

Clinical Pharmacology of Corticosteroids

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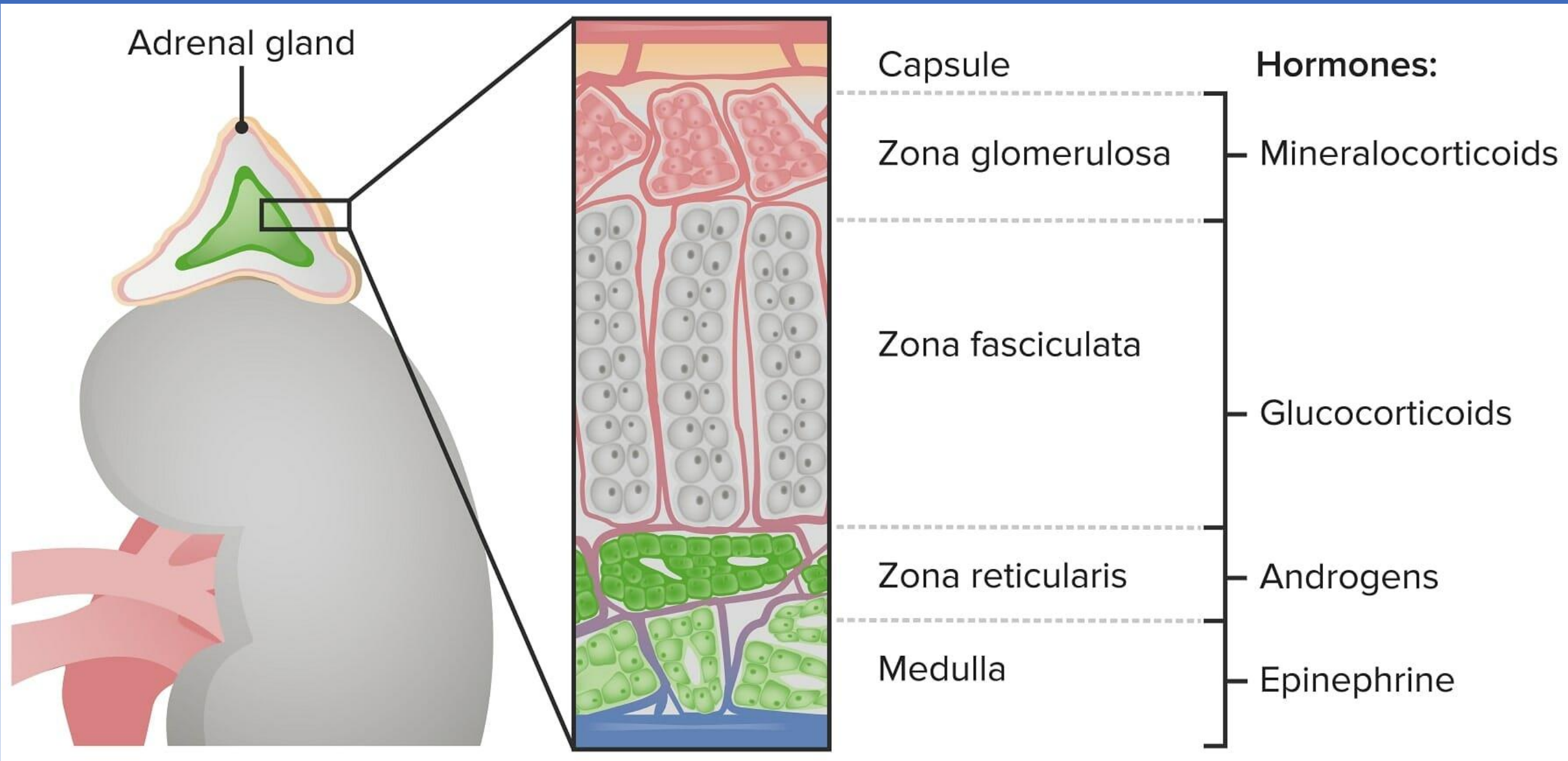


Case

- A 50-year-old woman being treated for SLE. She has long-standing dental phobia & has not been a compliant patient with her oral hygiene. She has rampant decay needs to be converted to dentures. Treatment plan is full mouth ext. alveoloplasty , bilateral mandibular tori removal & 4 implants to support the future prosthesis. She is currently taking 30mg/d of prednisolone.
- How do you go about managing this patient?

Definition

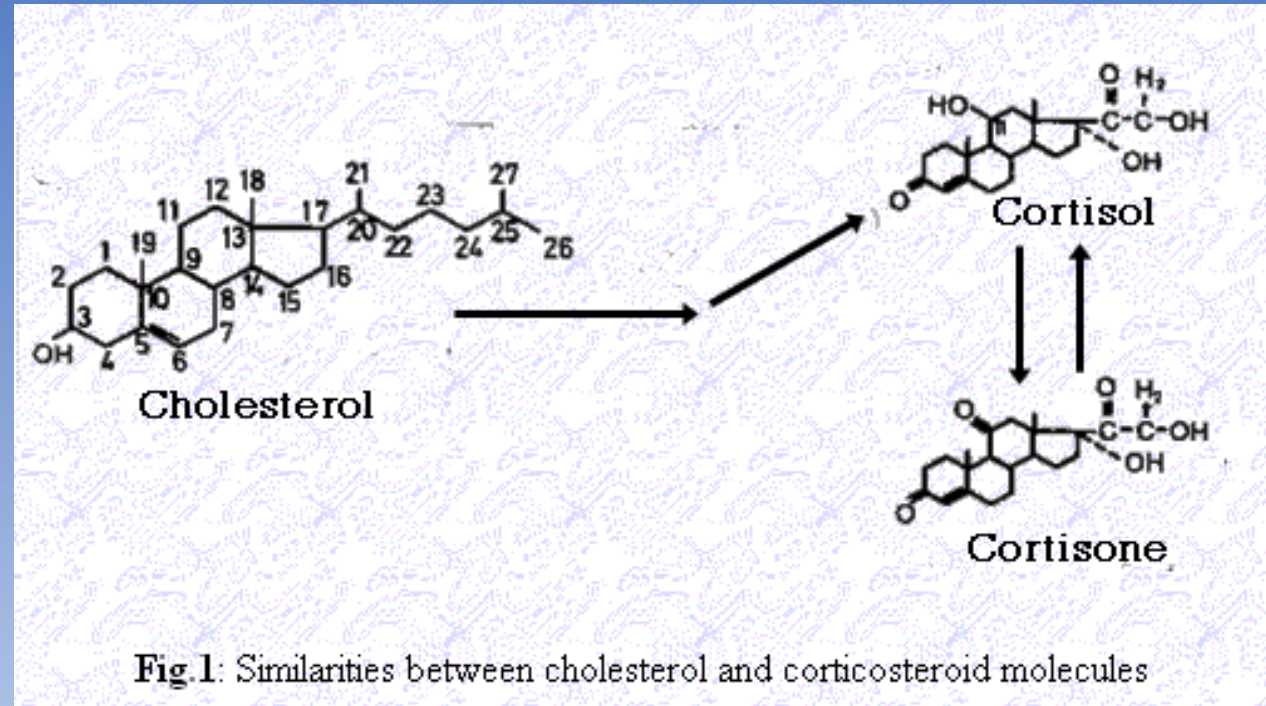
- Corticosteroids are important therapeutic agents used to treat inflammatory disorders or to suppress undesirable immune system actions.
- The term corticosteroid (steroid) is used clinically to describe agents with glucocorticoid activity.



