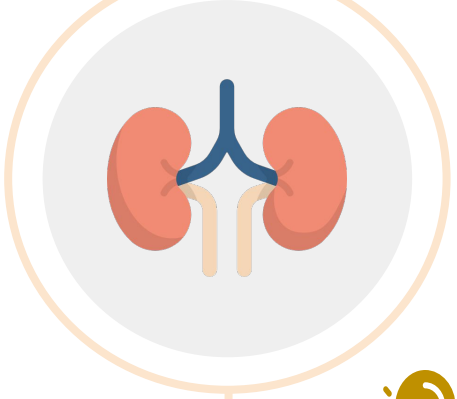
Chronic kidney failure



Online MedEds High-Yield Brilliant Summary!

Objectives :

- ★ Differentiate Chronic kidney disease from Acute Kidney Injury-AKI.
- ★ Describe the mechanism and pathophysiology of CKD progression and therapies to slow progression.
- ★ Compare the different causes of CKD and the risk factors of progression.
- ★ Identify recent updates in the diagnosis and therapy of CKD complications.
- ★ Classify CKD into 5 stages.
- ★ When to refer to nephrology
- ★ Discuss management choices of ESRD.

MED439

Medicine Team 439

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Chronic kidney failure

◀ Normal kidney function

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

Bones can break, muscles can atrophy, glands can loaf, even the brain can go to sleep without immediate danger to survival. But – should kidneys fail… neither bone, muscle, nor brain could carry-on.

Hamer Smith, PhD.

Definitions

CKD (CRF): 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,** irrespective to the cause.

ESRD: advanced CKD (Stage-5) requiring dialysis or kidney transplantation. It is defined as the loss of renal function leading to a collection of symptoms and laboratory abnormalities also known as uremia. **Not defined as a particular BUN or creatinine.**

◀ Etiology of CKD

- **Persistent** pre-renal or post-renal causes
- Glomerulonephritis
  - Diabetes mellitus[4] (DM) ⟶ 30%
  - Chronic GN ⟶ 15%
- Hypertension[4] ⟶ 25%
- Hereditary[1]
- Interstitial nephritis/pyelonephritis
- Tumours
- Miscellaneous
- Drugs[2]

◀ Risk Factors For CKD

1) Genetic[1] (family history of kidney disease)
2) Low socioeconomic status
3) Medical status, eg:
   a) diabetes
   b) hypertension
   c) cardiovascular disease
   d) smoking

◀ AKI vs CKD

- Acute kidney injury (AKI) is a **sudden** and **reversible** loss of renal function, which **develops over days or weeks** and is often accompanied by a reduction in urine volume.
- Distinction between AKI and CKD depends on the history, duration of symptoms and previous urinalysis. A normochromic anaemia, small kidneys on ultrasonography and the presence of renal osteodystrophy favour a chronic process.
- The persistence of the damage/decreased function for at least 3 months is necessary to distinguish CKD from AKI.
- Blood-wise, creatinine is elevated in both cases but stable in ESRD while changing in AKI

1- examples: polycystic kidney disease, and Alport syndrome (which is an x-linked recessive disorder most commonly cause by mutation or deletion of COL4A5. Characterized by a triad of hearing loss (Sensorineural deafness), vision (ocular) abnormalities, and ESRD in late teens or twenties.)

2- What drugs can cause nephrotoxicity?

- NSAIDS like (ibuprofen, naproxen).
- Antibiotics like (aminoglycosides, amphotericin B).
- PPI like (pantoprazole, in the elderly if used chronically it might have a low risk for developing CKD).

3- What determines our kidney function? serum creatinine, urine output, presence of proteins/blood in urine, biopsy findings (chronicity of kidney disease), US (decrease in size, increase in echogenicity, loss of corticomedullary differentiation). All these things point to chronic rather than acute kidney disease .

4- The most common causes of ESRD .

Chronic kidney failure

◀ Identifying CKD

- Compare to baseline if known
- Presence of complications of CKD
- Kidney imaging changes (US)
- Biopsy features of chronicity

◀ Pathophysiology

1. Loss of nephron mass, leading to hypertrophy of the remaining nephrons
2. increase plasma flow and glomerular pressure of The hypertrophied nephron (vasodilatation of the aff. Arterioles)
3.
   - Enhanced Proximal reab. of NaCl, Fluids and PO4 (causes edema and hyperphosphatemia)
   - Enhanced Collecting ducts secretion of K+ and H+

★ These adaptations initially restore homeostasis, But glomerular hyperfiltration leading to glomerular injury, glomerulosclerosis and further loss of renal function.

◀ Growth factors involved in CKD

➔ All lead to **Interstitial fibrosis**

1. **Transforming growth factor-B**
2. **Platelets derived growth factors**
3. **Osteopontin, angiotensin-II**
4. **Endothelin**

◀ CKD Stages ★ We calculate GFR using creatinine, assuming creatinine is stable (to baseline)

Stage	Description	GFR Stage Description (ml/min/1.73m2)
1	Kidney damage with normal or increased GFR	>90
2	Mild decrease in the GFR	60 – 89
3	Moderate decrease in the GFR	30 - 59
4	Severe decrease in the GFR	15 – 29
5	Kidney failure, **ESRD**	<15 or dialysis

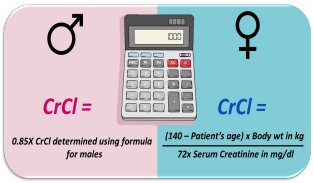
Chronic kidney failure

◀ Glomerular filtration rate (GFR)

