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.

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- Editing file
- Feedback

The basic information on staging, etiology and risk factors

★ Functions of normal kidneys: In order to know the disease we should know the normal function

What is GFR? Is it the rate at which the kidney filtrates blood.
A single kidney has about 1 million nephrons, they filter a total of 125 ml/minute which Is about 180 L/ 24 hours. 99% of which is reabsorbed.

- Fluid balance
- Electrolyte regulation
- Control acid base balance
- Waste removal Nitrogenous waste products
- Hormonal Function:
    - Erythropoietin (the most important) get secreted from Renal cell go to bone marrow → produce RBCs
    - Renin → Renin Angiotensin Aldosterone System (RAAS)
    - Prostaglandins
    - Active vitamin D3. Vit D is synthesized in skin or we get it from food then it goes to the liver but it is not in active form. after that it goes to the kidney to get activated into 1,25-dihydroxycholecalciferol, which is the active form of Vit D.

★ Etiology of CKD: I want you to remember the first 3 common cause

1. **Diabetes mellitus[1] 40% of cases.** (MOST common)
2. **Hypertension 30% of cases.** Through diffuse glomerulosclerosis.
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

[1] Through Hyaline depositions glomerulosclerosis (check diabetics nephropathy lecture)

★ Chronic kidney diseases: الكلية بتفشل كلو بيتعطل

- **CKD (CRF) means:** chronic progressive irreversible[2] loss of renal function. It is defined as the presence of clinical and/or pathologic evidence of kidney disease for at least 3 months[3]. (less than 3 months it is deemed as AKI)
- **ESRD:** advanced CKD (Stage-5 (last stage)) requiring dialysis or kidney transplantation

★ Risk factors for CKD:.

1. Genetic (family hx of kidney disease).As polycystic kidney disease, Alport syndrome[4].
2. Low socioeconomic status.
3. Medical status(Comorbidities): e.g. diabetes, hypertension, obesity, cardiovascular disease, smoking.

★ Stages of Chronic Kidney Disease: Depends on 1-presence evidence of kidney injury 2- GFR.

Stage	Description	GFR (ml/min/1.73m2)[5]
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. انتبهوا للنقطة هذي انه لازم يكون فيه evidence.	≥ 90 شخص سليم معافى طبيعي بيكون ال GFR عنده اكثر من 100، لكن ما نقول عنه انت ستيج 1 ليه؟ لأن ماعنده Evidence of kidney injury
2	evidence of kidney injury + Mild ↓ GFR	60 – 89
3	evidence of kidney injury Moderate ↓ GFR	30 – 59
4	evidence of kidney injury Severe ↓ GFR	15 – 29
5	Kidney failure, (ESRD)	<15 or dialysis

[2] Which differentiates it from Acute Kidney Injury which is reversible
[3] if it less than 3 month it could be reversible
[4] Alport syndrome is genetic disorder characterized by glomerulonephritis , ESRD and hearing loss
[5] Normal GFR is 125ml/min/1.73m^2

The mechanism and pathophysiology of CKD progression

https://youtu.be/E1myFSlpy-A

★ Pathophysiology:

It occurs by two correlated mechanisms:

1. Loss of nephron mass → hypertrophy of the remaining nephrons

The hypertrophied nephron plasma flow and glomerular pressure increase (vasodilatation of the afferent Arterioles) when there is nephron loss there will be a reduction in GFR, this activates the RAAS system which dilates the afferent arteriole leading to an increase in intraglomerular pressure.

النفرونز الباقية يصير لها Hypertrophy لأنها تحاول تعوّض، وبيزيد الدم الرايح لها عشان تشتغل أكثر فبالتالي بيزيد ال GFR per that nephron not the total GFR

➔ ↑ Intraglomerular pressure (due to ↑ blood supply) and ↑ Filtration (still the total GFR is decreased).

➔ Enhance proximal reabsorption of NaCl, Fluids and PO4. causing edema and hyperphosphatemia

➔ Enhance collecting ducts secretion of K+ and H+.

