCK, Peptide YY, GLP1, & PP
- satiety: prolongation of interval until hunger
→ insulin, glucagon, leptin

TQ

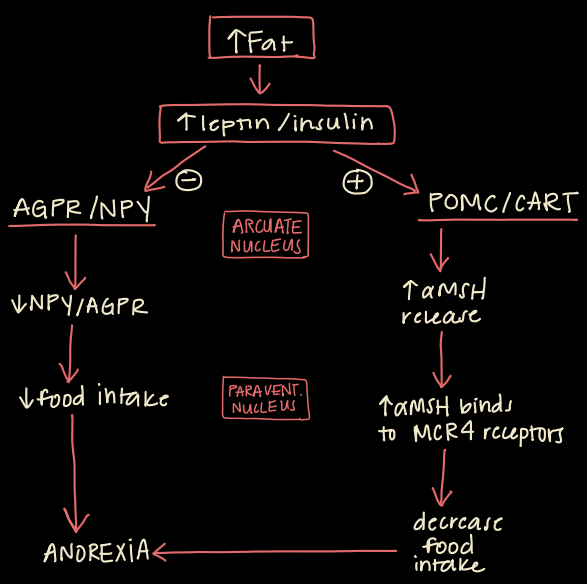


Primary feedback mechanisms that control food intake

- **Stretch receptors in the stomach** activate sensory afferent pathways in the vagus nerve and inhibit food intake. feeling of fullness
- **Peptide YY (PYY), cholecystokinin (CCK), and insulin**: Gastrointestinal hormones that are released by the ingestion of food and suppress further feeding. small intestine
- **Ghrelin:** released by the stomach, especially during fasting, and stimulates appetite.
- **Leptin:** Produced in increasing amounts by fat cells as they increase in size. It inhibits food intake. long term stimulant/inhibitor

LEPTIN LONG TERM adiposity signal (directly related to fat stores)
→ in starvation: ↓leptin = Hypogonadism
→ in obesity: ↑leptin = leptin resistance; brain ignores signal
→ stimulates RAAS → HTN

ADIPONECTIN inversely related to fat mass, ↑insulin sensitivity
* secreted by adipocytes
* mediated by AMPK
→ stimulates FA oxidation & glucose uptake in muscle by GLUT4
* thiazolidinediones ↑adiponectin



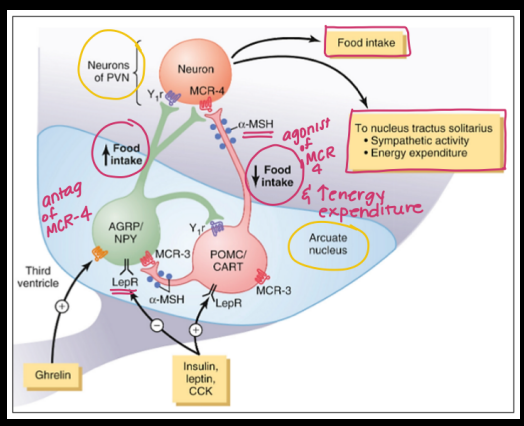
* causes & pathogenesis of obesity / pathophys. consequences & complications of obesity

* long-term consequences

Systemic Consequences of Obesity

- **Metabolic**
  - Adipose tissue = a metabolic ORGAN
    - Adipose tissue → stores energy AND acts as an endocrine organ releasing adipokines → pathophysiology of obesity and its complications
  - Obesity is a chronic inflammatory state cytokines!
- **Psychosocial**
  - Low self esteem – society looks down on overweight
  - Social and cultural standards for dietary patterns
    - Both close social and larger scale social connections increase likelihood of obesity
- **Mechanical**
  - Fat mass is heavy and hard on joints.
  - Increases in weight exponentially increase pressure on knees → osteoarthritis

social circle affects weight



* pathophys consequences & complications of obesity:
→ visceral fat = greater risk bc close to visceral organs
* adipokines: ↓adiponectin
- PAI-1 → atherosclerosis & thrombosis
- Angiotensinogen → HTN

TQ

★ MØ recruited w/ weight gain
- ↑TNFα & IL-1B → worsen insulin resistance

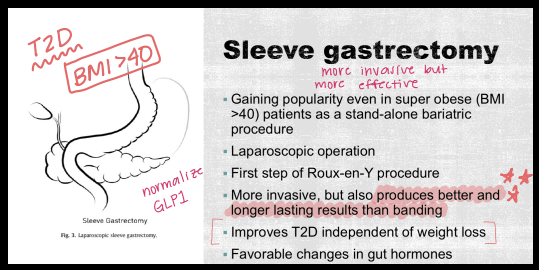
→ Cardio complications
★ 1 unit ↑BMI = ↑5% risk CVD men & ↑7% women
★ HTN, HF, CAD, PAD, Afib
★ altered hemodynamics

