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Chronic Kidney Failure

★ **Objectives:**

1. To understand the basic informations on etiology,staging, Diagnosis and treatment.
2. To know complications of CKD and their treatment.
3. To analyze the mechanism and pathophysiology of CKD progression and therapies to slow progression.

★ **Resources Used in This lecture:** Slides-StepUp-Davidson's

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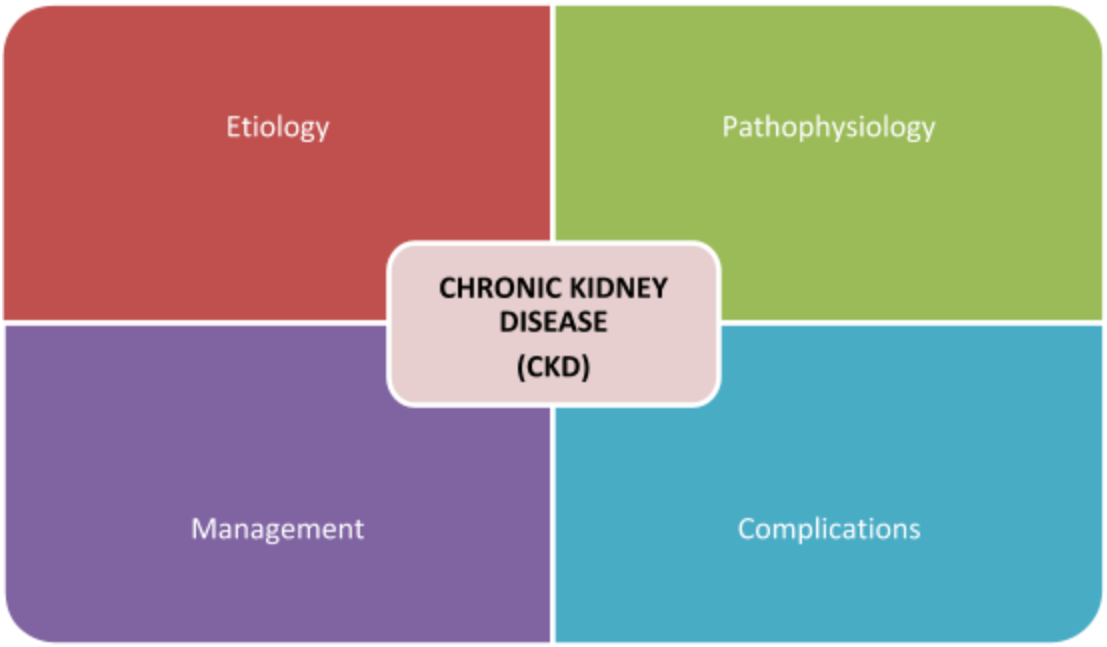


Functions of normal kidneys:

- Fluid balance
- Electrolyte regulation
- Control acid base balance
- Waste removal
- Hormonal function:
    - Erythropoietin
    - Renin
    - Prostaglandins
    - Active vitamin D3

Chronic Kidney Disease (CKD) previously termed as chronic renal failure

chronic progressive **irreversible** loss of renal function. It is defined as the presence of clinical and/or pathologic evidence of kidney disease **for at least 3 months**

ESRD: advanced CKD (Stage-5) requiring dialysis or kidney transplantation

Stages of Chronic Kidney Disease:

stage	Description	GFR (ml/min/1.73m2)
1	Kidney damage with normal or GFR Evidence by lab (e.g. ↑ urea, Creatinine, proteinuria, hematuria...) or by radiology (e.g. cysts, stones, atrophic kidney...) + or normal ↑ GFR.	>90
2	Mild ↓ GFR	60 – 89
3	Moderate ↓ GFR	30 - 59
4	Severe ↓ GFR	15 – 29
5	Kidney failure, ESRD	<15 or dialysis

Etiology of CKD include:

- Diabetes Mellitus (30% of cases)
- Hypertension (25% of cases)
- Glomerulonephritis
- Interstitial nephritis/pyelonephritis
- Congenital and inherited "polycystic disease"
- Miscellaneous
- Tumors

Risk Factors For CKD:

