

Chronic Kidney Disease

• Also known as IFTA-GS (Interstitial Fibrosis Tubular Atrophy Glomerulosclerosis)

• Rate of fall of GFR after 3rd decade – 0.8 ml/min/year

• Causes

• Diabetic Nephropathy

• Chronic Glomerulo Nephritis

• Ischemic Nephropathy

• Chronic tubulo interstitial disease

• ADPKD

Rate of GFR fall (ml/min/yr)
8-10

6-8

4-6

2-4

1-2

• KDIGO classification

Prognosis of CKD by GFR
and albuminuria categories:
KDIGO 2012

				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m ²) description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure [ESRD]	<15			

Manifestations of CKD

- Haematological
 - [Anaemia
 - [Abnormal Haemostasis
- Vascular / Cardiac
 - [Ischemic Vascular disease
 - [Heart failure
 - [Hypertension
 - [Left ventricular Hypertrophy (LVH)
 - [Pericarditis

- Bone mineral disease
- Fluid imbalance
- Hyperkalemia
- Endocrine Abnormalities
- Skin abnormalities
- GI and Nutritional abnormalities
- Uremia

- M/c cause of death - Coronary Artery disease
- Strongest Risk factor for progression - Proteinuria
- Strongest morphological predictor - Degree of tubulointerstitial damage (on biopsy)

Uremia

	Clinical features of uremia appear when $GFR < 15 \text{ ml/min/1.73 m}^2$
• <u>Pathophysiology</u>	① Consequence of accumulation of toxin that normally undergo excretion ② Consequence of loss of other kidney functions like fluid and electrolyte homeostasis & hormone regulation. ③ Progressive systemic inflammation and its vascular and nutritional consequences.
<u>Consequences</u>	• Increased levels of PTH, FGF-23, insulin, prolactin • Increased levels of acute phase reactants (Fibrinogen, C-reactive protein) • Decreased levels of negative acute phase reactants (Albumin, Fetuin) • Decreased levels of vitamin D, calcium, estrogen
	<u>Electrolyte disorders</u>
• <u>Sodium</u>	• Normal levels of sodium is seen in CKD. • Hyponatremia may be seen if water intake exceeds the capacity of renal water clearance. • If hyponatremia occurs, it responds to fluid restriction.
<u>Potassium</u>	• Hyperkalemia may be precipitated in certain settings like ↑ intake, hemolysis, haemorrhage, metabolic acidosis.
• <u>Acid base balance</u>	• Early CKD - Normal anion gap metabolic acidosis • Advanced CKD - High anion gap metabolic acidosis.

Anaemia in CKD

	• Hb $< 10 \text{ g/dl}$ is considered anaemia in CKD • Target Hb $\rightarrow 11 \text{ g/dl}$ • Hb $> 13 \text{ g/dl}$ can increase risk of stroke. • Anaemia Starts appearing in CKD stage III.
• <u>Effects</u>	① Can independently increase rate of GFR fall. ② Progression to LVH $\rightarrow$ diastolic heart failure $\rightarrow$ $\uparrow$ cardiovascular mortality
• <u>Causes in CKD</u>	① Absolute or relative erythropoietin deficiency Erythropoietin $\rightarrow$ Produced by peritubular fibroblasts in interstitium (cortex & outer medulla) in response to HIF [Hypoxia Inducible Factor] $\rightarrow$ Acts on JAK-2 receptors ② Anaemia of Chronic disease ③ Iron deficiency anaemia ④ $\uparrow$ Parathormone (PTH) $\rightarrow$ causes Bone Marrow fibrosis ⑤ Uremia $\rightarrow$ bleeding ⑥ B₁₂ / Folate / other nutritional deficiencies
• <u>Nature</u>	Hypoproliferative

