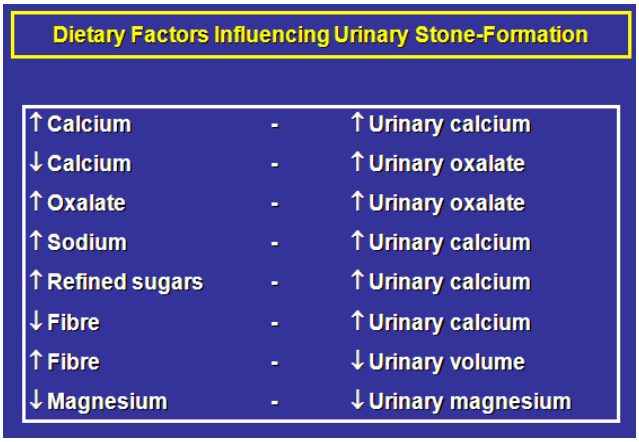
Urolithiasis

Lifetime risk of renal stone disease 10-15%
Peak incidence 30-50 years
Females have bimodal distribution – second peak after menopause
Males > females 2:1 [females have higher levels of urinary citrates; serum testosterone a/w higher production of hepatic oxalate]
Whites and asians > blacks and hispanics
More common in hot, dry climates, particularly those populated by fair-skinned races [KSA; UAE; USA; Canada; Japan are top five]
Risk factors intinsic and extrinsic

- Intrinsic — gender, genetic and metabolic (see below)
- Extrinsic — climate, occupational, fluid intake (<1200 ml/day) and diet:



Water hardness (high calcium carbonate) controversial
Low urinary volume a/w inadequate intake is the single most common cause of stone formation in adults
High animal protein causes high urinary oxalate, high urinary uric acid, low pH and low citrate (buffer used up) and high urinary calcium

Recurrence rate 50% at 10 yrs; 90% at 30 yrs
Risk factors for recurrent stone formation

- Early age of onset
- Strong family history
- Type of stone
  - Cystine
  - Calcium hydrogen phosphate (Brushite)
- Medical condition
  - Hyperparathyroidism
  - Hyperthyroidism
  - Sarcoidosis
  - Renal tubular acidosis
  - Primary hyperoxaluria
  - Cystinuria
  - Malabsorption
    - Crohn's disease
    - Jejunoileal bypass
    - Intestinal resection

- Drugs
  - Indinavir and triamterene
  - Vitamin D and megadose calcium supplementation
- Anatomical abnormality
  - PUJO
  - Calcyceal diverticulum
  - Medullary sponge kidney
  - Horseshoe kidney

Types

(i) Calcium stones (80%)
- Calcium oxalate
  - Calcium oxalate monohydrate*
  - Calcium oxalate dihydrate
- Calcium phosphate
  - Hydroxyapatite (tricalcium diphosphate)
  - Brushite* (calcium hydrogen phosphate dihydrate)

(ii) Infection stones (10-15%)
- Magnesium ammonium phosphate
- Carbonate apatite

(iii) Uric acid stones (5-10%)
- Uric acid**
- Ammonium urate
- Sodium urate

(iv) Other (1%)
- Cystine*
- Xanthine**
- Silica**
- Indinavir//Triamterene**

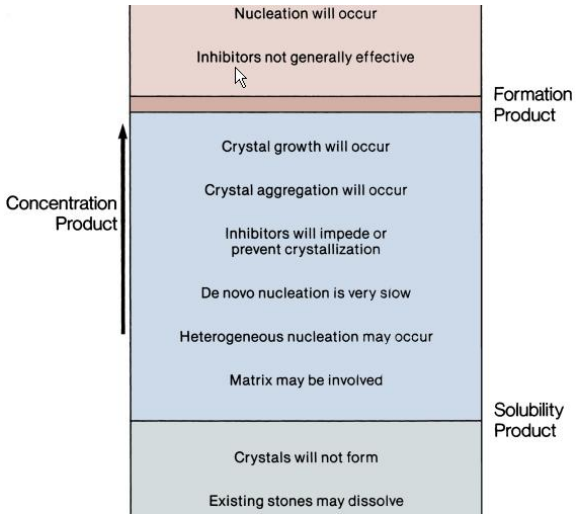
* Cystine, calcium oxalate monohydrate, brushite hardest stones
** Fully radiolucent, unlike cystine (ground-glass)

Chemical Type	Appearance
Calcium oxalate monohydrate	Hourglass
Calcium oxalate dihydrate	Envelope, tetrahedral
Calcium phosphate–apatite	Amorphous
Brushite	Needle shaped
Magnesium ammonium phosphate (struvite)	Rectangular, coffin-lid
Cystine	Hexagonal
Uric acid	Amorphous shards, plates