1. Genetic (family hx of kidney disease)
2. Low socioeconomic status
3. Medical status: diabetes, hypertension, Obesity, smoking & cardiovascular disease

Pathophysiology:

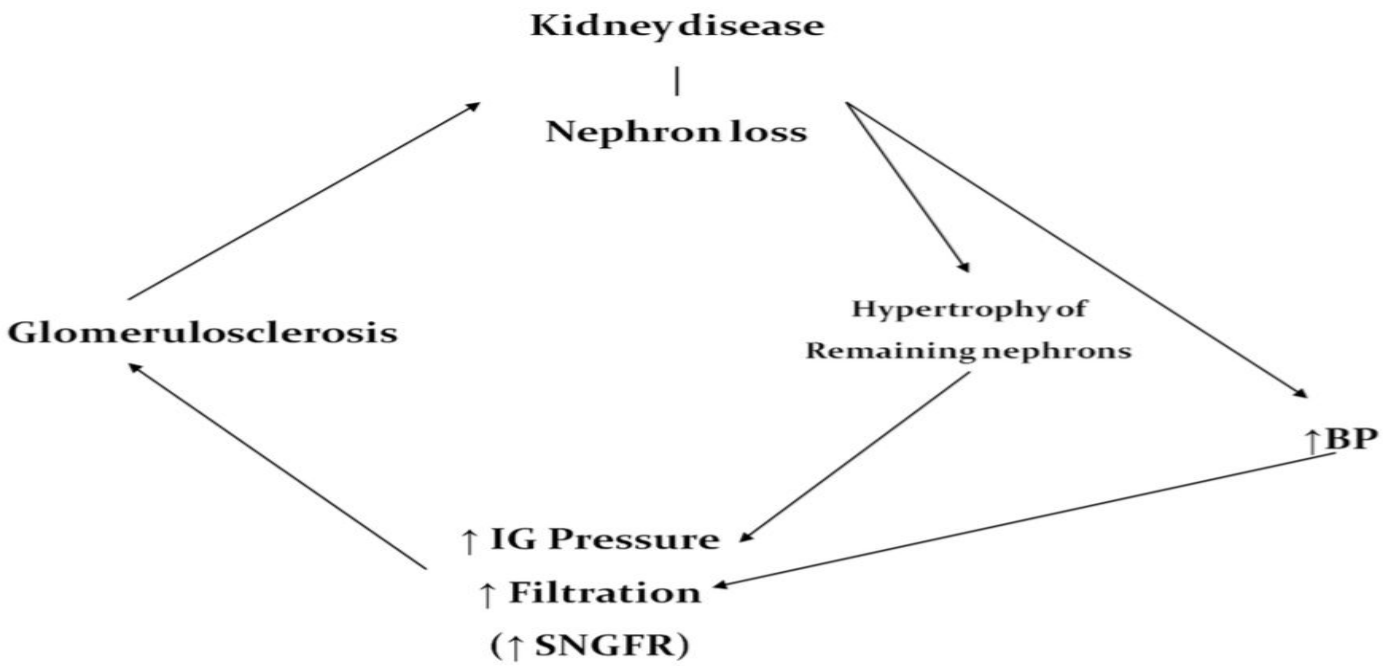
Underlying kidney disease → Loss of some nephrons → Kidney try to compensate by two mechanism:

1. Increase Blood pressure (Due to decreased GFR).
2. Increase single nephron GFR [SNGFR] in the remaining nephrons by hypertrophy and hyperfunction leading to:
   a. ↑ Intraglomerular pressure and ↑ Filtration (still the total GFR is decreased).
   b. Enhance proximal reabsorption of NaCl, Fluids and PO4.
   c. Enhance collecting ducts secretion of K+ and H+.

These adaptations **initially** restore hemeostasis. But **glomerular hyperfiltration → glomerular injury,** glomerulosclerosis and further loss of renal function.
Also will result in increase of some Growth factors such as:

- Transforming growth factor-B
- Platelets derived growth factors
- Osteopontin, angiotensin-II
- Endothelin.

leading to **further kidney damage and interstitial fibrosis.**



★ Factors contributing to the Progression of CKD

- Degree of hypertension
- Severity of proteinuria
- Hyperlipidemia
- Drugs (NSAID)
- High protein diet
- Persistent metabolic acidosis
- Extent of tubulointerstitial disease

★ Clinical Feature of CKD:

The typical presentation is with a **raised urea and creatinine** found during routine blood tests, frequently accompanied by hypertension, proteinuria or anaemia.

