Diabetes Pharmacology (Ch. 57)

Pathophysiology Review Slides

Diabetes Mellitus

Diabetes Mellitus (DM): Defective Insulin Secretion → Hyperglycemia

Type 1 DM:

- Cell-mediated autoimmune destruction of beta-cells
- Insulin-dependent
- Juvenile form (75% < 30 years old)
- Prone to ketoacidosis

Type 2 DM:

- Insulin resistance → decreased insulin OR increased secretions → increased resistance
- Associated with obesity; HTN & dyslipidemia
- Adult-onset form (but % childhood cases are increasing)
- Ketoacidosis only under stress
- Genetic predisposition

Gestational (GDM):

- Onset or 1st recognition during pregnancy
- Obesity; family history of GDM; ethnicity & > 25 y.o. = increased risk

Other specific types:

- Genetic defects in beta-cells or insulin action
- Pancreas impairments (cystic fibrosis; pancreatitis; infections)
- Endocrine disorders (ex. Hyperthyroidism; acromegaly; cushing's disease)

DM Diagnostic

Marker	Dx Threshold
Glycosylated Hemoglobin (HbA1c) - Measure avg. plasma glucose exposure to RBC	>6.5% (5.7% to 6.4% = increased risk)
Fasting plasma glucose (FPG) - Fasting = 8 hours minimum	> 126mg/dl or 7.0 mmol/L (100-125 mg/dl = increased risk)
Oral glucose tolerance testing (OGTT) - 2-hour plasma glucose with 75g glucose dose	> 200 mg/dl or 11.1 mmol/L (75-199 mg/dl = increased risk)
Random Glucose Levels (RGL) - Only in patients with classic hyperglycemia Sx	> 200 mg/dl or 11.1 mmol/L

Type 1 DM vs. Type 2 DM

Characteristics	Type-I (β-cell defect)	Type-II (Insulin resistance)
Incidence	Common childhood disease (0.17%)	45-64 yo: 10.5% 65-74 yo: 18.4%
Age of Onset	Peak = 11-13 years Rare < 1 or 30+	Highest Risk between 40-70
Gender	Similar	Similar
Racial Distribution	Whites ≈ 2x ↑ Risk	↑ Risk black & native Americans
Obesity	Usually Normal BMI	Important Contributing Factor ∝ Degree & Distribution of Obesity
Heredity	≈ 5-10%	≈ 10-15%
Antibodies	Islet Cell & Insulin Autoantibodies	Abs not Prevalent
Insulin	Resistance unusual Severe Deficiency to No Secretion	Resistance at Dx Secretion declines over time

Gestational Diabetes Mellitus (GDM)

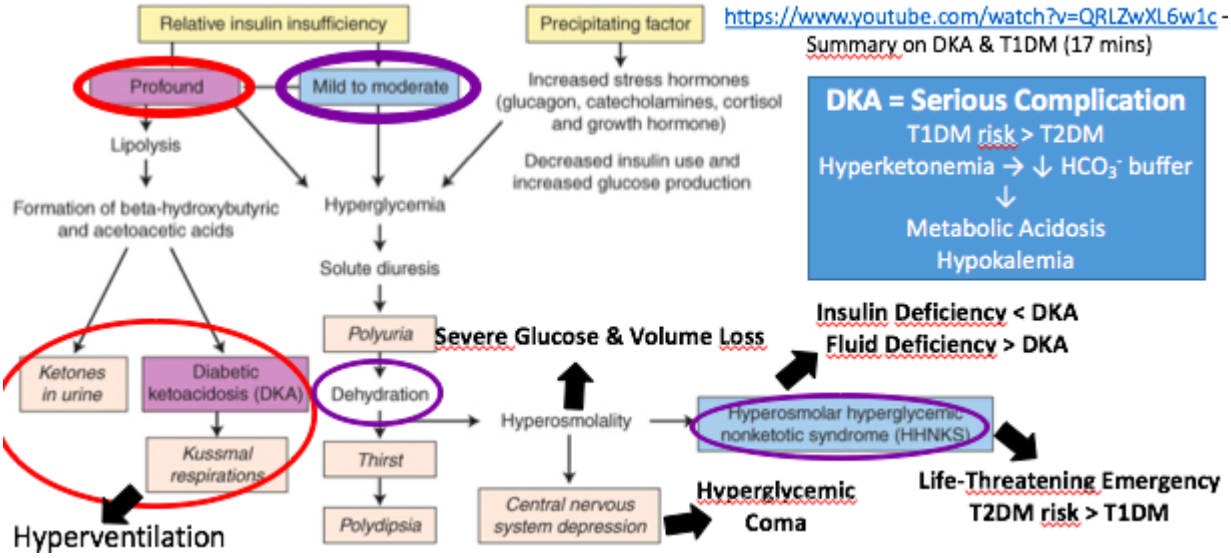
- Unknown pathophysiology
- Insulin resistance + hypoinsulinemia
- Prevention
  - Early screening
  - Glucose monitoring pre/post/during
  - Healthy diet + physical activity
- Pregnancy complications
  - Baby puts on extra weight → C-section
  - Increased T2DM risk for baby
  - Increased early delivery → respiratory distress
- Complications for mother
  - Increased T2DM risk & future GDM
  - Increased risk preeclampsia & HTN

Hypoglycemia

- Insulin shock
  - Plasma glucose < 45 mg/dl (<30 newborns)
  - T1DM risk > T2DM
  - Preventable with monitoring
- Neurogenic Sx = increases SNS activation
  - Tachycardia
  - Tremor
  - Anxiety
- Neuroglycopenic Sx = brain hypoglycemia
  - Dizziness
  - Confusion
  - Seizures
  - Coma

- Treatments
    - Exogenous glucose
    - Glucagon injections

Diabetic Ketoacidosis (DKA) & Hyperosmolar Hyperglycemic Nonketotic Syndrome (HHNKS)



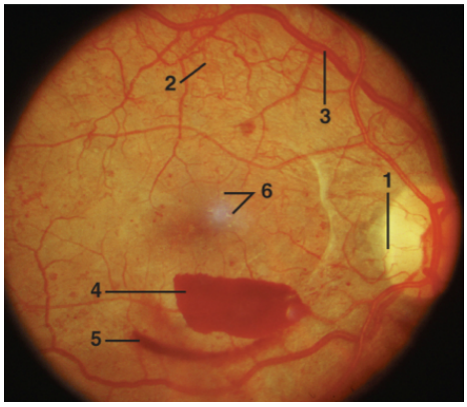
Microvascular Diseases

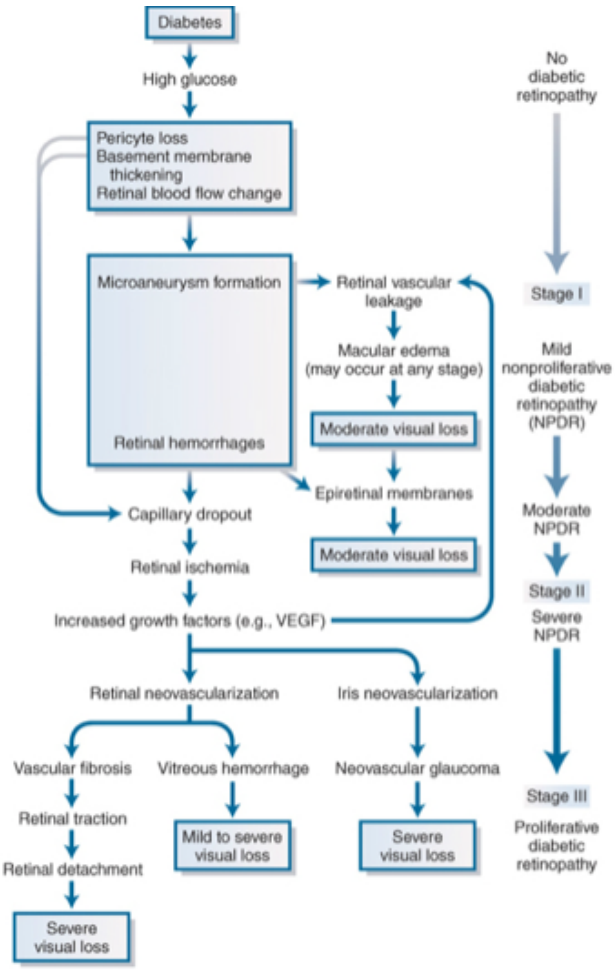
- Hyperinsulinemia + Hyperglycemia → oxidative stress → increased glycosylated hemoglobin → microvascular angiopathy
- Chronic hyperglycemia → T2DM patients have increased risk
- Organs most affected:
    - Retina → diabetic retinopathy
    - Kidneys → diabetic nephropathy
    - Nerves → diabetic neuropathy

Diabetic Retinopathy (DR)

- 1 & 2 = neovascularisation
- 3 = engorged veins
- 4 & 5 = hemorrhage
- 6 = solid exudate

- Increased risk of cataract; glaucoma; blindness





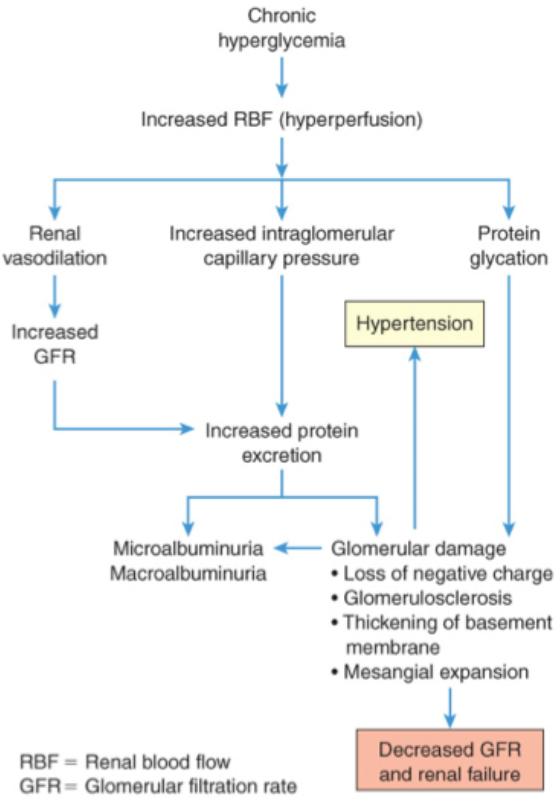
<u>Diabetic Nephropathy (DN)</u>

- Most common cause of end-stage kidney disease (ESKD)
- Microalbuminuria = loss 30-300mg/day → 1st sign