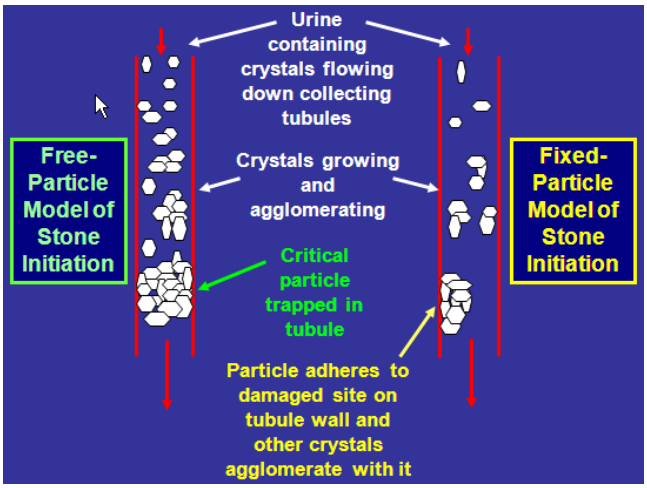
Physicochemistry

Relationship between salt and solute comprises 3 states: undersaturated, supersaturated but stable in solution (metastable), and supersaturated with spontaneous precipitation (unstable)

Concentration product = degree of saturation
Solubility product (Ksp) = concentration of ions in a pure solution at which no more chemical will dissolve (without a change in pH, temp, or composition)
Formation product (Kf) = the concentration product at which crystals actually form NB. For pure solutions Ksp effectively the same as Kf; however in urine the presence of inhibitors allows a degree of metastable super-saturation.



Supersaturation alone produces crystals in static solutions but cannot explain formation in urine. Believed to occur through nucleation, aggregation and retention. Crystal nuclei either form in pure solutions (homogenous) or on existing surfaces (rbc, epithelial cell, debris). Individual crystals too small to grow sufficently large to obstruct tubules within normal transit time. However if more than one clumps together may be retained in lumen and continue to grow (Free particle theory). Alternatively may attach to damaged tubular surfaces (Fixed particle theory)



Randall's plaques – subepithelial collection of calcified material at papilla; aetiology unknown. Arise within basement membrane of thin loops of Henle and extend through medullary interstitium to subepithelial location. Almost invariably composed of hydroxyapatite.

Inhibitors

Citrate	CaOx; CaPh
Magnesium	Ca Ox
Pyrophosphate	CaPh
Glycoproteins	
Nephrocalcin	CaOx
Tamm-Horsfall protein	CaOx
Uropontin (osteopontin)	CaOx

NB. All inhibit aggregation, but only nephrocalcin and uropontin inhibit nucleation and growth as well. There are no known urinary inhibitors of uric acid stones

Promotors

- Polymerised THP
- Matrix substance A

<u>Investigation of stone disease</u>

First stone

- U+E, Calcium, Urate
- Urinary dipstick (nitrites/leucocytes, pH, and cystine)
- pH > 7.5 suggests infection stones; pH < 5.5 uric acid stones
- Dipstick for cystine (sodium nitroprusside + urine = purple discolouration – Brandt's test)
- Stone analysis if possible
- Extended metabolic analysis not recommended in all patients because:
  - ~50% have a further stone at 10yrs
  - likelihood of recurrence not predicted by metabolic screening

Recurrent stones – who to investigate?

- Children
- Recurrent stone formers
- Bilateral stones
- Strong family history of stones
- Complex stones
- Stones in solitary kidney
- High likelihood on the basis of medical co-morbidity

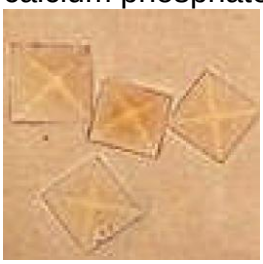
Recurrent stones – how to investigate?

- U+E, calcium, urate, venous bicarbonate (?RTA)
- Urine
  - Random pH urine
  - Fasting pH urine
  - Dipstick for nitrites and leucocytes
  - Spot test for cystine
  - 2 x 24 hour urine collections:
    - #1- HCl (prevents precipitation of calcium salts; prevents oxidation of ascorbate to oxalate)
      - Citrate
      - Oxalate
      - Calcium
      - Creatinine/volume

Others optional (typically not routine)
Magnesium & phosphate used to determine supersaturation of calcium salts
Sodium, urea, phosphate and K+ indicative of dietary habits
#2 – Sodium Azide (prevents precipitation of uric acid)
pH
uric acid

Calcium stone disease

Account for ~80% stone episodes in UK [~50% calcium oxalate; ~30% calcium phosphate]


Calcium oxalate dihydrate crystals

Causes

90% idiopathic

10% metabolic abnormality
Hypercalcaemia
Hypercalciuria
Hyperoxaluria
Hyperuricosuria
Hypocitraturia

