Urinary system

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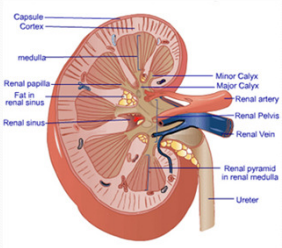
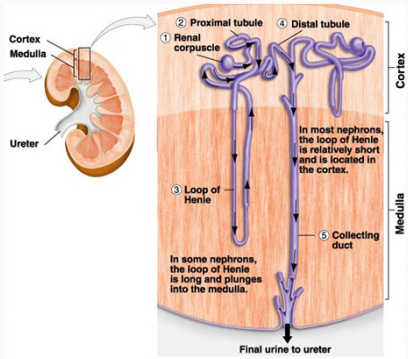
Normal kidney function

- Extra cellular fluid volume control
- Electrolyte balance
- Waste product excretion
- Drug and hormone elimination/metabolism
- Blood pressure regulation
- Regulation of haematocrit
- Regulation of calcium/phosphate balance
- Acid-bace balance

Urinary system

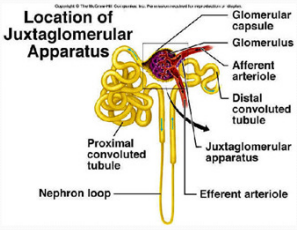
- Kidneys
- Renal arteries/ veins
- Ureter
- Urinary bladder





Nephron

- Glomerulus
- Proximal convoluted tubule
- Loop of Henle
- Distal tubule
- Collecting duct

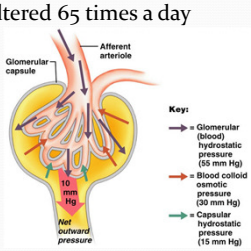


3 basic renal processes

- **Glomerular filtration**: filtering of blood into tubule forming primitive urine
- **Tubular reabsorption**: absorption of substances needed by body from tubule to blood
- **Tubular secretion**: secretion of substances to be eliminated from the body into the tubule from the blood

Glomerular filtration

- 1st step in urine formation
- 180 L / day filtered
- Entire plasma volume filtered 65 times a day
- Proteins not filtered

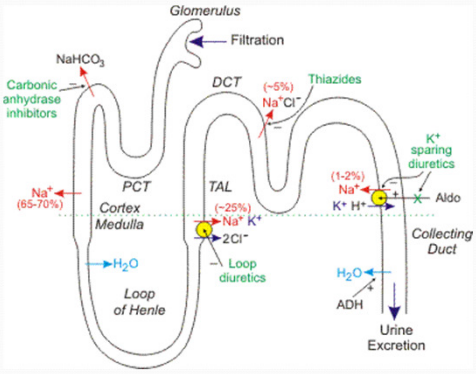


Tubular reabsorption

- Water: 99%
- Sodium: 99.5%
- Urea: 50%
- Phenol: 0%

Tubular secretion

- Protons (acid-base balance)
- Potassium
- Organic ions



Proximal tubule

- Epithelium is permeable to ions/H2O and permits passive flow in either direction
- 60-70% of filtered load of Na^+ and water is reabsorbed
- Na^+ transported out of cells into interstitial and into blood by primary active transport mechanism of nephron – Na^+/K^+ATPase in basolateral membrane
- Water reabsorbed as a result of osmotic pressure gradient
- Chloride absorption is passive
- Na^+ entry coupled with other solutes- glucose, amino acids
- Bicarbonate is returned to plasma – action of carbonic anhydrase

Loop of Henle

- Descending limb permeable to water – moves out passively
- Fluid reaching tip of loop has high osmolarity
- Ascending limb has low permeability to H2O
- 20-30% of filtered Na^+ reabsorbed
- Active reabsorption of NaCl, not accompanied by H2O
- Reduces osmolarity of tubular fluid
- $Na^+$and Cl^- move into cells by co-transport system involving $Na^+/K^+/2Cl^-$, process being driven by electrochemical gradient for Na^+ produced by Na^+/K^+ATPase
- Loop diuretics inhibit this process

Distal tubule

- Na^+ entering cells from lumen, accompanied by Cl^- by means of an electrochemical Na^+/Cl^-carrier
- Active NaCl transport dilutes the tubular fluid
- **Thiazide diuretics** inhibit this carrier
- Ca^{2+} excretion is also regulated
- K^+ions secreted into tubule