  ↓
- Macroalbuminuria = loss > 300mg/day

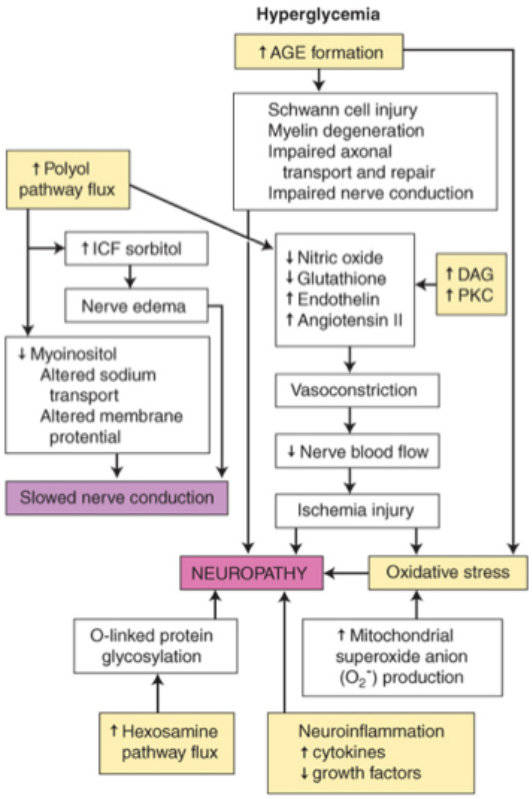
  ↓
- Clinical proteinuria → diabetic nephropathy

  ↓
- Acceleration of diabetic nephropathy & cardiovascular complications



Diabetic Neuropathy (DPN)

- Most common DM complication
- Nerves = vulnerable to hyperglycemia
- Sensory deficits → motor deficits
- Peripheral damage 1st; ANS 2nd
- Ex: neuropathic pain; decreased proprioception; decreased coordination; muscle weakness; autonomic GI & cardiac complications

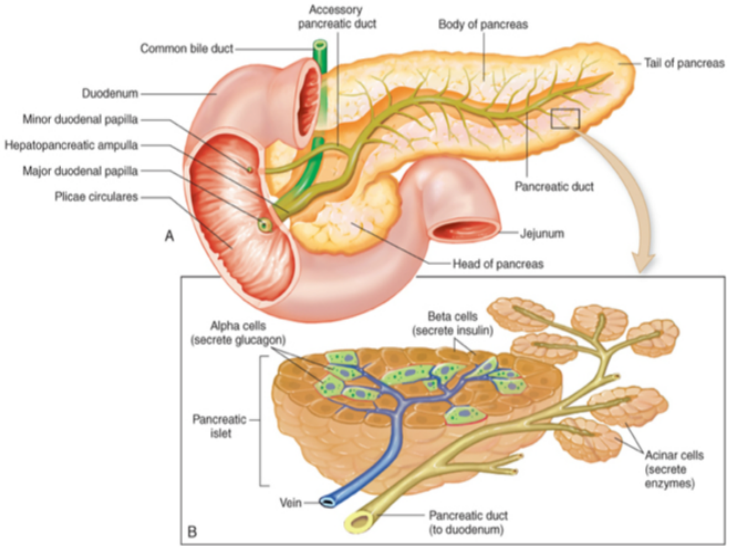


Macrovascular Diseases

- Coronary artery disease (CAD)
  - Accelerated damage → plaque instability
- Stroke
  - Risk is increased 2x vs. non-diabetic
- Peripheral arterial disease (PAD)
  - Very common with T2DM
  - Occlusion → ulcers → gangrene → amputation

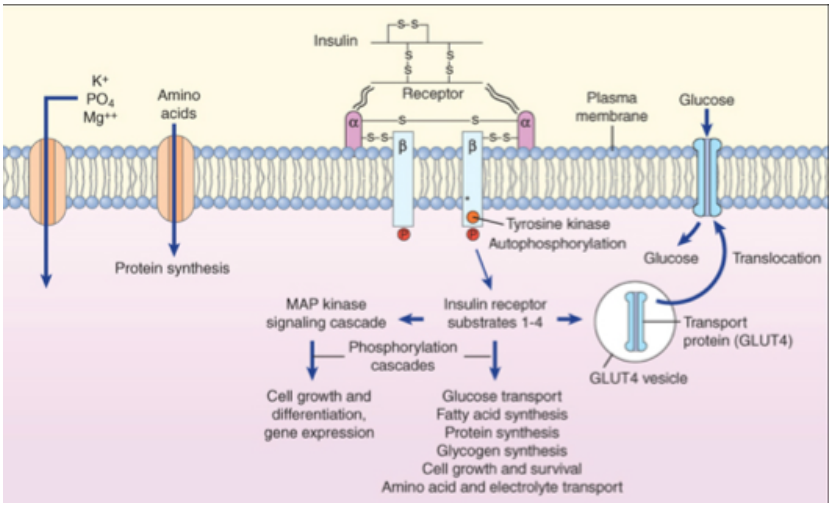
Endocrine Pancreas

- 99% exocrine (discussed in GI lectures)
- 1% endocrine → islet of Langerhans
  - Highly vascularized
- 4 hormone-secreting cells:
  - Alpha cells → glucagon
  - Beta cells → insulin & amylin
  - Delta cells → somatostatin & gastrin
  - F cells → pancreatic peptides



Insulin

- Anabolic peptide hormone
- Receptors on most cells
    - NOT THE BRAIN → hypoglycemic shock
- Primary action = decreased glucose
    - Increased GLUT4 channels → increased uptake
    - Increased usage as fuel
    - Decreased glycogenolysis



- Other actions:
    - @ liver: increased fatty-acid synthesis
    - @ adipose tissues: decreased lipolysis / increased fat storage
    - @ muscle tissues: increased amino acid uptake & protein synthesis

Factors increasing secretion	Factors decreasing secretion
• Increased glucose or amino acids • Increased GI hormones • Parasympathetic stimulation of beta-cells	• Decreased glucose • Increased insulin (Negative feedback) • Sympathetic stimulation of alpha-cells (glucagon)

BACK TO PHARM!!

Overview of Treatment

- **Primary goal**: keep glucose levels in “healthy range” (which will vary between individuals, which is why we need to get a baseline value for our patients)
- Prevent long-term complications (ex. Micro & macrovasculature diseases)
- Diet & physical activity = central components
- Physical activity increases glucose uptake & insulin-sensitivity

Type-1 DM

- Extensive patient education
- Must couple insulin replacement with carb intake (because these individuals do not produce insulin
- Weight maintenance with physical activity
- Combine with appropriate antihypertensive drugs
    - ACE-inhibitors; Statins

Type-2 DM

- Management of comorbidities = crucial
- Will not necessarily get insulin
- See Canadian guidelines at the end of the section

Tight glycemic control

- Around-the-clock blood glucose level maintenance

General Glycemic Treatment Targets for Nonpregnant Adults With Diabetes

A1C	<7.0%[a]
Premeal plasma glucose	80–130 mg/dL[a]
Peak postmeal plasma glucose	<180 mg/dL[a]

Type-1 DM

- Benefits outweigh the risks
- Drawbacks:
    - Increased hypoglycemia risk & weight gain
    - Increased cost/complexity of therapy

Type-2 DM

- Benefits limited to microvasculature complications (meaning we can reduce these, but not so much for the rest)
- Benefits increases in younger & recent-onset patients as compared to an older patient

Individualized goals based on:

- Duration of diabetes
- age/life expectancy
- Comorbid conditions
- microvascular/cardiac complications
- Hypoglycemia awareness
- Other individual considerations

Contraindications

- Advanced vascular complications
- Limited life expectancy
- Limited resources/support system
- Long-standing T2DM
- Severe hypoglycemia
- Extensive comorbidity

Insulin Deficiency Consequences

Catabolic state: increased breakdown of fat, glycogen & proteins

↓

Gluconeogenesis: fat & amino acid conversion to glucose

+

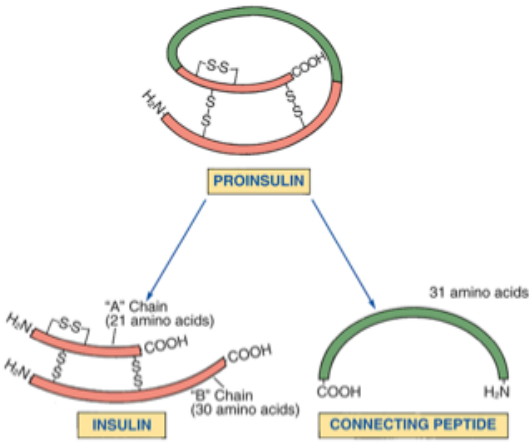
↓ glucose usage/cellular uptake

↓

Hyperglycemia

↓

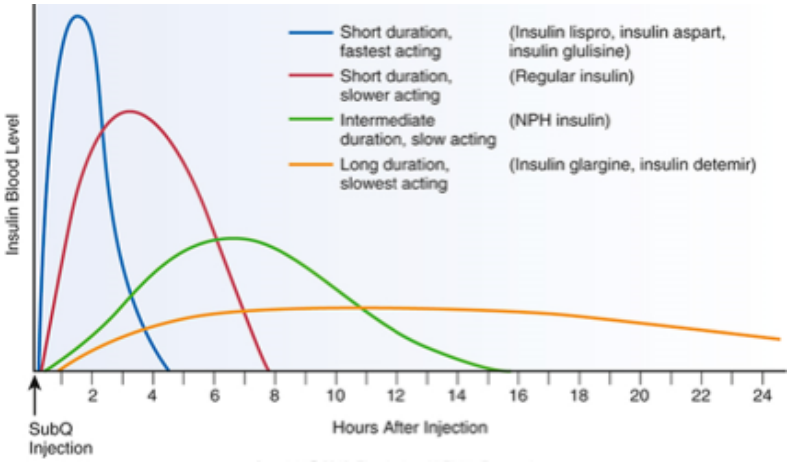
Diabetic signs & symptoms



The diagram to the right points out that one of the synthesis markers for the presence of insulin or lack thereof, is this connecting peptide when insulin is produced by the pancreas. It comes first in this long section (top image) and then it needs to be cut in two to form insulin. The connecting peptide is discarded and ends up in the bloodstream and excreted in the urine. Measuring the amount of this peptide will give us an indication of how much insulin (or lack of) is produced by the individual.