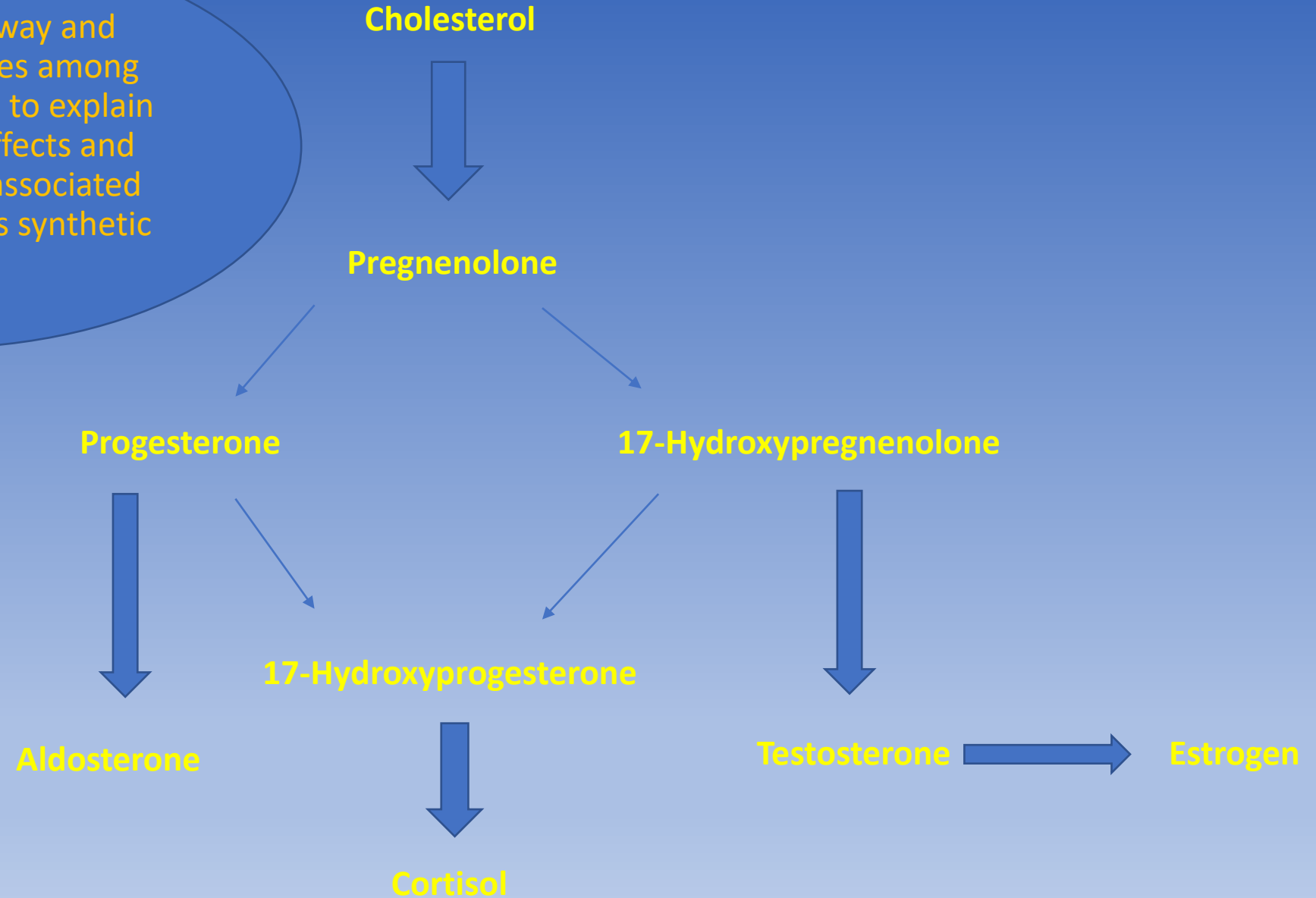
Structure

- All steroid hormones are derived from cholesterol metabolism.

The shared chemical feature of Pregnane.

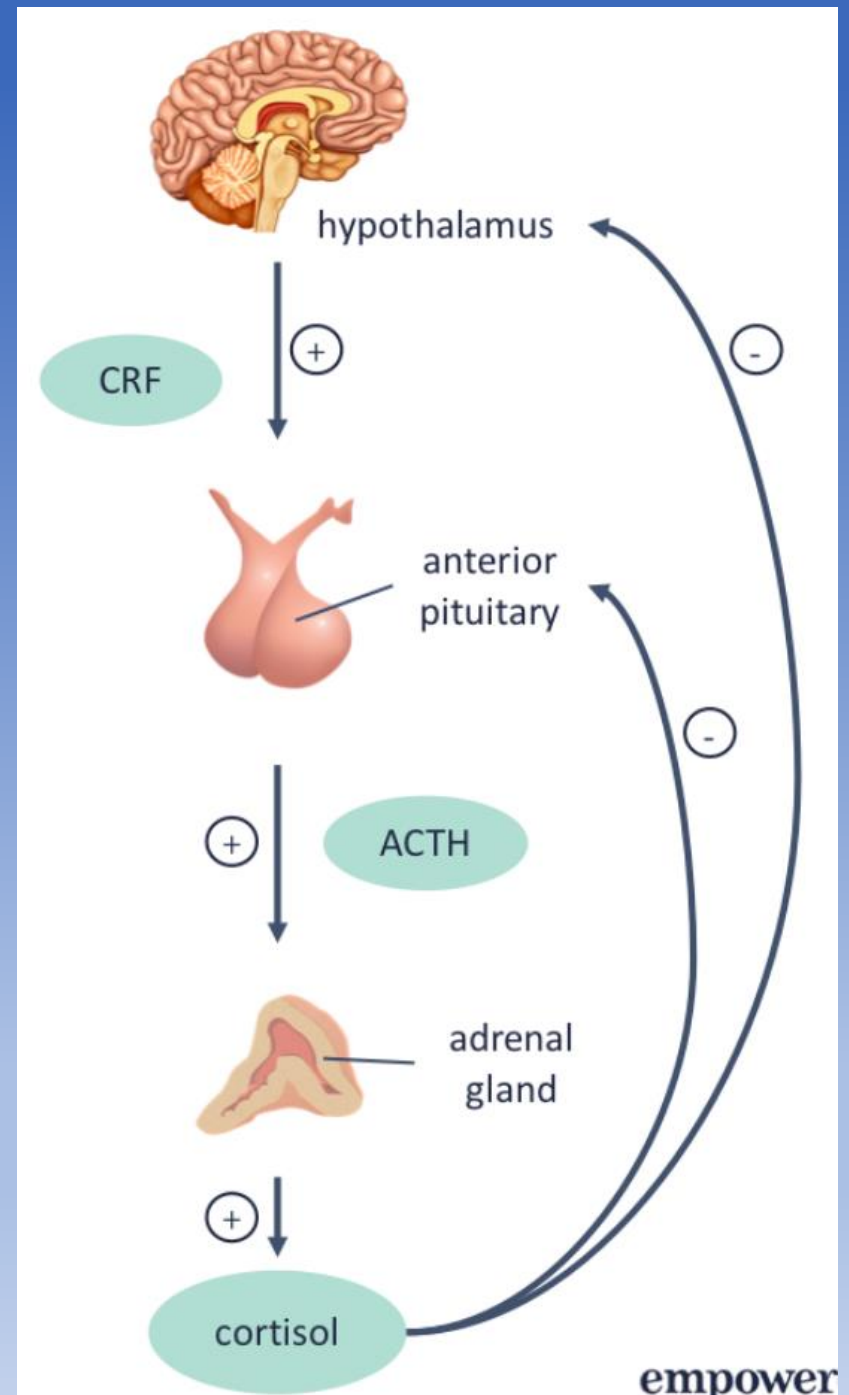


- This common pathway and structural similarities among the hormones help to explain some of the side effects and adverse reactions associated with cortisol and its synthetic analogues.