→ Hyperinsulinemia → β cell failure → T2DM

→ Non-Alcoholic fatty liver dz (70-90%)
★ TG deposition → cirrhosis & carcinoma

→ Cancer due to ↑ estrogens & androgens → Breast/endomet. CA
★ Hormonal component + inflammatory mediators

→ Repro:
★ PCOS: ↑LH but Ø surge; ↓FSH = Øovulation; hyperinsulinemia

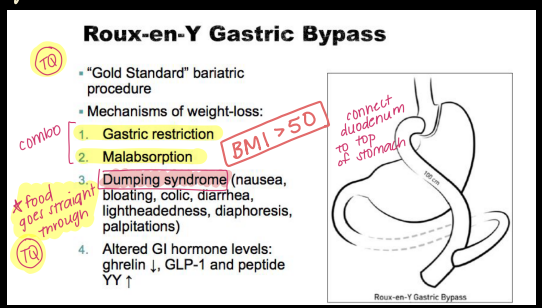


TQ ★★ to maintain WL: energy expenditure is more important than caloric restriction

★ WL strategies & maintenance
- monitored weight loss programs = most effective in maintaining long term weight loss
- 150 min exercise/week can prevent DM
- MEDS: work in brain; only work while you take em
  - phentermine/topiramate (↓appetite through dopamine)
  - bupropion (↑POMC activity)
  - orlistat (inhibits lipase)
- SURGERY: [BMI >40 or BMI >35 + comorbidities (T2D, CVD)] ★
  - ★ Restrictive: small meals, small insulin response (like low glycemic foods)
    MC = adjustable band
    Sleeve gastrectomy → improves T2D independent of WL
  - ★ Malabsorptive: long term WL; most effective BMI >50; tx T2D; need vitamins forever
    Roux-en-Y: "Gold Standard" → makes hormones normal

TQ?

TQ



L10 Path & Px of T2D:

- Understand the impact of obesity and Type 2 diabetes on the US population
- Diagnose T2D and "prediabetic" states by applying history and physical findings to currently accepted diagnostic criteria
- Describe pathophysiology of insulin resistance and beta cell destruction
- Describe mechanistically selected factors that reduce response to insulin
- Discuss systemic inflammation related to obesity as it contributes to insulin resistance and beta cell destruction
- Apply understanding of development of insulin resistance syndromes to prevention of diabetes

★ Gestational Diabetes: (after 24 weeks)
- ↑RF: obesity, FamHx DM, current insulin resistance (ex. PCOS), POC
- complications: macrosomnia, ↑mortality ↑risk of T2D in baby
- pathogenesis: human placental lactogen is analogue to IGF-1

Type 2 Diabetes:
- Highest risk in Native Americans/Alaskans
- prevalence ↑logarithmically

TQ?

★ Diagnostic Criteria:

TQ probably A1C question...

★★ Diagnostic criteria for diabetes

Table 2.2—Criteria for the diagnosis of diabetes
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L). → follow up w/ A1C
*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

polyuria/polydipsia

Prediabetes

- IFG = impaired fasting glucose
  - Fasting blood sugar ≥ 100mg/dL (100-125)
- IGT = impaired glucose tolerance post-prandial
  - Normal fasting glucose, elevated after glucose load or post-prandial
  - Typical of insulin resistance
- Oral Glucose Tolerance Test (OGTT)
  - 75g glucose load
  - Positive test is BG 140-199 mg/dL after 2h
- A1C 5.7-6.4%
- People with prediabetes have an increased risk of developing type 2 diabetes, heart disease, and stroke

Diabetic continuum → slow process down!

★ Screening for Adults:

★ 45yo w/ ØRF → every 3 years ★ EVERYONE!

★ any adult w/ RF → every 3 years if normal

ex: FamHx, POC, Hx CVD, HTN, PCOS, inactivity, prediabetes, GDM (every 3 years), HIV

★ Presenting symptoms:

- polyuria, polydipsia, polyphagia (more insidious onset than T1D)

MC ★ - blurry vision & nocturia, infections like Candidiasis

- peripheral neuropathy

★ HYPERINSULINEMIA down regulates insulin receptors → INSULIN RESISTANCE

★ ACANTHOSIS NIGRICANS = INSULIN RESISTANCE ∴ only T2D

TQ
- hyperkeratosis & hyperpigmentation
- caused by ↑insulin binding to IGF receptors on melanin containing cells

