STEROIDS COMPLICATIONS

MOUSA AL-AQAILEH
RAMI RIAD
RAMI BARHAM
AYA AL-AQTASH

OBJECTIVES

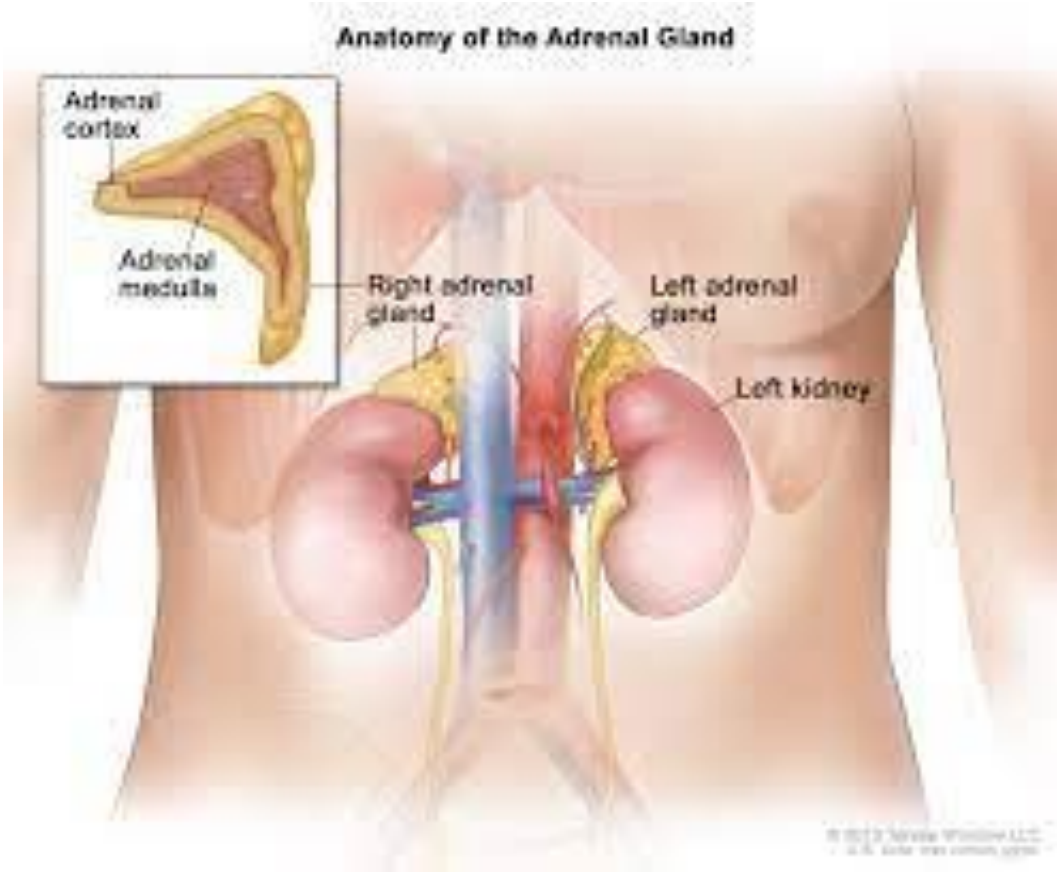
- **Introduction to steroids**
- **mechanism of action**
- **types of steroids**
- **short and long term side effects of steroids**
- **steroid monitoring and management of complication**

INTRODUCTION

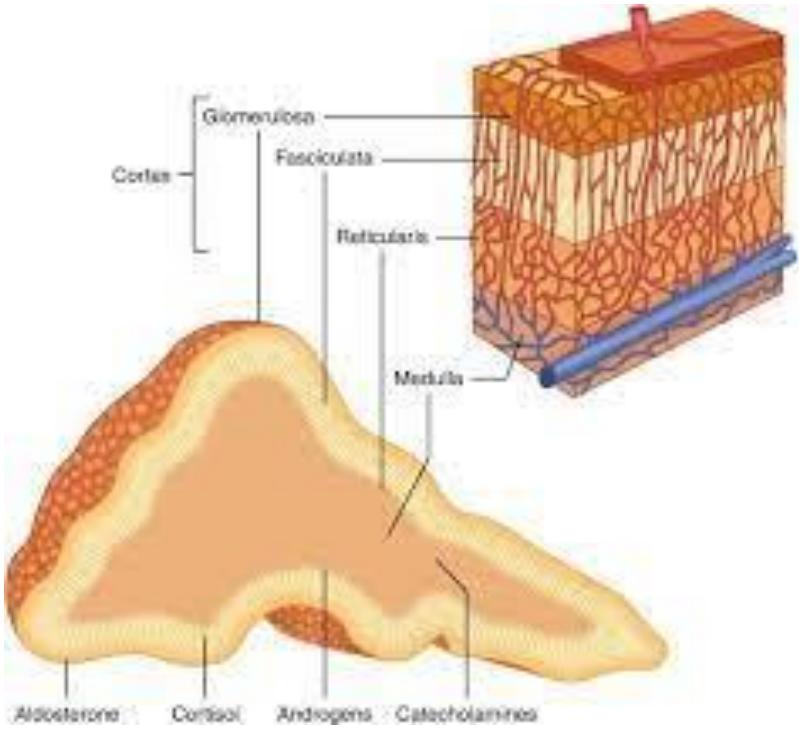
The adrenal gland consists of the cortex and the medulla.

medulla secretes catecholamines

cortex secretes two types of corticosteroids (glucocorticoids and mineralocorticoids and the adrenal androgens