(i) Hypercalcaemia
Hyperparathyroidism; malignancy, TB, sarcoid (sarcoid granulomas produce $1,25(OH)_2D_3$ leading to absorptive hypercalciuria)
Incidence of calcium stone disease in hyperparathyroidism only 1%
Treatment of cause

(ii) Hypercalciuria
Isolated hypercalciuria in ~ 50% patients with CaOx stones
Defined as > 4mg/kg/24 hrs or >7mmol (men) or >6mmol (women); Parks and Coe 1986. Other definition >200mg/day
Classification
Idiopathic (~50%)
Absorptive (from gut)
XS calcium absorption from gut – unknown cause
Increased filtration, reduced renal reabsorption (low PTH), raised phosphate, normocalcaemia, but fasting urinary calcium normal
Type 1 > 200mg/day on high or low ca diet
Type 2 > 200mg/day on high ca diet only
Renal leak
Impaired tubular resorption
Secondary hyperPTH, low phosphate, normocalcaemia, fasting calcium high
Resorptive (from bone)

Typically due to PTH or PTHrP
Hypercalcaemia, low phosphate, fasting urinary calcium high
Rx cause

	Absorptive	Renal	Resorptive
Serum calcium	Normal	Normal	Elevated
Parathyroid function	Suppressed	Stimulated (secondarily)	Stimulated (primarily)
Fasting urinary calcium	Normal	Elevated	Elevated
Intestinal calcium absorption	Elevated (primarily)	Elevated (secondarily)	Elevated (secondarily)

Diagnosis
- Resorptive hypercalciuria usually obvious: differentiation between idiopathic, renal and absorptive more difficult
- Traditionally 'fast and load' calcium test – absorptive has normal fasting urinary calcium cf. resorptive/idiopathic
- Fast and calcium load rarely performed as most patients get thiazides anyway

Management
- a) **High fluid intake**
- b) Calcium restriction
  - Low ca diets a/w increased stone formation (due to increased oxalate absorption) Curhan 1993; 1997
  - Studies did not separate patients with absorptive hypercalciuria – moderate restriction may have a role in these patients
- c) Sodium cellulose phosphate
  - Binds divalent cations and reduces urinary calcium, even in type 1 hypercalcuria
  - No evidence reduces recurrence; a/w severe GI side effects, hyperoxaluria, hypomagnesaemia
  - Largely historical due to side effect profile
- d) **Thiazide diuretics**
  - Prevent sodium for calcium exchange in distal nephron.
  - Used for both renal and absorptive
  - Hydrochlorothiazide 25mg bd usual
  - Absorptive
    - Treats hypercalcuria, not cause
    - Previous studies have shown limited long- term efficacy (Preminger 1987). Initial increase in BMD indicating skeletal accretion, but after a variable period, bone stores overwhelmed and leak occurs again. Thiazide holiday recommended.
  - Renal
    - Ideal Rx as corrects underlying abnormality
    - No worries re. loss of effectiveness
    - Certainly reduces urinary calcium, but less impressive vs. recurrence (15% rec. vs. 27%

controls) and only if taken for more than 2 yrs (?stone clinic effect)
Side effects problematic in 30%
Lethargy
Hypokalaemia}
Hypocitraturia } **supplement with KCit**
Impotence
Reduced libido
Rarely pancreatitis

e) Orthophosphate
Uro-Phos-K
Slow release neutral potassium phosphate, binds intestinal calcium and inhibits activated vitamin D
Reduces urinary calcium and increases citrate but no evidence that reduces stone recurrence rates.
No publications since initial reports 1998

(iii) Hyperoxaluria
Dietary oxalic acid predominantly absorbed in colon
Oxalic acid completely filtered, secreted but not absorbed
Defined as > 40mg/day oxalate in urine
< 80mg/day = dietary hyperoxaluria; > 80mg/day enteric or primary hyperoxaluria
Causes:
Dietary hyperoxaluria
Reduce intake of rhubarb, tea, chocolate, nuts, spinach and strawberries
Eliminate megadoses of vitamin C
Enteric hyperoxaluria
Most common cause of hyperoxaluria
Malabsorption syndromes (Crohn's etc.)
Bile salts increase permeability of intestinal mucosa to oxalate and calcium soap formation results in increased free gut oxalate
? role for *oxalobacter formigenes*
Primary hyperoxaluria
Rare autosomal recessive disease
Mutated AGT (see appendix) leads to very elevated levels of urinary oxalate (>100mg/day), causing CaOx stone disease, nephrocalcinosis and renal impairment (liver and kidney transplant required)
Management
High fluid intake
Low oxalate diet
[High calcium/magnesium diet proposed to chelate bile salts but hypercalciuria and diarrhoea problematic]

(iv) Hyperuricosuria
Urinary uric acid > 600mg/day
Only abnormality in ~10% calcium oxalate stone formers

