Chronic kidney failure

Objectives:

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

[Color index : Important | Notes | Extra]

Resources:

- 435 slide, team 434 and team 432

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- Done by: Omar Alqahtani & Hassan Albeladi
- Team sub-leader: Shamma Alsaad
- Team leaders: Khawla AlAmmari & Fahad AlAbdullatif
- Revised by: Ahmad Alyahya

The basic informations on staging, etiology and risk factors

Functions of normal kidneys:

- Fluid balance
- Electrolyte regulation
- Control acid base balance
- Waste removal
- Hormonal function:
  - ➔ Erythropoietin The most important, Goes to bone marrow to produce RBCs
  - ➔ Renin
  - ➔ Prostaglandins
  - ➔ **Active** vitamin D3 which regulates bone mineralization

Chronic Kidney Disease (CKD): used to be known as chronic renal failure

- Chronic progressive **irreversible**[1] 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/G5 requiring dialysis or kidney transplantation.**

Stages of Chronic Kidney Disease:

Stage	Description	GFR (ml/min/1.73m^2)[2]
1	**Kidney damage with normal or ↑ GFR** You need evidence of kidney injury either by: ➔ Lab tests: high urea high creatinine, hematuria, proteinuria or cast. ➔ Radiological evidence like cyst(s), shrinking kidney, kidney scars, kidney stones or hydronephrosis.	**≥ 90**
2	**Mild ↓ GFR**	**60 – 89**
3	**Moderate ↓ GFR**	**30 - 59** Stage A: 30-45 Stage B: 46-59
4	**Severe ↓ GFR**	**15 – 29**
5	**Kidney failure, (ESRD)**	**<15 or dialysis**

[1] Which differentiates it from AKI which is reversible
[2] Normal GFR is 125ml/min /1.73m^2

Etiology of CKD:

1. **Diabetes Mellitus** 40% of cases
2. **Hypertension** 30% of cases
3. **Glomerulonephritis** 15% of cases
4. Hereditary cystic and congenital renal disease "polycystic disease" 4% of cases
5. Interstitial nephritis/pyelonephritis 4% of cases
6. Miscellaneous 5% of cases
7. Tumors 2% of cases

Risk Factors For CKD:

- ➔ **Genetic** (family hx of kidney disease)
- ➔ Low **socioeconomic** status
- ➔ **Medical status:** Diabetes, hypertension, Obesity, smoking & cardiovascular disease

The mechanism and pathophysiology of CKD progression

Chronic kidney disease.

Pathophysiology of CKD:

It occurs by two correlated mechanisms:

1. **Underlying kidney disease**[3] **→ Loss of nephron mass → Kidneys try to compensate by:**

   Increasing Blood pressure due to decreased GFR and increased single nephron GFR (SNGFR) in the remaining nephrons by hypertrophy and hyperfunction leading to:

   - ➔ ↑ Intraglomerular pressure and ↑ Filtration (still the total GFR is decreased).
   - ➔ **Enhance proximal reabsorption of NaCl, Fluids and PO4.**
   - ➔ **Enhance collecting ducts secretion of K+ and H+**

   These adaptations initially restore homeostasis Since the basement membrane carries the hyperfiltration for a certain limit. If it continues it will get damaged.