Collecting ducts

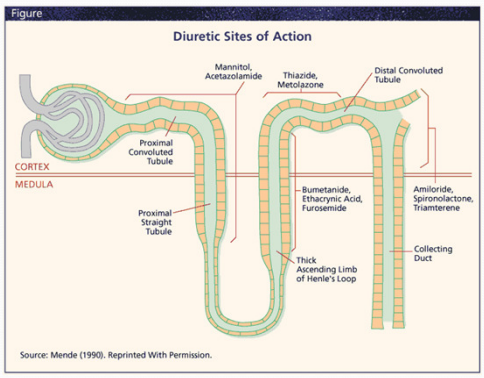
- Absorption of NaCl is under control of **Aldosterone** – mineralocorticoid hormone secreted by adrenal cortex
- If concentration of Na^+ is high- more Na^+will be absorbed
- K^+ and H^+ excreted
- **Spironolactone** antagonizes action of Aldosterone
- Water reabsorbed in collecting duct through special pores regulated by ADH – released by posterior pituitary
- More water absorption →more concentrated urine → decreased urine outflow
- **Amiloride and Triamterene** inhibit Na^+ channels

Diuretics

- Increase excretion of Na^+ and water from body by action on kidney
- Reduce reabsorption of Na^+ and Cl^- from filtrate , increase water loss secondary to excretion of NaCl
- Diuretics which have direct action on cells of nephron (except Aldosterone) act from within tubular lumen and reach their site of action by being secreted into proximal tubule

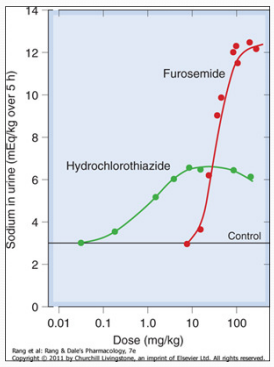
Classification

Name	Example
Carbonic anhydrase inhibitors (CAI)	Acetazolamide
Thiazides	Hydrochlorothiazide
Loop diuretics	Furosemide, Bumetanide, Torasemide
Phthalimidines	Chlorthalidone
Diverse	Indapamide, Metalazone
K^+ sparing diuretics	Spironolactone, Amiloride, Triamterene
Osmotic diuretics	Mannitol, Isosorbide, Urea
Acid forming salts	Ammonium chloride
Indirectly - acting urine drivers	Methylxanthines, Dopamine, cardiac glycosides



Diuretics

- **High vs low ceiling**



Loop diuretics

- Eg **Furosemide, Bumetamide, Torasemide, Piretanide**
- 15-25 % of Na^+ in filtrate can be excreted
- Act on thick segment of ascending Loop of Henle
- Inhibit the transport of NaCl out of tubule into interstitial tissue by inhibiting $Na^+/K^+/2Cl^-$carrier in the luminal membrane
- Direct inhibiting effect on carrier – act on Cl^- binding site
- More solute is delivered to distal portion of nephron where its osmotic pressure further reduces water reabsorption

Loop diuretics

- High sodium concentration that reaches distal tubules – results in loss of H^+ and K^+ (stimulates Aldosterone) – metabolic alkalosis
- Activation of Renin-Angiotensin-Aldosterone system due to fall in blood volume and arterial pressure
- Increased excretion of Ca^{2+} and Mg^{2+}
- Decreased excretion of uric acid
- Have venodilator action

Kinetics

- Absorbed from GIT
- IVI
- Plasma protein bound – does not pass into glomerular filtrate
- Secreted in proximal convoluted tubule by organic acid transport mechanism
- Excreted into urine
- Fraction metabolized in liver
- Peak within 30 min if given IVI
- Duration of action 3-6 hours

Side effects (SE)

- Hypokalaemia
- Metabolic alkalosis
- Hypotension
- Thromboemboli
- Allergic reaction
- Gout
- Deafness

Uses

- Pulmonary oedema
- Heart failure
- Cirrhosis
- Nephrotic syndrome
- Renal failure
- HT
- Hypercalcaemia
- Elimination of drugs during poisoning

Drug interactions

- **Aminoglycosides:** enhances ototoxicity, and nephrotoxicity

Thiazides

- Eg. **Hydrochlorthiazide, Cyclopenthiazide**
- Reduces active reabsorption of Na^+ and Cl^- by binding to Cl^- side of electroneutral NaCl co-transport system and inhibits its action
- K^+ loss is significant
- Excretion of uric acid ↓
- Mg^{2+} excretion ↑
- Hypochloraemic alkalosis can occur
- Vasodilatation
- Hyperglycaemia (inhibit Insulin secretion)
- Tolerance does not develop
- Body PH does not affect their action

Uses

- HT – (blood volume reduced, later direct effect on blood vessels)
- Mild heart failure
- Severe resistant oedema
- Nephrogenic diabetes insipidus (antidiuretic effect)
- Pt who form calcium kidney stones
- Nephrotic syndrome
- Liver cirrhosis