Causes include overingestion, xs production (gout, myeloproliferative disorders, and drugs (see uric acid stones)
pH <5.5 results in uric acid crystal precipitation, which act as nidus for CaOx crystal nucleation
Uric acid crystals also bind urinary inhibitors (GAGs)
Management
High fluid intake
Allopurinol (xanthine oxidase inhibitor) 300 mg/day irrespective of serum urate
Potassium citrate

(v) Hypocitraturia
Definition urinary citrate < 320mg/day
Implicated in up to 50% stone formers
Citrate reduces stone formation in 3 ways
Reduces free urinary calcium by complexing Ca+
Directly prevents spontaneous CaOx nucleation
Prevents aggregation of CaOx crystals
Typically reflects acid base balance; in metabolic acidosis tubular c citrate reabsoprtion increased
Common disorders a/w hypocitraturia include distal renal tubular acidosis (see appendix), chronic diarrhoea, ACEIs and thiazides (?intracellular acidosis)
Management
High fluid intake
Potassium citrate

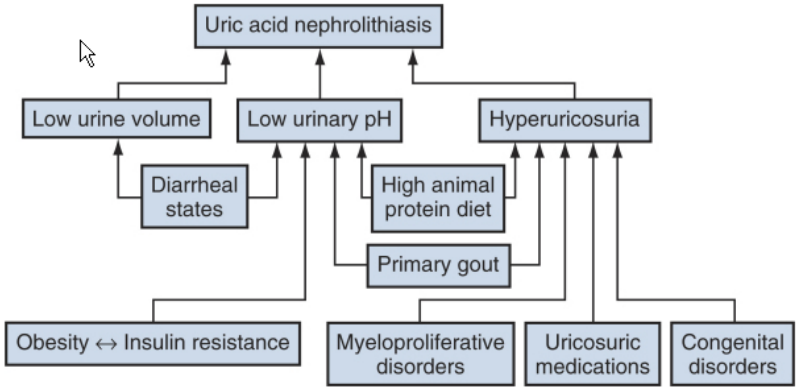
Infection stones
Common
Account for 10-15% of all stones
Females > males 2:1
Composed predominantly of magnesium ammonium phosphate hexahydrate ($MgNH_4PO_4 \cdot 6H_2O$) with a variable component of carbonate apatite ($Ca_{10}[PO_4]_6 \cdot CO_3$).
Caused by production of urease by bacteria (most commonly Proteus (mirabilis), Pseudomonas and Klebsiella and Staphylococcus species)
Urease producing bacteria act on urea to produce ammonia and carbon dioxide. Ammonia dissociates into ammonium ions and hydroxide (high pH)

$$(NH_2)_2CO + H_2O \rightarrow 2NH_3 + CO_2 \qquad NH_3 + H_2O \rightarrow OH^- + NH_4^+$$

Ammonium ions then complex with magnesium and phosphate ions to form struvite – only occurs in alkaline environments pH > 7
Aetiology
Congenital abnormality
Impaired bladder emptying (neurogenic bladder)
Urinary diversion
Medical managment
Limited
Antibiotics for acute infection, pre-operatively and following sucessful stone elimination in a patient with residual fragments

Hemacidrin for residual fragments a/w complications unless sterile urine
Acetohydroxamic acid (urease inhibitor 250mg tds) prevents new stones and reduced growth of pre-existing stones (Griffith 1991) but a/w low grade DIC and thrombosis and cessation rate up to 70%

Uric acid and urate stones
5-10% of all renal stones
More common in middle east ? genetic susceptibility
Dalmations, great apes and humans affected due to lack of uricase (converts uric acid to soluble allantoin for excretion by kidney)
Uric acid solubility very pH dependent; below pH <5.5 significant reduction in uric acid solubility
Requirements for uric acid calculi formation:
Low urinary pH
Low urine volume
High relative uric acid concentration



Aetiology
Low urinary pH
Most important factor, as most patients with uric acid stones have normal levels of urinary uric acid, but persistently low pH
Gouty diathesis*, diarrhoea, gout and high animal protein intake
*cause unknown but more common in patients with insulin resistance, possibly due to impaired urinary ammonia production
Low urinary volume
Diarrhoea, ileostomies, poor oral intake, xs sweating
Hyperuricosuria
With hyperuricaemia (3):
primary gout (aetiology unknown);
myeloproliferative conditions
Lesch-Nyhan syndrome
Without hyperuricaemia (2)
drugs (salicylates, thiazides)
dietary (organ meats and sardines)
Investigation
Urinary pH < 5.5
Elevated serum urate

24 hour urine collection (sodium azide) > 600mg/day
Negatively birefringent crystals on polarised light
Radiolucent calculus on plain imaging (also sodium urate, ammonium urate, xanthine, matrix, indinavir and triamterene)
Identifiable calculus on CT (350-400 Hounsfield units)