Normal GFR is 125ml/min, 70% is reabsorbed in Proximal tubule + 20% reabsorbed in ascending loop of Henle 5% in distal and 4% in collecting duct --> only 1 mL is going out as urine

These adaptations initially restore homeostasis.(by compensating Hyperkalemia and acidosis) Since the basement membrane carries the hyperfiltration for a certain limit. If it continues it will get damaged.

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

2. Increase of some Growth factors such as:

➔ Transforming growth factor-B.

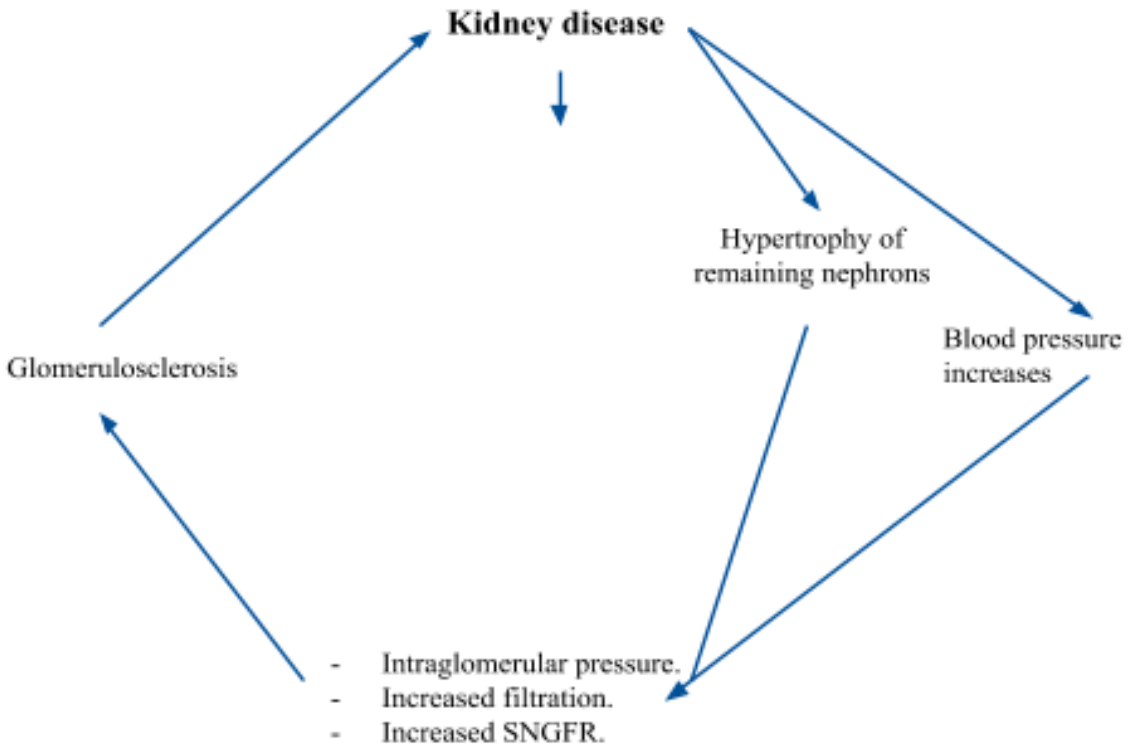
➔ Platelets derived growth factors.

➔ Osteopontin, angiotensin-II.

➔ Endothelin.

leading to further kidney damage and interstitial fibrosis

★ Vicious cycle of CKD that leads to ESRD:



★ Factors contributing to the Progression of CKD: If we control these factors this will delay the progression of CKD

- Degree of hypertension
- Severity of proteinuria increase in urinary protein causes injury to tubular cells, leading to interstitial inflammation and fibrosis
- Hyperlipidemia.
- Drugs (NSAID , aminoglycoside).
- High protein diet. High-protein intake lead to ↑ intraglomerular pressure and glomerular hyperfiltration → more damage
- Persistent metabolic acidosis.
- Extent of tubulointerstitial disease.