...also w/ insulin resistance:

Hyperandrogenism in women → anovulation (PCOS)

★ Insulin signaling pathway:

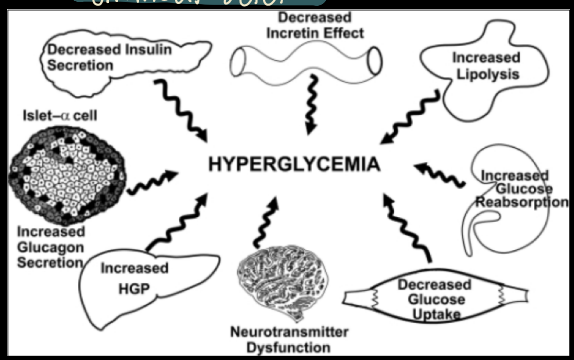
1. mitogenic, Øeffect by insulin resistance ∴ hyperinsulinemia → proliferation, inflammation, etc.
2. metabolic, via PI3 kinase activation → mTOR ↑protein synth; inhibition of mTOR = hyperglycemia
   → inhibit glycogen synthase kinase
   → increased expression of GLUT4

Ominous octet: manifestations/pathophys of T2D

@liver: makes more sugar! → glucotoxicity ↑G6P
↑glucagon
Lipotoxicity → gluconeogenesis

@muscle: lean T2D = more severe insulin resistance
down regulated insulin receptors
IRS1 dysfunction → Øvasodilation
NORMAL MAPK → inflammation, cell proliferation, & atherosclerosis

Ominous octet:



@βcell: insulin resistance forces βcells to overproduce
& eventually decompensate
★ Lipotoxicity
★ Glucotoxicity

TQ ★ IAPP - amyloid secreted 1:1 w/ insulin
↳ deposits in βcells → TOXIC!

@Adipocyte: resistance to antilipolytic effect of insulin
= ↑FFA
→ gluconeogenesis
→ hypertrophic adipocytes Østore fat well
∴ TG store in liver, βcells, & smooth m. → toxic lipid metabolites

↓adiponectin & ↑adipokines

@GI: incretin effect → oral glucose > IV glucose
↳ in T2D: ↓incretin effect bc ↓GLP1 & ↑resistance to GLP1
↑GIP but resistant to effects

TQ

EARLY MANIFESTATION of impaired glucose tolerance → T2D

@αcell: Hyperglucagonemia; ↓suppression by GLP1
liver is more responsive to ↑glucagon → makes more glucose

@kidney: ↑SGLT2 & SGLT1 → perpetuating hyperglycemia (maladaptive)

@brain: insulin resistance in cerebral tissue → Ø suppression of food intake

clinical utility

- Utilize mechanisms of action of antihyperglycemic medications to optimize pharmacologic treatment of Type 2 diabetes ✓
- Describe pathogenesis of clinical complications of Type 2 diabetes
- Understand screening protocols for complications of Type 2 diabetes
- Discuss pharmacologic approaches to prevention and treatment of diabetic complications

→ what, when, why
what population for which
why med works & HOW

INFLAMMATION:

↑CRP & IL-1β = predictive of T2D
★ ↑CRP best biomarker of CVD in T2D

L11 Complications of T2D:

Goals:
A1C < 7% DECREASES COMPLICATIONS
A1C ≤ 6.5 for newly dx young diabetics
A1C 7.5-8% = SHORT LIFE → 2 MEDS
Higher A1C = more intense therapy

#1 INITIAL CHOICE UNLESS CONTRAINDICATED: **METFORMIN**
→ weak insulin sensitizer in m.
★ ↓hepatic glucose production
↓A1C then ↑ w/ β-cell failure
LOW RISK OF HYPOGLYCEMIA

★ thiazolidinediones: Pioglitazone
★ ↓A1C ; preserve β cell fcx)
↳ protect against IAPP toxicity
★ PPARγ agonist mobilizes fat, prevents lipotoxicity
★ synergy w/ metformin
→ Risk of EDEMA → CI in HF

★ TZD = glitazone = PPAR
= edema Ø HF

★ GLIPTANS = DPPIV
= angioedema Ø ACEi

★ incretin mimetics:
injectable: GLP-1 agonist: "tide"
- long term preserve β cell fcx)
- restores normal glucose-stimulated insulin secretion
- WL

oral: DPP-IV inhibitor
- prevents breakdown of GLP
- Ø hypoglycemia
- Ø affect on weight