Insulin Types

- Types of insulin DOES NOT EQUAL time course
- High-alert agent = increased medication error risks



- Only available parenteral (SubQ) - it is completely digested if administered PO because it is a protein
- All synthesized via DNA recombination
    - Short duration - rapid acting : control postprandial blood glucose rise
    - Short duration - slower acting : control postprandial blood glucose rise, basal glycemic control
    - Intermediate : basal glycemic control between meals
    - Long duration & slowest acting : daily basal glycemic control of T1DM & T2DM
- Nursing Advice: insulin appearance
    - Clear, colorless solutions (except NPH insulin)
    - Always inspect insulin quality
    - Discard if colored or cloudy
    - NPH insulin must be gently mixed
    - Note date of bottle opening

<u>Insulin: Administration</u>

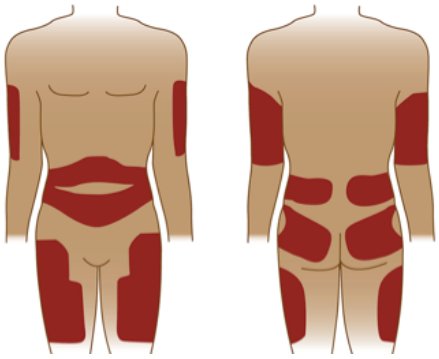
Administration

- Subcutaneous = preferred for all
- Via syringe/Pen/Jet injectors
- Pre-filled syringe stored in fridge upright
- Gently agitate to re-suspend prior to injection
- IV: emergency ketoacidosis

Concentrations	Indication
U-100 (units/mL) U-200	Routine replacement therapy
U-300	Daily basal insulin coverage
U-500	Specifically for insulin resistant patients

Nursing advice: Insulin Mixing

- Only NPH insulin can be mixed with short-acting insulins
- Premixed preparations = preferred to decrease errors

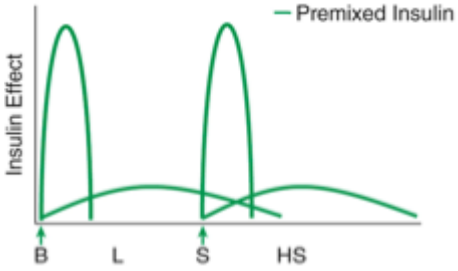


Fast absorption in the abdomen
Slow absorption in the thighs

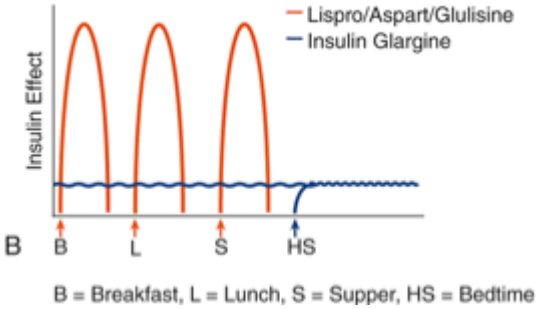
<u>Insulin: Diabetes Therapy</u>

- Major indication: required for all T1DM patients and many T2DM
- Dosing schedules: dosage should be adjusted proportionally to carbohydrate intake
- Twice-daily premixed (fig. A): Only 2 injections but less “need-based” adjustment

- Premixed (intermediate with short acting insulin)
- Should be administered around breakfast and then supper time
- Drawback: less need-based adjustments
- Benefit: fewer injections throughout the day



- Intensive basal-bolus (Fig. B): good meal & basal coverage → perfect for T1DM
  - Involves the use of a long-acting in addition to a short-acting
  - Goal is to have coverage for all three meals of the day.
  - At bedtime you get a long acting to cover you until bedtime the following day.
  - Drawback: more administrations per day.



B = Breakfast, L = Lunch, S = Supper, HS = Bedtime

- Continuous Subcut infusions (CSI): steady infusion + automated adjustments
- IV infusions: critical care

*** Patient education, healthcare team program & active patient participation ***

Insulin therapy complications:

- Major: hypoglycemia (see pathophys review slide)
- Risk factors: intense exercise, childbirth, meal skipping, excessive alcohol consumption
- Treat rapidly via fast acting oral glucose dose (ex. Orange juice, non-diet soda, etc.)
- Minor: hypokalemia, lipohypertrophy, allergic reactions (rare)

Drug interactions:

- Hypoglycemic agents (ex. alcohol) & hyperglycemic agents (ex. glucocorticoids)
- Beta-blockers → can hide/delay early detection signs

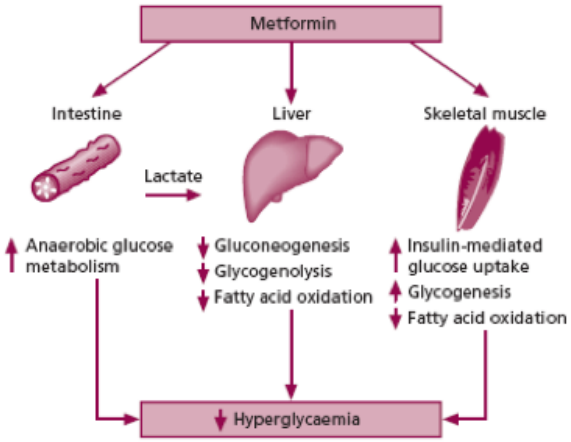
Non-Insulin Medications for Diabetes

Biguanides: Metformin

- Drug of choice for T2DM
- Weight neutral: it won't make you gain or lose weight (unlike other agents)

Pharmacokinetics	Orally Available No Metabolism → 100% Kidney Excretion
Adverse Effects (All GI Related)	↓ Vit. B12 & Folic Acid Absorption ↓ Appetite; Nausea & Diarrhea **'Weight-Neutral'**
Toxicity (Very Rare)	**Lactic Acidosis; ↑ risk if Renal Impairment**
Drug Interactions	Alcohol & Cimetidine (H2-Blocker)
Therapeutic Uses	
Glycemic Control	**↓ Blood Glucose without ↑ Insulin** **Hypoglycemia risks = Low** Synergy with other Antidiabetic Agents Safe for individuals skipping meals
T2DM Prevention	Delay T2DM development in High Risk Individuals **Not as much as Diet + Exercises!!**
Gestational Diabetes	Benefits = Insulin
PCOS	↓ Androgens levels + ↑ Insulin Sensitivity Off-Label Usage

- Mechanism of Action: acts directly on the organs.
  - At the intestine: it increases anaerobic glucose metabolism - increase the breakdown of glucose before it is absorbed.
  - At the liver: decreases the gluconeogenesis
  - At skeletal muscles: increase insulin sensitivity and glycogenesis (synthesis of glycogen)
- Metformin is decreasing the amount of glucose that is getting into the bloodstream.



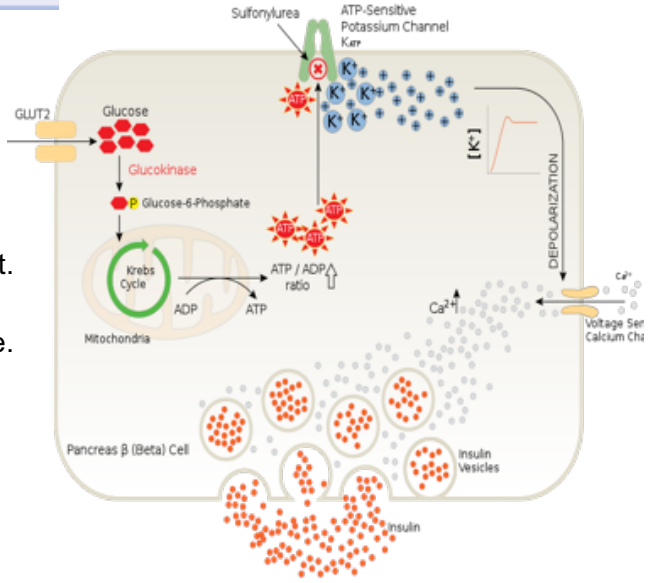
Sulfonylureas (2nd Gen) & Glinides

- Oldest oral antidiabetic agent
- 2nd Gen safety >>> 1st Gen
    - 2nd gen is much more potent and less drug-drug interactions