★ Symptoms and Signs:

Most patients with slowly progressive disease are asymptomatic until GFR falls below 30mL/min/1.73 m2 (stage 4 or 5) and some can remain asymptomatic with much lower GFR values **than** this.

★ Uremic syndrome:

Uremia results from retention of **end products of protein metabolism.** i.e. urea
Administration of urea causes only mild symptoms. Other potential uremic toxins:

- Guanidine
- Phenoles
- P2 microglobulin
- Phosphate
- Hipurate
- Polyamines
- Homocysteine
- Purines
- Parathyroid hormone (PTH)
- Dimethyl arginine

Changes occur in CKD patients

❖ Metabolic and electrolytes abnormalities in CKD:

A. Carbohydrate intolerance:

- Insulin is degraded by the liver and kidneys
- The decrease in insulin clearance is offset by peripheral insulin resistance
- Hyperparathyroidism inhibits insulin secretion
- Decrease in requirements for insulin and OHD in diabetic patients as they develop renal failure. Otherwise, they might develop hypoglycemia as they have decrease in insulin clearance.

B. dyslipidemia:

- ↓ HDL cholesterol
- ↑ TG and lipoprotein (α)

C. Fluid and Electrolytes:

- ↓ GFR and defective tubular function → expansion of plasma and ECF volumes, edema, and hypertension.
- **Hyponatremia** can result from failure to excrete free water when intakes exceed 1.5L/day. Hypertension is common unless Na+ intake is restricted to 100 meq/day.
- Patient with salt losing nephropathy require stepwise increases in Nacl and fluid intake.
- K+ elimination in CKD is **initially** maintained by:
    - enhanced K+ secretion in surviving nephrons
    - colonic K+ secretion (from aldosterone stimulated by hyperkalemia and metabolic acidosis)

However, as GFR decreases, K+ elimination is reduced → **hyperkalemia.**

D. Acid-Base abnormalities – metabolic acidosis

- The body produces about 80 mmol of non-volatile acids from metabolism everyday.
- These acids accumulates as renal failure progresses.
- Production of ammonia NH_3 (in distal and CD cells) decreases → limits distal tubular H^+ trapping as NH_4 and hence, decreases renal bicarbonate regeneration.
- Additionally, there may be proximal HCO_3 wasting or reduced distal H^+ secretion.

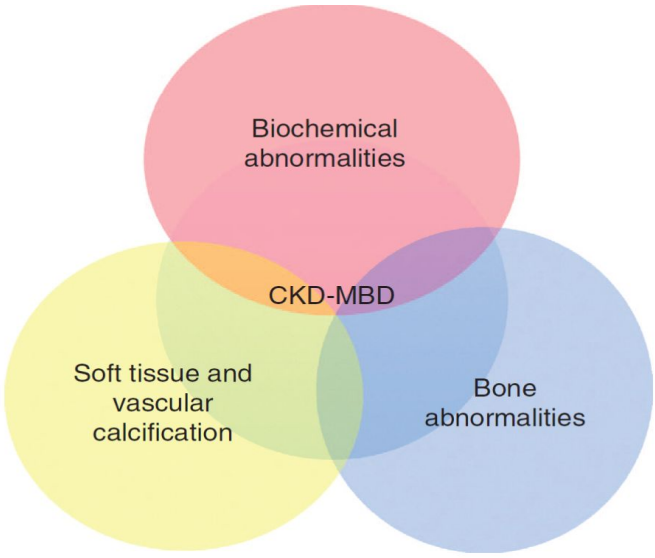
E. Chronic Kidney Disease-mineral and bone disorder CKD–MBD:

Indicates alterations in mineral bone metabolism, these alterations include:

1. biochemical abnormalities in **calcium, phosphorus,PTH, vitamin D and fibroblast growth factor-23.**
2. changes in bone morphology: volume, turnover,and mineralization
3. calcification of soft tissue and blood vessels

As GFR declines, the excretion of phosphorus is impaired, leading to a tendency to hyperphosphatemia.