Ø use together

GLIPTAN

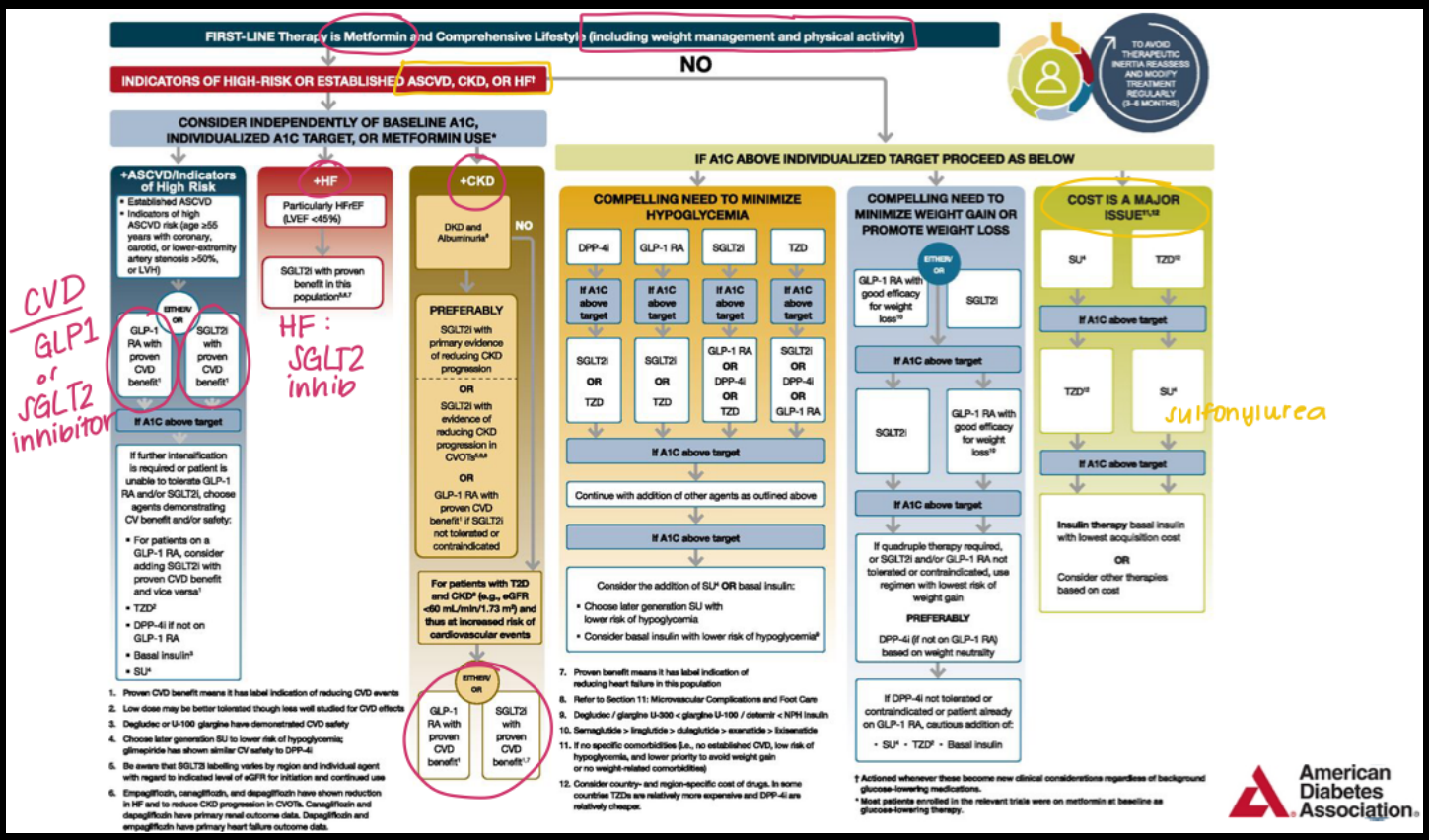
ANGIOEDEMA

★ SGLT2 inhibitors: "gliflozin" ptz w/ HF or CKD
TQ
→ @PCT, pee out glucose
→ good for active middle aged pt w/ CV dz
★ Risk of dehydration & genital yeast infections

★ Insulin → Basal Bolus
→ Risk of weight gain & hypoglycemia limits ↓A1C
→ protects β cells