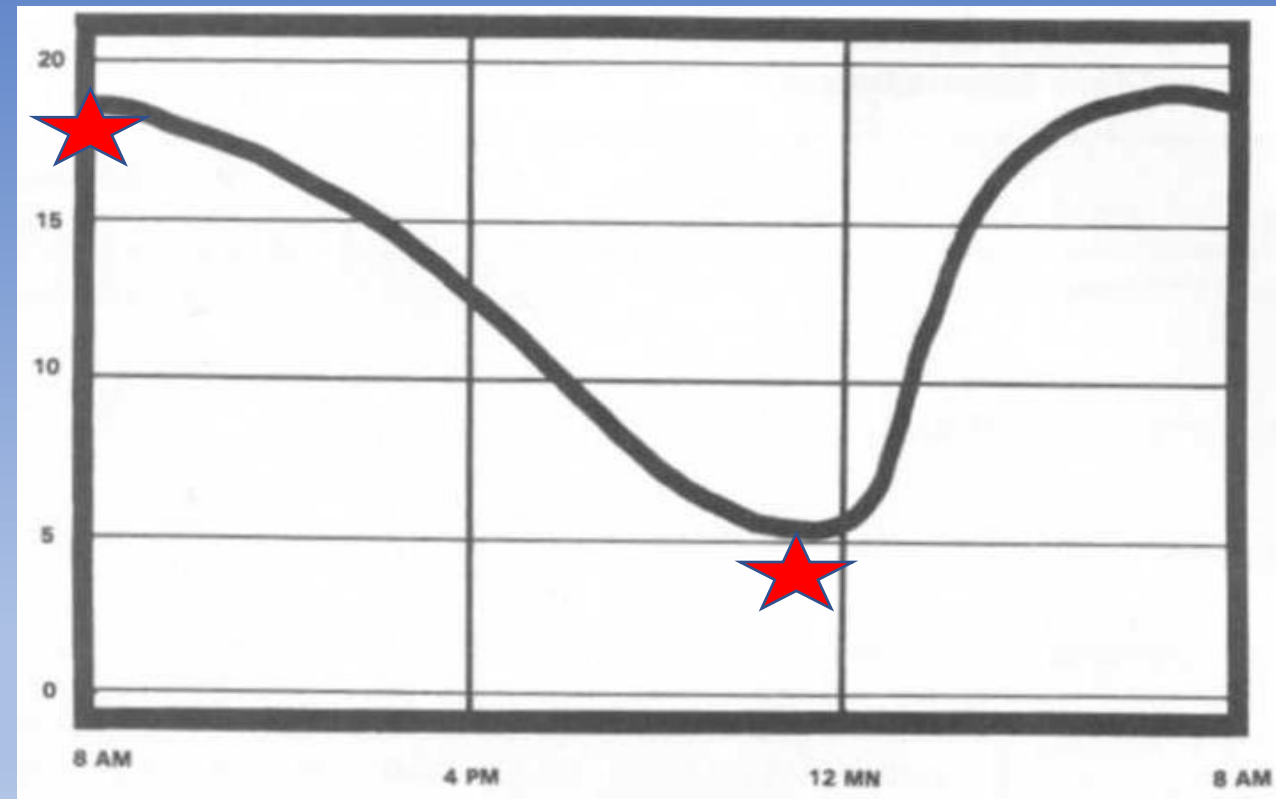
Hypothalamic-Pituitary-Adrenal Axis

Normal function of this axis is important for general health & metabolic functions.



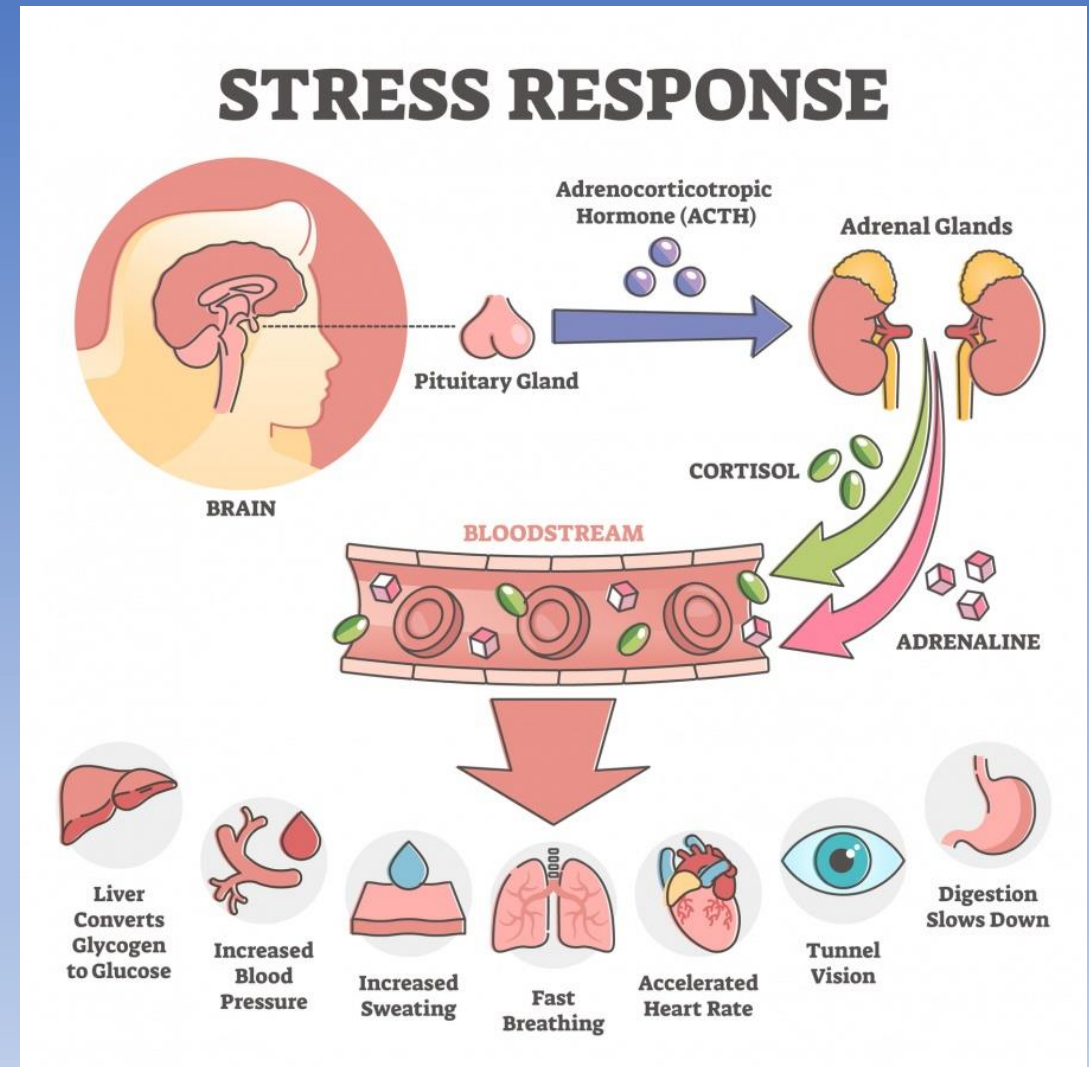
Normal Circadian Rhythm

- Plasma cortisol concentrations are typically highest in the morning (mg/mL) and lowest during the night while sleeping.
- Under non-stressed conditions, cortisol production is approximately 20 mg daily in adults.



Effect of Stress

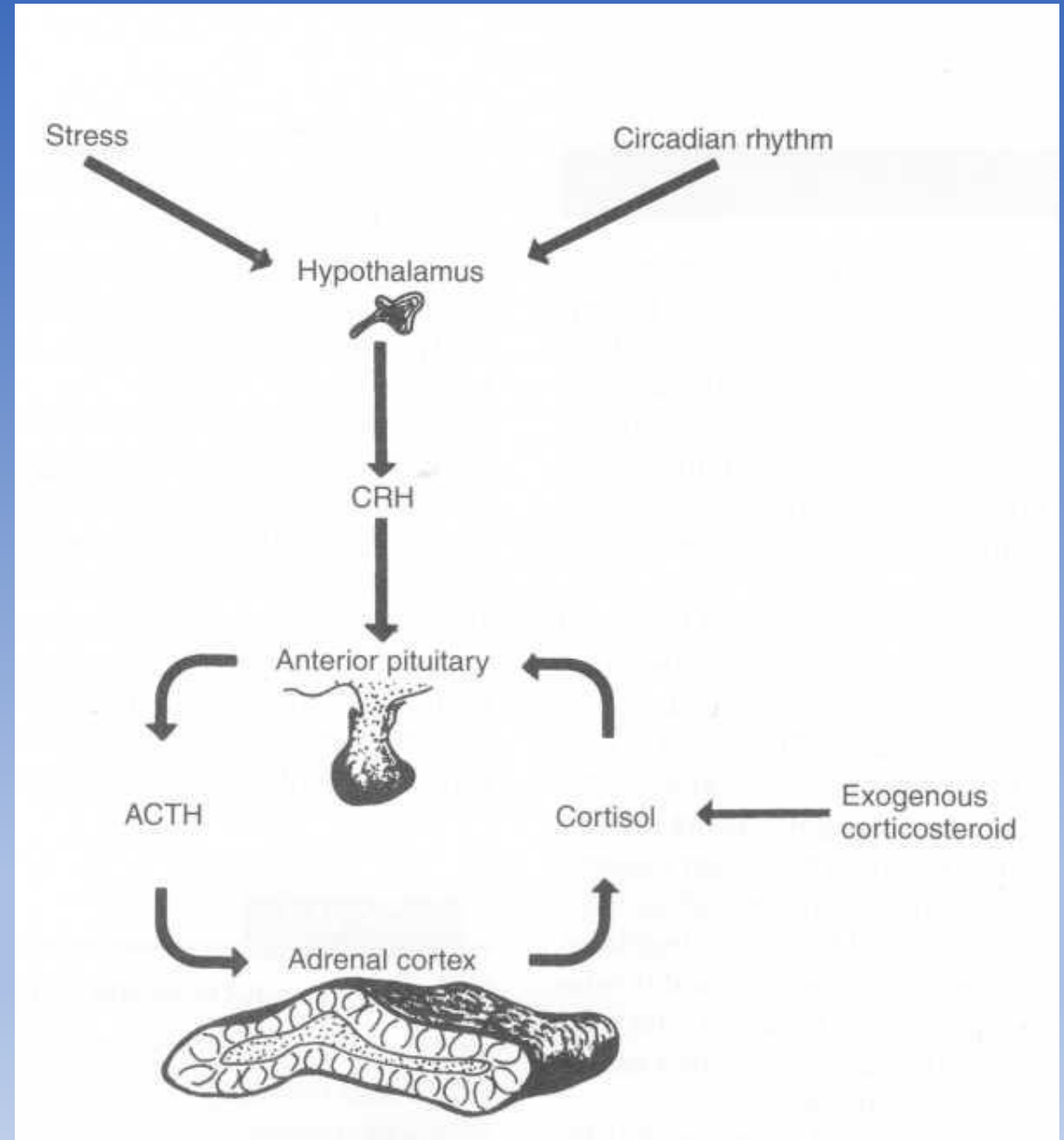
- Physical or psychological stress is associated with increased levels of cortisol.
- Daily production can increase to 150 –200 mg during stress.
- Triggers: surgery (fluid loss) , trauma , fever , burns , hypoglycemia , sepsis
- Pain response after surgery increases requirement for endogenous cortisol.