• Mx

① Correct Iron deficiency anaemia

- S. ferritin $\leq 500 \text{ ng/ml}$
PSAT $\leq 30\%$ } Indicative of IDA in CKD.
- Oral iron preparations are not useful.
- Parenteral iron preparations
 - Iron Sucrose (200mg in 1 dose)
 - ferric carboxymaltose (1g)
 - ferric isomaltose (1.5g)
- Fe deficit = $[2.2 \times \text{BW} \times (14 - \text{Hb})] + 1000$ (for iron stores)

② Erythropoietin therapy

- Can be given as:

a) Recombinant human erythropoietin (1st generation)

- $T_{1/2}$ - 8 hrs
- Dose - 20-50 units/kg x 3 times / week.
- Route - IV / Subcutaneous.

b) Darbepoetin alpha (2nd gen)

- Advantages -
 - ① long $T_{1/2}$ (25 hrs) [given once a week]
 - ② Increased carbohydrate content
 - ③ More sialic acid residues

c) Epoetin beta (2nd gen)

- longest $T_{1/2}$ (140 hrs) [given once / month]
- Other names
 - Methoxy Polyethylene Glycol
 - continuous erythropoietin receptor activator
 - [CERA]

- Problems in giving erythropoietin -
 - Stroke
 - MI
 - HTN

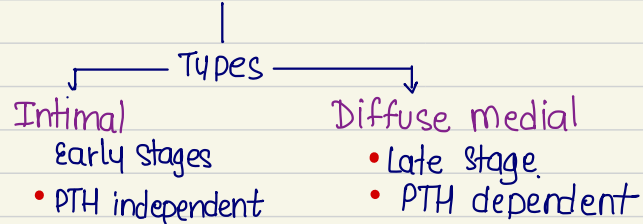
Vascular and Bone mineral disease in CKD

• CKD is a state of accelerated atherosclerosis due to:

- a) ↑ oxidised LDL
- b) ↑ Lipoprotein a
- c) Loss of fetuin in urine
- d) ↑ asymmetrical dimethyl arginine
- e) ↑ PTH

* Statins are not recommended in CKD.

CKD → Irreversible calcification



• Calcification

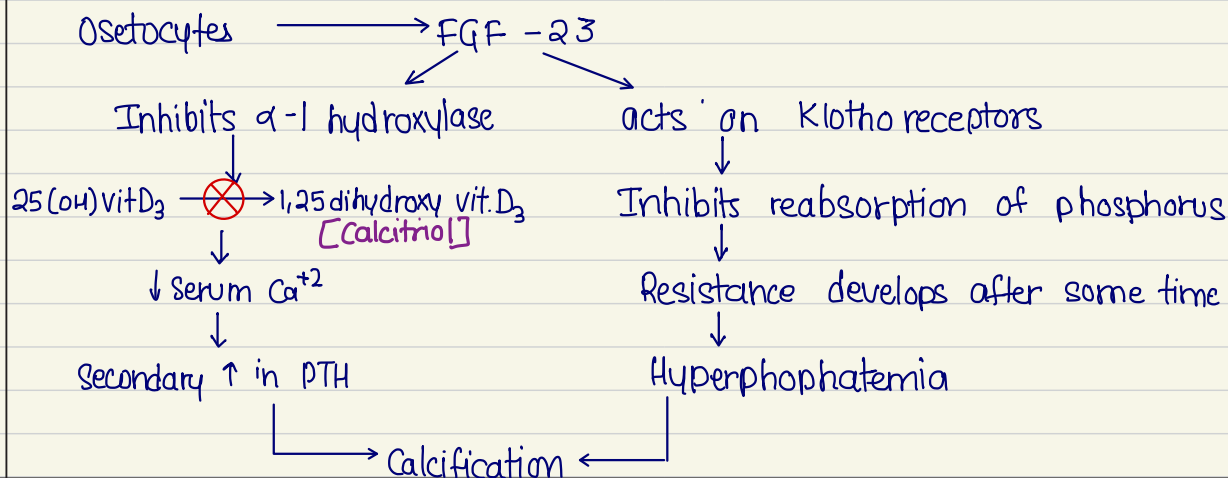
① CKD → ↓ Nephron number

↓
Hyperphosphatemia

↓
Converts normal endothelial cells to osteoblasts

↓
Osteoblasts trap Ca^+ and cause Irreversible Calcification

② In stage III/IV of CKD phosphatonin (FGF 23) is secreted from osteocytes.