- Decreased kidney function refers to a decreased glomerular filtration rate (GFR), which is usually estimated (eGFR) using serum creatinine and one of several available **equations:**

Estimation of GFR

- **Cockcroft-Gault formula:**



- **MDRD Study equation:**

$$eGFR_{MDRD}\ (mL/min/m^2) = 175.0 \times (Scr)^{-1.154} \times age^{-0.203} \times 0.742\ (\text{if female}) \times 1.212\ (\text{if black}),$$

- **CKD-EPI equation:**

$$GFR_{CKD\text{-}EPI} = 141 \times \min\left(\frac{serum-creatinine}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{serum-creatinine}{\kappa}, 1\right)^{-1.209} \times 0.993^{age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}] \quad (2)$$

◀ Prognosis of CKD

- The graph shows the most recent staging System for CKD prognosis, developed by **KDIGO:**

Every stage represent a range of GFRs, for example; G1 is GFR more than or equal to 90 which is normal. However, patient in G1 stage may still present with different albuminuria categories (divided A1, A2, and A3)

So to map a patient in this graph you need:

1. GFR
2. Urine albumin levels

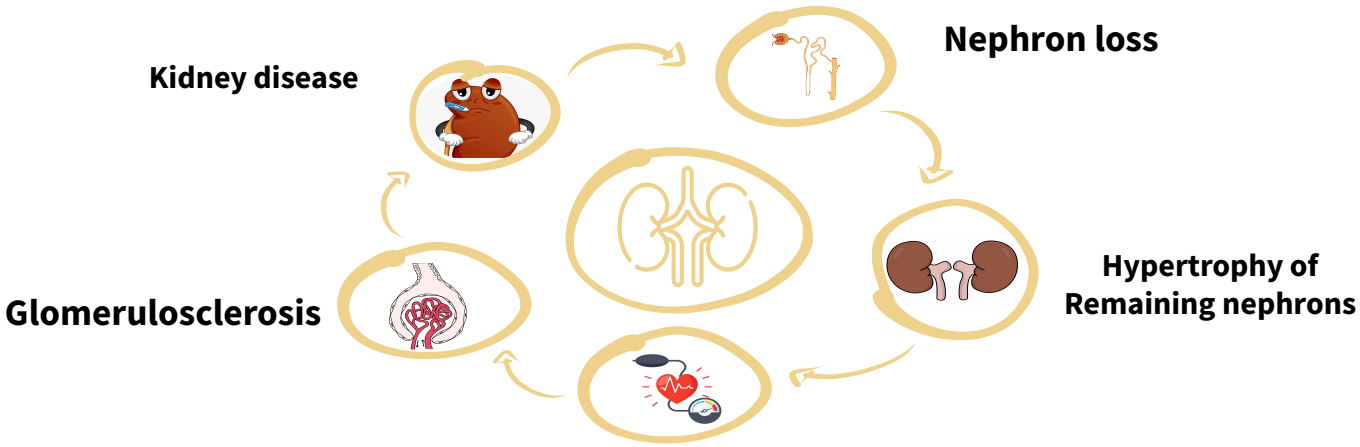
Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR[1] 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 m²) 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	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Level of proteinuria is increasingly being reported alongside GFR as it is associated with more rapid progression of CKD. A patient in the red zone has high risk of developing **ESRD** as well as **cardiovascular diseases (stroke, death, MI).** E.g. if a patient has a GFR=41 and albumin excretion of 41 mg/mmol the patient will be in (G3B with A2 which is a high risk of developing cardiovascular disease and end stage kidney disease)

◀ Vicious cycle of CKD that leads to ESRD



1- Basically, based on the KDIGO guidelines, kidney function depends on (other than biopsy findings) GFR decline and the increase of protein in the urine. This means that you can have elements of CKD even if you have a GFR of ≥90 (first row orange). The more proteinuria and the more decline in GFR, the higher risk (red).

Investigations of CKD

Test	Finding	Interpretation
Urinalysis	Haematuria	• glomerulonephritis
	Proteinuria	• glomerular disease (heavy proteinuria). • Urinary infection.
	Glycosuria	• (With normal blood glucose is common in CKD). • TB.
Urine microscopy	WBC	• Active bacterial urinary infection In CKD; sterile pyuria suggests: • papillary necrosis • renal tuberculosis.
	Eosinophiluria	• allergic tubulointerstitial nephritis • cholesterol embolization.
	Casts	• active renal disease

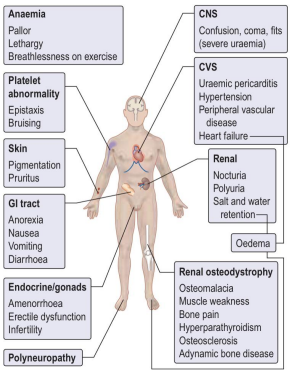
Urine biochemistry	Urine osmolality	Is a measure of concentrating ability.
		• **A low urine osmolality**:
		  ○ normal in the presence of a high fluid intake
		  ○ indicates renal disease when the kidney should be concentrating urine, such as in hypovolaemia or hypotension.