Pharmacokinetics	Orally Available Mix of hepatic metabolism & kidney excretion
Adverse Effects (All GI Related)	↑ Risk if Liver or Renal Impairment Hypoglycemia in normo & hypoglycemic patients Weight Gain → **'Weight-Positive'**
Drug Interactions	Alcohol & Other Hypoglycemic Agents Beta-Blockers (↓ Insulin release)
Therapeutic Uses	
Glycemic Control	↑ Insulin Secretion (so ineffective for T1DM) Most often used in combination

Glinides (Repaglinide & Nateglinide)	
Mechanism of Action & Adverse Effects	**Same as Sulfonyureas**
Pharmacokinetics	Vs. Sulfonylureas = Short Time Course Administered with meal intake

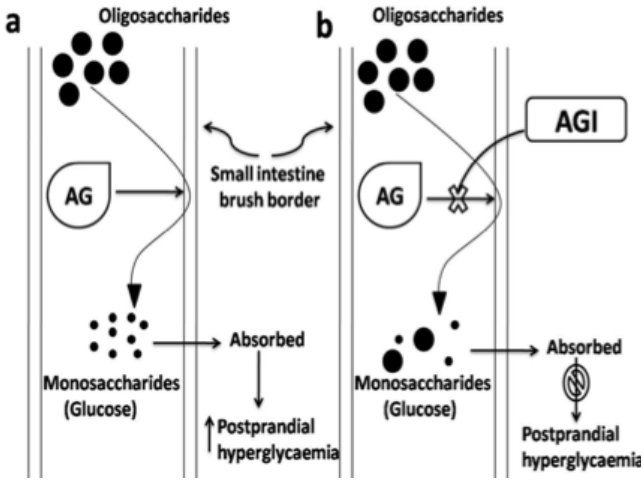
- Mechanism of action: it acts on the pancreatic beta cells. The little vesicles filled with insulin are released when the cell is activated. The drug activates the cells a bit more than they normally are by blocking a potassium channel. By blocking the K+ channel, it prevents the K+ from leaking out. As a result, the cell becomes depolarized, thereby permitting influx of calcium, causing insulin release.



Alpha-Glucosidase Inhibitors (AGI)

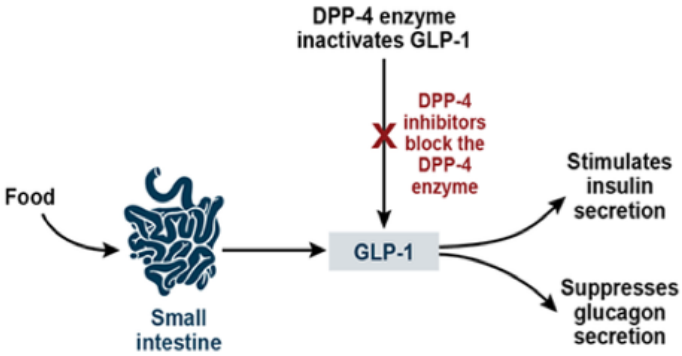
- AGIs: Acarbose & Migitol
- Therapeutic use:
    - T2DM glycemic control
    - Decrease A1C levels & postprandial glucose peaks
- Kinetics:
    - Only 2% absorbed → very few systemic effects
    - Stays where it acts (in the gut!!)
    - Inactivated by GI enzymes & bacteria
- Adverse effects:
    - GI distress (ex. Cramps, flatulence, diarrhea)

  - Decreased iron absorption → increased anemia risks
  - Hypoglycemia only in combination
  - Very rare risks of liver dysfunctions
- Mechanism of action: prevents the enzyme AG from breaking down larger structures from which glucose comes from. So if you prevent the breakdown of oligosaccharides into monosaccharides, the oligosaccharides are too large to be absorbed.
- Variable prescription pattern in North America due to GI adverse effects (not preferred drug)



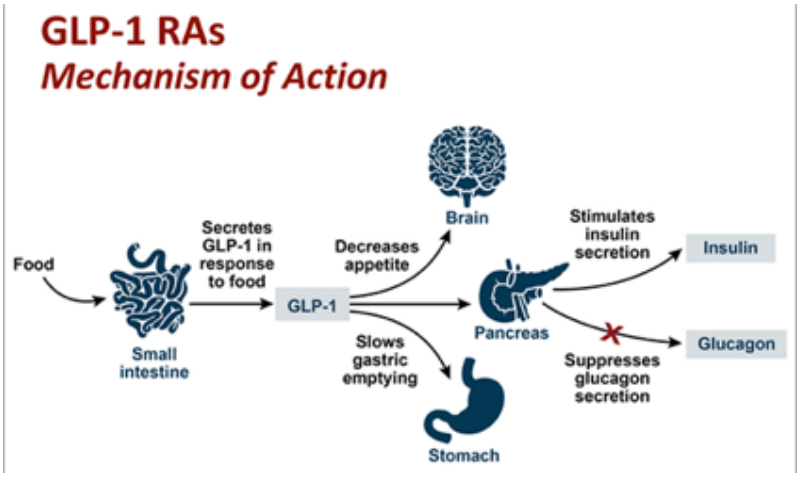
DPP-4 Inhibitors

- DPP-4 Inhibitors: Gliptins (ex. Sitagliptin)
- Therapeutic use:
  - second-line drug to T2DM therapy
  - Small decrease in A1C → yet clinically significant
- Kinetics: ~100% absorbed / ~100% kidney excretion
- Adverse effects: Very few → well tolerated
  - Hypoglycemia & respiratory infections = placebo
  - Severe pancreatitis (rare) → monitor
  - Unconfirmed allergic reactions → monitor
- Drug interactions:
  - Nothing significant → good benefit
- Mechanism of action: it acts on the incretin hormone GLP-1 pathway. GLP-1 is released by the small intestine when food arrives. Its goal is to increase the release of insulin and suppress glucagon. DPP-4 inhibitors blocks the DPP-4 enzyme, whose job is to inactivate the GLP-1 hormone.
  - NB. because it works on increasing insulin secretion, this drug will not work in T1DM.



Injectable GLP-1 Agonists: Liraglutide

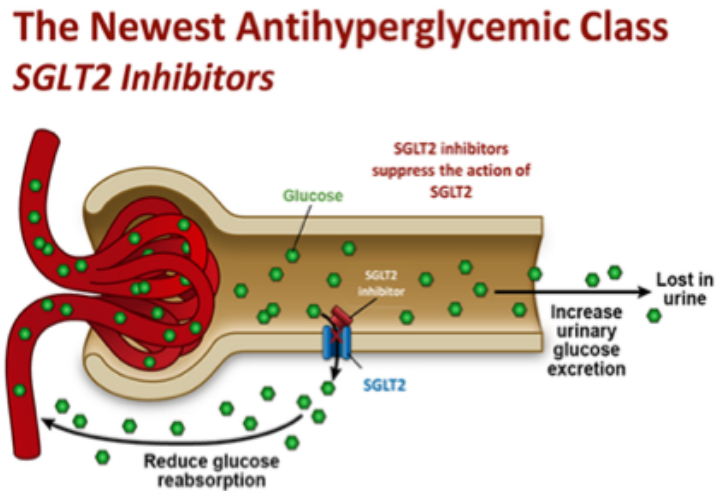
- Therapeutic use:
  - Improve glycemic control of T2DM
  - Weight - neutral
  - Injections: 2x/day or once a week extended release
- Kinetics:
  - Subcutaneous injections = best absorption
  - ~ 100% kidney excretion
- Adverse effects:
  - Frequent hypoglycemia with sulfonylureas
  - Some GI distress & risk of severe pancreatitis
  - Possible renal impairment
  - Possible teratogen → avoid during pregnancy
- Drug interactions:
  - Decreased absorption of PO drugs (contraceptives & antibiotics)
- Incretin Mimetics resistant to DPP-4 metabolism (it will not get inactivated by DPP-4)
  - Said to be a superior drug because of this
- Mechanism of Action: incretin mimetic (simulates the same action) as the one produced by your body.



SGLT2 Inhibitors

- SGLT2 = sodium glucose ligand transporter #2
- Drugs: Empagli**flozin** & Canagli**flozin**
- Action:
  - Decreased glucose kidney reabsorption
  - Weight loss via urinary caloric loss
- Specific Usage:
  - Best options for patients with CVD comorbidities already on Metformin
  - Improves cardiovascular & renal outcomes
- Adverse effects
  - Orthostasis & increased urinary tract infections
  - Rare: euglycemic DKA

- Mechanism of Action: it inhibits the SGLT2 transporter (which carries sodium and glucose) which are found in the kidney tubules. By blocking these transporters, it prevents the reabsorption of glucose, so it can be excreted, decreasing blood glucose.