• High Bone turnover state

• Seen in 90% cases of CKD

- Characterised by
 - ↑ PTH
 - ↑ Phosphorus
 - ↓ Ca^{+2}
 - ↓ Calcitriol

Due to ↑sed PTH, there is (a) ↑sed Bone formation
(b) ↑sed Bone Resorption

• Hence, bone does not get mineralised i.e. bone contains Calcium Phosphate instead of Calcium Hydroxyapatite

↓

- Bone pain
- Bone prone to fractures

• PTH promotes Bone marrow fibrosis & Diffuse medial Calcification.

Bone tissue which is replaced is not just replaced by bones. Fibrous tissue etc are involved in replacement.
Hence, it is called **Osteitis Fibrosa Cystica**.

• Radiological Findings of Osteitis Fibrosa Cystica

① Subperiosteal resorption on radial side of proximal & middle phalanges of 2nd & 3rd fingers.

② Brown's tumor (localised collection of macrophages)

• Types

• Secondary Hyperparathyroidism -

- ↑ PTH
- ↑ Phosphorus
- ↓ Ca

• Tertiary Hyperparathyroidism - Long standing cases of 2° Hyperparathyroidism.

- very High PTH > 1500 pg/ml
- ↑ calcium
- ↑ Phosphorus

• Mx

① Rx of Hyperphosphatemia

↳ Pure Phosphate binders

- Sevelamer
- Lanthanum
- Sucroferric oxyhydroxide

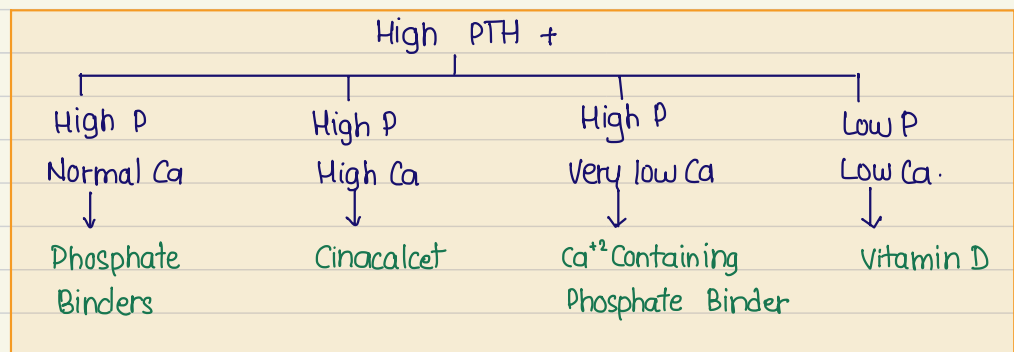
② Reduce PTH

↳ Calcium sensing receptor agonist - Cinacalcet
(Use only if Serum $\text{Ca}^{+2} > 9.5 \text{ mg/dl}$)

• If Calcium levels very low ($< 7.5 \text{ mg/dl}$)

Calcium containing phosphate binders [CaCO_3 ; Ca acetate]

• If Calcium & Phosphorus are low (Rare) - Vitamin D_3 (Cholecalciferol)
↳ 60000 IU/week X 6 times



* Restrict Phosphorus containing food (dairy, nuts etc).

• Parathyroidectomy

Indications in CKD

- ① Refractory Hypercalcemia & Bone disease
- ② Refractory pruritis
- ③ Severe Calcification.