- Cortex has three zones, and each zone synthesizes a different type of steroid hormone



zona glomerulosa → Mineralocorticoids (aldosterone)

zona fasciculata → glucocorticoids (cortisol)

zona reticularis → adrenal androgens

all these hormones made from cholesterol

Hypothalamo-pituitary adrenal axis

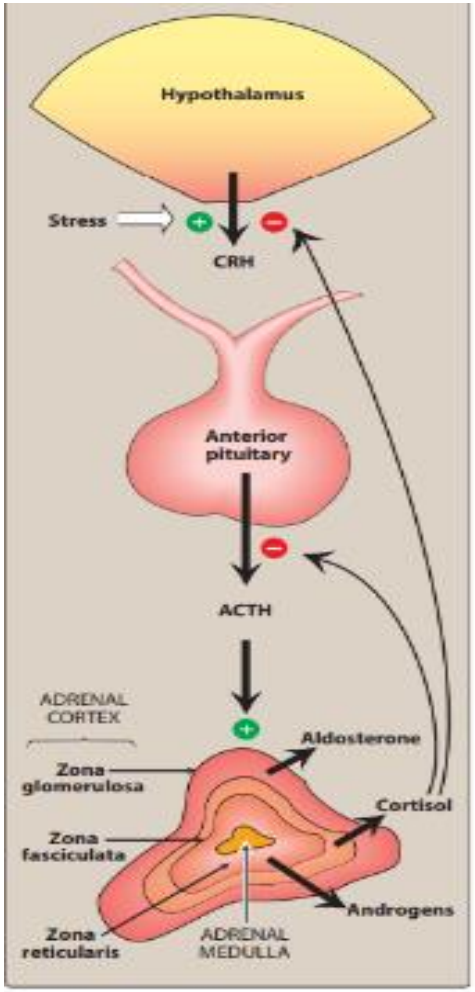


Figure 27.2
Regulation of corticosteroid secretion.
ACTH = adrenocorticotropic hormone;
CRH = corticotropin-releasing hormone.

Penetrate cell membrane

↓

bind to specific intracellular cytoplasmic receptors in target tissues

↓

((receptor–hormone complex))

↓

translocates into the nucleus by(corepressor proteins)

↓

attaches to gene promoter elements

it acts as a transcription factor to turn genes on or off depending on the tissue

This mechanism requires time to produce an effect.
However, other glucocorticoid effects are immediate, such as the interaction
with catecholamines to mediate relaxation of bronchial musculature

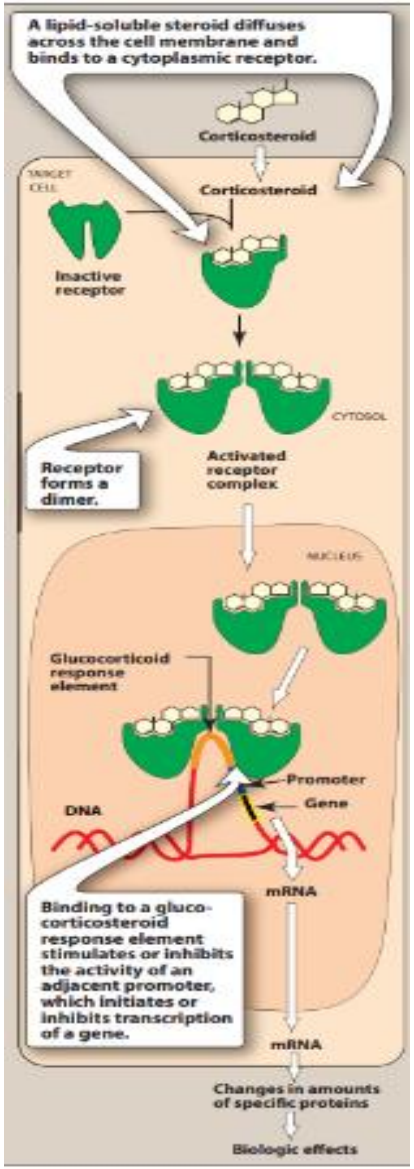


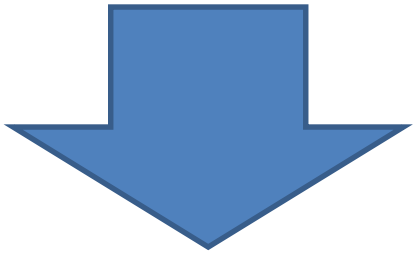
Figure 27.3
Gene regulation by glucocorticoids.

Therapeutic uses of the corticosteroids

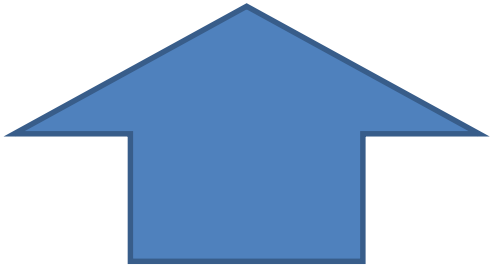
- Replacement therapy for primary adrenocortical insufficiency (Addison disease)
- Replacement therapy for secondary or tertiary adrenocortical insufficiency
- Diagnosis of Cushing syndrome
- Replacement therapy for congenital adrenal hyperplasia(CAH)
- Relief of inflammatory symptoms
- Treatment of allergies
- Acceleration of lung maturation

Glucocorticoids (normal action)