Serum biochemistry	• Urea and creatinine. • Calculation of eGFR. • Electrophoresis and immunofixation for myeloma. • Elevations of creatine kinase and a disproportionate elevation in serum creatinine and potassium compared with urea suggest rhabdomyolysis.	
Hematology	Eosinophilia	• vasculitis • allergic tubulointerstitial nephritis • cholesterol embolism.
	Fragmented red cells and/or thrombocytopenia	• intravascular haemolysis due to accelerated hypertension • haemolytic uraemic syndrome • thrombotic thrombocytopenic purpura.
Immunology	Complement components, Autoantibody screening, Cryoglobulins, Antibodies to HIV, Antibodies to streptococcal antigens (antistreptolysin O titre (ASOT), anti-DNAse B), Antibodies to hepatitis B and C.	
Radiological investigation	• **US:** for renal size and to exclude hydronephrosis • **CT:** for retroperitoneal fibrosis, other causes of urinary obstruction, and may also demonstrate cortical scarring. And exclude low-density renal stones or nephrocalcinosis that can be missed in US • **MRI**.	

Complications of Chronic kidney failure

◀ Uremic syndrome[1]

- Uremia results from **retention** of end products of protein metabolism
- Administration of urea causes only mild symptoms
- Other potential uremic toxins:
  - Guanidine
  - Phenoles
  - Phosphate
  - Polyamines
  - Purines
  - Dimethyl arginine
  - β2 microglobulin[2]
  - Hippurate
  - Homocysteine
  - Parathyroid hormone (PTH)



◀ Metabolic and electrolytes abnormalities in CKD

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.

Dyslipidemia[3]

- Low HDL cholesterol
- High TG and lipoprotein(a)

Acid-Base abnormalities – metabolic acidosis

- The body produces about 80 mmol of nonvolatile acids from metabolism everyday.
- These acids accumulates as renal failure progresses.
- Production of ammonia NH_3 (in distal and CD cells) decreases, which limits distal tubular H^+ trapping as NH_4 and hence, decreases renal bicarbonate regeneration.
- Additionally, there may be proximal **HCO3 wasting** or reduced distal H+ secretion.

Fluid and Electrolytes[4]

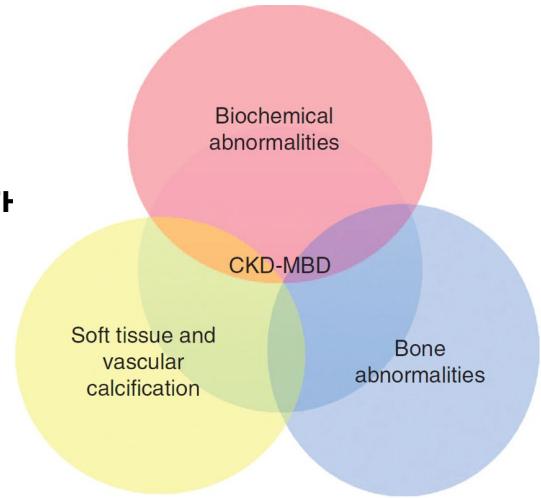
- GFR and defective tubular function → expansion of plasma and ECF volumes, edema, and hypertension.
- **Hyponatremia** can result from failure to excrete free water when intakes exceed 1.5 L/day
- Hypertension is common unless Na+ intake is restricted to 100 meq/day
- **K+ elimination in CKD is initially maintained by:**
  - enhanced K+ secretion in surviving nephrons
  - colonic K+ secretion (from **aldosterone**[5] stimulated by hyperkalemia and metabolic acidosis)

  However, as GFR decreases, K+ elimination is curtailed → hyperkalemia

1: **MTB:** Uremia is defined as the presence of : metabolic acidosis, fluid overload, encephalopathy, hyperkalemia and pericarditis.
2: β 2-microglobulin: This molecule (a component of HLA proteins on most cell membranes) is normally excreted by the kidneys, but is not removed by dialysis .so accumulation and polymerization of it leads to Amyloidosis. Deposition results in the carpal tunnel syndrome and joint pains, particularly of the shoulders.
3: Correction of lipid abnormalities: e.g. HMG-CoA reductase inhibitor therapy (statins), is used in patients with CKD, although without formal proof of survival benefit.
4: In a patient with CKD, symptomatic volume overload and severe hyperkalemia are the most common complications that require urgent intervention.
5:any cause of hypoaldosteronism May lead to hyperkalemia

Complications of Chronic kidney failure

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



- **Indicates alterations in mineral bone metabolism**
- **These alterations include :**
  - biochemical abnormalities in **calcium, phosphorus, PTH, vitamin D** and fibroblast growth factor-23.
  - changes in bone morphology : volume, turnover, and mineralization.
  - calcification of soft tissue and blood vessels.
- **The classic biochemical abnormalities:**
- **Hypocalcemia**
- **Hyperphosphatemia**
- **Secondary hyperparathyroidism** (due to low Ca^{+2})
- **Hypovitaminosis D**
- **Elevated FGF-23**
- Bone density measurement is recommended for CKD stage 3a and lower if results will impact treatment. Also if needing confirmation bone biopsy is an ungraded recommendation

Pathogenesis of CKD- MBD[1]

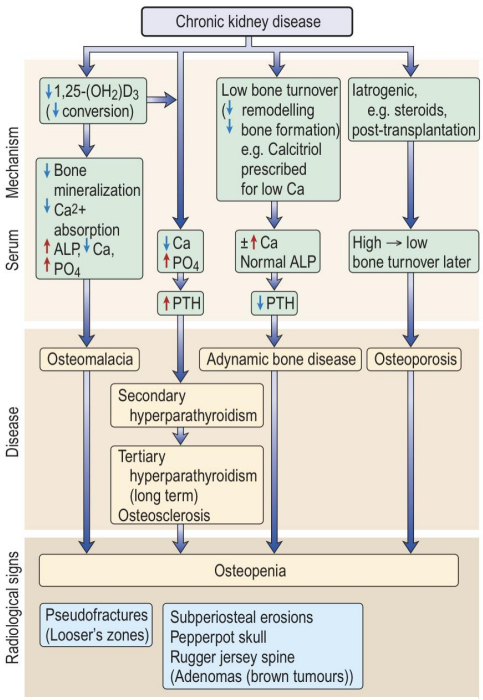
As GFR declines, the excretion of phosphorus is impaired, leading to phosphate retention.