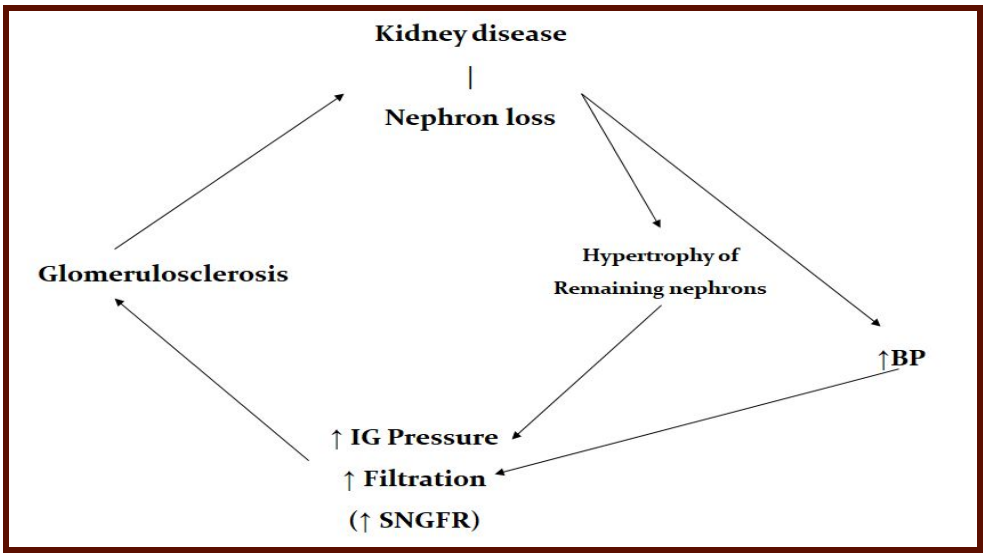
   Glomerular hyperfiltration → glomerular injury → glomerulosclerosis → further loss of renal function.

2. **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 **Tubulointerstitial fibrosis**.

[3] DM or glomerulonephritis

Vicious cycle of CKD that leads to ESRD:



Factors contributing to the Progression of CKD:

- Degree of **hypertension** the most important factor
- Severity of **proteinuria**
- **Hyperlipidemia**
- Drugs: **NSAID** and **Aminoglycoside**
- High **protein** diet
- Persistent **metabolic acidosis**
- **Extent** of **tubulointerstitial** disease.

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 just go through them:

  - ➔ Guanidine
  - ➔ Phenoles
  - ➔ P_2 microglobulin
  - ➔ Phosphate
  - ➔ Hipurate
  - ➔ Polyamines
  - ➔ Homocysteine
  - ➔ Purines
  - ➔ Parathyroid hormone (PTH)
  - ➔ Dimethyl arginine

Changes in CKD patients.

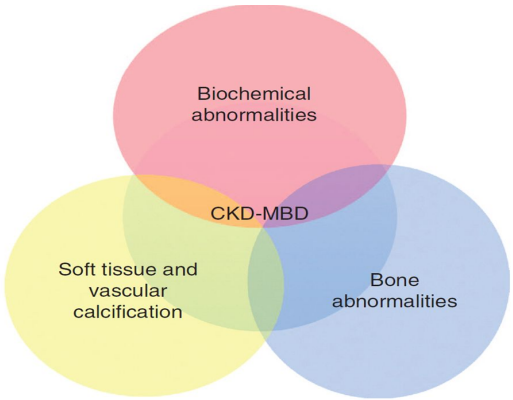
A. Metabolic and electrolytes abnormalities in CKD:

Abnormality	Information
Carbohydrate intolerance	➔ Insulin is degraded by the liver and kidneys. ➔ ↓ in insulin clearance is offset by peripheral insulin resistance. ➔ **Hyperparathyroidism inhibits insulin secretion.** ➔ ↓ in requirements for insulin and OHD[4] in diabetic patients as they develop renal failure. Otherwise, they might develop hypoglycemia as they have decrease in insulin clearance.
Dyslipidemia	➔ ↓ HDL cholesterol. ➔ ↑ TG and α lipoprotein.
Fluid and Electrolytes:	➔ ↓ **GFR** and **defective tubular** function → **Expansion of plasma and ECF volumes**, edema and hypertension. ➔ Water intake exceeds 1.5L/day + ↓ salt intake → failure to excrete free water → Hyponatremia. ➔ Water intake less than 0.5 L/day + ↑ salt intake → Hypernatremia. ➔ Hypertension is common **unless Na+ intake is restricted to 100 meq/day** → Patients 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 as 20% of the total secretion - hyperkalemia and metabolic acidosis → aldosterone stimulation → ↑ Colonic K+ secretion. However, **as GFR and K+ secretion ↓ → hyperkalemia.**
Acid-Base abnormalities: metabolic acidosis	➔ The body produces about **80 mmol of non-volatile acids**[5] daily from metabolism. ➔ These acids accumulate as renal failure progresses. ➔ Production of **ammonia NH3** (in distal and CD[6] cells) ↓ → limits distal tubular H+ trapping as NH4 and hence, ↓ renal bicarbonate regeneration. ➔ Additionally, there may be proximal HCO3 waste or reduced distal H+ secretion.