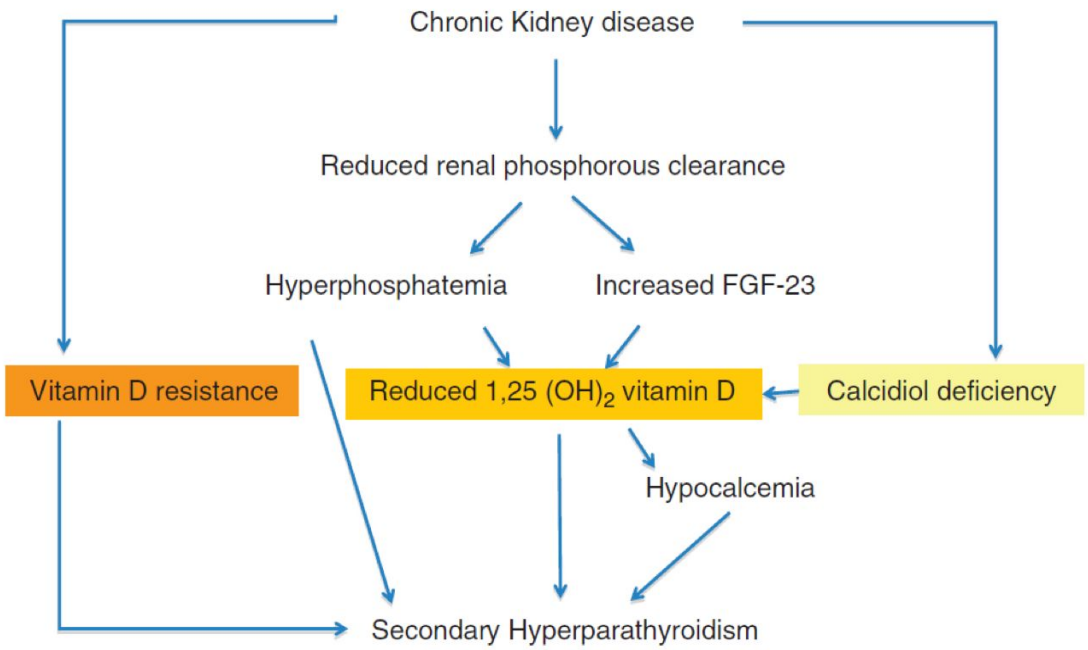
Hyperphosphatemia is an independent risk factor for the increased morbidity and mortality of stage 5 CKD from cardiovascular events.



Recently, it has been demonstrated that fibroblast growth factor 23 (FGF-23) is stimulated by **phosphorus retention.**
FGF-23 causes phosphaturia (via both parathyroid-dependent and independent mechanisms) and maintain serum phosphorus in the normal range **until GFR declines to < 30 ml/min/1.73m2.**

FGF-23 also decreases 1,25-dihydroxyvitamin D (calcitriol) formation which in conjunction with hyperphosphatemia, will lead to parathyroid hyperplasia and an increase in PTH secretion.

★ **The classic biochemical abnormalities:**
- hypocalcemia
- hypophosphatemia
- hyperparathyroidism
- hypovitaminosis D
- elevated FGF-23



E.Renal Osteodystrophy (ROD)

is a complex disorders of bones in uremic patient resulting from abnormalities of mineral ions (Ca, po4, Mg) ,PTH , Vit-D and FGF23 metabolism in the presence of factors related to the uremic state.
Spectrum of bone abnormalities in ROD:

1. *Osteitis fibrosa cystica* (high bone turnover), due to:
   a. PTH
   b. activity of both osteoclast and osteoblast

2. *Adynamic bone disease* (low bone turnover): A defect in osteoblast development or activity caused by factors related to the uremic state.
   Risk factors for adynamic bone disease:
   - Advanced age
   - CAPD
   - Diabetes mellitus
   - Calcitriol therapy
   - Parathyroidectomy
   - Flouride and iron intoxication
3. *Osteomalacia* (low turnover accompanied by under mineralized bone tissue)
4. *Combination of the above*

Patients with these bone abnormalities may be asymptomatic or may develop symptoms related to bone pain or fractures.
ESRD patients on dialysis have > 3-4 times increased risk of vertebral and hip fractures compared to general population even after adjustment for age, gender and race.