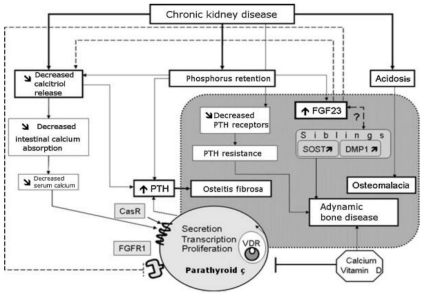
Hyperphosphatemia is an independent risk factor for the increased morbidity and mortality of stage 5 CKD from cardiovascular events.

Recently, it has been demonstrated that fibroblast growth factor 23 (FGF-23) is stimulated by phosphorus retention

FGF-23 causes phosphaturia and maintains serum phosphorus in the normal range until GFR declines to < 30 ml/min/1.73m2.

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





1- decreased activation of vit. D (decreased conversion from inactive to active)→ PTH is stimulated ↑**PTH→ ↑phosphate, ↓Ca++**
Explanation: because there is no excretion of phosphate (Phosphorus excretion is only from kidney) , there is no reabsorption of Ca++→ Ca++ gets excreted and the phosphate gets reabsorbed (Ca++ doesn't go up because it's not absorbed in the intestine).
As this goes on, the body senses that it does not have enough Ca++ → bone buffering/bone changes. so it either has high turnover or low turnover (adynamic bone disease or osteomalacia; respectively)
Persistent sPTH can lead to tPTH (Tertiary) which is manifested by Hypercalcemia due to increased bone turnover

Complications of Chronic kidney failure

◀ Bone abnormalities = 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[1] metabolism in the presence of factors related to the uremic state.

Spectrum of bone abnormalities in ROD:

- Osteitis fibrosa cystica (high bone turnover)
  - Due to:
    - **High Parathyroid Hormone**
    - Increase activity of both osteoclast and osteoblast
- Adynamic bone disease (low bone turnover)
- Osteomalacia (low turnover accompanied by under mineralized bone tissue)
- 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.

(two primary factors are related renal bone disease: **impaired excretion of phosphate** and **failure of the kidney to form active vitD**. The reduced vitD levels impairs intestinal absorption of calcium. In addition, raised levels of serum phosphate make complex with calcium in the extracellular space, leading to calcium phosphate deposition. All of this cause hypocalcaemia which stimulates PTH production by the parathyroid glands. A sustained excess of PTH results in skeletal decalcification.)

Adynamic bone disease

- A condition of which both bone formation and resorption are depressed
- Risk factors:
  - Advanced age
  - CAPD
  - Diabetes mellitus
  - Calcitriol therapy
  - Parathyroidectomy
  - Fluoride and iron intoxication
- Mechanism
  - Defect in osteoblast development or activity caused by factors related to the uremic state

1-Phosphate retention results in the release of fibroblast growth factor 23 (FGF 23) by osteoblasts as a compensatory mechanism. FGF 23 causes phosphaturia to bring the plasma phosphate level to within the normal range. However, consistently elevated levels of FGF 23 after a while cannot control phosphate levels and its effects are overwhelmed by development of secondary hyperparathyroidism. Elevated FGF 23 levels are the strongest independent predictor of mortality in patients with CKD. This underscores the necessity of controlling phosphate levels during very early stages of CKD.
2-calcium and phosphate deposition, causes vascular calcifications that may result in necrotic skin lesions. This is called calciphylaxis.

Complications of Chronic kidney failure

◀ Cardiovascular abnormalities of ESRD (CKD-5)

1 Hypertension[1]

- **CKD is the most common cause of 2ry hypertension**
- Occurs in 90% of patients with ESRD (most common complication of CKD)
- Causes:
  - **Salt and water retention (the primary cause)**
  - **Inappropriate secretion of RAAS**
  - High sympathetic tone
  - High generation of vasoconstrictors (endothelin)
  - Low generation of vasodilators (nitric oxide)

2 Cardiomyopathy

- left ventricular hypertrophy (LVH)
  - A risk factor for early death in CKD
  - Anemia aggravates LVH
- Coronary artery disease (CAD)
  - Coronary artery calcification is more common in patients with ESKD than in normal individuals and it is highly likely that this contributes significantly to cardiovascular mortality.
- Congestive heart failure (CHF)
- Diastolic dysfunction

- 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
- Hyperparathyroidism amyloidosis, and iron overload also cause cardiac dysfunction.

3 Pericarditis and pericardial effusion

- **Pericarditis usually resolves with intensive dialysis.**
- **Dialysis pericarditis:** occurs as a result of an intercurrent illness or surgery in a patient receiving apparently dialysis.

◀ Cardiovascular risk factors in CKD patients

- **classical risk factors for atherosclerosis:**
  - A raised (calcium × phosphate) product
  - Hyperparathyroidism: contribute by increasing intracellular calcium.
  - Vascular calcification: in uraemia is now thought to be an active process whereby vascular smooth muscle cells acquire osteoblast-like characteristics
  - Inflammation: a potent mediator of vascular calcification by inhibition of **fetuin.**
- **Other cardiovascular risk factors**: homocysteinaemia, Chlamydia pneumoniae infection, oxidative stress and elevated endogenous inhibitor of nitric oxide synthase and asymmetric dimethyl arginine (ADMA) levels

1- The immune system (lymphocytes) helps keep arteries clear of lipid. White blood cells don't work normally in a uremic environment. Leading to accelerated atherosclerosis. This is the most common cause of death in those on dialysis.