Adrenal Insufficiency

- In serious chronic disease associated with inflammation, including sepsis, the adrenal gland's ability to produce cortisol at maximal levels is impaired.
- In this “adrenal insufficiency” supplementation with hydrocortisone may be warranted.
- Corticotropin test is an older therapy that has limited clinical utility today (250 microgram exogenous inj. Of ACTH and test the blood 30-60 minutes after. subnormal response in cortisol is suggestive of adrenal insufficiency).

- The risk and extent of HPA suppression is related to the corticosteroid dose, duration, time of daily administration, specific agent chosen, and route of administration.



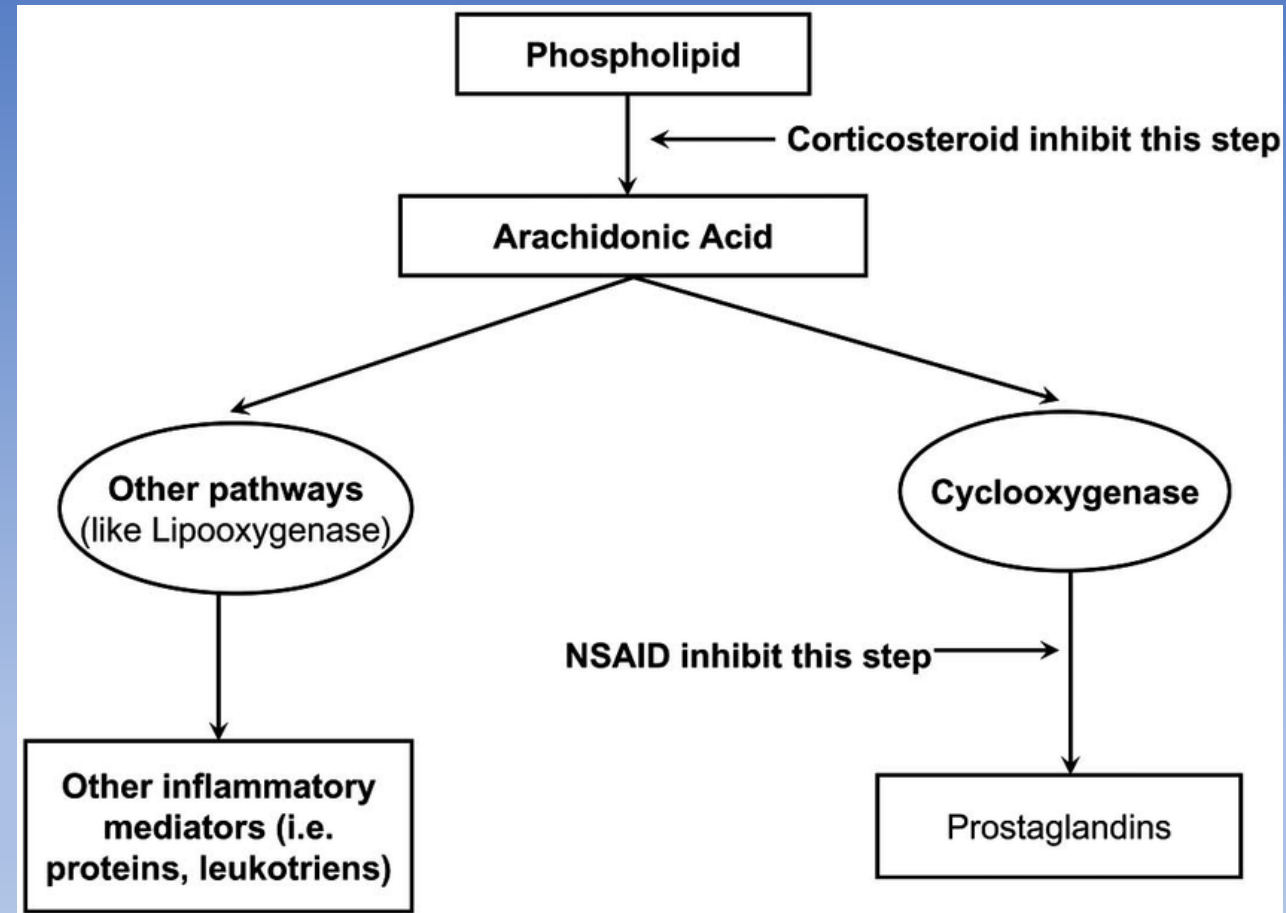
Laboratory Findings

- Serum cortisol level (by RIA)
- ACTH (high in primary adrenal insufficiency and low in secondary)
- Insulin tolerance test (assess the entire HPA axis) when secondary adrenal insufficiency is suspected but this test induces severe hypoglycemia.
- (Aldosterone , renin , Na , K) level

Mechanism of Action

Affect numerous steps in the inflammatory pathway:

- Inhibition of phospholipase A2.



Anti-inflammatory Effect

- In general , glucocorticoids support cell membrane integrity which results in :
- Suppressing vasodilation & vascular permeability.
- Preventing the release of damaging lysosomes.
- Suppressive effect on lymphocytes , macrophages , Neutrophils (reduce migration to inflammatory sites) , IL-1 , IL-2 , IL-6 , TNF- α

Pharmacodynamics and Pharmacokinetics

- Corticosteroids systemically used are classified according to potency, mineralocorticoid effects, and duration of HPA suppression.
- Potency is expressed relative to hydrocortisone and is useful in determining comparable doses.

Systemic Corticosteroid Properties

Medication	Anti-Inflammatory Potency (relative)	Equivalent Potency (mg)	Duration of Effect (hypothalamic-pituitary-adrenal axis) (h)	Mineralocorticoid Potency (relative)
Short acting				
Hydrocortisone	1	20	8–12	1
Intermediate acting				
Prednisone	4	5	18–36	0.8
Prednisolone	4	5	18–36	0.8
Methylprednisolone	5	4	18–36	0.5
Long acting				
Dexamethasone	25	0.75	>36	0

- Beclomethasone : 8 puffs 4 times a day = 14 mg oral prednisone once a day.
- Structural modifications to the steroid molecule are designed to increase potency as well as to minimize mineralocorticoid effects. More potent agents exhibit fewer mineralocorticoid effects.

- The structural modifications result in improved specificity for the glucocorticoid receptor, a longer duration of receptor occupancy, increased lipophilicity, and reduced aqueous solubility.
- These features are desirable pharmacologic properties to enhance efficacy and safety.

Onset of Action

- The onset of effect of systemic corticosteroids is often delayed for 3– 8 h, regardless of the route of administration.
- This may be related to the intracellular and nuclear effect of these therapies.
- For acute life-threatening conditions?

Duration of Action

- The duration of action for specific corticosteroids is often based on how long effects on the HPA persist, whereas the actual therapeutic action is longer (Because corticosteroid action occurs intracellularly, the effects persist, even when detection in the plasma is absent).

Absorption & Excretion

- The steroids are well absorbed from the GI tract.
- Significant amounts may also be absorbed from sites of local applications (skin , mucous membranes , eye).
- More than 90% are bound to α -globulin (transcortin) & albumin.
- Cortisol is rapidly degraded in the liver , conjugated with glucuronic acid & excreted in urine.
- The major metabolic products : 17-hydroxycorticosteroids & 17-ketosteroids (former to measure the HPA axis).