❖ Cardiovascular:

1. Hypertension Occurs in 90% of patients with ESRD
   - Secondary to **Salt and water retention.**
   - Inappropriate secretion of RAA system.
   - ↑ sympathetic tone
   - ↑ generation of vasoconstrictors (endothelin)
   - ↓ generation of vasodilators (nitric oxide)
2. Cardiomyopathy
   - left ventricular hypertrophy (LVH)
   - Coronary artery disease (CAD)
   - Congestive heart failure (CHF)
   - Diastolic dysfunction
3. Pericarditis and pericardial effusion
   - Due to Uremia. It's an indication of Dialysis.
4. Congestive heart failure
   - Due to Volume overload, HTN, and Anemia.

◆ These abnormalities increase 2-5 folds in ESRD
◆ About one-half of all hemodialysis patients have significant ischemic heart disease
◆ Dyslipidemia, HTN, homocystin, DM, and insulin resistance contribute to atherosclerosis
◆ Anemia aggravates LVH
◆ Hyperparathyroidism amyloidosis, and iron overload cause also cardiac dysfunction.

❖ GI:

- Nausea, Vomiting.
- Loss of appetite (Anorexia).
- Uremic faetor, stomatitis, esophagitis, gastritis, and peptic ulcer disease
- ↑ Gastrin in CKD

❖ Neuromuscular abnormalities

CNS dysfunction:

- Decreased attention, agitation, confusion, insomnia, and impaired memory
- May develop also: depression, hallucinations, delusions, hiccups, cramps, **flapping tremor,** "sign of encephalopathy and indication of hemodialysis"
- myocloms, fasciculation, and uremic seizures.
- Lethargy, Confusion, Tetany due to **Hypocalcemia**

Peripheral neuropathy:

- usually symmetric, lower limbs
- Sensory precedes motor dysfunction
- Hyperreflexia
- Restless leg syndrome, in which the patient's legs are jumpy during the night. and burning feet
- Postural hypotension (autonomic dysfunction)
-

❖ Hematological:

Anemia:

- Develops as serum creatinine increases > 180 mcm/L and GFR declines to <30 ml/minute
- Normocytic,normochromic anemia
- Main cause: decreased production of EPO

Platelet Dysfunction:

- Bruising, ecchymoses, bleeding from mm
- Platelets dysfunction (count is normal): ↓ VWF, which facilitate the interaction between platelets and endothelium through its binding to platelet glycoprotein (IIb, IIIa) receptors.

❖ Immunologic:

Impair cellular and humoral immunity → increased susceptibility to infections " degranulation is impaired"

❖ Dermatologic abnormalities

Uremic pruritus is related to:

- Calcium and phosph deposition (secondary to ↑ PTH)
- Hypercalcemia
- Peripheral neuropathy
- Dry skin
- Anemia
- Inadequate dialysis

★ Natural History of CKD:

Early: usually asymptomatic in its early stages.

Late: symptoms and signs usually related to:

- sodium and water retention **(HTN, Edema)**
- metabolic and hormonal complications **(anemia, vit–D deficiency, ↑ PTH)**
- Increased incidence of CVD, infection, and Impaired physical function.