Complications of Chronic kidney failure

◀ Neuromuscular abnormalities

1 CNS dysfunction

- Decreased attention, agitation, confusion, insomnia, and impaired memory
- May develop also: depression, hallucinations, delusions, hiccups[2], cramps, flapping tremor[2], myocloms, fasciculation, and seizures.

2 Peripheral neuropathy

- usually symmetric, lower limbs
- Sensory precedes motor dysfunction
- Restless leg syndrome[1] and burning feet
- Postural hypotention (autonomic dysfunction)
- Median nerve compression: avoided by haemofiltration and haemodiafiltration.

◀ Hematologic abnormalities

1 Anemia[3]

- KDIGO guidelines identifies anemia as **below 130 for males** and **below 120 in females.**
- Develops as serum creatinine increases > 180 mcm/L and GFR declines to < 30 ml/minute
- Normocytic, nomochrome anemia
- Screening for anemia should be done **annually for CKD stage 3**, **biannually for stage 4** and **every 3 months for stage 5**
- Main cause: decrease production of EPO
- Other causes: retention of bone marrow toxins, bone marrow fibrosis secondary to hyperparathyroidism, deficiency of (iron, vit B_{12}, folate), ↑RBC destruction, abnormal RBC membrane, and use of ACE inhibitors (may cause anaemia in CKD, probably by interfering with the control of endogenous erythropoietin release)
- If anemia is found, approach the patient as any person with anemia and do an anemia work up prior to labeling them as anemia of CKD.

2 Platelet Dysfunction[4]

- Bruising, ecchymosis, bleeding from MM
- Platelets dysfunction (count is normal): low VWF (von-willebrand disease), which facilitate the interaction between platelets and endothelium through its binding to platelet glycoprotein (IIb, IIIa) receptors.

1-neuropathic pain in the legs that is only relieved with movement. Difficult to treat. correction of anaemia by erythropoietin. Clonazepam is sometimes useful. Renal transplantation cures the problem.
2-Flapping tremor and hiccups are imp signs of encephalopathy
3- What causes anemia? A decrease in the production of EPO (→less hematopoietic cells go into erythropoietic pathway →less erythrocytes).
4- Platelets don't work normally in a uremic environment. They do not degranulate. If a platelet does not release the contents of its granules, it will not work. Platelet count is investigated by bleeding time.

Complications of Chronic kidney failure[2]

◀ Gastrointestinal abnormalities

- Common in CKD patients
- Anorexia, nausea, and vomiting
- Uremic fetor, stomatitis, esophagitis, gastritis, and peptic ulcer disease
- High Gastrin in CKD

◀ Dermatologic abnormalities

★ Uremic pruritus is related to:
  - Calcium and phosphate deposition (2° high PTH), Hypercalcemia, Peripheral neuropathy, Dry skin, Anemia, Inadequate dialysis.

★ porphyria cutanea tarda (PCT): a blistering photosensitive skin rash.

◀ Nephrogenic systemic fibrosis (NSF)

Definition: NSF is a systemic fibrosing disorder with predominant skin involvement. It is seen only in patients with moderate to severe CKD (eGFR <30 mL/min), particularly patients on dialysis.
Cause: Gadolinium-containing contrast agents (MRI)

◀ Other metabolic abnormalities

- Gout: treated by **Colchicine** (for acute attacks), and **allopurinol** should be introduced under colchicine cover to prevent further attacks.
- Insulin: insulin requirements in diabetic patients **decrease** as CKD progresses (Insulin is catabolized by and to some extent excreted via the kidneys). By contrast, end-organ resistance to insulin is a feature of advanced CKD resulting in modestly impaired glucose tolerance. Insulin resistance may contribute to hypertension and lipid abnormalities.

◀ Other abnormalities

- Endocrine abnormalities: hyperprolactinemia, increased LH hormone, decreased serum testosterone, absence of female sex hormone cyclical changes **(anovulatory)**, GH abnormalities, abnormal thyroid hormone (measured by TSH).
- **Calciphylaxis[1]**: calcific uraemic arteriolopathy due to reduced serum levels of a calcification inhibitory protein (fetuin-A) and abnormalities in smooth muscle cell. increasingly recognized as a contributing factor to death in dialysis patients.
- Malignancy: The incidence of malignancy is raised in patients with CKD and with dialysis. Malignant change can occur in multicystic kidney disease. Lymphomas, primary liver cancer and thyroid cancers also occur.

1- Mentioned in slide 7 The patient will have ↑**PTH,** ↑**phosphate,** ↓**Ca++**. Which abnormality to we target first? The ↑phosphate because it results in calciphylaxis. It increases the risk of atherosclerosis. Decreased blood supply to skin/organs, it looks like gangrenous changes (legs, arms, abdomen, organs, etc.)