★ Uremic syndrome:

Uremia results from retention of end products of protein metabolism.as urea and cr.

* Administration of urea causes only mild symptoms.

* Other potential uremic toxins:

- Guanidine
- P2 microglobulin
- Hippurate
- Homocysteine
- Parathyroid hormone (PTH)
- Phenols
- Phosphate
- Polyamines
- Purines
- Dimethyl arginine

Metabolic & electrolytes abnormalities in CKD

★ Metabolic & electrolytes abnormalities in CKD:

a. Carbohydrate intolerance: (Skipped)

- 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 oral hypoglycemic drugs in diabetic patients as they develop renal failure.

b. Dyslipidemia: (Skipped)

- Decrease in HDL (yes, the good cholesterol) cholesterol.
- Increase in TG and lipoprotein(a).

c. Fluid and Electrolytes: هذي المصيبة الكبرى.

- **Decreased GFR** and defective tubular function causing expansion of plasma and ECF volumes, edema, and hypertension.
- **Hyponatremia** can result from failure to excrete free water when intakes exceed 1.5 L/day. Water intake less than 0.5 L/day + ↑ salt intake → Hypernatremia.
- **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:
    1. enhanced K+ secretion in surviving (hypertrophied) nephrons.
    2. colonic K+ secretion (from aldosterone stimulated by hyperkalemia and metabolic acidosis).In the beginning of kidney failure the colon will start to secret K . Normally it will not secret K because the kidney usually does this job.

However, as GFR decreases, K+ elimination is curtailed which will lead to **hyperkalemia**.

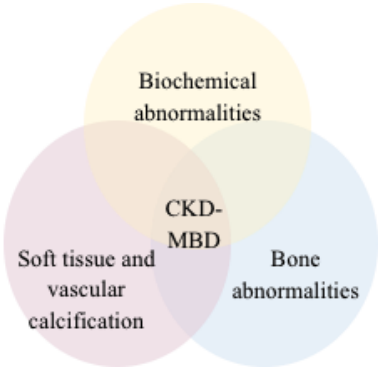
d. Acid-Base abnormalities – metabolic acidosis

- The body produces about 80 mmol of non-volatile acids[6] from metabolism everyday.
- These acids accumulates as renal failure progresses
- Production of ammonia NH3 (in distal and CD cells) decreases which limits distal tubular H+ trapping as NH4 and hence, decreases renal bicarbonate regeneration. (H is excreted from the body when it combine with NH3 (produces by kidney) becoming NH4, if we have a kidney injury no NH3 production → accumulation of H+ → acidosis)
- Additionally, there may be proximal HCO3 wasting (Instead of reabsorbed HCO3 it will be excreted) or reduced distal H+ secretion.

★ Chronic Kidney Disease-mineral and bone disorder (CKD- MBD)

Indicates alterations in mineral bone metabolism. These alterations include : What happens to the bones

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.



★ Biochemical abnormalities:

- As GFR declines, the excretion of phosphorus (nonvolatile) is impaired; 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 (stimulate kidney to excrete PO2) (via both parathyroid-dependent and independent mechanisms) and maintains serum phosphorus in the normal range until GFR declines to <30ml/min/1.73m2.

➔ FGF-23 (it is harmful by itself) also ↓ 1,25-dihydroxyvitamin D (calcitriol) formation which in conjunction with hyperphosphatemia → parathyroid hyperplasia and an ↑in PTH secretion.