Medical Management

- Primary adrenal insufficiency with glucocorticoid & mineralocorticoid replacement.
- Secondary deficiency needs lower dose of glucocorticoid replacement than primary form.
- Tertiary deficiency : controlled by alternate day therapy and tapering the dosage.

Cortisol Functions

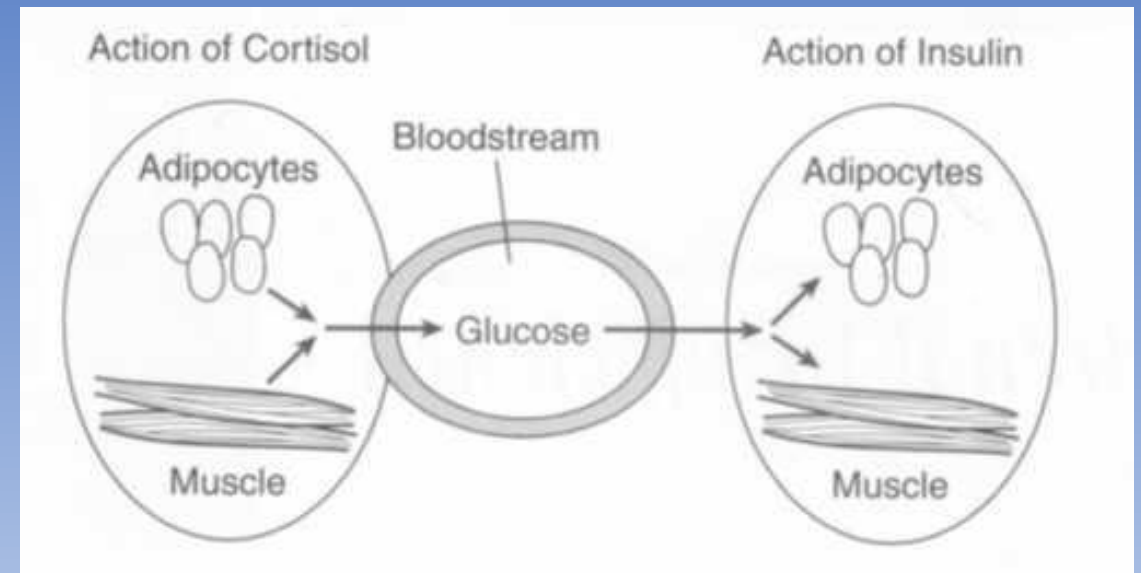
- Cortisol has a variety of physiologic effects in humans , affect nearly every organ and metabolic process in the body.
- Immunity
- Stress
- Homeostasis
- Insulin antagonist
- Lipolysis
- BP↑
- Activate osteoclasts

Effects on Carbohydrate Metabolism

- Glycogenolysis.
- Steroids can increase blood glucose level and insulin resistance.
- An increase in the morning insulin dose may be effective in reducing steroid induced hyperglycemia.
- At the commencement of corticosteroid therapy in people considered at risk of steroid induced diabetes, capillary blood glucose (CBG) testing should be initiated once daily. This should be prior to or following lunch or evening meal when the hyperglycemic effects of morning steroid dosing is likely to be greatest.

Effect on Lipid Metabolism

- Fatty acid mobilization : redistribution of fat from peripheral to central location (centripetal)
- Cutaneous striae on trunk , flushing







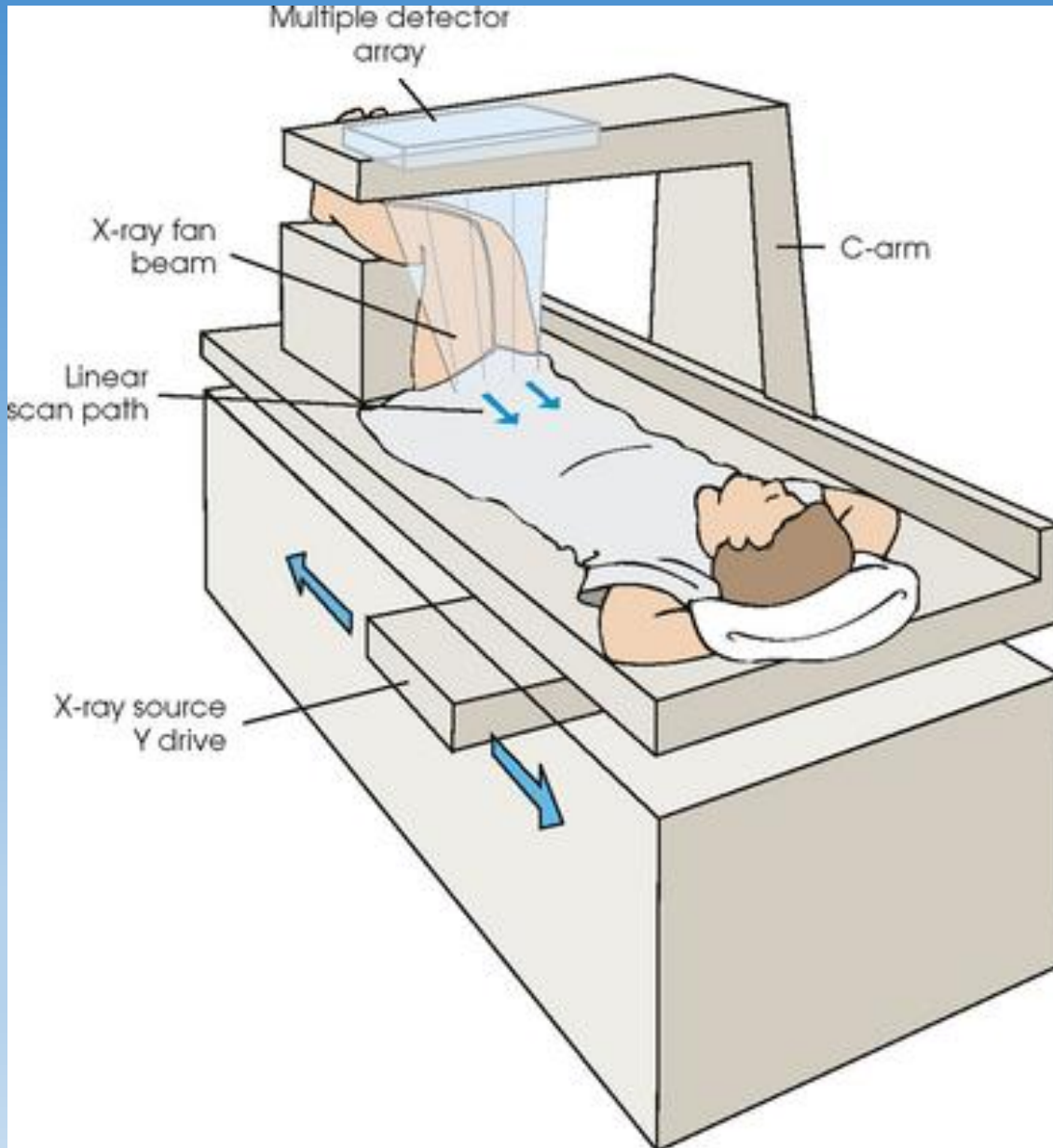
Effect on Protein Metabolism

- Inhibiting protein synthesis=anti-anabolic effect
- Protein wasting (catabolism)
- Retardation of growth
- Increased capillary fragility
- loss of muscle : weakness
- Urinary nitrogen excretion = Negative nitrogen balance