2-Kidney OUTAGES: hyperKalemia, Osteodystrophy, Uremia, Tryglyceridemia, Acidosis, Growth delay, EPO deficiency (anemia), Sodium and water retention

Chronic kidney failure

◀ 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 –D deficiency, high PTH)
- increased incidence of CVD, infection, and impaired physical function

◀ Evaluation[1] of Patients with CKD

- Kidney damage refers to **pathologic abnormalities**, whether established via renal biopsy or imaging studies, or inferred from markers such as urinary sediment abnormalities or increased rates of urinary albumin excretion.
- **History:** 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 (e.g.: Alpert syndrome)
- 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	Indication
Serum creatinine	The first appropriate test to do when you suspect CKD
CBC	Normocytic, normochromic anemia
Urinalysis	**Haematuria** and **proteinuria**: may indicate glomerular disease and need for biopsy. Proteinuria indicates risk of progressive CKD requiring preventive ACE inhibitor or ARB therapy.
Urea and electrolytes (Ca, P, Mg, K)	Uremia, hyperkalemia, hypocalcemia, hypermagnesemia, and hyperphosphatemia
PTH	Secondary hyperparathyroidism
Vit-D	Hypovitaminosis D
Cr clearances ★	**To estimate GFR**
Renal ultrasound	To evaluate size of kidneys/rule out obstruction
Urine pro/cr ratio	
LFTs	

★ Further evaluations will depend on initial findings and likely diagnostic possibilities

1-Investigations main aims are: to exclude AKI. to identify the underlying cause if possible (since this may influence the treatment). to identify reversible factors that may worsen renal function (such as hypertension or urinary tract obstruction).to screen for complications of CKD (such as anaemia and renal osteodystrophy). to screen for cardiovascular risk factors.

Management of CKD

01 Salt and water retention

- Salt intake restriction – daily Na+ < 100 meq
- fluid restriction 1 – 1.5 L/day
- Loop diuretics

02 Nutrition

- ↓**protein**; not less than 0.8mg/kg/day[1] if GFR <30. And not exceed 1.3gm / kg/ day with CKD at risk of progression.
- ↓**phosphate**
- ↓**sodium:** salt intake less than 2 gm/ day
- ↓**potassium**

03 Hyperkalemia[2]

★ Treatment of hyperkalemia
- **IV calcium gluconate**[4]**:** 10 cc of 10%
- Followed by 25 ml of **50% dextrose** solution with 5-10 units **regular insulin**
- B2-adrenergic agonist nebulizer (**salbutamol**[5])

Causes of hyperkalemia (discussed in more details in a future lecture)

- **Exogenous sources:**
  - **dates**
  - dried fruits
  - citrus fruits
  - **banana**
  - chocolate
  - salt substitute.

★ **Medications**:
- **ACEI**
- ARBs
- NSAID
- K+- sparing diuretics
- B-Blockers
- heparin
- Digitalis
- succinylcholine

04 Metabolic acidosis

- Firstly, Need rule out other causes of acidosis prior to starting treatment
- **NaHCO3** IV/**oral**: prevent bone buffering and progression of CKD (t**arget: serum bicarb > 22**)
- (↑HCO3 excretion and ↑H+ reabsorption). The problem is that this continues, CKD gets even worse and bone buffering (bc of the acidosis) gets worse leading to more osteomalacia

1-Severe protein restriction is not recommended, because there is no evidence that this reduces the rate of decline in renal function but may lead to malnutrition.
2-Hyperkalaemia menefists on ECG as a peaked T-wave. often responds to dietary restriction of potassium intake. Drugs which cause potassium retention should be stopped.
3: other causes of hyper kale is include internal K+ balance shift, for example: anything that may cause cell lysis (leading to K+ leakage into the ECF): crush injuries, tumor lysis syndrome and rhinomyolysis.
4- First step to **shift K inside cells** and protect cardiac cells
5- second line if the above did not work

Management of CKD

05 Hypocalcemia (vit D and hyperparathyroidism)

★ **Calcium:**
- levels to be checked **every 6-12 months for stage 3**, **3-6 months for stage 4** and **1-3 months for stage 5**.
- Ca^{+2} levels should reach normal; however, asymptomatic hypocalcemia (mild hypocalcemia) can be tolerated.

★ **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/phosphorus.

★ **PTH:**
- PTH levels in CKD pre dialysis should reach normal levels
- Treatment high PTH includes **Vitamin D (monitor Ca and phosphorus as it may increase it)**
- **Cinacalcet** is another option to reduce PTH, (if you have ↑ Ca++ and want to ↓ PHT) it lowers calcium x phosphate product **but can lead to hypocalemia**
- parathyroidectomy:
  - Indications: PTH > 800 pg/ml with symptoms of bone disease (myopathy, bone pain) persistent hyperphosphatemia soft tissue calcifications.
  - Side effects: May cause hypocalcemia.

06 Hyperphosphatemia ★

★ phosphorus levels to be checked **every 6-12 months for stage 3**, **3-6 months for stage 4** and **1-3 months for stage 5**.

★ **First hormone to target in treatment is Phosphorus[2]:**
- Reduce phosphate intake to < 10 mg/kg/day (**Diet control**)
- Phosphate binders[3]:
  - **Calcium carbonate**[1]
  - **Sevelamer** (Renagel) (Non-calcium phosphate binder. causes acidosis)
  - Lanthanum carbonate

★ phosphorus levels should reach normal.

07 Hyperlipidemia

the goal is to keep low density lipoprotein cholesterol < 100 mg/dl by diet control and **statin** group. Use of statin however shows no evidence of survival improvement.

1-Tackles hypocalcemia AND hyperphosphatemia. contraindicated with hypercalcaemia or hypercalciuria. The problem is that people treat it as a supplement (don't take it with meals) causes hypercalcemia and constipation.
2- Why? The ↑phosphate results in calciphylaxis. It increases the risk of atherosclerosis. Decreased blood supply to skin/organs, it looks like gangrenous changes (legs, arms, abdomen, organs, etc.). How? First, must start off with low phosphate **diet** because phosphate binders wont work otherwise.
3- Given with meals.