★ sulfonylureas

BAD LONG TERM by exhausting βcells

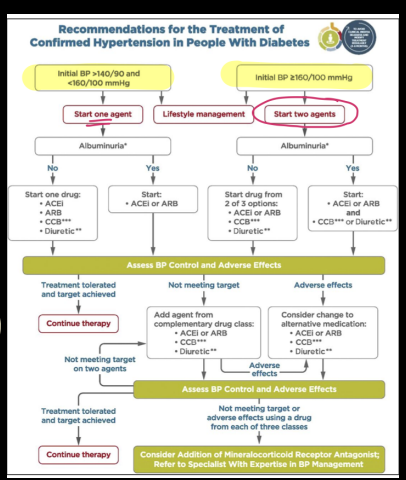


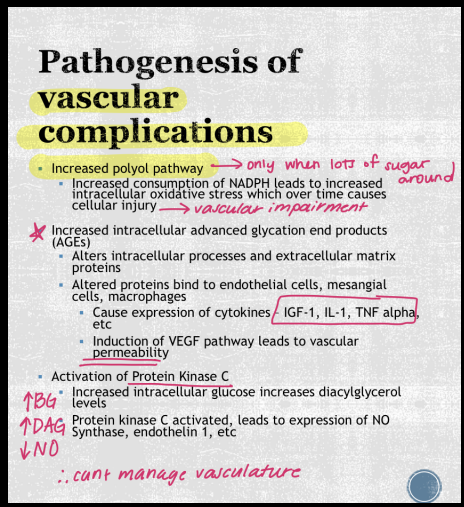
CVD GLP1 or SGLT2 inhibitor

HF: SGLT2 inhib

Chronic complications:

★ HTN: goal = get BP as low as pt can tolerate
= 130/80 mmHg
tx: ACE-i / ARBs +/- CCB or thiazide
guidelines →





★ Diabetic Nephropathy: systemic HTN → glom hyperfiltration
→ vasoconstricts efferent (AngII)
→ fibrotic glomerulus

management: BP each visit
urine albumin & Cr annually

tx: ACE-i or ARB

★ antiplatelet therapy (aspirin) for:

★ 1° prevention; T1D/T2D w/ CVD risk over 50 w/ ø bleeding risk
★ 2° prevention; T1D/T2D w/ known CVD

★ dyslipidemia:

① weight loss
② age 20-39 → statin
age 40-75 → statin
③ manage glucose to manage TG

GIVE STATIN EVEN W/O dyslipidemia ↓mortality in CVD

★ Somatic Neuropathy: carpal tunnel, gastroparesis, impaired sensation

TQ ★ screening: comprehensive foot exam w/ monofilament every 6mos

★ pathogenesis: ↓ K^+ channel; ↑ Na^+ channel → impaired Na/K pump

★ Diabetic Retinopathy: MC cause of blindness

★ RF: duration, hormonal Δs

TQ ★ screen w/ ANNUAL DILATED RETINAL EXAM

Nonproliferative	Proliferative
▪ Earliest stage of retinopathy	▪ Growth of new capillaries and fibrous tissue in retina
▪ Retinal capillaries leak proteins, lipids, red cells into retina	▪ Due to small vessel occlusion causing tissue hypoxia and resulting in angiogenesis
▪ If occurs in macula - macular edema leads to decrease visual acuity	▪ More common in T1D
▪ Most common cause of visual issues in T2D	▪ Leads to retinal detachment and blindness

★ Bariatric surgery

all w/ BMI >40

BMI 35-40 if cannot acheive WL

BMI 30-35 if cannot acheive WL + comorbidities

WANG PQs

✓ 1. D

✓ 2. C

✓ 3. A

✓ 4. B T1D DKA

✓ 5. E

✓ 6. C

✓ 7. E GUPS Hx T2D ★ → would it be T2D or GD

✓ 8. D

✓ 9. C

✓ 10. A

✓ 11. B

12. E

✓ 13. B

✓ 14. C DDx: impaired glucose tolerance & T2D

★ ~~15. C~~ E T2D

16. E

17. D

18. A

19. D

✓ 1. E

✓ 2. D

✓ 3. D

✓ 4. B

✓ 5. B

✓ 6. C

✓ 7. E

✓ 8. B

✓ 9. B

✓ 10. C

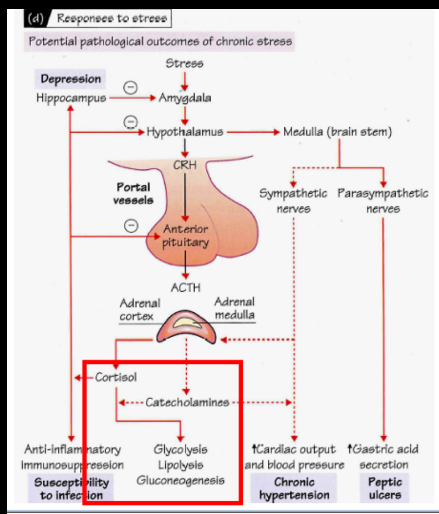
✓ 11. A

✓ 12. B

✓ 13. B

✓ 14. D pruritic rash, WL, ↑A1C, ↑glucose = Glucagonoma
✓ 15. A
✓ 16. E
✓ 17. E
✓ 18. D

LOS Babos



Adrenal medullary catecholamines are part of an integrated stress response. Catecholamines work with cortisol (from adrenal cortex) and other stress hormones and neurotransmitters).