- **Cortisol** is the principal human glucocorticoid. Normally, its production is diurnal, with a peak early in the morning followed by a decline and then a secondary, smaller peak in the late afternoon. Factors such as stress and levels of the circulating steroid influence secretion
- **Promote normal intermediary metabolism**
- **Increase resistance to stress**
- **Alter blood cell levels in plasma**



Eosinophils
basophils
monocytes
lymphocytes



Hemoglobin
Erythrocytes
platelets
PML

PML:- polymorphonuclear leukocytes

CONT…

- **Have anti-inflammatory action**
- **Affect other systems**

  High levels of glucocorticoids (-ve feed back of ACTH and suppress further synthesis of glucocorticoids and thyroid-stimulating hormone),

  In addition adequate cortisol levels are essential for normal glomerular filtration

Mineralocorticoids (normal action)

- **Mineralocorticoids** help to control fluid status and concentration of electrolytes, especially sodium and potassium.
- Aldosterone acts on distal tubules and collecting ducts in the kidney, causing reabsorption of sodium, bicarbonate, and water. Conversely, aldosterone decreases reabsorption of potassium, which, with H+, is then lost in the urine. Enhancement of sodium reabsorption by aldosterone also occurs in gastrointestinal mucosa and in sweat and salivary glands

Types of steroid

- **Short acting**

(hydrocortisone,cortisone)

- **Intermmediate acting**

(prednisone,prednisolone,methylprednisolone, triamcinolone)

- **Long acting**

(betamethasone,dexamethasone)

- **Mineralocorticoids**

(fludrocortisone)

Short acting

- Duration of action(1-12hours)
- It’s the only natural corticosteroids
- Its anti inflammatory effect the same as salt retaining effect
- Route of administration:

Cortisone(oral)

Hydrocortisone(IV,IM)

Intermediate acting

- Duration of action:(12-36hours)
- Its synthetic in orgin
- Its anti inflammatory effect not the same as salt retaining effect
- Route of administration:

Prednisone(oral)

Prednisolone,methylprednisolone(IV,IM)

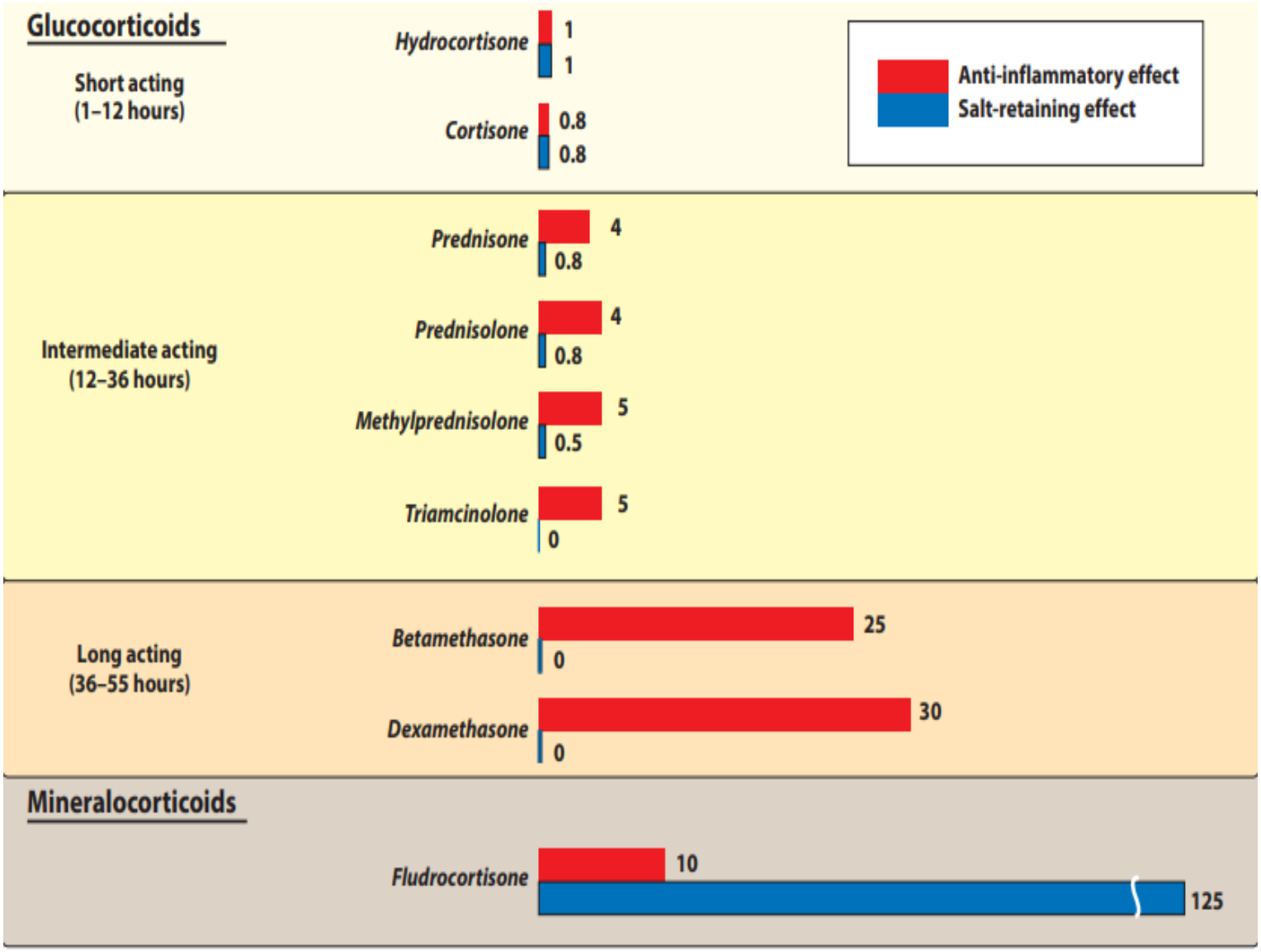
Triamcinolone(IM)