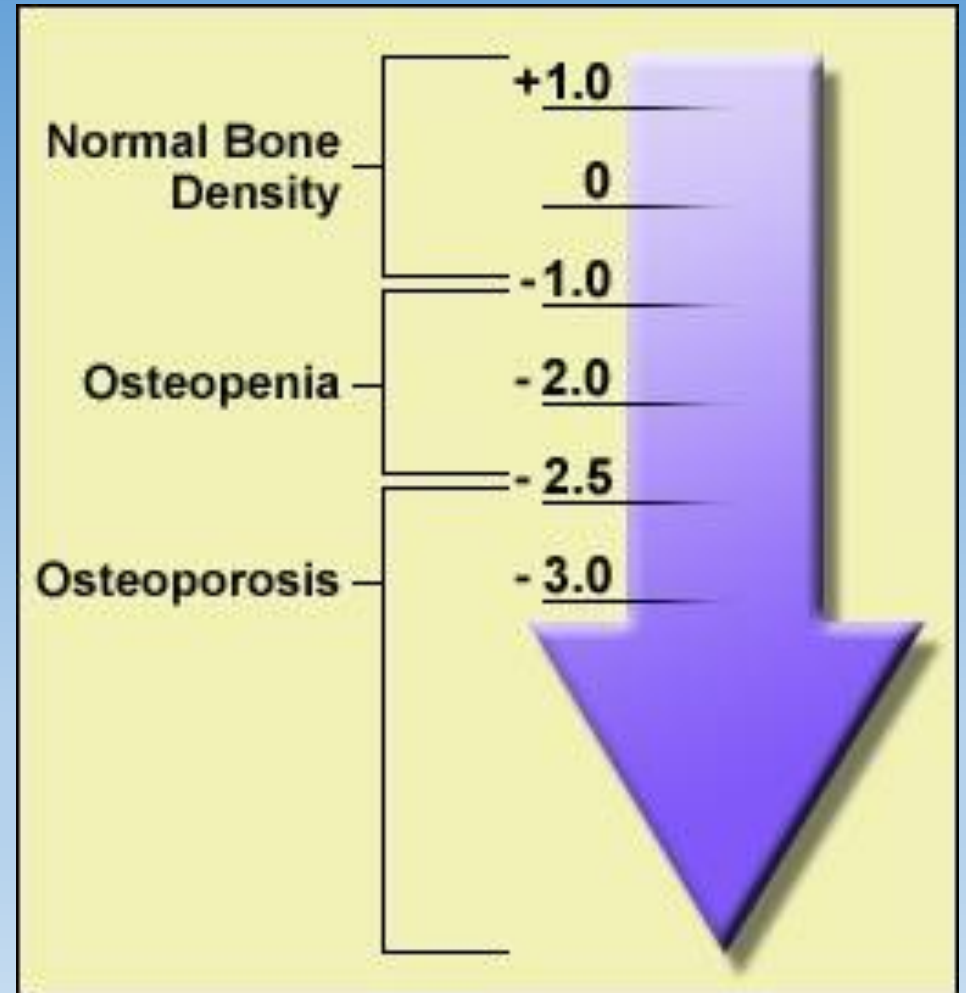
Effect on Bone metabolism

- Reduce Ca absorption
- Bone resorption
- Risk of OP in menopausal women
- 1000-1500 mg/d Ca & 400-800 IU Vitamin D3



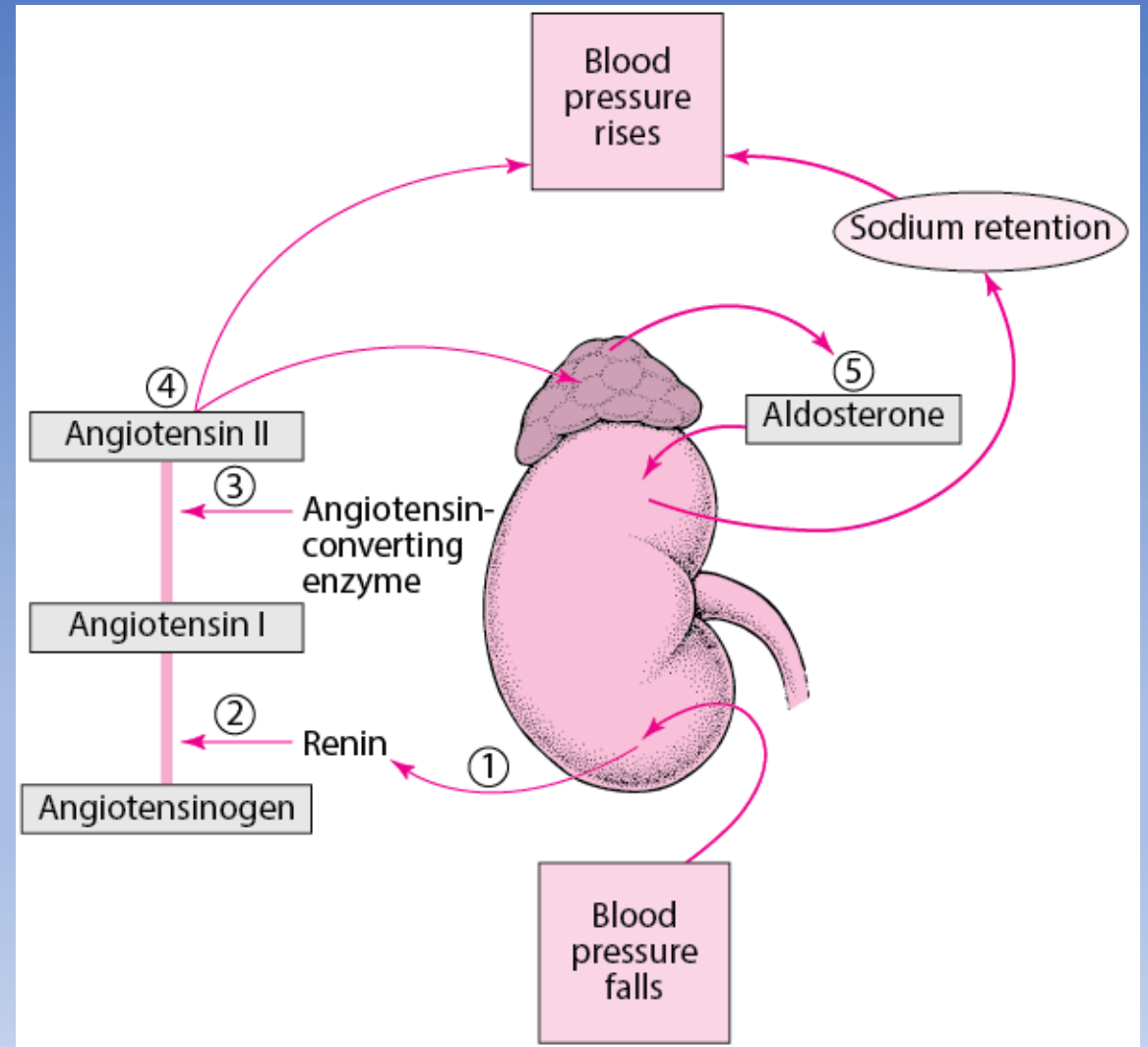


T Score



Effects on Cardiovascular System

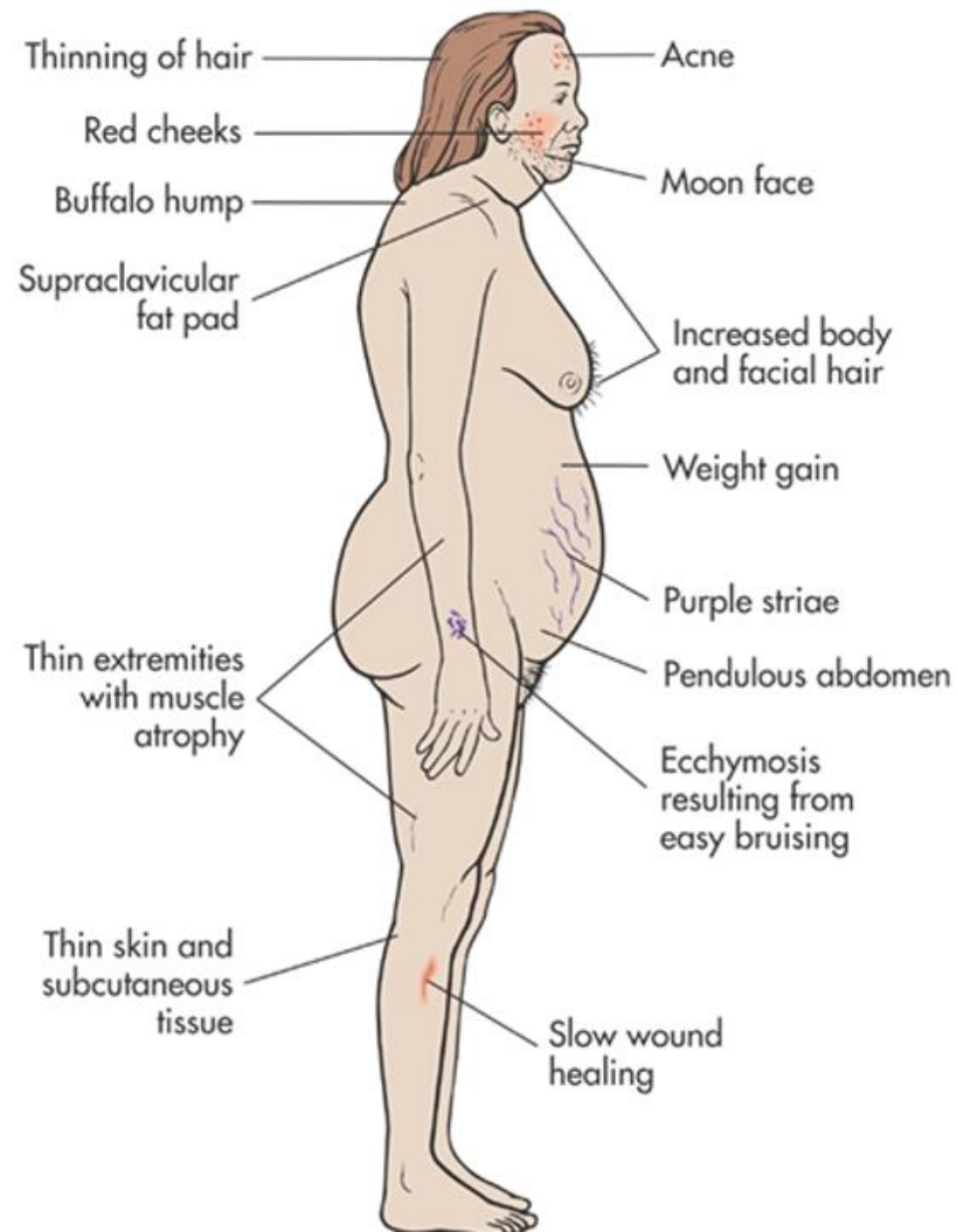
- Mineralocorticoid activity.
- Expanded extracellular fluid volume , edema , hypertension , LVH & CHF