B. 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**.

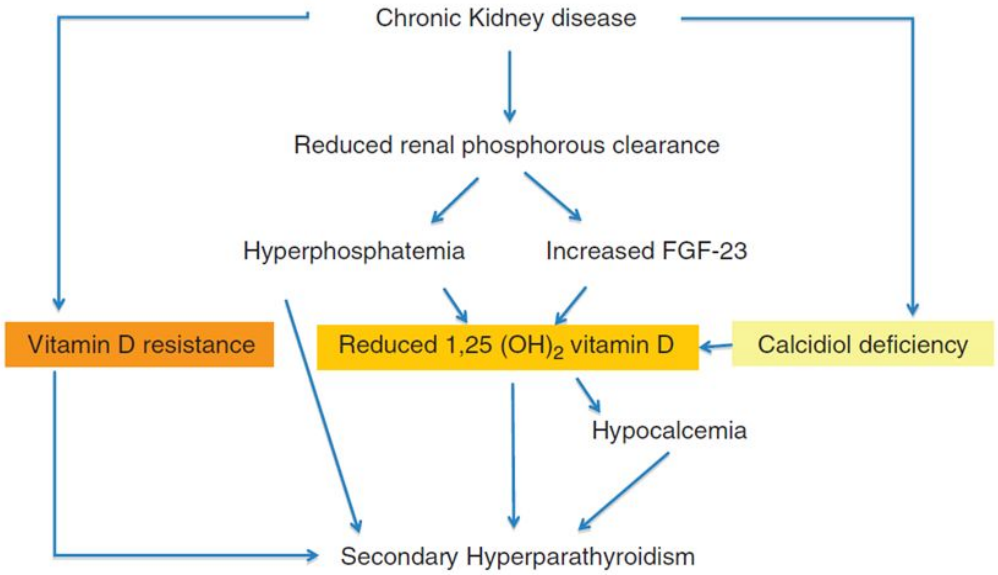


[4] Oral hypoglycemic drugs
[5] A nonvolatile acid (also known as a fixed acid or metabolic acid) is an acid produced in the body from sources other than carbon dioxide, and is **not excreted by the lungs** for example : phosphoric acid (excreted via the kidneys). Volatile acids (HCO3) are **excreted by the lungs.**
[6] Collecting ducts

1. Biochemical abnormalities:

- As **GFR declines**, the **excretion of phosphorus is impaired;** **as the only way to excrete phosphorus is through the kidney,** leading to a tendency for **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 **maintains serum phosphorus in the normal** range until **GFR** declines to **< 30** ml/min/1.73m^2.
  - ➔ **FGF-23** also ↓ 1,25-dihydroxyvitamin D (**calcitriol**) formation **which in conjunction with hyperphosphatemia → parathyroid hyperplasia** and an ↑ **in PTH** secretion.



Secondary Hyperparathyroidism is stimulated by hyperphosphatemia, Hypovitaminosis D or Hypocalcemia

- **What are the reasons for altered vitamin D metabolism in CKD?** (just go through them)
  1. **Calcidiol deficiency:** Reduced sun exposure, reduced skin synthesis, reduced ingestion of foods rich in vitamin D, loss of DBP with proteinuria.
  2. **Calcitriol deficiency:** Reduced calcidiol availability, reduced renal 1-α hydroxylase availability, down regulation of renal 1-α hydroxylase from hyperphosphatemia and FGF-23, reduced endocytotic uptake by megalin, increased degradation of calcitriol by PTH and FGF-23.
  3. **Calcitriol resistance:** Loss of VDR in parathyroid glands, impaired binding of active vitamin D to VDR and impaired binding of vitamin D–VDR complex to the VDR element.