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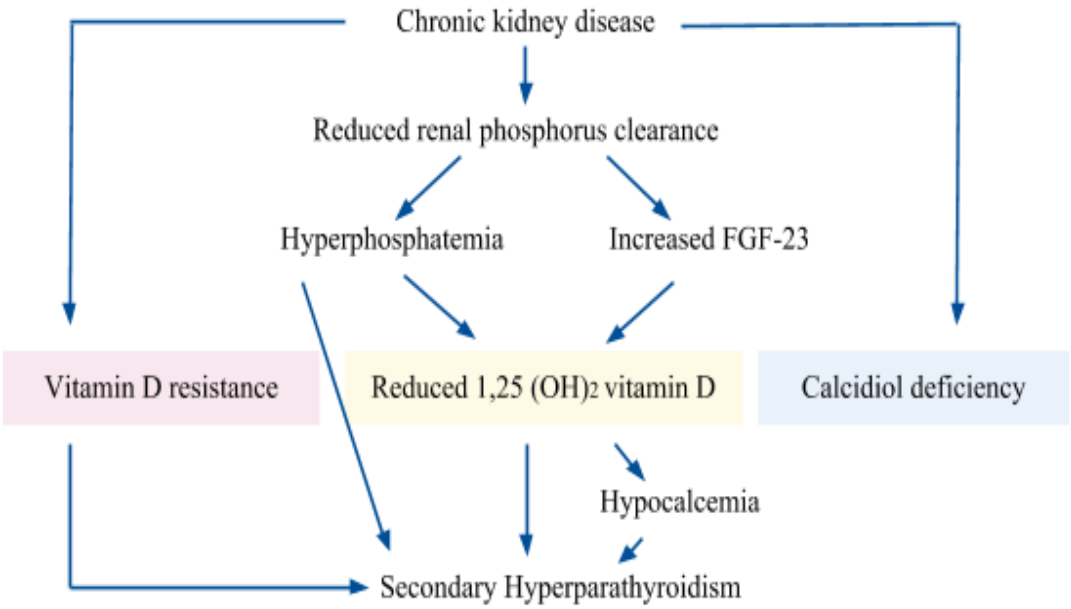
[6] Like phosphate which can only be excreted by the kidney. So, when the kidney fails this will cause these acids to accumulate. (hyperphosphatemia). Volatile acids like H2CO3 can be degraded into H2O and CO2 which is then exhaled by the lung.

الزبدة:



so hyperphosphatemia lead to direct effect to 2ndary Hyperparathyroidism and indirect effect by ↓ 1,25-dihydroxyvitamin D which lead to hypocalcemia → strong stimulator to Parathyroid gland → hyperparathyroidism (اذا عرفتوا هذي ٣ العوامل فهذا يكفيني)

★ Reasons for altered vitamin D metabolism in CKD (doctor: I don't need you to know 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-αhydroxylase availability, down regulation of renal 1-αhydroxylase 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 (vitamin D receptor) 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: what we see in blood analysis

- hypocalcemia.
- hyperphosphatemia.
- hyperparathyroidism.
- hypovitaminosis D.
- elevated FGF-23.

★ Bone abnormalities = Renal Osteodystrophy (ROD)

it Is a complex disorder 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. Increased PTH

b. increased activity of both osteoclast and osteoblast

2. Adynamic bone disease (low bone turnover)

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.

★ Adynamic bone disease (Skipped By The Doctor)

Risk factors:

- Advanced age.
- CAPD[7].
- Diabetes mellitus.
- Calcitriol therapy.
- Parathyroidectomy.
- Fluoride and iron intoxication.

Mechanism:

Defect in osteoblast development or activity caused by factors related to the uremic state.

[7] continuous ambulatory peritoneal dialysis: is a 'do it yourself' option that does not require a machine. It involves a tube permanently inserted through the abdomen to allow a fluid called dialysate to be emptied and replaced every day.