Diet Instruction

- Na restriction
- K supplement
- High protein (1.5g/kg/d)
- low fat diet(limit cholesterol & saturated fats)
- Carbohydrates in the form of fresh fruits and vegetables.
- Small frequent meals

Potassium Rich Foods			
JustChartit.com			
100 Grams  Avocados 485 mg Potassium	100 Grams  Pumpkins 340 mg Potassium	100 Grams  Pomegranate 236 mg Potassium	100 Grams  Banana 358 mg Potassium
100 Grams  Lentils 369 mg Potassium	100 Grams  Mushrooms 318 mg Potassium	100 Grams  Coconut Water 250 mg Potassium	100 Grams  Peas 244 mg Potassium
100 Grams  Watermelon 112 mg Potassium	156 Grams  Spinach 540 mg Potassium	136 Grams  Potatoes 515 mg Potassium	100 Grams  Cucumbers 147 mg Potassium
JustChartit.com			

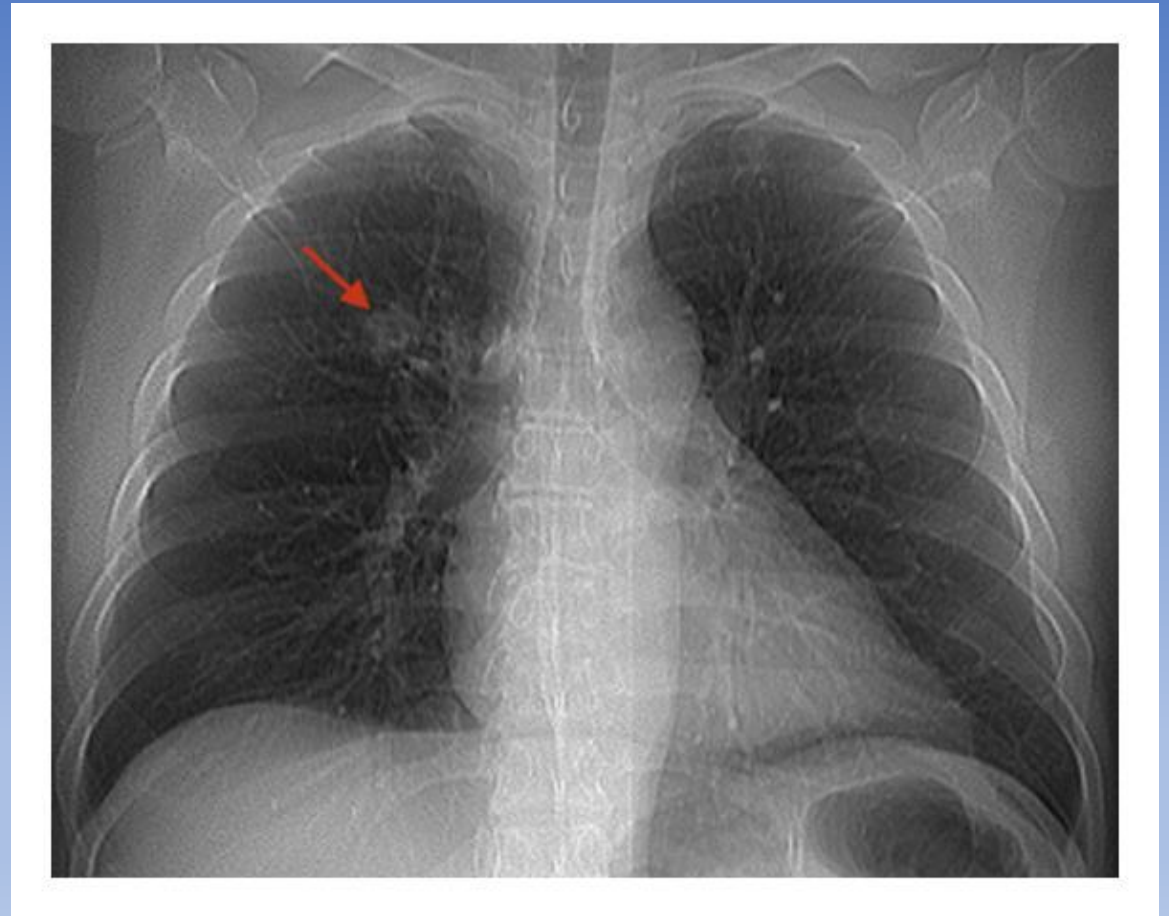


Peptic Ulcer

- Mechanism?
- The risk is higher when NSAIDs or Aspirin are used concurrently.
- Take with food and full glass of water or food.
- Consider prescribing a PPI (before steroid use) for GI protection in people at high risk of gastrointestinal bleeding or dyspepsia.
- Omeprazole Cap 20 mg

Latent Infections

- Re-activation of latent Tuberculosis



- An upper lobe nodule

Other Effects

- Hirsutism
- Poor wound healing
- Aseptic osteonecrosis in the head of femur
- Increased intraocular pressure (children and diabetic susceptible) cataract
- Psychosis (euphoria , insomnia , nervousness , manic-depressive disorder)

Careful Monitoring

- BP
- FBS
- BUN , Creatinine
- Physical activity
- Diet
- BDM , Calcium , Vitamin D prescription
- Omeprazole
- CXR
- Eye examination
- Psychologist consultation?
- In children and adolescents, growth velocity should be monitored.

Adverse Effects of steroids

Hypothalamic-pituitary-adrenal axis suppression
Physical appearance changes: moon facies, buffalo hump, central trunk obesity
Growth suppression
Hirsutism
Acne
Insomnia
Increased appetite
Hyperglycemia
Muscle wasting
Reduced bone mineral density and osteoporosis
Increased bruisability
Atrophy of skin
Immunosuppression
Cataracts
Glaucoma
Weight gain
Psychiatric disturbances

Contraindications of Systemic Steroid Therapy

- Peptic ulcer
- Diabetes mellitus
- Hypertension
- Viral and fungal infections
- Tuberculosis and other infections
- Osteoporosis
- Psychosis
- Epilepsy
- CHF
- Renal failure

Therapeutic Uses

- Pharmacologic use of corticosteroids (exceed the normal physiologic doses) commonly to suppress or prevent signs and symptoms of allergic responses or inflammation, or to suppress an unwanted immune response.
- Less commonly, hydrocortisone is used for physiologic replacement of cortisol when circulating cortisol is deficient due to a primary or secondary adrenal insufficiency (Replacement therapy)
- Even in hepatitis , lymphoma , Crohn , uveitis

Replacement Therapy

- Hydrocortisone is the agent of choice
- Usual dosing strategies to mimic normal cortisol production is 20 mg each morning and 10 mg at 4:00 PM.
- During periods of stress, doses of up to 300 mg daily may be required to prevent signs and symptoms of adrenal insufficiency, including hypoglycemia, hypotension, and cardiovascular collapse
- Fludrocortisone is a synthetic form of aldosterone that can be added to improve overall control of adrenal insufficiency and is generally dosed at 0.1 mg daily.

Systemic Steroids

- Systemic corticosteroids are not considered first-line therapy for chronic management because of the significant adverse consequences.
- Chronic systemic corticosteroid therapy may be required in diseases that are unresponsive to first-line therapies but require close monitoring for the numerous adverse effects.
- Synthetic products with increased potency and minimal mineralocorticoid activity are preferred.