• Low Bone turnover State Adynamic Bone disease

- Seen in
 - ┌ Females
 - ├ Caucasians
 - ├ Diabetics
 - └ Patients on peritoneal dialysis
- More risk for fractures & Calcification.
- Characterised by low PTH Levels
 - ↳ Causes in CKD
 - ┌ Calcium supplements
 - ├ Vitamin D
 - ├ High Calcium in dialysate
 - └ Aluminium in dialysate

Mx Cut off all Calcium supplements-

Cardiac Manifestations in CKD

• manifestations

• CKD is state of accelerated atherosclerosis

① Acute Coronary Syndrome / Ischemic vascular disease.

• Best marker of ACS in CKD - **Troponin I**

↳ standard marker for myocardial injury

* cardiac troponins are elevated in CKD without evidence of ischemia.
Hence serial measurements are needed.

• Inducible Ischemia test $\begin{cases} \text{① Treadmill test} \\ \text{② Dobutamine Stress Echo.} \end{cases}$

• Angiogram

* Baseline EKG is has no value

• m/c cause of death in CKD - Myocardial Infarction.

② Heart failure

③ Hypertension (low BP carries a poorer prognosis in CKD as it signifies poor left ventricular function)

④ Left ventricular Hypertrophy

⑤ Pericarditis - due to advanced uremia.

* A form of low pressure pulmonary edema can also occur in advanced CKD.
↳ Shows **Bat wing** distribution of alveolar edema fluid on chest x-ray.

Nervous system manifestations in CKD

• <u>Uremic Encephalopathy</u>	• Occurs when $GFR < 10 \text{ ml/min}$ • Occurs due to accumulation of Guanido Succinic acid. • Shows 100% response to dialysis. • C/F - Altered sensorium, Gait & Speech abnormalities.
• <u>Uremic Neuropathy</u>	• Small fibre ; Distal to proximal involvement. Sensory motor in nature • Lower limbs involved predominantly • Polyneuropathy
• <u>Dialysis dementia</u>	Due to Aluminium
• <u>Others</u>	• Seizures • Twitching • Restless leg syndrome • Hiccups • Cramps

* Most common neurological manifestation- Peripheral Neuropathy.

* Most common cause of convulsions in CKD- Water Intoxication

Endocrine manifestations in CKD

Hypoglycemia

- Insulin removal impaired due to CKD. Plasma levels of insulin remain slightly to moderately elevated.
- Decreased renal gluconeogenesis also contributes to hypoglycemia.
- Levels of
 - a) LDL - Normal
 - b) Triglycerides - ↑
 - c) HDL - ↓
 - d) Oxidised LDL - ↑
 - e) Lipoprotein a - ↑
 - f) Apo B & Apo C - ↑

Hormone Levels

- Prolactin ↑
- Testosterone / Estradiol ↓
- FSH & LH ↑
- Cortisol ↑
- GH ↑
- Insulin like growth factors ↓
- T₄ ↑
- T₃ ↓
- reverse T₃ ↑

Skin Manifestations in CKD

- Xerosis
- Uremic Pruritis
 - ↳ Rx - Opioid Kappa agonist - Nalfurafine
- Classical skin lesion in CKD - Prurigo Nodularis
- Calcemic uremic arteriopathy / Calciphylaxis
 - ├ Occlusion of dermal vessels producing severe skin necrosis
 - ├ Precipitated by warfarin
 - ├ Rx
 - ├ Sodium thiosulphate
 - ├ Vitamin K
 - └ Stop Ca^{+2}
- Nephrogenic fibrosing dermatopathy
 - ↳ Progressive subcutaneous induration (especially arms & legs)

GIT manifestations in CKD

- Uremic fetor - Urine like odour on breath
- Gastritis / Peptic disease / Mucosal ulcers -
- Uremic GI bleeding
- Malnutrition - CKD is state of protein catabolism.
- Anorexia
- Constipation - worsened by iron & Calcium supplements.
- Malnutrition Inflammation Atherosclerosis Syndrome