Management

High fluid intake

Dissolution therapy (chemolysis)

Sodium bicarbonate 500mg qds
Potassium citrate 20mEq tds
Occasionally intravenous 1/6 molar lactate or sodium bicarbonate solution used for patients with nausea and vomiting
Rarely intravesical or intrarenal sodium bicarbonate for direct chemolysis

Prevention

Allopurinol 300mg/day for all patients with hyperuricosuria (with or without hyperuricaemia) – not indicated in patients with merely low urinary pH or low volume
Allopurinol (xanthine oxidase inhibitor): side effects rare but include, rash, hypersensitivity (Stephens Johnson syndrome), hepatitis and renal failure

<u>Ammonium urate stones</u>

Rare in developed countries; common cause of endemic bladder stones in developing world
Typically form constituent of other stones but occasionally predominant component
A/w conditions of salt and water loss and low urinary pH; inflammatory bowel disease, laxative abuse and metabolic syndrome
Rx cause; alkalise urine

<u>Lesch Nyhan syndrome</u>

Rare
Males only
X-linked hereditary defect of hypoxanthine-guanine phosphoribosyl transferase (HPRT)
Hyperuricaemia and hyperuricosuria
Choreoathetosis, mental retardation, self-mutilation, gouty arthritis and renal stones

Cystine stones

Relatively uncommon; accounts for 1-2% of renal stones (10% kids)
Autosomal recessive inheritance of defect in tubular resorption of ‘COLA’ amino acids (C=Cystine, O=Ornithine, L=Lysine, A=Arginine)

Mutations affect heteromeric amino acid transporters on chromosomes 2 and 19. Ornithine, lysine and arginine all highly soluble in urine; therefore only cystine a problem. Cystine more soluble at higher urinary pH and at higher ionic strengths (more dissolved salts)
Heterozygotes 1:200; Homozygotes 1:20,000, but some heterozygotes produce stones. Therefore incidence of symptomatic cystine stones 1:10,000
Median age of stone formation 20-30 years
Cystinuria; normal individuals excrete <100mg/day; heterozygote carriers excrete 150-300mg/day; homozygote affected individuals typically excrete >400mg/day (solubility limit ~250-300mg/day)
Investigation
- Sodium nitroprusside spot test (Brandt's test)
  - Cystine + sodium cyanide = cysteine (pink)
  - Cysteine + nitroprusside = purple discoloration
  - Positive when urinary cystine > 75mg/L
  - False positives
    - Homocystinuria
    - Sulpha drugs
    - N-acetylcysteine
- Ground glass appearance on plain film (disulphide bonds)

Medical management
- High fluid intake (to produce 2.5 to 3 litres/day)
- Limit sodium intake
- Avoid red meat, fish and poultry (high levels of methionine – precursor of cystine)
- Urinary alkalisation (aim for pH 6.5-7.0 to improve solubility)
- Cystine binders (disulphide bond to soluble drug cf. insoluble cystine)
  - (i) D-penicillamine (250mg/day: side effects nephrotic syndrome, dermatitis and pancytopenia; 70% cessation rate; rarely used)
  - (ii) Alpha mercaptopropionylglycine (aka Thiola; 100mg bd, titrated to urinary cystine < 250mg/day: better tolerated than penicillamine, but side effects asthenia, GI upset, rash; cessation rate 30%)
  - (iii) Captopril (no reported clinical trials – not currently recommended)

<u>Other stones</u>

a) Matrix stones
- Mucoproteins and mucopolysaccharide
- Radiolucent
- Extremely rare

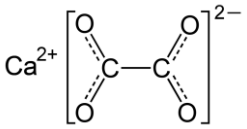
b) Bladder calculi
- Migrant (from upper tracts)
- Primary endemic
  - Children with low phosphate, cereal-based diets (low animal protein): high urinary ammonium and oxalate – typically ammonium urate +/- calcium oxalate
- Secondary
  - BOO

- UTI
- Foreign body

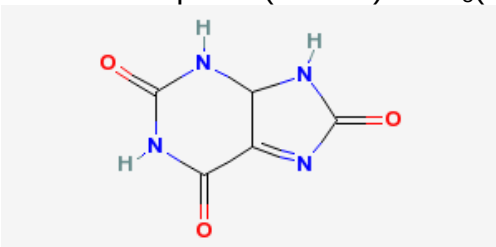
c) Drug associated stones
- Stones made of drug
  - Indinavir HIV protease inhibitor
  - Triamterene K sparing diuretic
  - Guaifenesin
  - Ephedrine
  - Ciprofloxacin
- Stones increasing risk clacium stones
  - Bumetanide
  - Frusemide
  - Acetozolamide