Minimizing HPA Suppression

- Multiple daily doses of corticosteroids for pharmacologic effects are generally required only in acute intensive situations.
- When the same daily dose is used, multiple doses have a higher risk for HPA suppression (eg, 10 mg three times a day has a greater risk than 15 mg twice a day, which has a greater risk than 30 mg daily).

- Daily doses that are administered at times other than early morning have a higher risk for hypothalamic-pituitary-adrenal axis suppression.
- Longer durations of therapy present a higher risk of hypothalamic-pituitary-adrenal axis suppression compared with shorter courses, and agents with a longer duration of action have a higher risk compared with a medium or short duration of action therapies.

Tapering of Corticosteroid Therapy

- General recommendations regarding the need to consider a tapering regimen are:
- (1) Prednisone 30 mg daily (or equivalent) for at least 2 weeks.
- (2) any dose of any systemic corticosteroid for at least 1 month.
- (3) when signs and symptoms of HPA suppression are already present.
- Some clinicians also use tapering to avoid an exacerbation or flare of the condition that is being treated.

- If more than 20-30 mg of hydrocortisone (or its equivalent) is given daily for more than a week results in suppression of HPA axis.
- It is generally unnecessary to taper doses in patients who receive corticosteroids for 5–10 d, which is among the most common regimens used for acute treatment.
- Unfortunately, the use of tapering in these situations can lead to longer exposure to the corticosteroid than necessary and the attendant risks associated with continued use.

Examples of Taper

1. The patient received prednisone 60 mg daily for 3 wk for flare of an autoimmune condition, which is now under control

Tapering strategy (duration of taper was 2 wk): Decrease by 10-mg increments every 2 d until 20 mg daily is reached, then decrease by 5 mg daily every 2 d until finished

2. The patient received prednisone for 3 mo for treatment of idiopathic thrombocytopenic purpura, with a current dose of 40 mg daily and the condition is controlled

Tapering strategy (duration of taper was 7 wk): Decrease by 10-mg increment weekly for 2 wk (20 mg); decrease by 5 mg weekly for 2 wk (10 mg); decrease by 2.5 mg weekly until complete

- When using prednisone as an example, tapering of daily doses of 20 mg adjustments made every few days to weeks, depending on the duration of the taper.
- When a daily dose of 20 mg daily is reached, it is useful for the patient to see the clinician for evaluation about how the tapering regimen is being tolerated. At this point, reducing the daily dose in 2.5- or 5-mg is often successful.
- At any point during a tapering regimen, if the patient develops signs of adrenal insufficiency, then the taper can be stopped or slowed until the patient is stable.

- Tapering of corticosteroids, when appropriate, is an art rather than a science and may require frequent adjustments to the tapering schedule, depending on how the patient is tolerating the taper. Although there is no one correct strategy for tapering, general recommendations based on clinical experience are provided for consideration.

Alternate-day Regimen

- A method for minimizing the adverse effects of long-term systemic steroid therapy.
- This method consists of giving steroids in the morning every other day instead of daily but at a higher dose to maintain an elevated serum level.
- This regimen allows the adrenal gland to function normally during the off day and thus does not tend to cause HPA suppression.

Drug Interactions

- Are often based on cytochrome P450 3A4 isoenzyme interactions. Corticosteroids are metabolic substrates for cytochrome 3A4, so any agents that inhibit or induce 3A4 activity will either increase or decrease corticosteroid activity.

ACE inhibitors	Antagonize hypotensive action of ACE-inhibitors
Amphotericin B	Increased risk of hypokalemia
Antidiabetic agents	Antagonism of blood glucose lowering; hyperglycemia
Antihypertensives	Antagonism of hypotensive effects
Carbamazepine	Increased metabolism of corticosteroid
Cobicistat and ritonavir	Increased concentration of corticosteroid
Estrogens	Increased concentration of corticosteroid
Grapefruit juice	Increased concentration of corticosteroid
Inhaled β_2 agonist	Increased risk of hypokalemia
Ketoconazole and itraconazole	Increased concentration of corticosteroid
NSAIDs, including salicylates	Increased risk for gastrointestinal bleeding
Phenobarbital	Increased metabolism of corticosteroid
Rifampin	Increased metabolism of corticosteroid
Vaccines	Reduced effect of vaccines
Warfarin	Increased or decreased effect of warfarin
Cyclosporine	Increased concentration of cyclosporine

Data from Reference 16.

ACE = angiotensin-converting enzyme

NSAID = nonsteroidal anti-inflammatory drug

Contraindications of Topical Steroids

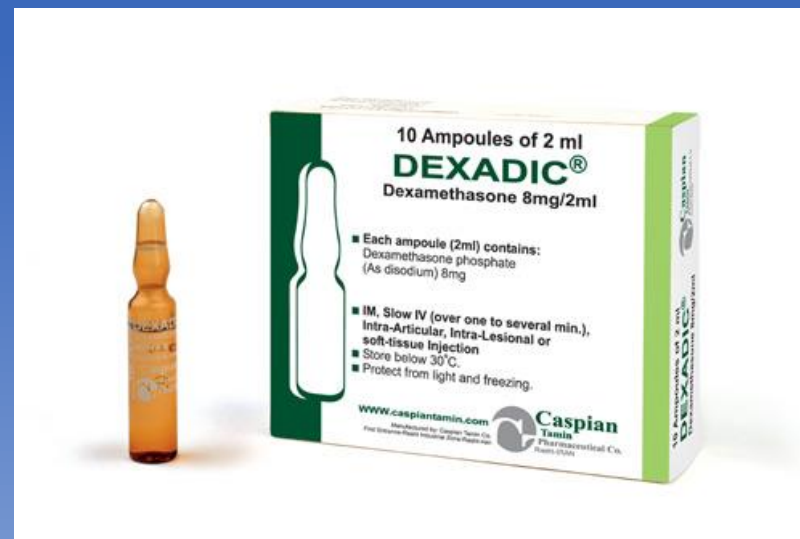
- Immunocompromised patients
 - Fungal infection
 - Herpes infection
-
- Potent topical steroids can cause purpura & ulceration , especially in thin mucosal areas.

Therapeutic Uses in Dentistry

- Oral ulceration (traumatic ulcers , RAS , erosive LP , EM , PV)
- TMJ disorders (the best response of intraarticular injection in persons free of radiographic changes).
- Post-operative sequelae (for trismus & edema).
- Allergic reactions (not the urgency drug as EP).









Case

- Medical consultation
- The stress is best managed with short-acting benzodiazepine
- Post-operative pain with long-standing local anesthetic
- Note NSAIDs while not contraindicated (the risk of peptic ulcer)
- One can delay the placement of the implants until the ability to heal is well assessed.

The Approaches Fall into Three Categories

- 1- Add a single dose of additional steroid. Dexamethasone 6-10 mg is the most common.
- 2- Increase the pre-operative steroid (2-3-fold) and taper back over several days until the baseline dose is re-achieved.
- 3- Do not change the steroid dose & use sedation & pain control. This is by far the most common choice to steroid supplementation in the dental arena.

- Patients who took 5-50 mg/d prednisone for several years and their medication discontinued within 1 week before surgery have withstood general surgical procedures without the development of adrenal crisis.
- Prolonged procedure : >1 hour stressful and can require the need for supplementation)
- Surgery : minor(25mg)moderate(50-75mg)major(100-150mg hydrocortisone) (moderate and major need tapering in 2-3 days after surgery)

Dental Management

- Anticoagulants potentiate by corticosteroids resulting in increased risk of bleeding.
- Monitoring BP (systolic under 10 and diastolic under 6 represent hypotension)(head lower than feet , fluid replacement)
- It is recommended to delay treatment for patients at risk for adrenal crisis until have been stabilized.
- Currently only patients with primary deficiency recommended to receive supplementation only when surgery or G.A. is performed.
- Fasting state can mimic features of an adrenal crisis.

- Patients with well-controlled secondary deficiency and those who take daily, or alternate-day corticosteroids generally have enough cortisol to handle routine dental procedures if their dose is taken the morning of the procedure.
- Routine dental procedures do not require supplementation even in patients with well controlled primary insufficiency.
- Surgery should be done in the morning.
- Proper stress reduction
- Barbiturates should be used with caution because reduce blood level of cortisol.

- Because recovery of chronic steroid-induced suppression may be slow , patients formerly treated for prolonged periods with steroids and assume to have adrenal suppression may need to receive steroids during stressful situations for 3-12 months after cessation of steroid therapy.