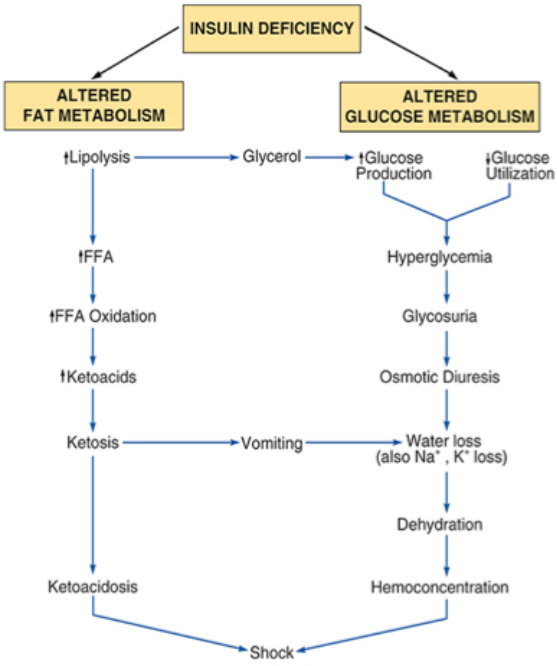


<u>Poor Glycemic Control</u>

Diabetic Ketoacidosis (DKA) therapy

*****Life threatening emergency*****

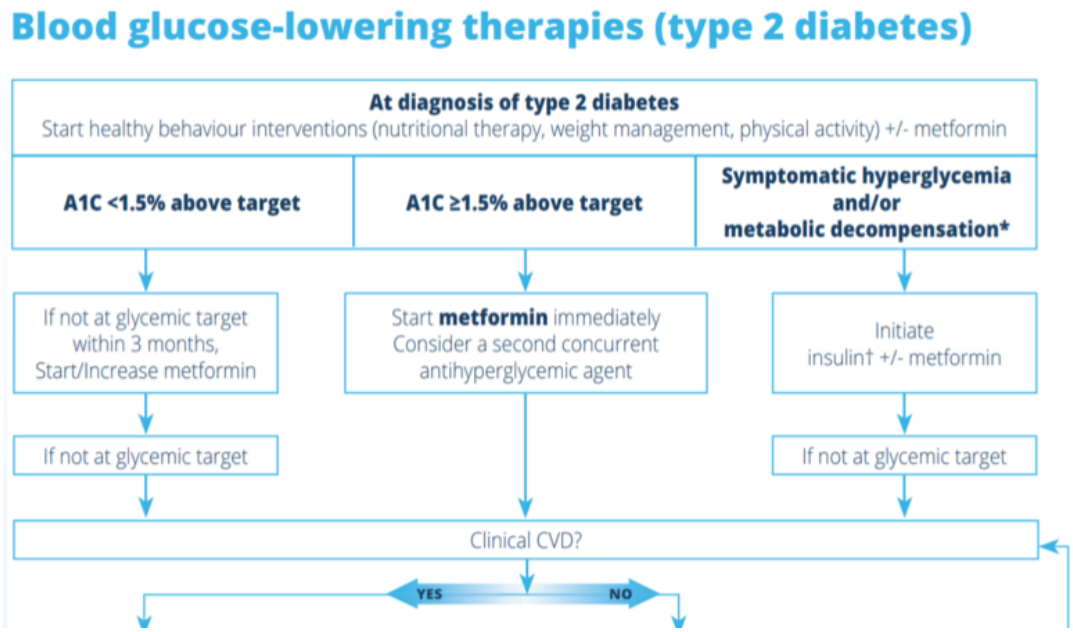
- Must correct hyperglycemia & acidosis
- IV fluids & electrolytes for rehydration
- IV insulin to gradually decrease blood glucose
- Rapid decrease in blood glucose can exacerbate condition

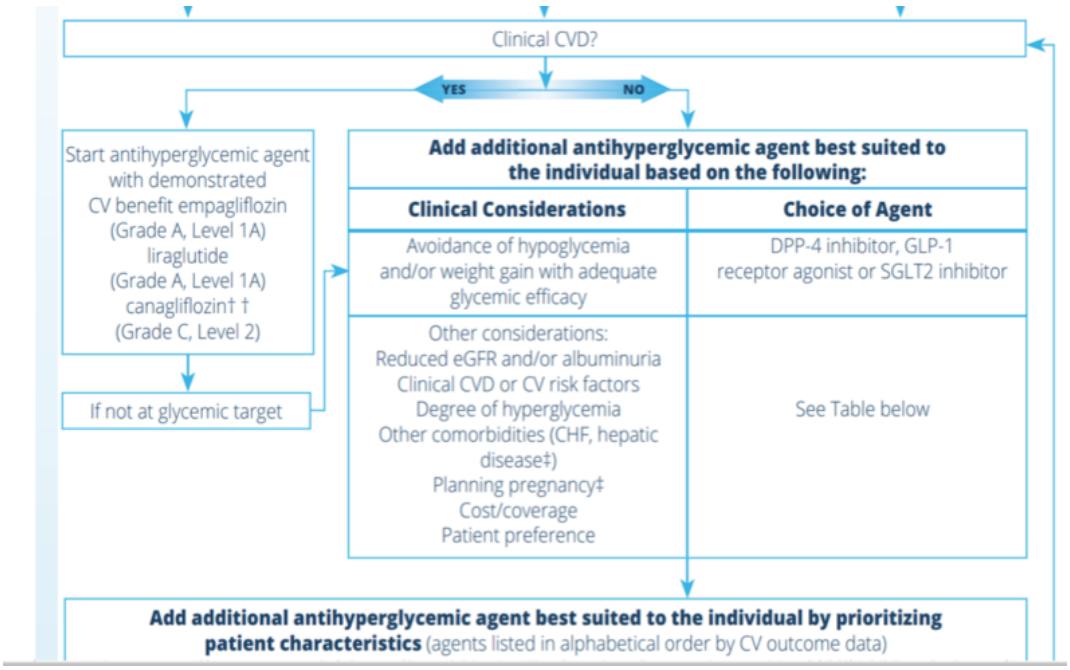


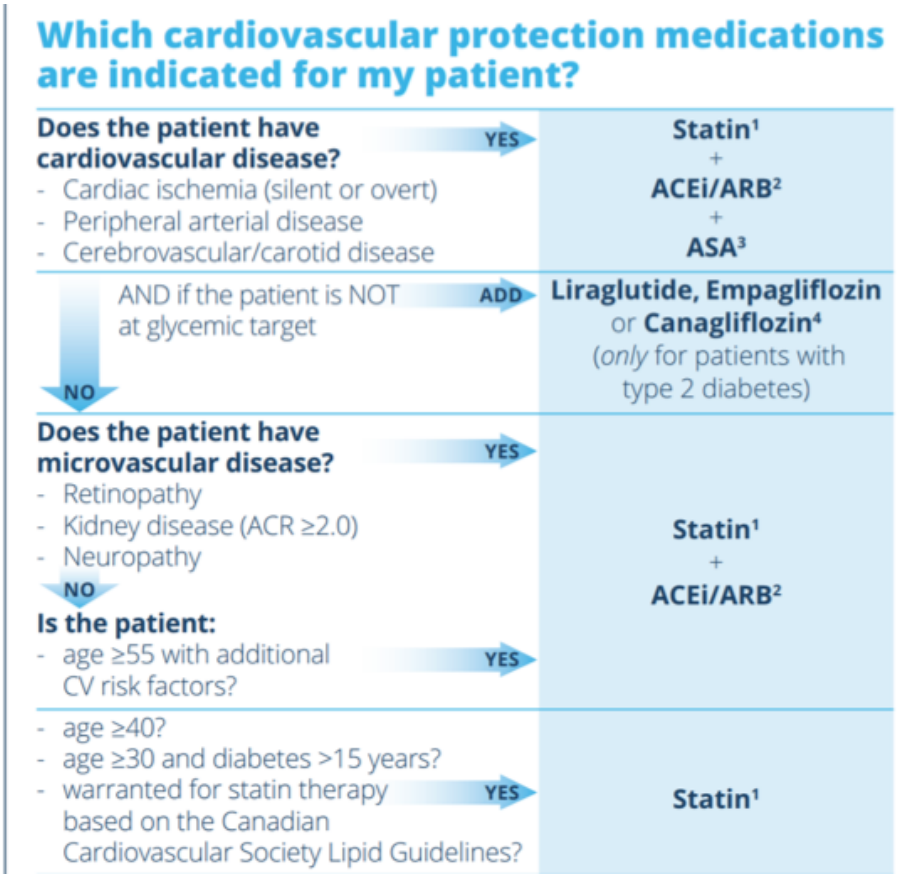
Severe hypoglycemia therapy:

- When self-treatment with oral carbohydrates fails:
  - IV glucose = preferred option (immediate effect)
  - If not an option (ex. Unconscious at home) → glucagon subcut

Canadian Diabetes Guideline
See following site: http://guidelines.diabetes.ca/docs/CPG-quick-reference-guide-web-EN.pdf







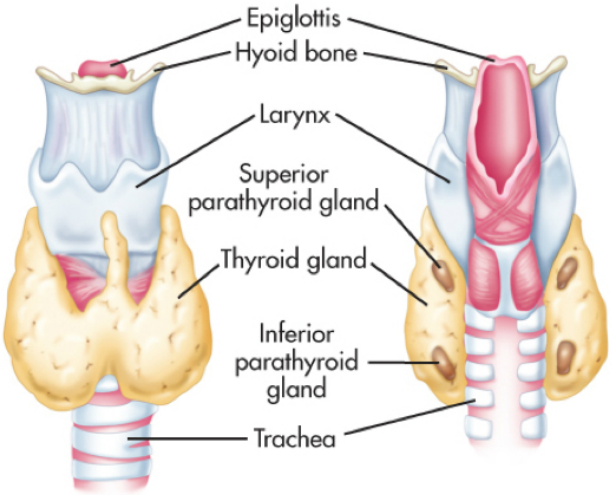
Key Nurse Takeaway

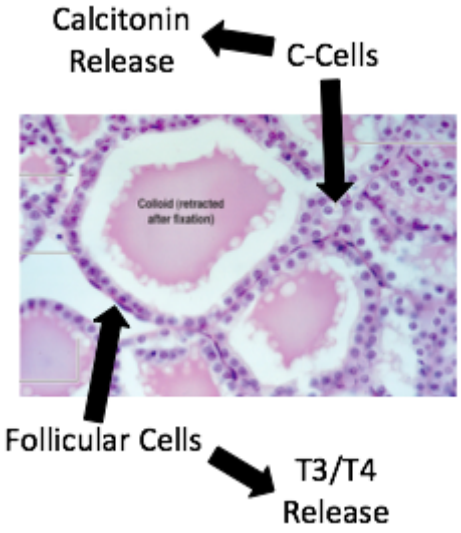
- Risk of hypoglycemia with insulin vs. oral antidiabetic Rx
- Insulin increases uptake by almost all cells (except brain!!!)
- Oral antidiabetic Rx do not influence insulin levels as much
    - Works via decreasing glucose entry into the circulation so levels don't drop drastically, they simply stop increasing too much.
- Patients are often confused with this and confuse the causal relationship between meal intake and insulin or metformin administration
    - They must eat because they took insulin
    - NOT take insulin because they ate