Appendix

Chemical formulae



Calcium oxalate monohydrate (Whewellite) = $C_2H_2CaO_5$
Calcium oxalate dihydrate (Weddellite) = $C_2H_4CaO_6$
Tricalcium diphosphate (Hydroxyapatite) = $Ca_3O_8P_2$
Calcium hydrogen phosphate dihydrate (Brushite) = CaH_5O_6P
Magnesium ammonium phosphate (Struvite) = H_4MgNO_4P
Carbonate apatite (Dahlite) = $Ca_5(PO_4,CO_3)_3F$

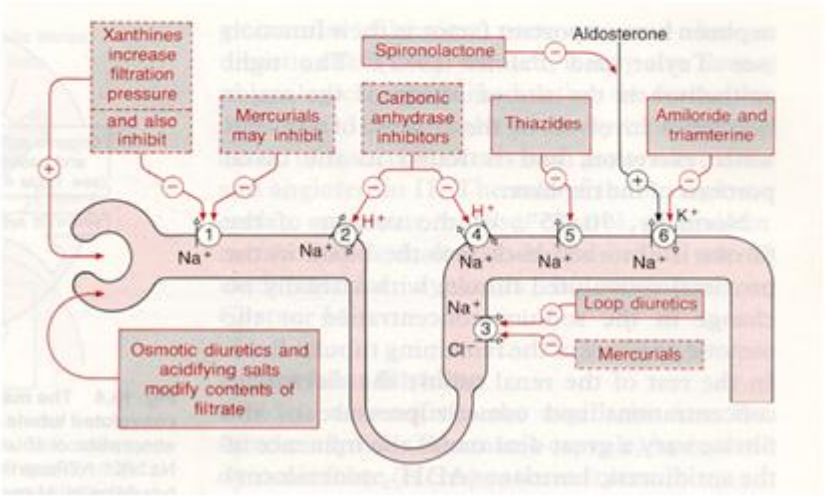


Uric acid (above) = $C_5H_4N_4O_3$
Ammonium urate = $C_5H_7N_5O_3$
Sodium urate = $C_5H_3N_4NaO_3$

Renal physiology

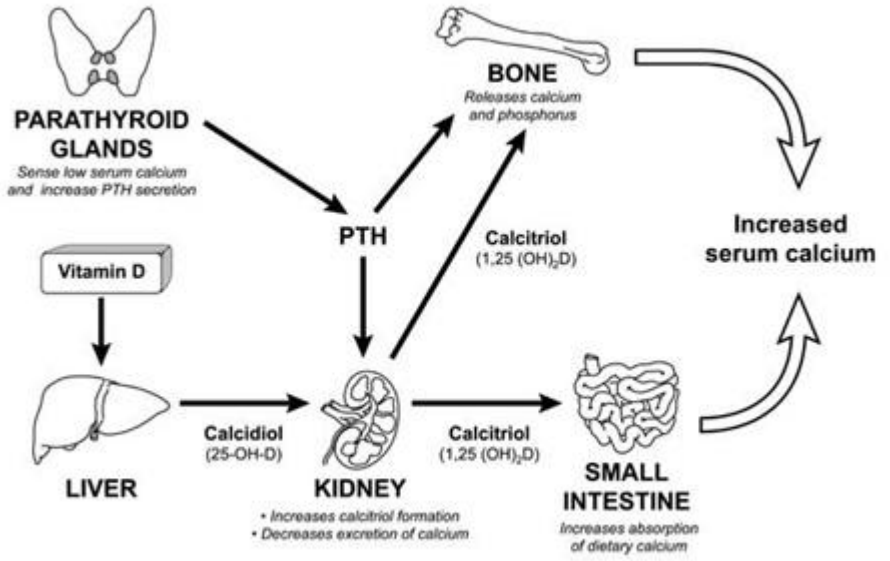
	Proximal nephron	LOH	Distal nephron
Na+ reabsorption*	67%	25%	8%
Water reabsorption*	65%	15%	20%
Ca++ reabsorption	65%	15%	15%
Mg++ reabsorption	15%	60%	10%

* maximum values

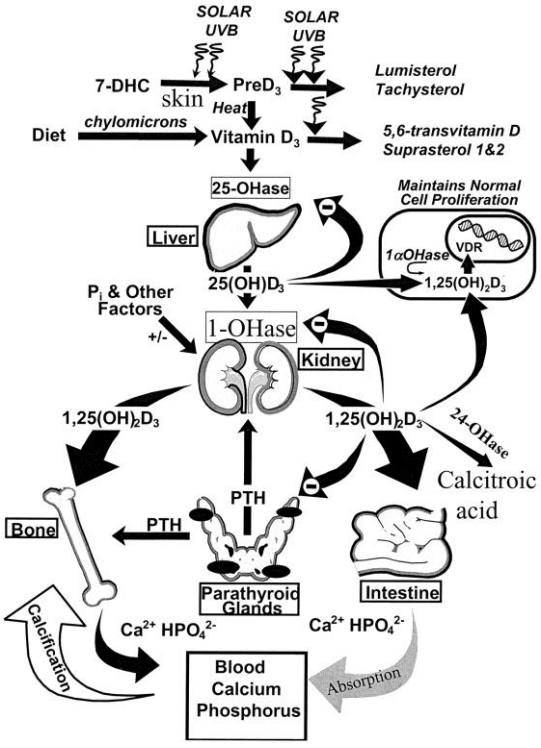


Calcium metabolism

40% dietary calcium absorpted; 90% small intestine, 10% colon
Only ionised non-complexed calcium absorbed, usually transcellular
When dietary calcium low, vitamin-D dependent channels increase fractional absorption