Long acting

- Duration of action(36-55hours)
- Its synthetic in origin
- Its anti inflammatory effect not the same as salt retaining effect
- Route of administration:

Betamethasone(IV,IM)

Dexamethasone(IV,IM,Oral)


Glucocorticoids
Short acting
(1–12 hours)
Hydrocortisone
1
1
Cortisone
0.8
0.8
Anti-inflammatory effect
Salt-retaining effect
Intermediate acting
(12–36 hours)
Prednisone
4
0.8
Prednisolone
4
0.8
Methylprednisolone
5
0.5
Triamcinolone
5
0
Long acting
(36–55 hours)
Betamethasone
25
0
Dexamethasone
30
0
Mineralocorticoids
Fludrocortisone
10
125

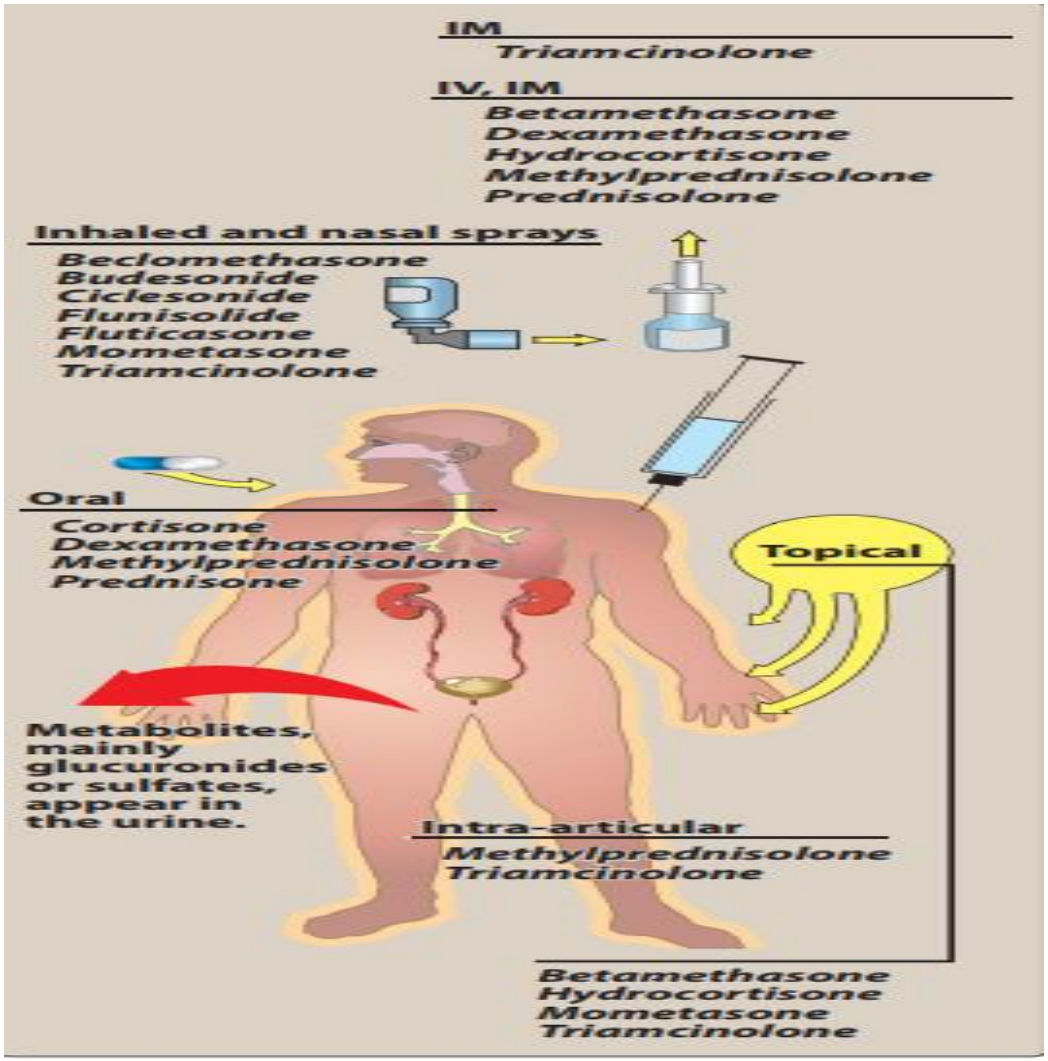
Pharmacokinetics

- 90% of absorbed glucocorticoids are bound to plasma proteins, mostly corticosteroid-binding globulin or albumin.
- Corticosteroids are metabolized by the liver microsomal oxidizing enzymes.
- The metabolites are conjugated to glucuronic acid or sulfate, and the products are excreted by the kidney.

Cont…

- **Dose**: Many factors should be considered in determining the dosage of corticosteroids, including glucocorticoid versus mineralocorticoid activity, duration of action, type of preparation, and time of day when the drug is administered.
- **Discontinuation**:

Sudden discontinuation of these drugs can be a serious problem if the patient has suppression of the HPA axis. In this case, abrupt removal of corticosteroids causes acute adrenal insufficiency that can be fatal, coupled with the possibility that withdrawal might cause an exacerbation of the disease, means that the dose must be tapered slowly according to individual tolerance and the patient must be monitored carefully.