★ Changes to other body systems:

1. Cardiovascular abnormalities of ESRD (CKD-5)

Hypertension Very common.	➔ Occurs in 90% of patients with ESRD ➔ Secondary to Salt and water retention *(the primary cause and most important).* ➔ Inappropriate activation of RAAS ➔ ↑ 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, ↑ homocysteine, 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) Angina + MI due to Vascular and soft tissues calcification, especially in Coronary arteries , carotid and cerebral arteries. ➔ Congestive Heart Failure (CHF) ➔ Diastolic Dysfunction	
Pericarditis and pericardial effusion	Due to Uremia → pericardial effusion (يكون مدمى) → need intense dialysis	
Congestive Heart Failure	Due to volume overload, HTN, and Anemia	

50% of ESRD patient die from cardiovascular abnormality , not from the ESRD itself

2. Neuromuscular abnormalities

1. CNS dysfunction

- Decreased attention, agitation, confusion, insomnia, and impaired memory.
- May develop also: depression, hallucinations, delusions, hiccups important sign in Encephalopathy, cramps in muscles , flapping tremor[8] which is also an important sign of encephalopathy, myoclonus, fasciculation, and seizures.
- Flapping tremor (Asterixis) causes: 1- Renal Failure 2- liver failure 3- Respiratory failure
- Patient present with hiccups and flapping tremor → Emergency dialysis
- Lethargy, Confusion, Tetany due to **Hypocalcemia.**

2. Peripheral neuropathy

- Usually symmetric, lower limbs.
- Sensory precedes motor dysfunction.
- Restless leg syndrome and burning feet.
- Postural hypotension (autonomic dysfunction).

3. Hematologic abnormalities

1. Anemia

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

2. Platelet dysfunction[9] Platelet count is normal but the function is abnormal.

- Bruising, ecchymosis, bleeding from mucous membrane.
- Platelets dysfunction (count is normal): low VWF (VWF lies in the storage granules, the platelets do not release their granules in uremic environment so there will be a decrease of VWF in the blood) which facilitate the interaction between platelets and endothelium through its binding to platelet glycoprotein (IIb, IIIa) receptors the platelets cannot function properly in a uremic state.

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[8] Usually means one of three things: Liver failure, Renal failure OR Respiratory failure

[9] *We can find this abnormality by measuring bleeding time that will be increased (note) . *Uremia will inhibit coagulation by preventing the sticking of platelets.
*Normal bleeding time is 5min(note)

4. Gastrointestinal abnormalities

- Anorexia, nausea, and vomiting.
- Uremic fetor (urine smell in their mouth) , stomatitis, esophagitis, gastritis, and peptic ulcer disease.
- Increased Gastrin in CKD. (it is the cause of stomatitis, esophagitis, gastritis, and peptic ulcer disease.)

5. Immunologic abnormalities

Impair cellular and humoral immunity → increased susceptibility to infections

6. Dermatologic abnormalities

Uremic pruritus is related to:

- Calcium and phosphate deposition (secondary to increased PTH)
- Hypercalcemia.
- Peripheral neuropathy.
- Dry skin, Anemia.
- Inadequate dialysis.

★ Natural Hx 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–Ddeficiency, ↑PTH.
- Increased incidence of CVD, infection (the neutrophils will also suffer in uremia and they will not degranulate so this will predispose patient to recurrent infections), and Impaired physical function.

★ Evaluation of Patients with CKD (Skipped By The Doctor)

- 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 (polycystic kidney disease) 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:

Test	Indications
Serum creatinine	The first appropriate test to do when you suspect CKD
CBC	Normocytic, normochromic anemia
Urinalysis	➔ Proteinuria → risk of progressive CKD → requiring preventive ACE inhibitor or ARB therapy. ➔ Hematuria.
Urea & electrolytes	Uremia Hyperkalemia, hypocalcemia, hypermagnesemia and hyperphosphatemia
PTH	Secondary hyperparathyroidism.
Vit-D	Hypovitaminosis D.
Cr clearance	To estimate GFR.
Renal ultrasound	To evaluate size of kidneys/rule out obstruction. a. Small kidneys are suggestive of chronic renal insufficiency with little chance of recovery. b. Presence of normal-sized or large kidneys does not exclude CKD.
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.