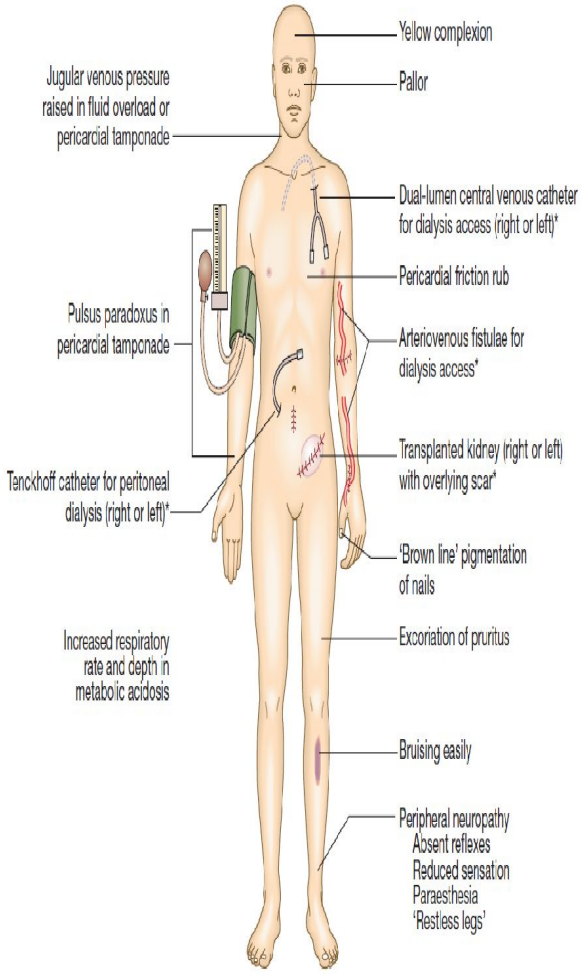


Fig. 17.13 Physical signs in advanced chronic kidney disease. (*Features of renal replacement therapy)

★ Evaluation of Patients with CKD

- The history should document the presence of uremic symptoms and possible etiology from: Diabetes Mellitus, Hypertension, congestive Heart Failure, MM, NSAID
- Family history can suggest PCKD or hereditary nephritis
- Volume depletion and obstructive nephropathy should be identified and treated promptly
- Ultrasound – small, shrunken kidneys
- Normal kidney size with CKD: DM, amyloid, MM

All patients with CKD should have a basic evaluation including : CBC, urinalysis, U&E, LFTs, Ca, P, magnesium, PTH, Vit-D, urine pro/cr ratio.

Further evaluations will depend on initial findings and likely diagnostic possibilities

Investigation

- **CBC:** Anemia, thrombocytopenia
- **Urinalysis**: Hematuria and proteinuria may indicate cause. Proteinuria indicates risk of progressive CKD requiring preventive ACE inhibitor or ARB therapy
- **Measure Cr clearance to estimate GFR**
- **Serum electrolytes** (K^+, Ca^{2+}, PO_4^{3-}, Serum protein)
- **Renal ultrasound:** evaluate size of kidneys/rule out obstruction
    - Small kidneys are suggestive of chronic renal insufficiency with little chance of recovery.
    - Presence of normal-sized or large kidneys does not exclude CKD.
- **Renal biopsy**—in select cases to determine specific etiology.

Management of CKD Patients

1. Nutrition: restriction intake of:

- protein; not less than 0.8mg/kg/day
- Phosphate
- sodium
- potassium

2. Salt and water retention:

- Salt intake restriction "daily Na^+ < 100 meq
- fluid restriction 1 – 1.5 L/day
- Loop diuretics
- RAS inhibition (ACEi, ARB) if HTN w proteinuria

3. Hyperkalemia:

- Exogenous sources of K^+ : dates, dried fruits, citrus fruits, banana, chocolate, salt substitute
- Medications that ↑ K^+: ACEI, ARB, NSAID, K^+- sparing diuretics, B-Blockers, and heparin.

Treatment of hyperkalemia:

- IV calcium gluconate 10 cc of 10%
- Followed by 25 ml of 50% dextrose solution with 5-10 units regular insulin
- B_2-adrenergic agonist nebulizer **(salbutamol)**
- $NaHCO_3$ IV/oral

4. Hyperphosphatemia and secondary hyperparathyroidism:

a. Reduce phosphate intake to < 10 mg/kg/day

b. Phosphate binders: **Calcium carbonate, Sevelamer (Renagel), Lanthanum carbonate**

c. Vitamin D (Calcitriol) 0.125 mcq/day

- Must be withheld until s. phosphate concentration have been controlled to < 6 mg/dl **because it may cause severe soft tissue calcifications.**
- Vitamin D compounds can cause hypercalcemia and hyperphosphatemia, which may increase coronary calcification, **so parcicalcitrol (Zemplar) is an analogue that inhibits PTH synthesis without elevation of calcium/phos.**

d. Indication for parathyroidectomy: **PTH > 800 pg/ml with symptoms of bone disease (myopathy, bone pain) persistent hyperphosphatemia soft tissue calcifications.**

5. Hyperlipidemia

the goal is to keep low density lipoprotein cholesterol < 100 mg/dl by diet control and statin group.