IM
Triamcinolone
IV, IM
Betamethasone
Dexamethasone
Hydrocortisone
Methylprednisolone
Prednisolone
Inhaled and nasal sprays
Beclomethasone
Budesonide
Ciclesonide
Flunisolide
Fluticasone
Mometasone
Triamcinolone
Oral
Cortisone
Dexamethasone
Methylprednisolone
Prednisone
Topical
Metabolites, mainly glucuronides or sulfates, appear in the urine.
Intra-articular
Methylprednisolone
Triamcinolone
Betamethasone
Hydrocortisone
Mometasone
Triamcinolone

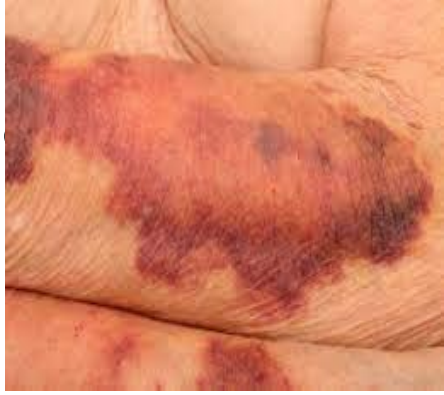
Short and Long-Term Complications of Steroids

- Several retrospective reviews have shown that long-term glucocorticoid use, even in low doses, is a significant independent predictor of numerous adverse effects and that the risk is both dose- and duration-dependent

- Glucocorticoids have adverse effects on many organ systems. Adverse effects range from those that are not necessarily serious but are displeasing to patients (eg, Cushingoid appearance) to those that are life-threatening (eg, serious infections).

- With the exception of cataracts, a potential acceleration in atherosclerotic vascular disease, and bone effects (osteoporosis and osteonecrosis), all glucocorticoid toxicity is at least partially reversible over time with glucocorticoid discontinuation.