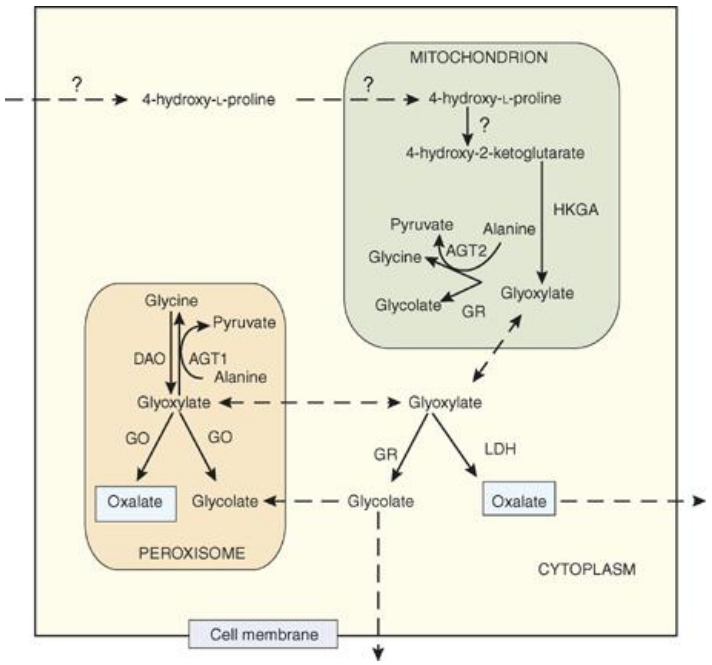
Vitamin D metabolism



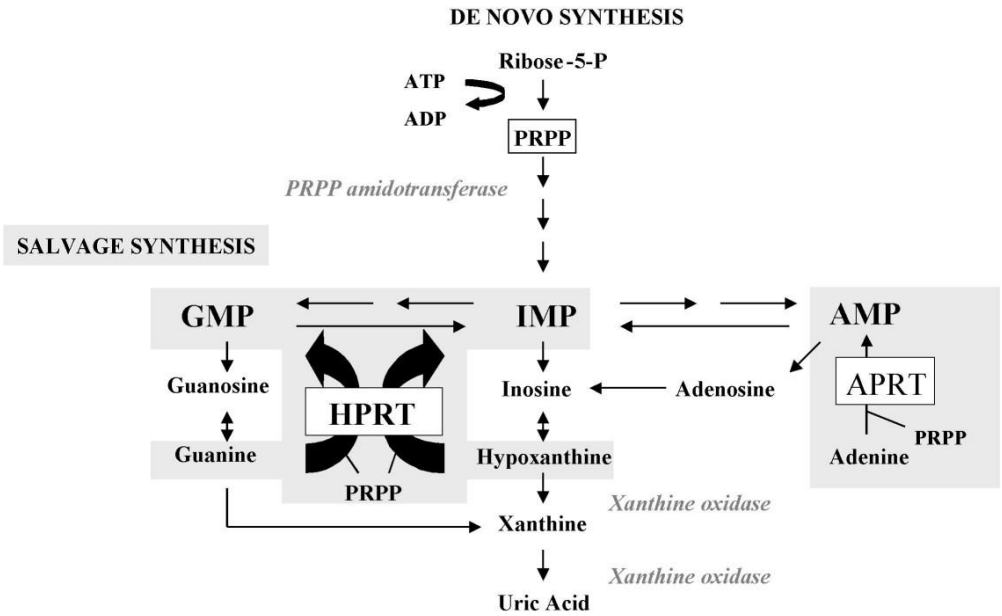
Oxalate metabolism

Only 10-15% of ingested oxalate absorbed (50% small bowel; 50% colon)
May be significantly reduced in patients with enteric colonisation with *oxalobacter formigenes*. ? therapeutic benefit
Most oxalate appearing in urine from hepatic metabolism (50% glycine breakdown; 50% ascorbic acid breakdown)

Primary hyperoxaluria (type 1) caused by a deficiency of the hepatic enzyme alanine-glycoxylate aminotransferase (AGT). Results in failure of conversion of glycoxylate to glycine, leading to increased production of oxalic, glycolic and glycoxylic acids (see below)