6. Anemia

Target Hb/Hct:

- K DOQI → Hb 11-12
  Hct 33-36%

- Anemia will cause left ventricular hypertrophy, decrese quality of life and reduces survival in patients on HD

- Conversely: Hb > 13 and Hct > 42 are associated with more coronary events and increased mortality as evidenced by CHOIR (USA) and CREATE (Europe) studies

target iron levels:

- percent transferrin saturation (T-SAT) reflects iron available for erythopoiesis
- serum ferritin reflects overall iron stores
- in CKD, target T-Sat > 20 (20 – 50)
- target S. ferritin > 100 ng/ml
- **iron supp should be withheld, if T-sat > 50 , S. ferritin > 800 ng/ml**

Treatment Guidelines (Anemia):

A. Oral iron

- *in non-dialysis patients (CKD stages 1-4)*: 100-200 mg elemental iron should be given daily in 2-3 days, either one hour before meals or two hours post. (1 tab Ferrous fumerate, 200 mg contains 66 mg elemental iron)
- *In dialysis patients (CKD 5):* IV iron should be given as ongoing iron losses tends to be higher

B. IV iron

- 1 gr of iron saccharate (ferrosac) divided into 10 doses of 100 mg given with each dialysis session.

C. Recombinant Erythropoeitin–epoeitin alfa (eprex):

- patients on: starting dose 120 – 180 IU/kg/week, IV
- pre-dialysis patients and PD patients: 80-120 IU/kg/week subcutaneously weekly dose
- Hb/Hct monitoring every 4 weeks
- the most common side effects: headache, HTN, arthralgia, and diarrhea
- resistance to epoeitin:

1. inadequate Epo dose
2. anemia of chronic disease (infection, inflammation)
3. functional iron deficiency
4. secondary to hyperparathyroidism
5. carnitine deficiency
6. hemoglobinopathies
7. aluminum toxicity
8. B_{12}/folate deficiency
9. Malnutrition

D. Darbepoetin Alfa (Aranesp)

- Recombinant Epo
- Half-life: three folds longer IV and two folds longer S/C than that of epoetin
- Recommended starting dose 0.45 mcg/kg S/C weekly or double the dose every 2 weeks.

Transplantation is the only cure.

Medications:

- **Loop diuretics** (fursemide) (Salt and water retention).
- **RAS inhibition** (ACEi, ARB) if HTN with proteinuria.
- **Phosphate binders** (Calcium carbonate, Sevelamer (Renagel), Lanthanum carbonate). given with meals.
- **Statin** (hyperlipidemia).

- **Parcicalcitrol (Zemplar)** inhibits PTH synthesis without elevation of Ca^{2+}/PO_4^{3-} (vitamin D compounds → Hypercalcemia + Hyperphosphatemia → coronary calcification). Parathyroidectomy when PTH 800 pg/ml + bone disease symptoms (myopathy, bone pain) + persistent hyperphosphatemia soft tissue calcifications.
- **Hyperkalemia** (temporary protect the heart from arrhythmia by shifting the K^+ into the cell): IV calcium gluconate 10 cc of 10% → 25 ml of 50% dextrose solution with 5-10 units regular insulin → B2-adrenergic agonist nebulizer (salbutamol) → $NaHCO_3$ IV/oral.
- **Erythropoietin** for anemia (Hemoglobin should not go back to normal but around 11-12, if more than 12 high chance of strokes and cardiac problems).
- **Oral Iron** (100-200mg) if not on dialysis, IV Iron if on Dialysis divided into 10 doses of 100 mg given with each dialysis session.