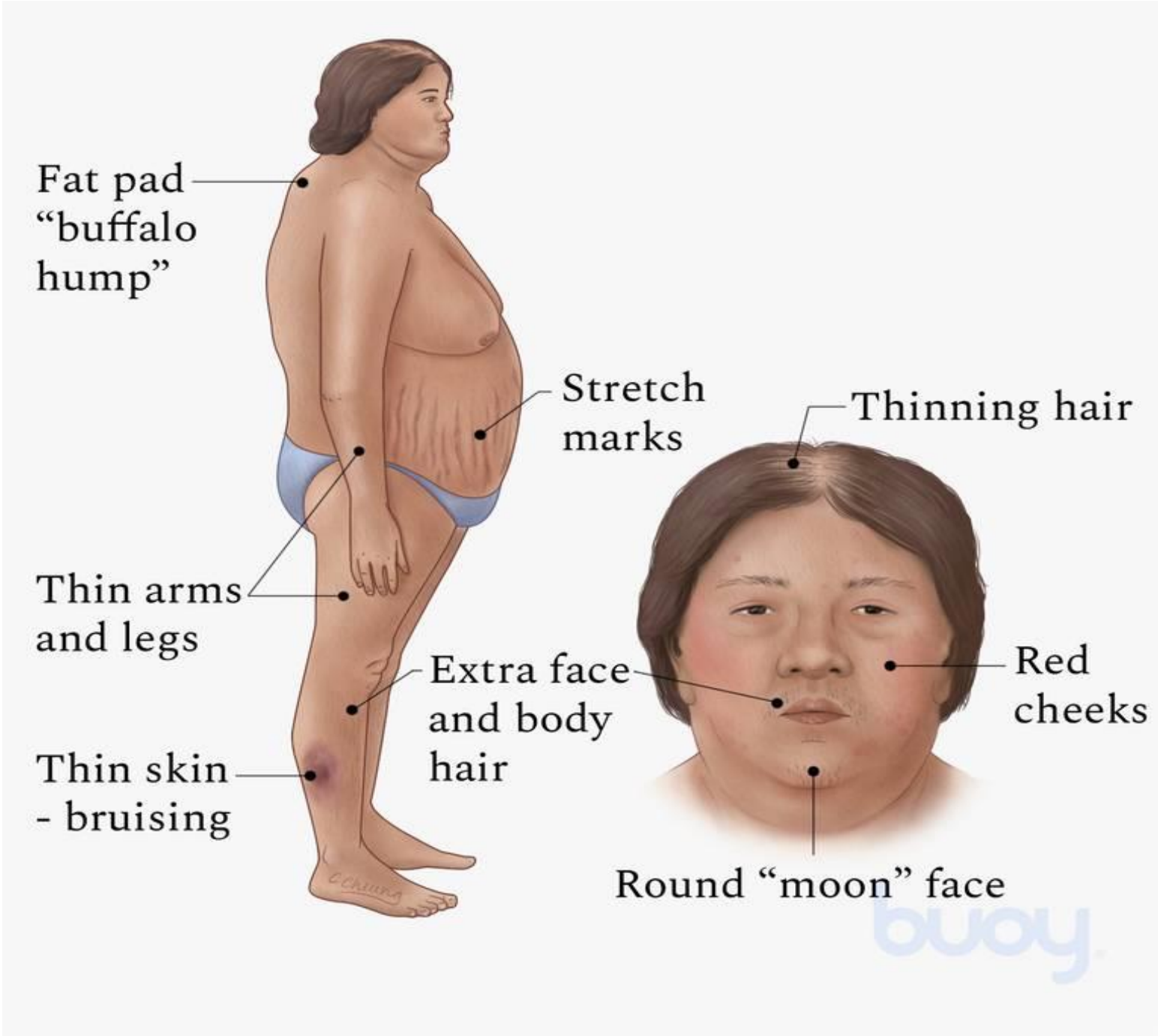
Dermatologic effects and appe



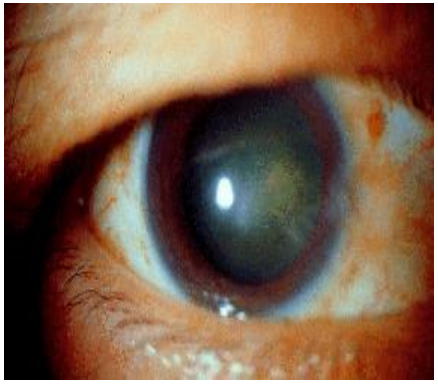
1. **Skin thinning and ecchymosis**
   - The ecchymosis or purpura associated with glucocorticoid use often affects the sun-exposed areas of the dorsum of the hand and forearm and is not accompanied by palpable swelling.

2. **Cushingoid features**
   - Redistribution of body fat with truncal obesity, buffalo hump, moon face, hirsutism, and increased appetite (early SE) can develop within the first two months of therapy.

3. **Weight gain**
   - Weight gain was more frequent in patients treated with at least 5 mg/day of prednisone or equivalent for at least six months.


Fat pad "buffalo hump"
Stretch marks
Thin arms and legs
Extra face and body hair
Thin skin - bruising
Thinning hair
Red cheeks
Round "moon" face

Ophthalmologic effects



1. **Cataracts**
   - They are usually bilateral and develop slowly. They typically occur in a posterior subcapsular location and can usually be distinguished from senile. cataracts.
   - risk is dose- and time-dependent and is more common with prednisone doses greater than 10 mg/day.
2. **Increased intraocular pressure**
   - most commonly in patients who use glucocorticoid eye drops, although it has been observed in chronic and, to a lesser extent, acute systemic glucocorticoid use.
3. **Exophthalmos**
   - Exophthalmos and swelling of the lids and ocular muscles are rare.

Cardiovascular effects

1. **Fluid retention and hypertension**
   - Hypertension is a known adverse effect of glucocorticoids and has been observed in up to 20 percent of patients with iatrogenic Cushing's syndrome; however, it is a dose-related adverse effect and is unlikely to occur at lower doses of glucocorticoids.
2. **Premature atherosclerotic disease**
   - Glucocorticoid use has been associated with increased rates of cardiovascular events (myocardial infarction, angina, coronary revascularization, hospitalization for heart failure, transient ischemic attack [TIA], or stroke).

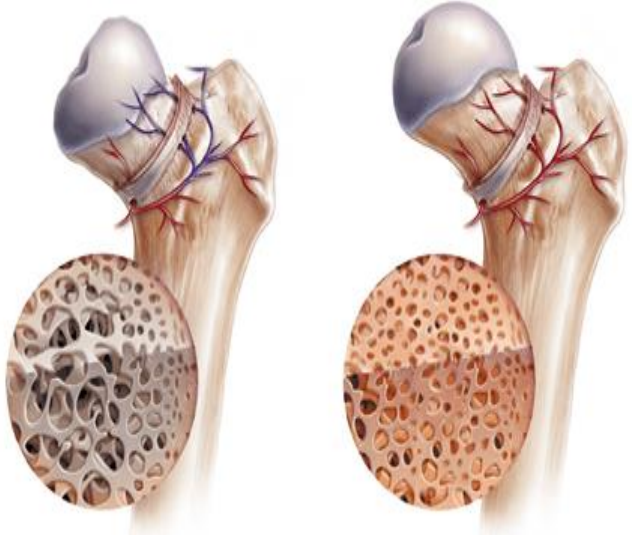
3. **Arrhythmias**
   - Currently using glucocorticoids was associated with a significant increased risk of atrial fibrillation or flutter, compared with never having used glucocorticoids.
   - Risk was increased for new users and long-term users was unrelated to whether or not pulmonary or cardiovascular disease was present.
4. **Pulmonary emboli and venous thrombotic events**

Gastrointestinal effects

- Glucocorticoids increase the risk for adverse gastrointestinal effects, such as **gastritis (short-term)**, **ulcer formation**, and **gastrointestinal bleeding.**
- The use of NSAIDs and glucocorticoids is associated with a fourfold increased risk of a gastrointestinal adverse effect compared with nonuse of either drug
- Other complications associated with glucocorticoid use include visceral perforation and hepatic steatosis (fatty liver).

Bone and muscle effects

1. **Osteoporosis**
   - Glucocorticoids increase bone resorption, reduce bone formation, decrease intestinal calcium absorption, and increase renal calcium excretion.
   - Glucocorticoid therapy appreciably increases bone loss, which is most pronounced in the first few months of use.
   - Glucocorticoids increase the risk of fracture, particularly vertebral fractures, which occur early after exposure.
   - The incidence of fracture is higher with advanced age, larger dose, and longer duration of glucocorticoid therapy.
   - The increased risk of fracture has been reported with doses of prednisone or its equivalent as low as 2.5 to 7.5 mg daily.



2. Osteonecrosis

- Avascular or ischemic necrosis
- long-term use of prednisone more than 2
- Particularly with high doses

3. Myopathy

- Presents as painless proximal motor weakness in both the upper and lower extremities.
- Can occur with any of the glucocorticoid preparations but is more common with systemic glucocorticoids. The risk is increased in patients who are older, physically inactive, and in those with cancer.
- Initiation of 40 to 70 mg/day of prednisone can result in steroid myopathy within 30 days.
- Muscle enzymes are normal; electromyography (EMG) may be normal or can show a non-irritable myopathy, biopsy reveals nonspecific atrophy.