Production of epinephrine is dependent on cortisol
(PNMT activation by cortisol)

↑⊕ cortisol

WBOT

**Beta blockers

Don't forget that beta blockers will block may symptoms of hypoglycemia...except sweating!
Ø tachycardia, Ø anxiety

→ educate diabetic pts that sweating = hypoglycemia if they're on insulin or secretagogues

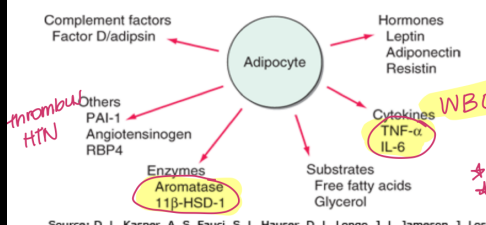
Adrenocortical steroids, primary action

→ what med are they most likely taking?

Table 9-11 Actions of Adrenocortical Steroids

Actions of Glucocorticoids	Actions of Mineralocorticoids	Actions of Adrenal Androgens
Increase gluconeogenesis	Increase Na^+ reabsorption	Females: stimulate growth of pubic and

Adipocytes



↑thrombus HTN

Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com

WHY do appearance-conscious adolescents skip their insulin???

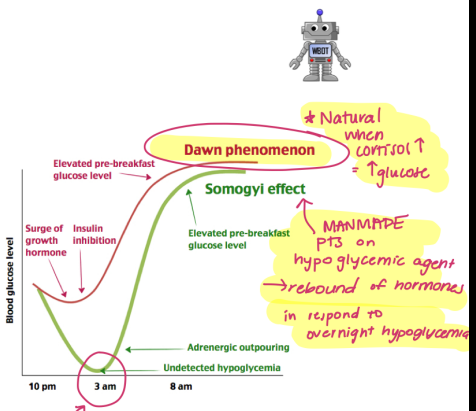
WBOT
- T1D teenager compliant w/ insulin
→ DKA
- skipped insulin dose to lose weight

– Increased expression of GLUT4 transporters and activation of fat synthesis in fat cells
-formation of triacylglycerols (fat synthesis and storage)
-inhibition of hormone sensitive lipase activated by cortisol
-fat cells are immunologically active, secreting TNFa, IL6, and adipokines that modify insulin actions

Answer

- A 64 year old female uses Novolin 70/30 twice daily to control her type 2 DM. Her morning glucose is consistently elevated. What action is most appropriate?
- Add basal insulin (e.g., Lantus)
- Add metformin
- **Check blood glucose at 0300** WBOT
- Decrease PM dose of insulin
- Increase PM dose of insulin

Elevations in AM glucose in patients on hypoglycemic agents may be due to lack of insulin (Dawn phenomenon) or rebound from adrenergic response to hypoglycemia (Somogyi effect). Check 0300 glucose to determine whether to increase insulin (Dawn phenom) or decrease insulin/add slow carbohydrate (Somogyi)



* Natural when cortisol ↑ = ↑glucose

MANIPULATE PTs on hypoglycemic agent → rebound of hormones in respond to overnight hypoglycemia

Hypoglycemic @ 3am = stop what caused it
→ decrease bed time glucose
or → add long term agent

LOW BaBOS

- Drugs that cause hyperglycemia
  - Antilipid: statins, niacin
  - Calcium channel blocker (overdose): nifedipine (Procardia)
  - Diuretic: hydrochlorothiazide (HydroDiuril)
  - Glucocorticosteroids: e.g., prednisone (Deltasone)
  - Thyroid hormone: levothyroxine (Synthroid)
  - Calcineurin inhibitors: cyclosporine (Sandimmune) tacrolimus (Prograf)
  - Atypical antipsychotics: Clozapine, Olanzapine, Quetiapine
  - Protease inhibitors (-avirs that are –navirs) eg ampreNAVIR, ritoNAVIR