Management

★ Management of Patients with CKD

1. Nutrition:	restriction intake of: • protein; not less than 0.8mg/kg/day. • phosphate (Meat , Dairy products, canned foods and food addatives) • sodium. To avoid hypertension. • potassium.
2. Salt and water retention: (Skipped)	• Salt intake restriction – daily Na+ < 100 meq. • Fluid restriction 1 – 1.5 L/day. • Loop diuretics. • RAAS inhibition(ACEi, ARB) if HTN w/proteinuria.
3. Hyperkalemia:	• Exogenous sources of K+: dates, dried fruits, citrus fruits, banana, chocolate, salt substitute. • Medications that increase K+: ACEI, ARB, NSAID, K+- sparing diuretics (spironolactone), B-Blockers, and heparin. **Treatment of hyperkalemia:** - IV calcium gluconate 10 cc of 10% which is the first step (it works by shifting K into the cells) - Followed by 25 ml of 50% dextrose solution with 5-10 units regular insulin - B2-adrenergic agonist nebulizer (salbutamol). Patiromer is a drug that binds to potassium in the gut, it is used as the second step if the first step fails - NaHCO3 IV/oral. If all fails and hyperkalemia is refractory then you should consider dialysis
4. Hyperphosphatemia and secondary hyperparathyroidism:	**a.** Reduce phosphate intake to < 10 mg/kg/day. **b.** Phosphate Binders مواد تربطه وتمنع امتصاصة: Calcium Carbonate (given to Pt with low Ca) , Sevelamer (Renagel), Lanthanum carbonate(given to Pt with high/ normal Ca) . Our food are full of PO4 so so we give them this drug It will bind to phosphate and Excreted in feces. **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: paricalcitol (Zemplar) is an analogue that inhibits PTH synthesis without elevation of calcium/phosphates. **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[10] → Hemoglobin 11-12 hematocrit 33-36% Don't raise it to the normal range because if we increased it more than 12 it leads to CVD - 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 erythropoiesis. - Serum ferritin reflects over all iron stores. - In CKD, target T-Sat>20 (20–50). - Target S.ferritin > 100ng/ml. - Iron supp should be withheld, if T-sat > 50 , S. ferritin > 800ng/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 fumarate, 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:** (due to low absorption)

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

- **Recombinant Erythropoietin – epoetin alfa (eprex)** (short Acting)

- 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 aim is to keep Hb around 11-12

- The most common side effects: headache, HTN, arthralgia, and diarrhea.

[10] **Kidney Disease Outcomes Quality Initiative** (National Kidney Foundation)

Resistance to epoetin:

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. B12/folate deficiency.
9. malnutrition.

- **Darbepoetin Alfa (Aranesp)**

- Recombinant Epo.
- Half-life: three fold longer IV and two fold 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/morbidity.
- May decrease the rate of progression of CKD.

Dialysis:

Should be delayed until their **GFR** drops to **8-6 mL/min/1.73m2** 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.

A suitable treatment for CKD is Kidney transplantation.

Summary

Chronic Kidney Disease	
Etiology	Diabetes mellitus in 40% of cases. Hypertension in 30% of cases. Glomerulonephritis in 15% of cases and other causes.
Stages	1.Kidney damage with normal or ↑ GFR (≥ 90) 2.Mild ↓GFR (60-89) 3.Moderate ↓ GFR (30-59) 4.Severe ↓ GFR (15-29) 5.Kidney failure, (ESRD) GFR: <15 or dialysis
Mechanism and pathophysiology	1. Loss of nephron mass → hypertrophy of the remaining nephrons the hypertrophied nephron plasma flow and glomerular pressure increase (vasodilatation of the afferent Arterioles) > ↑ Intraglomerular pressure (due to ↑ blood supply) and ↑ Filtration (still the total GFR is decreased). ▯ Enhance proximal reabsorption of NaCl, Fluids and PO4. causing edema and hyperphosphatemia ▯ Enhance collecting ducts secretion of K+ and H+ These adaptations initially restore homeostasis. 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 interstitial fibrosis.
Factors contributing progression	Degree of hypertension, Severity of proteinuria, Hyperlipidemia, Drugs (NSAIDs, aminoglycoside), High protein diet, Persistent metabolic acidosis, Extent of tubulointerstitial disease.
Changes in other body systems	1.CVS changes: HTN, Cardiomyopathies, pericarditis due to uremia and CHF 2.Neuromuscular: CNS dysfunction (Decreased attention and agitation…) And peripheral neuropathy 3. Hematologic: Anemia that develops as serum creatinine increases And platelet dysfunction with normal count and low VWF 4. GI: Anorexia, nausea and vomiting 5. Dermatologic: Uremic pruritus
Management	Management: Restriction of protein, phosphate, sodium and potassium intake. Salt and water restriction RAAS inhibition if required. Reduce phosphate intake to < 10 mg/kg/day, Vitamin D (Calcitriol) 0.125 mcq/day, The goal is to keep low density lipoprotein cholesterol < 100 mg/dl by diet control and statin group, Control anemia.
● CKD (CRF) means: 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 (last stage)) requiring dialysis or kidney transplantation, happens secondary to water and salt retention which is one of the leading causes of developing it. ● Fluid and electrolytes of the body get disrupted during CKD there will be: Decreased GFR leading to plasma and ECF expansion, Hyponatremia and Hypertension (unless sodium intake is restricted to 100 meq/day)	