- **The classic biochemical abnormalities of CKD–MBD:**
  - ➔ Hypocalcemia
  - ➔ Hyperphosphatemia
  - ➔ Hyperparathyroidism
  - ➔ Hypovitaminosis D
  - ➔ Elevated FGF-23

2. **Bone abnormalities = Renal Osteodystrophy (ROD):**

- **A complex disorders of bones in uremic patients** 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:
        - ➔ ↑ PTH
        - ➔ ↑ 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: (just go through them)
        - ➔ Advanced age
        - ➔ CAPD [7]
        - ➔ Diabetes mellitus
        - ➔ Calcitriol therapy
        - ➔ Parathyroidectomy
        - ➔ Fluoride 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 more than 3-4 times increased risk of vertebral and hip fractures** compared to general population even after adjustment for age, gender and race.

3. **Calcification of soft tissue and blood vessels.**

Most CKD mortalities result from vessel calcification,predominantly in the heart (e.g. angina and MI) and brain

C. Changes to other body systems			
Cardiovascular: Abnormalities of ESRD	**Hypertension**	➔ Occurs in 90% of patients with ESRD ➔ Secondary to Salt and water retention *(the primary cause).* ➔ Inappropriate secretion of RAA[8] system. ➔ ↑ sympathetic tone ➔ ↑ generation of vasoconstrictors (endothelin) ➔ ↓ generation of vasodilators (nitric oxide)	➔ **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.
	Cardiomyopathy	➔ **Left Ventricular Hypertrophy (LVH)** ➔ **Coronary Artery Disease (CAD)** due to calcification → Angina and MI ➔ **Congestive Heart Failure (CHF)** ➔ **Diastolic Dysfunction**	
	Pericarditis and pericardial effusion	**Due to Uremia** **Hallmark : Bloody fluid**	
	Congestive heart failure	**Due to volume overload, HTN, and Anemia**	

[7] continuous ambulatory peritoneal dialysis
[8] renin angiotensin aldosterone system

GI	**↑ Gastrin in CKD**	➔ Nausea, vomiting and anorexia[9] **Very common** ➔ Uremic faetor, Stomatitis, Esophagitis, Gastritis, and peptic ulcer disease
Neuromuscular abnormalities	**CNS dysfunction**	➔ ↓ attention, agitation, confusion, insomnia, and impaired memory ➔ May develop also: Depression, hallucinations, delusions, **hiccups**, cramps, **flapping tremor[10]. Dialysis must immediately be applied to patients with a flapping tremor. Otherwise they will develop seizures, epilepsy and coma** ➔ Myoclonus, fasciculation, and uremic seizures ➔ Lethargy, Confusion, Tetany due to **Hypocalcemia**
	Peripheral neuropathy	➔ Usually symmetric, lower limbs ➔ Sensory precedes motor dysfunction ➔ Hyperreflexia ➔ Restless leg syndrome and burning feet ➔ Postural hypotension (autonomic dysfunction)
Hematological	**Anemia**	➔ Main cause: **↓ production of EPO** ➔ Develops as **serum creatinine** increases > 180 mcm/L and GFR declines to <30 ml/minute ➔ Normocytic,normochromic anemia
	Platelet Dysfunction	➔ Bruising, ecchymoses, bleeding from mm[11] ➔ 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**	
Dermatologic abnormalities	**Uremic pruritus**	is related to: ➔ Calcium and phosph deposition (secondary to ↑ PTH) ➔ Hypercalcemia ➔ Peripheral neuropathy ➔ Dry skin ➔ Anemia ➔ Inadequate dialysis

[9] Loss of appetite

[10] Flapping tremor is a sign of encephalopathy which occurs in in Renal failure, liver failure and respiratory failure type two due to CO_2 retention

[11] Mucous membrane

Diagnosis

General Features of CKD:

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

Natural History of CKD:

- ➔ **Early: usually asymptomatic in its early stages**[12] [13].
- ➔ **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

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[14], NSAID
- ➔ Family history can suggest PCKD (Polycystic kidney disease) or hereditary nephritis
- ➔ Volume depletion and obstructive nephropathy should be identified and treated promptly
- ➔ Ultrasound: Evaluate size of kidneys and to rule out obstruction.
  - Small, shrunken kidneys
  - Normal kidney size with CKD[15]: DM, amyloid, MM
- ➔ All patients with CKD should have a basic evaluation including :

Test	Indications
CBC	Normocytic, normochromic anemia
Urinalysis	➔ Proteinuria → risk of progressive CKD → requiring preventive ACE inhibitor or ARB therapy ➔ Hematuria
Urea and electrolytes[16]	Uremia **Hyperkalcemia, hypocalcemia and hyperphosphatemia**
PTH	Secondary hyperparathyroidism
Vit-D	Hypovitaminosis D
Cr clearance	To estimate GFR
Urine pro/cr ratio.	
LFTs	

- ➔ **Further evaluations will depend on initial findings and likely diagnostic possibilities:**
  Renal biopsy: In selected cases to determine specific etiology.