Neuropsychiatric effects

1. **Mood disorders**
   - The prevalence of depression is greater in patients on more longstanding therapy, even on low to moderate doses.
   - Improved sense of well-being within several days of starting the medications; mild euphoria. (early)
2. **Psychosis**
   - Approximately 10 percent of patients have persistent symptoms that may require treatment despite reduction of glucocorticoid dose.
3. **Memory impairment**
   - A report found that patients treated with prednisone doses of 5 to 40 mg/day for at least one year had a partial loss of explicit memory.
4. **Insomnia**
   - Early after initiation of glucocorticoids.

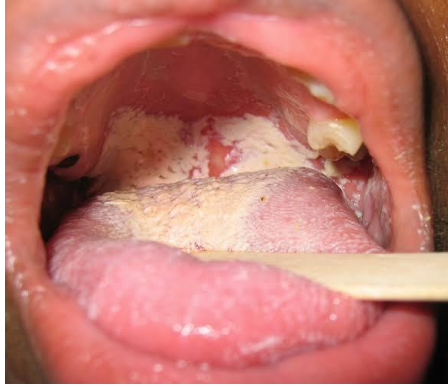
Metabolic and endocrine effects

1. **Hyperglycemia**
   - Systemic glucocorticoids cause a dose-dependent, usually mild, increase in fasting glucose levels and a greater increase in postprandial values in patients without preexisting diabetes mellitus, but the development of de novo diabetes in a patient with initially normal glucose tolerance is uncommon.
2. **Hypothalamic-pituitary-adrenal axis suppression**
   - Administration of exogenous glucocorticoids can suppress the hypothalamic-pituitary-adrenal (HPA) axis.
   - Abrupt cessation or rapid withdrawal of glucocorticoids in such patients may cause symptoms of adrenal insufficiency.

Immune system effects

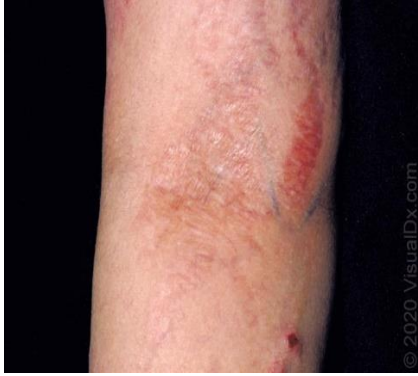
- Systemic glucocorticoids have many effects upon innate and acquired immunity that predispose to infection, resulting in a dose-dependent increase in the risk of infection, especially with common bacterial, viral, and fungal pathogens.
- Inhaled and topical glucocorticoids are usually not implicated in increased risk of systemic infections, in contrast to the effects seen with systemic agents.

Inhaled glucocorticoids



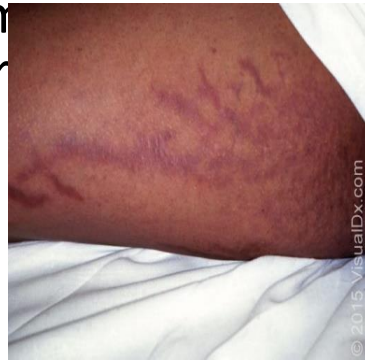
- Inhaled glucocorticoids (inhaled GC or ICS) have fewer and significantly less severe adverse effects compared with orally-administered glucocorticoids.
- Concerns about adverse effects arise with ICS because these medications are typically used over many years and are administered to infants, children, and older adults who may be more susceptible to the adverse effects, Such as **deceleration of growth velocity.**
- Local deposition of ICS in the oropharynx and larynx most commonly causes dysphonia or thrush. Dysphonia may be less common with devices that produce smaller-sized particles.
- Thrush can often be avoided by use of a large volume spacer/chamber with metered dose inhalers (MDI) and rinsing of the mouth.
- An individual's risk of systemic side effects from ICS is influenced by the cumulative dose, delivery system, individual differences in response to the glucocorticoid, and degree to which the drug is absorbed at different sites.
- ICS can increase intraocular pressure and enhance the formation of cataracts.

Topical corticosteroids



- Topical corticosteroids are safer than systemic glucocorticoids.
  Nevertheless, cutaneous and systemic side effects can occur, particularly with superpotent and potent drugs or extensive use of lower-potency agents

1. **Cutaneous**
   - Cutaneous atrophy, telangiectasias, and striae are potential adverse effects of topical corticosteroid therapy and are more likely to occur with the use of higher-potency agents.
2. **Systemic**
   - Systemic – Hypothalamic-pituitary axis suppression m
     occur with prolonged use of high-potency corticoster



Practical recommendations for the monitoring,prevention and management of systemic corticosteroid-induced adverse events

- Monitoring Before initiating long-term systemic corticosteroid therapy, a thorough history and physical examination should be performed to assess for risk factors or pre-existing conditions that may potentially be exacerbated by steroids therapy,such as diabetes, dyslipidemia, CVD, GI disorders, affective disorders, or osteoporosis.

- At a minimum, baseline measures of body weight, height, Bone mineral density and blood pressure should be obtained, along with laboratory assessments that include a complete blood count (CBC), blood glucose values , and lipid profile.

- In children, nutritional and pubertal status should also be examined.
- Symptoms of exposure to serious infections should also be assessed as steroids are contraindicated in patients with untreated systemic infections.