SE

- Hyperglycaemia
- ↑Plasma cholesterol, triglycerides, LDL, VLDL
- Male impotence (reversible)
- Gout
- Hypokalaemia
- Hypersensitivity reaction (sulphonamide derivative)

Rare SE

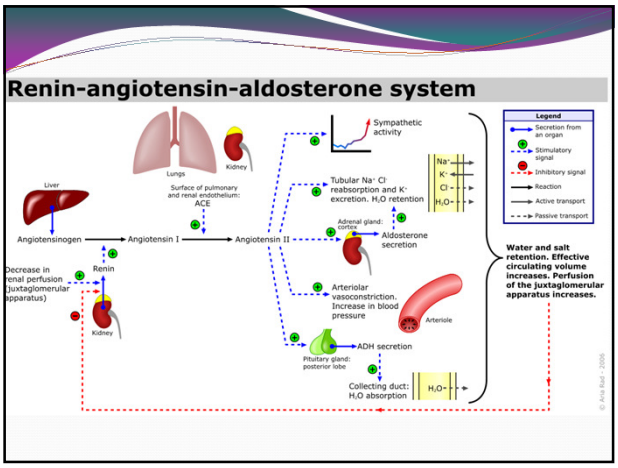
- Skin rash
- Parasthesia
- Weakness/tiredness
- Bone marrow depression
- Pancreatitis

Drug interactions

- **NSAIDs**: reduced diuretic efficacy
- **Beta blockers**: potentiate hyperglycaemia/hyperlipidaemia
- **Steroids**: enhance hypokalaemia
- Hypokalaemia potentiates digitalis toxicity
- **Lithium**: diuretics increase reabsorption of lithium in proximal convoluted tubule

Spironolactone

- Competitive antagonist of Aldosterone
- Competes for intracellular aldosterone receptors in cells of distal tubule
- Inhibit Na^+ retaining action of aldosterone
- ↓ K^+ secreting stimulation
- ↓ H^+ secretion



Uses

- Severe heart failure
- Resistant hypertension
- Combination with thiazides/loop diuretics to prevent potassium loss
- Primary hyperaldosteronism (Conn's syndrome)
- Secondary hyperaldosteronism
- Cirrhosis/ascites
- Nephrotic syndrome
- Chronic diarrhea

Side effects

- GIT disturbances
- Hyperkalaemia
- Metabolic acidosis
- Gynaecomastia
- Menstrual disturbances
- Testicular atrophy
- Peptic ulcers

Eplerenone

- New aldosterone antagonist
- No oestrogenic effects of Spironolactone
- Hypertension
- Post myocardial infarction with impaired left ventricle function

Amiloride/Triamterene

- Inhibit Na^+ reabsorption and reduce K^+ secretion in collecting tubules/ducts
- Block luminal Na^+ channels by which Aldosterone produces main effect
- Promotes excretion of uric acid
- K^+ sparing ability
- **Co-amiloside: Amiloride/HCTZ**

SE

- Metabolic acidosis
- Hyperkalaemia
- GIT disturbances
- **Triamterene**: folic acid deficiency – avoid in pregnancy

Drug interactions

- **K^+sparing diuretics and ACE inhibitors**: potentiate hyperkalaemia

Osmotic diuretics

- **Mannitol, Isosorbide, urea, glucose**
- Osmotically active molecule filtered by glomeruli but not absorbed by tubules
- Draw water osmotically with them and reduce concentrating ability of kidney, as concentration gradient of Na^+ from the tubular fluid to the cells is smaller

Uses

- Prophylaxis against ATN in shock and hepato-renal syndrome. Protects kidney by maintaining adequate flow of diluted urine
- Acute poisoning
- ↑ICP
- ↑IOP
- Initiate diuresis in pt with chronic dilutional hyponatraemia

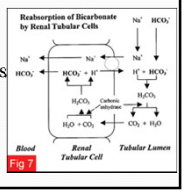
SE

- Expansion of extracellular fluid volume
- Hyponatraemia
- N+V
- Headache

CAI

- Carbonic anhydrase catalyzes carbon dioxide hydration/dehydration reaction
- **$H^+ + HCO^-_3 \rightleftarrows H_2CO_3 \rightleftarrows CO_2 + H_2O$**
- Hydrogen ions that are formed are exchanged for sodium
- Diffusible carbon dioxide taken up by the tubular cells to form bicarbonate again
- CAI prevent formation of hydrogen ions

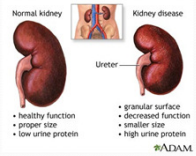
1. H^+ accumulate in body – metabolic acidosis
2. Na^+ and K^+ lost with water in urine
3. Urine alkaline due to lack of H^+



Uses

- Glaucoma – production of aqueous humor is reduced
- Alkalinize urine in treatment of poisoning with weak acids such as salicylates
- Prophylaxis against mountain sickness – metabolic acidosis enhances hyperventilation and respiratory alkalosis which occurs during acclimatization, develops more quickly. Hyperventilation increases the arterial oxygen saturation and reduces tissue hypoxia.