THYROID DISORDER DRUGS (Ch. 58)

Pathophysiology Review

Thyroid Hormones (TH)





Thyroid Hormone Regulation

TRH secretion → release of glycoprotein TSH

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TSH binds to TSH-receptors on follicular cells

↓

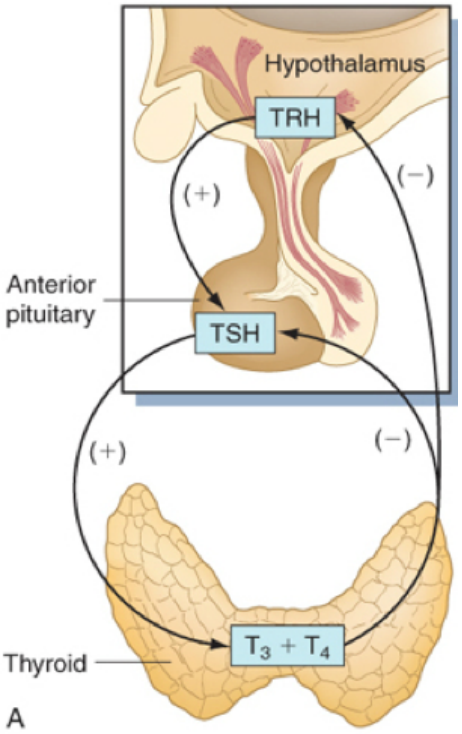
Increases release of T3 & T4

+

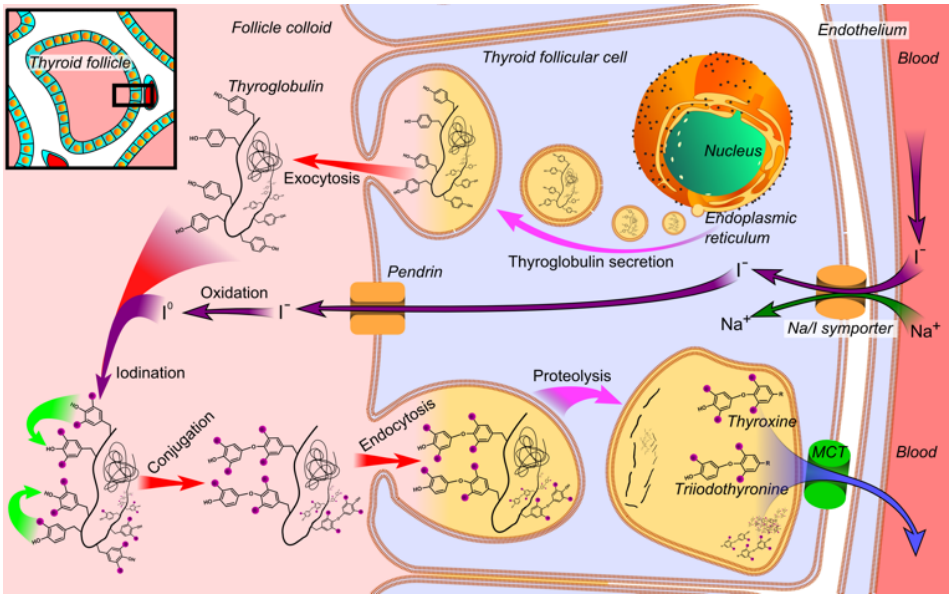
Increased iodine uptake & T3/T4 synthesis

+

TSH increases thyroid gland hypertrophy & hyperplasia



Thyroid Hormone Synthesis



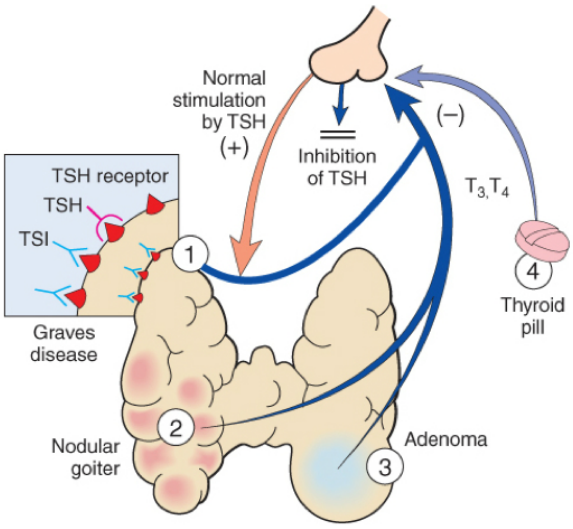
Thyroid Hormone Functions

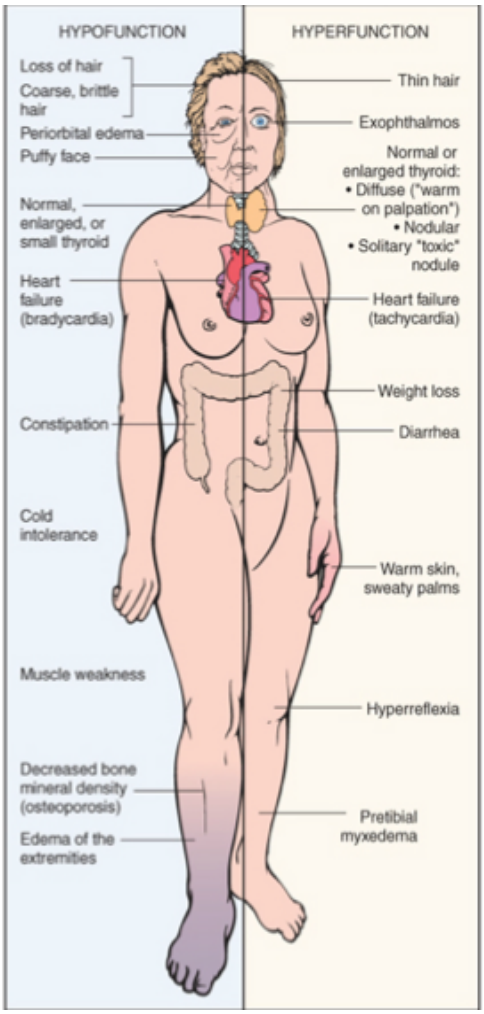
- TH are amines but act like steroids!! → alter protein synthesis
- T3-T4 transported bound within the bloodstream → T4 metabolised into T3 → T3 binds intracellular receptors

Main effects of T3 & T4:

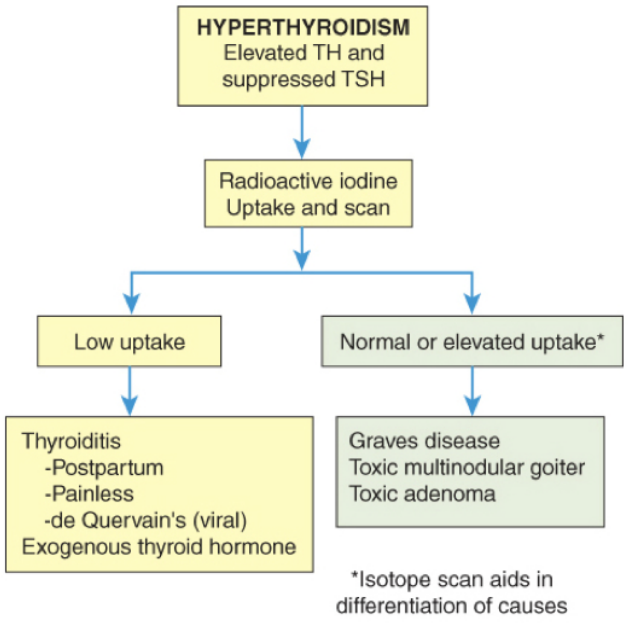
- Fetal + infant CNS development (neurogenesis)
- Increased basal metabolic rate (BMR) → especially lipid turnover & cholesterol synthesis
- Increased BMR → increased body heat & oxygen consumption
- Increased GH secretion + skeletal/muscular maturation
- Pathophysiological levels → increased cardiac contractility, HR & CO

Hyperthyroidism





Hyperthyroidism Evaluation



Graves Disease

- 50-80% of thyrotoxicosis
- Type-II hypersensitivity reaction
- Thyroid-stimulating immunoglobulins (TSI) → thyroid hyperplasia + T3/T4 synthesis = toxic goiter.
- Symptoms:
    - Exophthalmos (50% cases) - TSI interact with ocular fibroblast receptors
    - Visual impairments & pain
    - Fat accumulation
    - Edema
    - Inflammation
    - Subcutaneous swelling & erythematous skin
    - Pretibial myxedema/Graves dermopathy (smaller fraction of cases) - fibroblasts & T-cells stimulate hyaluronic acid production

Nodular Thyrotoxicosis & Thyroid Storm

Nodular Goiter:

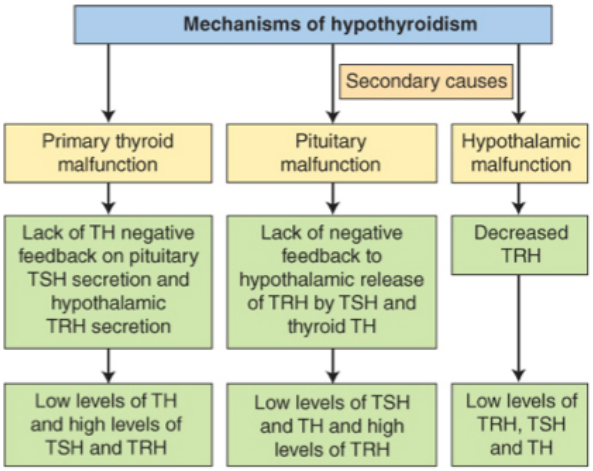
- Thyroid hyperplasia in response to increase TSH (ex. Puberty; pregnancy; iodine-deficiency)
- Follicular cells continuing to secrete excessive T3/T4 after response = toxic nodules
- Increased risk of thyroid cancer
- No exophthalmos or pretibial myxedema
- Other manifestations develop slowly

Thyroid storm or crisis:

- Drastic increase in T3/T4
- Rare but potentially lethal
- Patients with undiagnosed or mistreated
- Hyperthyroidism = increase risk
- Cause: acute stress (ex. Surgery, infection, emotional distress)
- Manifestations: hyperthermia, tachycardia, delirium

Hypothyroidism

- Normal TH + increased TSH = **subclinical hypothyroidism**
- Hashimoto Disease (autoimmune)
- surgery/radiotherapy
- Congenital
- Iodine deficiency → rare in developed countries thanks to enriched salt!