WBOT

hyperglycemia & weight gain

FYI: Current Drugs for Diabetes

	Drugs that increase insulin sensitivity or decrease carb absorption or increase carb clearance	Drugs that increase insulin level in blood stream (thus may cause hypoglycemia when used as monotherapy, will cause weight gain) could cause hypoglycemia & WG
Drugs that affect PPG> fasting PPG = post-prandial blood glucose level	**Amylin analog** Pramlintide (Symlin®) **α-glucosidase inhibitors** **Acarbose (Precose®)**, Miglitol (Glyset®) **Bile acid sequestrant** Colesevelam (Welchol®) **Dipeptidyl peptidase 4 inhibitors** Alogliptin (Nesina®), Linagliptin (Tradjenta®), Saxagliptin (Onglyza®), **Sitagliptin (Januvia®)** **Dopamine 2 agonist** Bromocriptine (Cycloset®) **Incretin mimetics** Albiglutide (Tnazeum) **Exenatide (Byetta®)**, dulaglutide)rulicity), Liraglutide (Victoza®) Lixisenatide (Adlyxin). Semaglutide (Ozempic®) **Thiazolidinedione** **Pioglitazone (Actos®)** Rosiglitazone (Avandia®) **SGLT2 antagonist** **Canagliflozin** (Invokana), Dapagliflozin (Farxiga). Ertugliflozin (Steglatro) Empagliflozin (Jardiance)	**Rapid insulin** (used preprandially) **Insulin aspart (Novolog®)** Insulin lispro (Humalog®) Insulin glulisine (Apidra®) **Short acting insulin** (preprandially) **Regular insulin (Humulin or Novolin R®)** **Intermediate insulin** **NPH insulin (Humulin N® or Novolin N®)** **Inhaled rapid insulin** Insulin Powder (Afrezza) **Sulfonylureas** *Chlorpropamide (Diabinese)* Tolazamide (Tolinase) Tolbutamide (Orinase) Glimepiride (Amaryl®) Glipizide (Glucotrol®) **Glyburide (DiaBeta® or Micronase®)** **Meglitinides** Nataglinide (Starlix®)(a d-phenylalanine derivative) **Repaglinide** (Prandin®)
fasting>PPG	Biguanide **Metformin (Glucophage®)** stop overnight/ daytime gluconeogen.	Long-acting basal insulin at bedtime **Insulin glargine (Lantus®)**— if still making w/ TBG *Insulin determir (Levemir®); Insulin decludec (Tresiba)*

Effects of metformin

- Metabolic/overdose
  - Rare risk of lactic acidosis (next 2 slides)
  - Minimal risk of hypoglycemia
  - Helps **normalize fasting blood glucose** (important, because if you awaken with high BG, it only rises from the starting point when carbs are consumed!)
- GI:
  - Upset, diarrhea flatulence — take w/ food
- Nutritional:
  - B12 deficiency
    - ?diarrhea
    - ?interference with Calcium dependent B12 absorption
    - ?inhibition of intrinsic factor secretion
  - Weight neutral

don't have to take w/ food tho

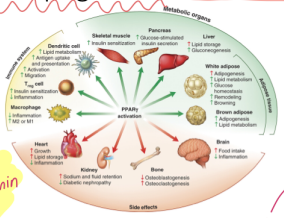
hypersegmented PMNs

WBOT

- can cause B12 deficiency → ↑MMA; megaloblastic anemia & peripheral neuropathy

Advantages	Disadvantages	Cost*
• Extensive experience • Rare hypoglycemia • ↓ CVD events (UKPDS) • Relatively higher A1C efficacy	• Gastrointestinal side effects (diarrhea, abdominal cramping, nausea) • Vitamin B12 deficiency • Contraindications: eGFR <30 mL/min/1.73 m², acidosis, hypoxia, dehydration, etc. • Lactic acidosis risk (rare)	Low

PPARγ agonists: thiazolidinediones



Nat Med. 2012; 99: 560

Pioglitazone (Actos)

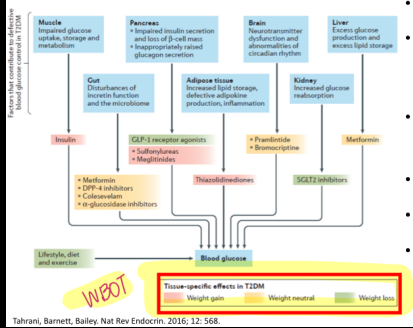
FYI rosiglitazone (Avandia)

- Mechanism: activate PPARγ to increase insulin sensitivity of muscle and fat (increases expression of GLUT4 among other effects)
  - Small reduction in hepatic glucose production
- Other effects:
  - Decreased inflammation
  - Weight gain
  - Edema (contraindicated in CHF)
  - Hepatotoxic
  - Macular edema
  - Fracture, weakened bones
  - Anemia
  - Cancer?