Renal impairment



- **History**
- **Examination:**
- Pallor, volume status, BP, urinalysis
- **Special investigations**:
- HB
- U&E
- Calcium, phosphate

Serum creatinine

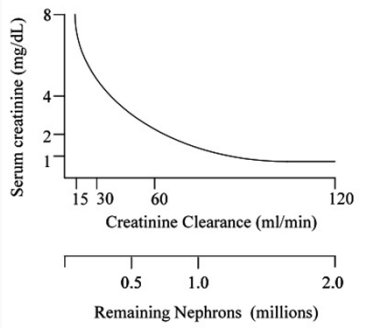
- Inverse relationship between serum creatinine and renal function
- Renal function declines steadily with age, not reflected in serum creatinine
- Renal function has linear relationship with lean body mass.
- Women have lower muscle mass than men of equivalent weight and age.

Creatinine clearance

- mL/min
- Volume of serum that is cleared of creatinine in that time
- "poor man's" equivalent of formal measurement of GFR
- **Cockcroft-Gault formula**: relies on age, weight, gender and serum creatinine

$$\text{mL/min} = \frac{(140\text{-age}) * \text{kg}}{\text{serum creatinine}}$$

- **MDRD formula**



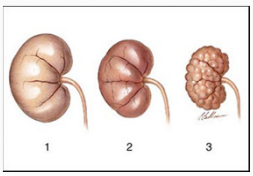
Medscape® www.medscape.com

Stages of Chronic Kidney Disease[18]

Description	Stage	GFR (mL/min/1.73 m²)
Kidney damage with normal or high GFR	1	≥ 90
Kidney damage with mild decrease in GFR	2	60-89
Moderate decrease in GFR	3	30-59
Severe decrease in GFR	4	15-29
Kidney failure	5	< 15 (or dialysis)

Prescribing in kidney disease

- Pt with renal impairment
- Pt on dialysis
- Pt with renal transplants



Principles

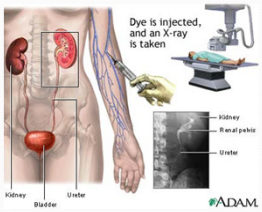
- Establish type of kidney disease
- Multiple drugs
- Interactions common
- Avoid drug toxicity

Dosing in renal impairment

- Adjust dose if creatinine clearance is below 60 mL/min
- Loading dose does not change
- Maintenance dose or dosing interval changes
- T½ prolonged:
- **Reduce dose**
- **Increase dosing interval**
- Active metabolites are excreted renally – **warfarin, diazepam**

Nephrotoxic drugs

- **NSAID's**
- **Aminoglycosides**
- **Radio opaque contrast media**
- **Gold**



Commonly prescribed drugs that require dose adjustment

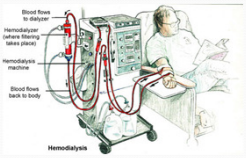
Class	Examples
Antibiotics/antifungals	Vancomycin, piperacillin, ciprofloxacin, fluconazole, carbapenems
Antivirals	Famciclovir, aciclovir, ganciclovir
Anticoagulants	LMWH
Cardiac drugs	Digoxin, sotalol, atenolol
Diuretics	Avoid potassium -sparing diuretics
Opioids	Morphine, codeine, pethidine
Psychotropics/ anticonvulsants	Lithium, topiramate, gabapentin, amisulpride
Hypoglycaemic drugs	Metformin, glibenclamide, glimepiride, insulin
Gout Rx	Allopurinol, colchicine

Other medication

- **St John's wort and ginko**: accelerate metabolism
- **Dandelion, noni juice**: hyperkalaemia
- **Heavy metals**: toxic to kidney
- **Ephedra-like compounds**: HT
- **Chinese herbal medicine**: nephrotoxic

Dialysis patients

- Pt have creatinine clearance/GFR less than 10mL/min
- Certain drugs actively removed during dialysis – take drug after dialysis session

Factors that may reduce extent to which drug is dialysed:

- Large molecular size of drug
- High protein binding
- Large volume of distribution
- High lipid solubility
- Type of dialyser membrane