Hypothyroidism Manifestations

- Edema
- Tongue thickening (myxedema) → slurred speech
- Cretinism → hypothyroidism at birth or childhood
    - Mental and physical retardation

BACK TO PHARM

General Strategy

Adult hypothyroidism

- Lifelong hormone replacement
- T4 alone > T3/T4 combination
- Adequate replacement eliminates all symptoms

Infantile Hypothyroidism

- Initiate replacement ASAP (because it has an effect on the brain)
- Within days of birth: normal development
- 3-4 weeks delay: some permanent disabilities
- Assessment after 3 years: determine if permanent therapy necessary

Grave's disease (hyperthyroidism)

1. Surgical thyroidectomy + replacement
2. Thyroid destruction via radioactive iodine
3. Anti-thyroid drug to decrease synthesis

- Best option for adults is #2
- Best option for younger patients = #3
- For exophthalmos: surgery or glucocorticoids
- Beta-blocker = adjunct therapy (quick action!!)

Toxic Nodular Goiter (hyperthyroidism)

- #1 or 2 preferred

Levothyroxine (T4)

General Information:

- Should be taken on an empty stomach in the morning
- Rapidly converted into T3 by the body
- 99.9% protein-bound → Half-life = 7 days → therapeutic delay
- Indication: all forms of hypothyroidism
- Therapeutic doses = very few adverse effects
- Toxic doses = hyperthyroidism symptoms
- Biggest drawback: several known drug interactions
    - Ex: warfarin, catecholamine, GI drugs

Therapeutic Goal

- Compensate deficiency precisely (dosage changes from pt to pt)
- Use clinical symptoms + Lab tests to adjust dosage
- TSH levels 6-8 weeks post-inhibition = best test
    - Low TSH levels are indicative of treatment success
- Symptomatic relief DOES NOT EQUAL cure

Nursing Consideration: Brand Equivalence

- Several brands/generic formulations: no one can own a patent on a hormone our bodies produce.
- Debate over the equivalence & interchangeability
- Recommendations:
    - Maintain patients on same product when possible
    - If switch: retest TSH serum at 6 weeks & adjust

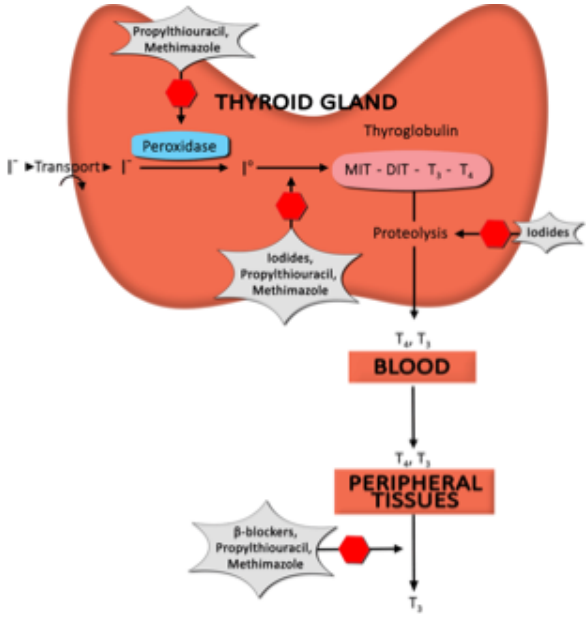
Lyothyronine (T3)

- Short action & increased cost
- Only better if require speedy onset
    - Ex: myxedema coma

Antithyroid Drugs: Thionamides

- Decrease thyroid hormone synthesis

	Methimazole	Propylthiouracil (PTU)
Kinetics	Half-Life long enough for 1-day dosing Very Lipid-Soluble → Placenta X-ing	Short Half-Life → 2-3x/day Poor Placental X-ing
Therapeutic Uses	Graves' Disease Radiation Therapy Adjunct Thyroidectomy Preparation Thyrotoxic Crisis Prophylaxis	**When PTU > Methimazole:** Thyroid Storm 1st Trimester Pregnancy Methimazole Intolerance
Adverse Effects	Avoid during 1st Trimester & Breast-Feeding Monitor for **Agranulocytosis (↓ WBC)** Hypothyroidism	Severe Hepatotoxicity ↑ Risk in Infants Agranulocytosis



- Mechanism of Action: used to decrease thyroid hormone synthesis. They block the conversion/introduction of iodine in the thyroid hormone synthesis pathway.

Radioactive Iodine (^{131}I)

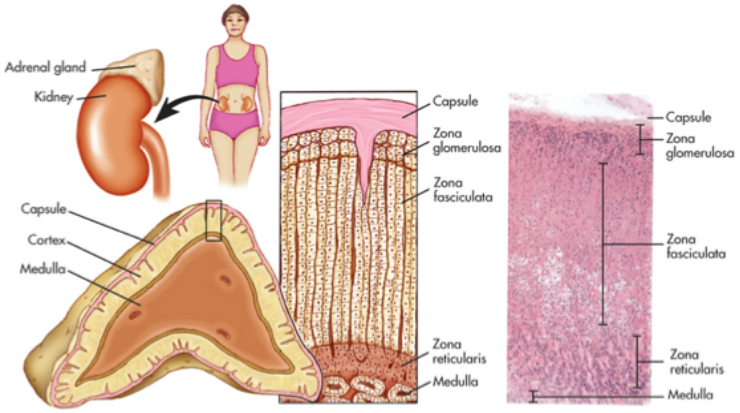
- Partial destruction of thyroid tissue
  - Damage to thyroid only
  - Delayed hypothyroidism
- Graves disease cured with single treatment in 66% patients
  - Delayed therapeutic effect → maximal = 2 months
- Indication for: adults with hyperthyroidism
- Inappropriate for: young children, pregnancy & lactation
- Advantages: low cost, no surgery, no risk of death, no effect on other tissues
- Disadvantages: delayed effect onset, delayed hypothyroidism (90%)
- Other usages:
  - Smaller doses → thyroid function diagnostic
  - Higher doses → thyroid cancer

DRUGS FOR ADRENAL CORTEX DISORDERS (Ch. 60)

Pathophysiology Review

Adrenal Glands

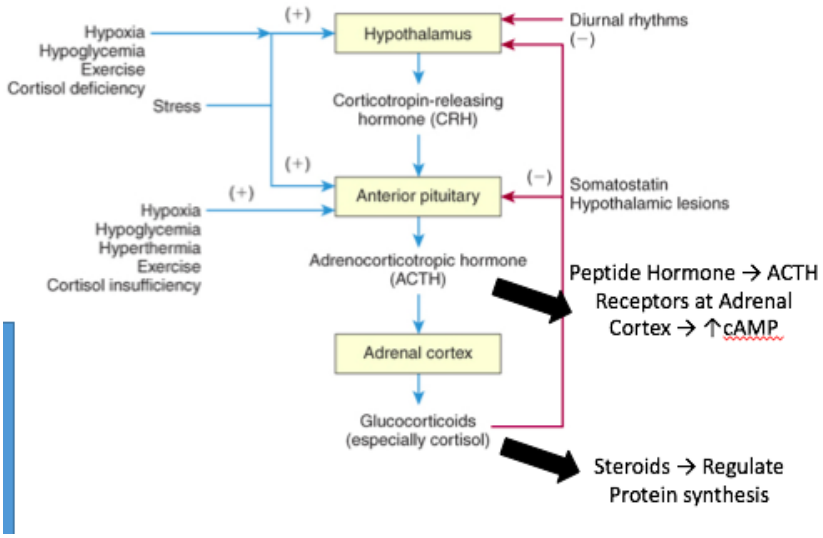
- 2 glands in 1!
- Cortex → glucocorticoids, mineralocorticoids, & a bit of estrogen & testosterone
    - Zona fasciculata → glucocorticoids (cortisol)
    - Zona glomerulosa → mineralocorticoids (aldosterone)
- Medulla → Epinephrine (adrenaline) & Norepinephrine



Glucocorticoids (GCC)

3 main regulators:

1. Cortisol levels
2. Stress
3. Diurnal rhythms

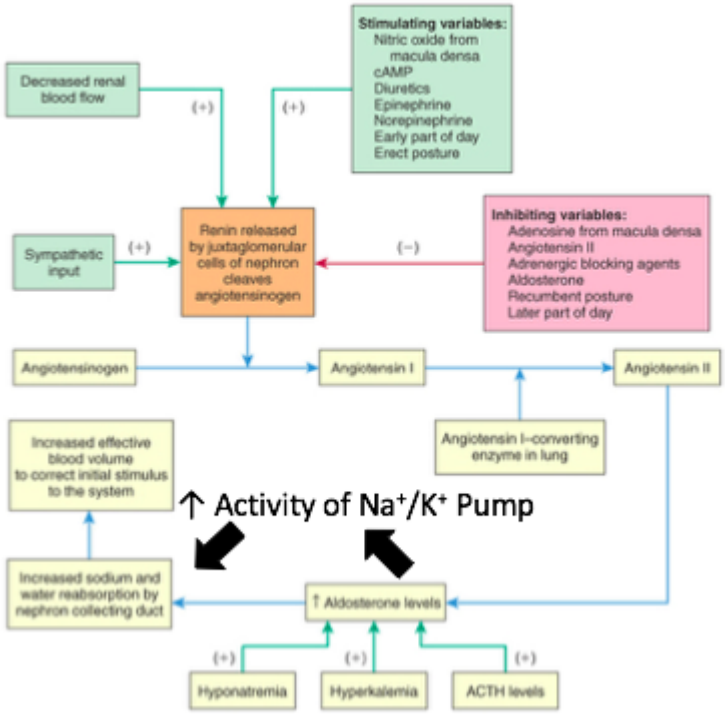


Main effects:

- Increase blood glucose
- Increase glycogen & protein catabolism
- Increase neuronal functions
- Powerful anti-inflammatory
- Anti-growth (ex. Decreased bone deposition)

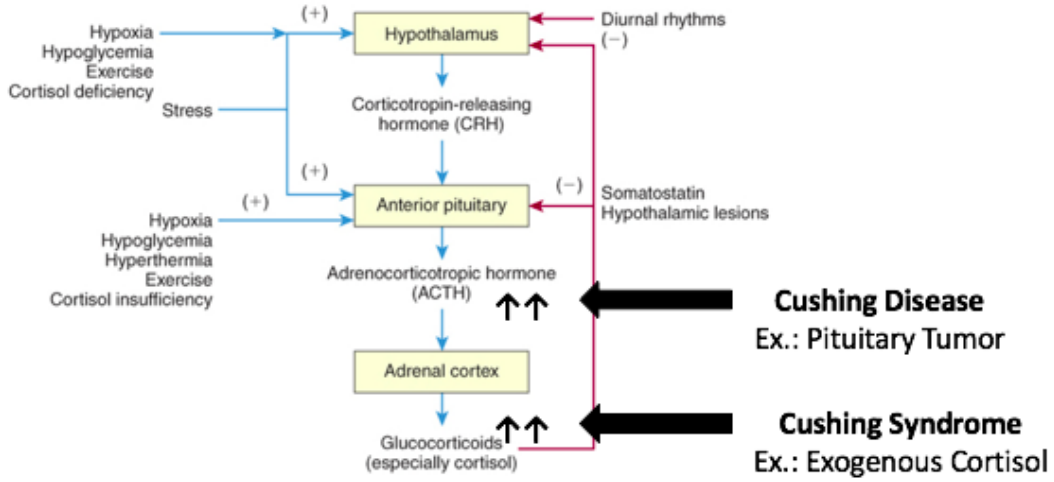
Aldosterone

- Main regulator = renin-angiotensin system activation
    - Decreases blood volume
    - Increases sympathetic input & ACTH
    - Hyperkalemia or hyponatremia
- Main effects → ionic regulation
    - Increased Na+ & water retention
    - Increased K+ & H+ excretion



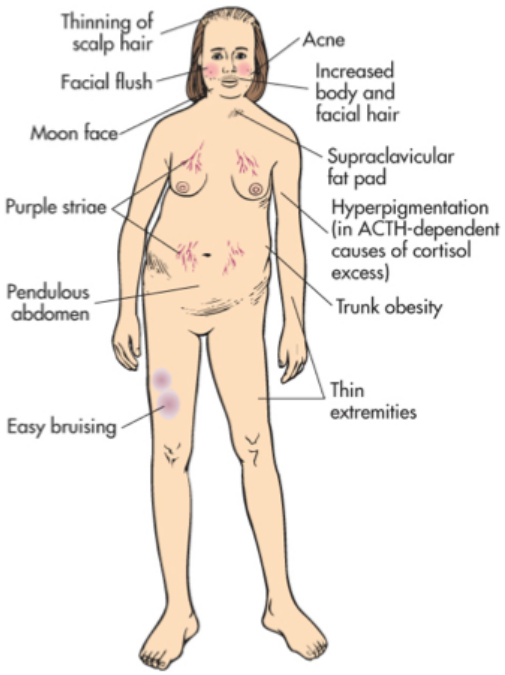
Cushing's Disease vs. Syndrome

- High levels of cortisol
- HP-adrenal gland axis shut down
- No circadian rhythms & stress response



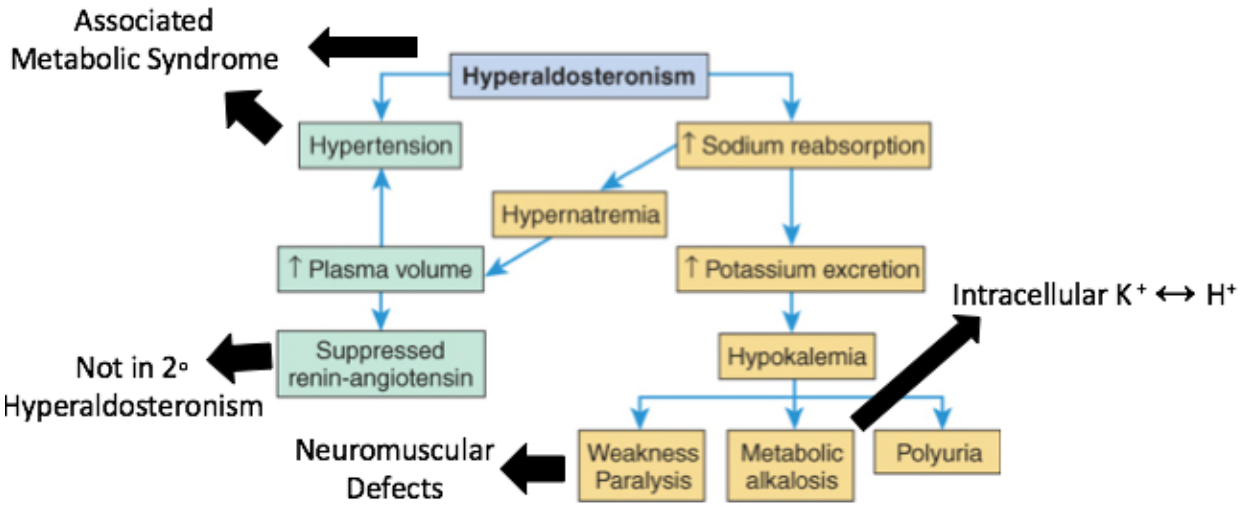
Cushing's Manifestation

- Insulin-resistance → diabetes in 20% of cases
- Increased catabolism → osteoporosis & muscular atrophy
- Hypertension → increased risk of metabolic syndrome & CVS events
- Immunosuppression → increased infections
- Physical Sx:
  - Weight gain
  - Moon face
  - Acne
  - Increased body/facial hair



Hyperaldosteronism

- 1° hyperaldosteronism = adrenal cortex tumor
- 2° = extra-adrenal stimulus (ex: increased renin/angiotensin II)



Addison's Disease

- Insufficient adrenal stimulation (ex. Exogenous cortisol → decreased ACTH) or insufficient cortisol synthesis or secretion
- Most common cause = autoimmune destruction of adrenal cortex
  - Can lead to adrenal atrophy & decreased cortisol or aldosterone or both
- Main manifestations:
  - Hypocortisolism
  - GI distress → nausea, vomiting, diarrhea
  - Hypoglycemia → fatigue, weakness, confusion

- Severe hypotension → vascular collapse & shock

BACK TO PHARM

Adrenocortical Alterations Management

Red = Adrenal Hypofunction vs. Green = Adrenal Hyperfunction

Pathology	Strategy
Cushing's Syndrome	**Adrenal Adenoma:** Surgical Removal + Hormonal Replacement **Pituitary Adenoma:** Partial Surgical Removal to ↓ ACTH Levels Ketoconazole ↓ Cortisol Synthesis but High Toxicity (not preferred)
Primary Hyperaldosteronism	**Adrenal Adenoma:** Surgical Removal + Hormonal Replacement **Bilateral Adrenal Hyperplasia:** Aldosterone Antagonists (ex.: Spironolactone)
Addison's Disease	**Hormonal Replacement (ex.: Hydrocortisone)**
Secondary & Tertiary Adrenal Insufficiency	**Glucocorticoid Replacement Only** Mineralocorticoid levels are usually ok!
Acute Adrenal Crisis	**Rapid Replacement of: Fluid + Salt + Glucocorticoids** Ex.: Hydrocortisone IV Bolus → Saline + Dextrose IV Infusion
Congenital Adrenal Hyperplasia	Genetic Enzyme Deficiency → ↓ Glucocorticoid → ↑↑ ACTH Release **Exogenous Hydrocortisone → ↓ ACTH → Stabilise Symptoms**

Adrenocortical Agents

Drug	Hydrocortisone	Prednisone	Dexamethasone
Action	Glucocorticoid & Mineralocorticoid activity	Only available mineralocorticoid	Glucocorticoid activity only
Replacement therapy	Preferred agent for adrenal insufficiency	Alternative to hydrocortisone	N/A
Non-endocrine therapy	Allergic reactions/anti-inflammation cancer therapy	Asthma, COPD, rheumatoid arthritis	Cushing syndrome diagnosis, brain tumors, cancer-induced nausea/vomiting
Adverse effects	Only at high and chronic doses Cushing's syndrome / hyperglycemia / osteoporosis / increased infection risk Hyperaldosteronism if mineralocorticoid activity only		

*At high chronic doses, you can develop Cushing's syndrome: because of the negative feedback loop, the drugs overtime will shut down the adrenal glands, relying exclusively on the drugs.