- Concomitant use of other medications should also be assessed before initiating therapy as significant drug interactions have been noted between steroids and several drug classes. –as shown in the table-

Table 6 Major drug interactions with systemic GCs [1,8]

Interacting drug class	Effect	Recommendation/comment
Anticonvulsants (e.g., carbamazepine, phenobarbital, phenytoin)	• ↓ GC exposure and efficacy; may persist for weeks following discontinuation of anticonvulsant	• Closely monitor outcomes of concomitant use • GC dose alterations may be required
Anticoagulants (e.g., warfarin)	• May ↑ anticoagulant effects of warfarin and ↑ risk of GI bleeding	• Monitor INR closely • Significant alteration in warfarin dose will likely be required within 3–7 days of GC initiation
Antifungals (e.g., itraconazole, ketoconazole)	• ↑ GC exposure and toxicity	• Monitor concurrent use for signs of GC overdose (fluid retention, hypertension, hyperglycemia) • Dose alteration of methylprednisolone and dexamethasone may be needed (prednisone and prednisolone not affected to a clinically relevant degree by this interaction)
Antidiabetic agents	• GC initiation can lead to glucose dysregulation, thereby counteracting the effects of antidiabetic drugs	• ↑ frequency of BG monitoring when initiating GC therapy • Adjust antidiabetic therapy based on BG results
Antibiotics (macrolides) (e.g., clarithromycin)	• ↑ GC exposure and toxicity	• Monitor concurrent use for signs of GC overdose (fluid retention, hypertension, hyperglycemia) • Dose alteration of methylprednisolone and dexamethasone may be needed (prednisone and prednisolone not affected to a clinically relevant degree by this interaction)
Antivirals (e.g., atazanavir, indinavir, ritonavir, saquinavir)	• ↑ GC exposure and toxicity • Dexamethasone may ↑ levels of indinavir and saquinavir	• Monitor concurrent use for signs of GC overdose (fluid retention, hypertension, hyperglycemia) • Dose alteration of methylprednisolone and dexamethasone may be needed (prednisone and prednisolone not affected to a clinically relevant degree by this interaction) • Monitor antiviral efficacy of indinavir and saquinavir if patient is taking dexamethasone
Anti-infectives (e.g., efavirenz, nevirapine, rifampin)	• ↓ GC exposure and efficacy; may persist for weeks following discontinuation of anti-infective	• Closely monitor outcomes, especially in transplant recipients • ↑ GC dose accordingly
Diuretics, potassium wasting (e.g., furosemide, HCTZ)	• GCs may ↑ kaliuretic effects of these diuretics	• Monitor potassium levels to determine whether alteration of diuretic therapy and/or potassium supplementation is needed
Live vaccines	• Immunization with live vaccines while taking immunosuppressive GC doses (40 mg/day of prednisolone [or equivalent] for > 7 days) may increase risk of both generalized and life-threatening infections	• Postpone live vaccines for at least 3 months after high-dose GC therapy is discontinued
NSAIDS	• May ↑ risk of GI ulcers when given concomitantly with corticosteroids	• Consider use of PPI if person is at risk of GI ulcers

GC glucocorticoid, *INR* international normalized ratio, *BG* blood glucose, *GI* gastrointestinal, *HCTZ* hydrochlorothiazide, *PPI* proton pump inhibitor, *NSAIDS* non-steroidal anti-inflammatory drugs.

- Females of childbearing age should also be questioned about the possibility of pregnancy. Steroids use in pregnancy may increase the risk of cleft palate in offspring ,although the absolute risk appears to be low.
- The above-mentioned parameters should be monitored-regularly.
- Specific recommendations for the assessment and monitoring of bone mineral density and fracture risk, diabetes, CVrisk and dyslipidemia and growth are provided in the this table.

Table 5 Assessment and monitoring of patients scheduled for long-term systemic corticosteroid therapy

Baseline:	*Physical:*	*Investigations:*
	• Weight	• CBC
	• Height	• Glucose
	• BMI	• Lipids
	• Blood pressure	• BMD
Subsequent monitoring:	*Bone health (adults):*	
	• Annual height measurement, and questionnaire for incident fragility fracture	
	• BMD 1-year post GC initiation	
	→ If stable: assess every 2–3 years	
	→ If decreased: assess annually	
	• Lateral spine x-ray in adults ≥65 years to examine for vertebral fractures	
	• Consider referral to endocrinologist/rheumatologist if fracture risk is high and/or BMD is decreasing	
	Bone health (children):	
	• Consider a baseline spine BMD and lateral spine x-ray in children receiving ≥3 months of GC therapy	
	• Repeat at intervals (typically yearly) if there is persistence of risk factors:	
	→ Ongoing steroid therapy	→ Declines in spine BMD
	→ Low trauma extremity fractures	→ Growth deceleration
	→ Back pain	
	• Referral to a pediatric bone health specialist if there is evidence of bone fragility (low-trauma extremity or vertebral fractures)	
	Growth (Children & Adolescents):	
	• Monitor every 6 months	
	• If growth velocity inadequate, refer to pediatric endocrinologist for further assessment	
	Dyslipidemia and CV Risk (adults):	
	• Assess lipids 1 month after GC initiation, then every 6–12 months	
	Hyperglycemia/Diabetes:	
	• Screen for classic symptoms at every visit: polyuria, polydipsia, weight loss	
	• Monitor glucose parameters:	
	→ For at least 48 hours after GC initiation [38]	
	→ Then every 3–6 months for first year; annually thereafter	

THANK YOU

- Sources:
- Uptodate
- Lippincott
- Pubmed