Management of CKD

08 Anemia[4]

★ **Target Hb/Hct**

- KDOQI → **Hb 10-12 (10-11.5) g/dL**, Hct 33-36%
- Anemia: 1)High LVH, 2)low quality of life. Both reduces survival in patients on HD
- Conversely: Hb > 13, Hct > 42 associated with more coronary events and increased mortality[1] as evidenced by CHOIR (USA) and CREATE (Europe) studies.

★ **target iron levels**

- After ruling out other causes of anemia[5], **first line of management is to tackle iron deficiency[6]** by supplementing iron (po as first line in CKD)
- percent transferrin saturation (T-SAT) reflects iron available for erythropoiesis
- Serum ferritin reflects overall iron stores
- For CKD: Target **T-Sat > 0.3, Target S. ferritin > 500 ng/ml[2]**
- Iron supplementation should be withheld if : T-sat > 50, S. ferritin > 800 ng/ml

Treatment Guidelines (Anemia)

Oral iron

Non-dialysis patients (CKD 1-4): 100-200 mg elemental iron should be given daily after meals. (1 tab Ferrous fumerate, 200 mg contains 66 mg elemental iron)

IV iron

- Dialysis patients (CKD 5): IV iron should be given as ongoing iron losses tends to be higher.
- 1g of iron saccharate (ferrosac) divided into 10 doses of 100 mg given with each dialysis session.

Recombinant Erythropoeitin (EPO)[3]

Epoeitin alfa (eprex)

- pre-filled injections: 1000, 2000, 3000, 4000 IU
- 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

Darbepoetin Alfa (Aranesp)

- Half-life: IV: three-fold longer and S/C: two-fold longer than that of epoetin
- Recommended starting dose 0.45 mcg/kg S/C
- weekly or double the dose every 2 weeks.
- Pre-filled injections: 20, 40, 60, 80 mcg

1- because correcting haemoglobin to normal levels associated with hypertension and thrombosis
2- 437 slides: For CKD: Target T-Sat > 20 (20 – 50), Target S. ferritin > 100 ng/ml.
3: initiated if iron **targets achieved** and **anemia persisted.** examples: darbepoetin, epoetin
4- In the normal population, the anemia Hb target is over 13 for males and over 12 for females, but in CKD patients are targets are different. The Hb target in this group is between 10-11.5. Why do we intentionally not reach the levels of normal people? Targeting a Hb >12/13 has an increased risk of developing malignancy, HTN, stroke, and CVD events. **What is the only/most likely disease that even without EPO-stimulating medications their Hb never drops CKD?** Why? Polycystic Kidney disease. Because the kidney is larger in size =more cells that produce EDO. This means that the disease can advance/go on for very long before their Hb begins to drop. They can live on dialysis/CKD without any EPO.
5- You have to treat this person like any other person with anemia. Don't just assume that the anemia is due to their CKD. They can still get GI bleeds, DIC, sickle cell disease, and other diseases that cause anemia, so you **must rule out other causes first**.
6- Checking iron stores is the first step. Why? If you give EPO-simulating agents to a patient with a low iron store, its not gonna work .

Management of CKD

Resistance to EPO

inadequate Epo dose	anemia of chronic disease (infection, inflammation)		B12/folate deficiency
functional iron deficiency	hemoglobinopathies	malnutrition	carnitine deficiency
secondary to hyperparathyroidism		aluminum toxicity	

09 Reduce cardiovascular risk:

- ★ **First line of therapy is RAAS blockade** regardless if there was DM or albuminuria but of coarse indication is stronger if there was DM or albuminuria
- ★ Optimal control of blood pressure: New KDIGO guidelines recommend that **SBP should be lower than 120** in CKD irrespective of concomitant DM or not based on the SPRINT trial
- ★ Reduction of proteinuria
- ★ Statins to lower cholesterol to <4.5 mmol/L

Book summary of CKD management

Goals of treatment
- BP <120/80
- Proteinuria <0.3 g/24 h

Treatment

Patients with chronic kidney disease and proteinuria >1 g/24 h:
- ACE inhibitor increasing to maximum dose
- Add angiotensin receptor antagonist if goals are not achieved[a]
- Add diuretic to prevent hyperkalaemia and help to control BP
- Add calcium-channel blocker (verapamil or diltiazem) if goals not achieved

Additional measures
- Statins to lower cholesterol to <4.5 mmol/L
- Stop smoking (three-fold higher rate of deterioration in CKD)
- Treat diabetes (HbA_{1c} <7%, 53 mmol/mol)
- Normal protein diet (0.8–1 g/kg bodyweight)

[a]*In type 2 diabetes start with angiotensin receptor antagonist.*

◀ Other preventive measures to delay CKD progression

- Smoking cessation
- Avoid nephrotoxic medications
- Weigh benefits vs risks prior to doing imaging with
- Optimize diabetic control, HbA1c <7%
- Exercise for 30 minutes 5 days a week

◀ Referral to nephrology

1. **AKI** or abrupt sustained fall in GFR <30 ml/min/1.73 m2 (GFR categories 4-5)
2. Consistent finding of **significant albuminuria** (ACR >300 mg/g [>30 mg/mmol][1]
3. **Progression of CKD or Hereditary kidney disease.**
4. Urinary **red cell casts, RBC >20/hpf** (sustained and not readily explained)
5. **CKD & HTN refractory to treatment[2]**
6. **Persistent abnormalities of serum potassium** recurrent or extensive nephrolithiasis.