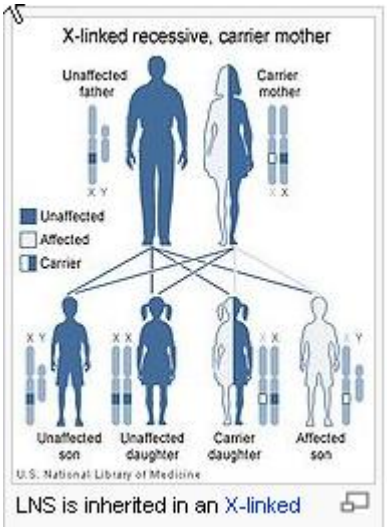


Purine metabolism



HPRT = hypoxanthine-guanine phosphoribosyl transferase. Deficiency of HPRT seen in Lesch-Nyhan syndrome

Allopurinol – structural isomer of hypoxanthine; acts as xanthine oxidase inhibitor. High levels may be a/w formation of xanthine stones (hypoxanthine more soluble than xanthine)



Renal tubular acidosis

Family of diseases characterized by failure of tubular H+ secretion and urinary acidification:

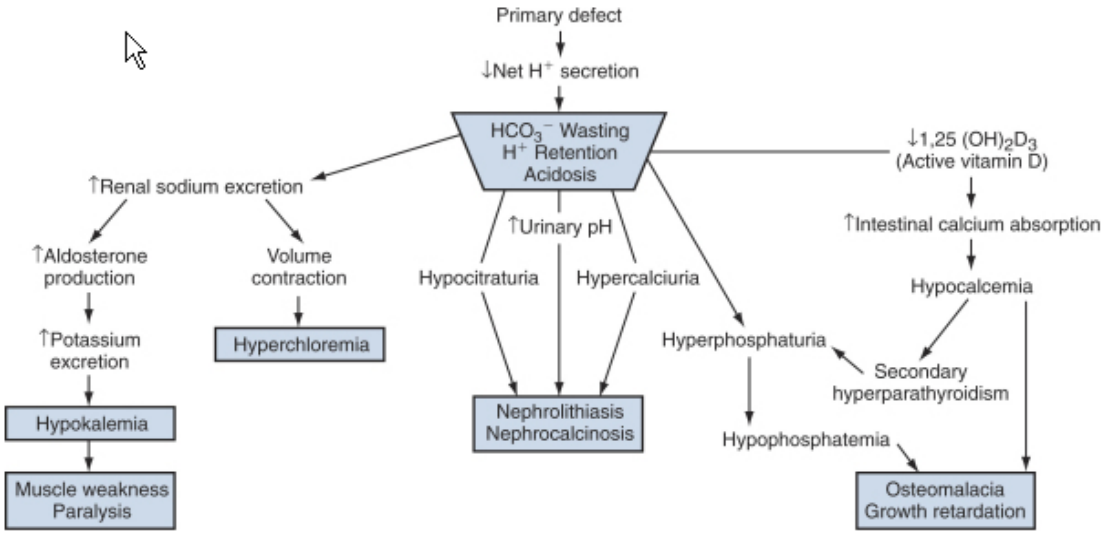
Type 1 Distal failure of H+ secretion
Diagnostic triad
Hyperchloraemic metabolic acidosis
High urinary pH (>5.5)
Low serum HCO3
80% female; 70% form stones, typically calcium phosphate
Associated low sodium, hyperaldosteronism, low potassium,
Low citrate predisposes to calcium stone disease (especially calcium phosphate) – Rx with potassium citrate

Type 2 Proximal failure of bicarbonate reabsorption
Same triad as above, with low sodium and potassium
Citrate normal - no stone disease
Usually children - growth retardation and osteomalacia (Tiny Tim)

Type 3 Actually type 1

Type 4 Impaired distal H+ and K+ secretion. As above but with hyperkalaemia – therefore cannot treat with potassium citrate

Many patients with milder forms of disease not particularly acidotic. Single best test is ammonium chloride (100mg/Kg) urinary acidification test. Ammonium chloride dissociates into ammonium ions and H+ ions – requires buffering by kidney. A urinary pH of <5.5 indicative of a failure of urinary acidification.


Primary defect
↓Net H+ secretion
HCO3− Wasting
H+ Retention
Acidosis
↓1,25 (OH)2D3
(Active vitamin D)
↑Renal sodium excretion
↑Intestinal calcium absorption
↑Aldosterone production
Volume contraction
↑Urinary pH
Hypocitraturia
Hypercalciuria
Hypocalcemia
↑Potassium excretion
Hyperchloremia
Hyperphosphaturia
Secondary hyperparathyroidism
Hypokalemia
Nephrolithiasis
Nephrocalcinosis
Hypophosphatemia
Muscle weakness
Paralysis
Osteomalacia
Growth retardation