HF makes metformin worse; PPAR makes HF worse

make HF WORSE; ↑expression of ENaCs

Major actions of drugs for type II DM



Tahrani, Barnett, Bailey. Nat Rev Endocrin. 2016; 12: 568.

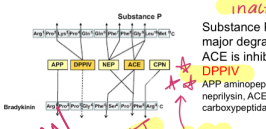
- Alpha glucosidase inhibitors – prevent absorption of disaccharides
- GLP1 agonists (incretin mimetics) – increase glucose dependent insulin release, increase satiety, delay gastric emptying
  - DPPIV inhibitors block breakdown of GLP1
- Insulin increase glucose uptake and utilization
  - Secretagogues (sulfonylureas and glitinides) increase insulin release
- Metformin – decreased hepatic and renal gluconeogenesis
- Thiazolidinediones – increase insulin sensitivity
- SGLT2 inhibitors – urinary loss of glucose

WBOT

anything that ↑insulin = weight gain & hypoglycemia

DPPIV inactivates more that incretins

inactivates DPPIV → ↑GLP



Substance P contributes to angioedema; DPPIV is a major degradation pathway for substance P when ACE is inhibited. Bradykinin is partially degraded by DPPIV

APP aminopeptidase P, DPP-IV dipeptidyl peptidase IV, NEP neprilysin, ACE angiotensin converting enzyme CPN carboxypeptidase N (Hypertension. 2009;54:516-523)

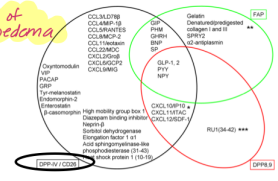
↑pain; infection

WBOT

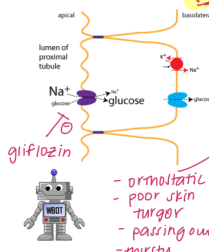
risk of angioedema

GLIPTAN

neuropeptide Y is also degraded by DPP-IV, there is an increased risk of arthralgia and pain



SGLT2 inhibitors



-gliflozin

- **Canagliflozin (Invokana)** dapagliflozin (Farxiga), empagliflozin (Jardiance), ertugliflozin (Steglatro)
- Inhibit glucose reabsorption in proximal tubule
  - Benefit in heart failure (empagliflozin)
- Adverse effects:
  - Bone loss and fracture risk (FDA bulletin 9.10.15)
  - Genitourinary infection UTI
  - Hypovolemia/hypotension
    - Increased urination, thirst
  - Hyperkalemia
  - Hypersensitivity reactions
  - Increases in LDL
  - necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene. (FDA 8.29.18)
  - Impaired renal function (FDA bulletin 6.14.16)
    - CI in renal failure (eGFR < 30ml/min/1.73m²
  - Increased amputation risk (canagliflozin)? (FDA 5.16.17)
  - Increased hepatic glucose production, increased fatty acid oxidation (FDA bulletin 12.1.15)
    - Euglycemic ketoacidosis
  - Pancreatitis (Health Canada 2018)
- Advantage
  - Weight loss
  - Oral tx
- Disadvantage
  - Recently intro'd to market

WBOT

↓reabsorbing sodium

risk of hyperkalemia

- dermatitis
- poor skin turgor
- passing out
- yeast

make CKD worse

Summary Drugs and weight

- Promote weight loss/ weight neutral
  - Metformin
  - GLP1 agonists (loss)
  - DPPIV inhibitors
  - Alpha-glucosidase inhibitors (loss)
  - SGLT2 inhibitors (loss)
- Weight gain
  - Drugs that increase insulin in body
    - Insulin
    - Secretagogues
  - Thiazolidinediones

WBOT

Clinical Applications

T2D

* Metformin = first line

>7.5 -8%. → use two anti-hyperglycemics (dual therapy)

↓ complications

- lifestyle Δs
- balanced macros & ↓calories
- statins
- ACE-i/ARB

T1D:

dehydration → get A1C & metab profile

RF: age, autoimmunities, genetic component
HLADR3,4,5

tx: insulin (exogenous)

amp kinase: ↑insulin sensitivity
↑Metformin = good!

↑GLUT 4
activates AMPK
↓inhibits gluconeogenesis

ARB: renal & cardioprotective

add statin, hypertensive, & SGLT2 inhibitor, + aspirin over 50.

PPAR = edema "glitazone"

DPPIV = angioedema "gliptan"

* GLP1 doesn't work in obesity
↓leptin sensitivity & insulin sensitivity
↑risk of HTN
→ increased BV & ↑TPR
→ stimulates RAAS from adipose tissue

Exercise, monitored WL programs

* SLEEVE bc longterm WL
(need extreme obesity for ROUX EN Y