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[12] Slowly progressive
[13] Until GFR falls below 30 mL/min/1.73 m^2 which occur in stage 4 and some can remain asymptomatic with much lower GFR values than this
[14] Multiple myeloma
[15] Presence of normal-sized or large kidneys does not exclude CKD
[16] $K+$, $Ca+^2$, PO_4 $-^3$ Mg

Management

Management of CKD Patients	
Nutrition	Restriction intake of: ➔ **Protein**; not less than 0.8 mg/kg/day ➔ **Phosphate** ➔ **Sodium** ➔ **Potassium**
Salt and water retention	➔ Salt intake restriction. Daily Na+ less than 100 meq or less than 2 g of salt per day ➔ Fluid restriction 1 – 1.5 L/day ➔ Loop diuretics even if they did not develop edema since they have tendency to get fluid retention ➔ RAS inhibition (ACEi, ARB) if HTN with proteinuria If the pt does not have tendency for hyperkalemia
Hyperkalemia	➔ **Causes :** - 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 ➔ How to treat hyperkalemia: First check the ECG 1. IV calcium gluconate 10 cc of 10% It will not decrease the K but will help stabilize the heart cells → prevents arrhythmia 2. Followed by 25 ml of 50% **dextrose solution with 5-10 units regular insulin** 3. B2 -adrenergic agonist nebulizer (salbutamol) 4. NaHCO3 IV/oral Shifting K inside the cells temporarily returns serum K to normal for 2 to 4 hours, after which it will return to serum → you get calcium resonium or sodium kayexalate to catch the k in the capillaries of the colon and get it into the stool Persistence of high K for more than 24 hours requires putting the patient on dialysis
Hyperphosphatemia and secondary hyperparathyroidism	➔ Reduce phosphate intake to < 10 mg/kg/day ➔ Phosphate binders: **Calcium carbonate, Sevelamer (Renagel), Lanthanum carbonate** the choice depends on pt situation: Low Ca → Ca carbonate. Normal Ca → Sevelamer. ➔ Vitamin D (Calcitriol) 0.125 mcq/day You need to give vit d to suppress hyperparathyroidism but make sure that the ph is back to normal before you give it otherwise you are pushing the pt towards phosphors calcification Just go through them - Must be withheld until s. phosphate concentration have been controlled to less than 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 ➔ Indication for parathyroidectomy: **PTH > 800 pg/ml with symptoms of bone disease (myopathy, bone pain) persistent hyperphosphatemia soft tissue calcifications**
Hyperlipidemia	The goal is to keep LDL cholesterol < 100 mg/dl by diet control and **statin group.**

Anemia	Just go through them ➔ Target Hb/Hct: - K DOQI → Hb 11-12 Hct 33-36% - Anemia will cause left ventricular hypertrophy, decrease 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):

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

Erythropoietin types: Short acting and long acting

- ➔ **Short acting eprex during hemodialysis**
  Twice to three times per week
- ➔ **Long acting Darbepoetin peritoneal dialysis**
  once or twice per week and can be given once per month depending on the patient situation

Just go through them

- **Recombinant Erythropoietin: 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:
  Inadequate Epo dose, Anemia of chronic disease (infection, inflammation), Functional iron deficiency, Secondary to hyperparathyroidism, Carnitine deficiency. Hemoglobinopathies, Aluminum toxicity, B12/folate deficiency or Malnutrition.
- **Recombinant Erythropoietin**: Darbepoetin Alfa (Aranesp)
  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.

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 and morbidity.
- ➔ May decrease the rate of progression of CKD.

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:**

- ➔ 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

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

Questions

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 ml/min/1.73m^2 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

1	2	3	4
C	B	B	D