1: or AER 300 mg/24 hours, approximately equivalent to PCR >500 mg/g [>50mg/mmol] or PER 500 mg/24 hours.
2: with 4 or more antihypertensive agents

Progression of CKD

◀ Introduction

- CKD tends to **progress inexorably to ESRD**, although the rate of progression may depend upon the underlying nephropathy.
- Patients with chronic glomerular diseases tend to deteriorate more quickly than those with chronic tubulointerstitial nephropathies.
- Indicators of bad prognosis:
  - Hypertension.
  - heavy proteinuria.

◀ What causes ESRD in CKD patients?

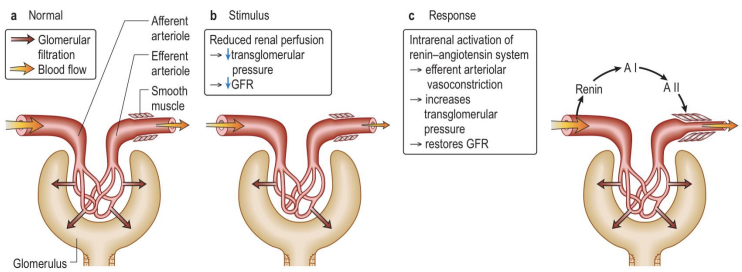
- A nonspecific **renal scarring** process common to renal disorders of different aetiologies may be responsible for progression.
- Possible causes of glomerular scarring and proteinuria include:
  - A rise in intraglomerular capillary pressure
  - Adaptive glomerular hypertrophy due to reduced arteriolar resistance and increased glomerular blood flow when there is reduced nephron mass.

increased intraglomerular capillary pressure:

Since the afferent arteriolar tone decreases more than efferent arteriolar tone, intraglomerular pressure and the amount of filtrate formed by a single nephron **rises**.

Rule of Angiotensin II:

1. Angiotensin II produced locally modulates intraglomerular capillary pressure and GFR, predominantly causing **vasoconstriction of postglomerular arterioles**, thereby increasing the glomerular hydraulic pressure and filtration fraction
2. **Its effect on mesangial cells and podocytes:** increases the pore sizes, impairs the size-selective function of basement membrane for macromolecules.
3. **modulates cell growth:** directly and indirectly by upregulating **TGF-β**, increases collagen synthesis and causes epithelial cell transdifferentiation to myofibroblasts.
4. **upregulating plasminogen activator inhibitor-1 (PAI-1):** inhibits matrix proteolysis by plasmin, resulting in accumulation of excessive matrix and scarring both in the glomeruli and interstitium.



Renal interstitial scarring

Caused by:

1. non-haemodynamic effects of angiotensin II
2. proteinuria per se (by exposing tubular cells to albumin and its bound fatty acids and cytokines) promotes secretion of pro-inflammatory mediators, which promote interstitial inflammatory cell infiltrate and further augment fibrosis and progression of CKD.

Progression of CKD *(cont.)*

◀ Prognosis

- prognosis for renal function in chronic glomerular disorders is judged more accurately by interstitial histological appearances than by glomerular morphology.

◀ Factors contributing to the Progression of CKD ★

Persistent metabolic acidosis | **Extent of tubulointerstitial disease** | Hypertension | Drugs (NSAID)

High protein diet | Proteinuria

◀ How do we slow the progression of CKD to ESRD?

★ Therapeutic manoeuvres aimed at inhibiting angiotensin II and reducing proteinuria mainly by **ACEI** and **angiotensin-receptor antagonists** have beneficial effects in slowing the rate of progression of CKD in both diabetic and non-diabetic renal diseases in humans.

◀ Management of ESRD

1. **Conservative management**
2. **Hemodialysis- HD**
   Vascular Access:
   AVF, AVG, Permcath
3. **Peritoneal Dialysis- PD**
   CAPD, CCPD, NIPD
4. **Kidney Transplantation**
   Living related,
   Living Unrelated, Cadaveric

Summary

Chronic Kidney Failure	
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 & 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 to Progression	Degree of hypertension, severity of proteinuria, Hyperlipidemia, Drugs (NSAIDs/aminoglycosides), high protein diet, persistent metabolic acidosis, extent of tubulointerstitial disease.
Changes in Other Body Systems	**CVS changes:** Hypertension, cardiomyopathies, pericarditis due to uremia and congestive heart failure. **Neuromuscular:** CNS dysfunction (decreased attention and agitation...) & peripheral neuropathy. **Hematologic:** Anemia that develops as serum creatinine increases, and platelet dysfunction with normal count and low VWF. **GI:** Anorexia, nausea and vomiting. **Dermatologic:** Uremic pruritus.
Management	• Restriction of protein, phosphate, sodium and potassium intake. • Salt & 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, and control anemia.

• CKD (CRF) means: chronic progressive irreversible loss of renal function. It is 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.
• Fluid and electrolytes of the body get disrupted during CKD causing a decrease in GFR leading to plasma and ECF expansion, Hyponatremia and Hypertension (unless sodium intake is restricted to 100 meq/day)

Lecture Quiz

Q1: 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

Q2: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 35 mL/min/1.73m2. You also notice the patients cholesterol levels are moderately raised. The most appropriate management is:

A- Sevelamer
B- Parathyroidectomy
C- Oral vitamin D
D- Cinacalcet

Q3: Typical biochemical features of chronic kidney failure include:

A- Hypophosphatemia
B- Hypercalcemia
C- Metabolic acidosis
D- Polyuria

Q4: 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

Q5: 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

Answers: Q1:C | Q2:A | Q3:C | Q4:A | Q5:C |

Answers Explanation File!

GOOD LUCK !

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