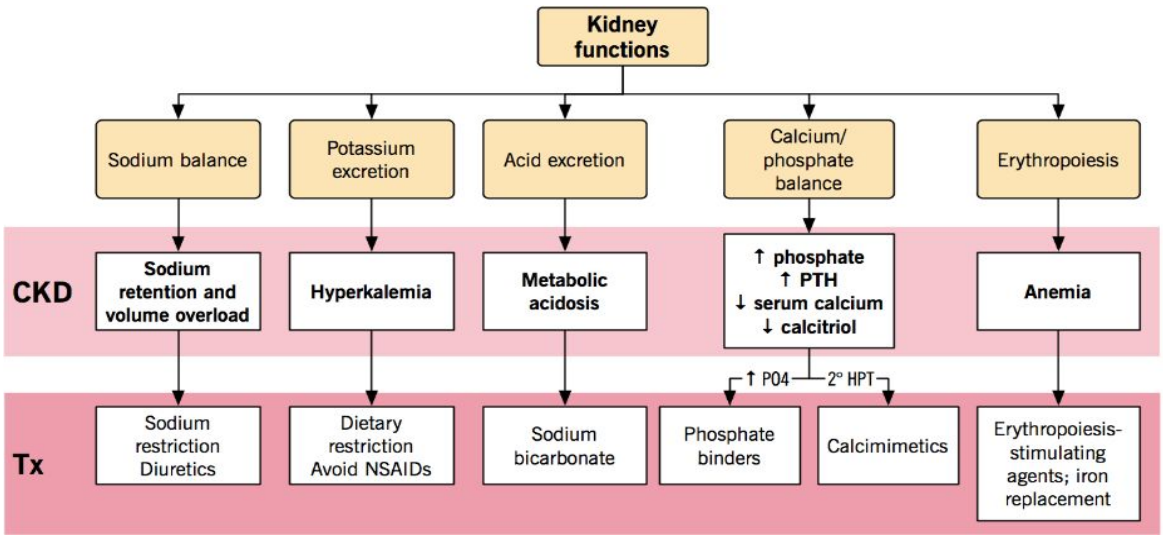
Dialysis:

Should be delayed until their GFR drops to 8-6 mL/min/1.73 m^2 or until the first onset of a clinical indication.

(The overall aim is to commence Dialysis by the time symptoms of CKD have started to appear but before serious complications have occurred.)

- Clinical indication:
- Symptoms of uremia: Pericarditis, Lethargy, deterioration in mental status, encephalopathy, seizures.
- Fluid overload: Pulmonary edema, Hypertensive emergency.
- Refractory hyperkalemia or Acidosis.
- Intoxications: methanol, ethylene glycol, lithium, aspirin.

Cr and BUN levels are NOT absolute indications for dialysis.



Exercise

Aerobic exercise and resistance training have been shown to:

- decrease inflammation, oxidative stress, endothelial dysfunction and insulin resistance.
- reduce blood pressure.
- improve hyperlipidemia, proteinuria, and obesity.
- decrease CV mortality/morbidity.
- may decrease the rate of progression of CKD.

Treatment of the Manifestations of ESRD	
Manifestation	**Treatment**
Anemia	Erythropoietin replacement and iron supplementation
Hypocalcemia and osteomalacia	Replace vitamin D and calcium
Bleeding	DDAVP increases platelet function; use only when bleeding
Pruritus	Dialysis and ultraviolet light
Hyperphosphatemia	Oral binders: see "Treatment of Hyperphosphatemia"
Hypermagnesemia	Restriction of high-magnesium foods, laxatives, and antacids
Atherosclerosis	Dialysis
Endocrinopathy	Dialysis, estrogen and testosterone replacement

MCQs

1) Which of the following is due to hyperparathyroidism in CKD?

a. Osteomalacia

b. Adynamic bone disease

c. Osteitis fibrosa cystica

d. Osteosarcoma

2) CKD patient with GFR of 68. Which stage is he at?

a. Stage 1

b. Stage 2

c. Stage 3

d. Stage 4

3) CKD causes:

a. Decreased TG levels

b. Decreased HDL levels

c. Increased glucose levels

d. Increased PH levels

4) Insulin is used in CKD to:

a. Manage hypokalemia

b. Manage hypophosphatemia

c. Manage hyperphosphatemia

d. Manage hyperkalemia

Answares:

1. C
2. B
3. B
4. D