Questions

1- A 50-year-old man comes to the physician for a routine follow-up visit. He has hypertension, diabetes mellitus, secondary hyperparathyroidism, and end-stage renal disease. He has been on hemodialysis for the past three years. He was admitted three months ago for line sepsis, which was treated with antibiotics. He had a right below-the-knee amputation two years ago following a non-healing foot ulcer. Physical examination shows a right carotid bruit. If this patient dies within the next five years, what would be the most likely cause of his death?
A. Cardiovascular disease
B. Stroke
C. Infection
D.Cancer

2 - Which substances of the following do the kidney produces ?
A. 25 - hydroxycholecalciferol , prostaglandins PGE2 , Erythropoietin
B. 25 - hydroxycholecalciferol , prostaglandins PGE2 , aldosterone
C. Angiotensin converting enzyme , Erythropoietin , prostaglandins PGE2
D. Angiotensin converting enzyme , aldosterone , prostaglandins PGE2

3- Typical Biochemical features of chronic kidney failure includes ?
A. Hypophosphatemia
B. Hypercalcemia
C. Metabolic acidosis
D.Polyuria

4. At a routine checkup, a 42-year-old male with diabetes is found to have an eGFR of 32 ml/min/1.73 m2. When repeated 3 months later, it is 35 ml/ min/1.73 m2. His albumin:creatinine ratio (ACR) is 35 mg/mmol (310 mg/g). Macroalbuminuria is defined as ACR >30 mg/mmol (>300 mg/g). What stage of CKD does he have?
A. Stage 1
B. Stage 2
C. Stage 3
D.Stage 4

5- Which of the following statements about parathyroid hormone synthesis is true ?
A. It is stimulated by activated vitamin D3
B. It is stimulated by hypocalcaemia
C. It is inhibited by hyperphosphatemia
D.It is inhibited by FGF-23

6- all of the following describe the natural history of Chronic kidney disease Except ?
A. hyperfiltration of non-injured nephrons cause eventual sclerosis
B. Hypertension develops as consequence of CKD
C. Proteinuria itself contribute to glomerular damage and progression of chronic kidney disease
D.progression of chronic kidney disease is reversible depending on the underlying cause

7- A 49-year-old woman attends your clinic suffering from chronic renal failure due to progressive glomerular disease. She appears well and her blood pressure is 141/92 mmHg. Blood tests reveal elevated phosphate, serum creatinine and urea, while calcium levels are low. Her estimated glomerular filtration rate is 35mL/min/1.73m2. You also notice the patient's cholesterol levels are moderately raised. The most appropriate management is:

a. Sevelamer
b. Parathyroidectomy
c. Oral vitamin D
d. Cinacalcet

Answers : 1.A 2.C 3.C 4.C 5.B 6.D 7.A