Chronic kidney disease and end- stage renal disease

- Chronic kidney disease (CKD) is defined as abnormalities in kidney structure or function (reduction in the glomerular filtration rate (GFR) and/or urinary abnormalities or structural abnormalities of the renal tract), present for 3 months or longer, with implications for health.
- Structural abnormalities include
- Albuminuria of more than 30 mg/day,
- Presence of hematuria or red cell casts in urine sediment,
- Electrolyte and other abnormalities due to tubular disorders.
  - **The severity of CKD is classified from 1 to 5 depending upon the level of GFR.**[1]

Table 18.1 Classification of chronic kidney disease

Stage of CKD	Glomerular filtration rate	Description
1	≥90 mL/min + proteinuria/haematuria or structural damage	Kidney damage with normal or increased GFR but other evidence of kidney damage
2	60–89 mL/min + proteinuria/haematuria or structural damage	Slight decrease in GFR with other evidence of kidney disease
3a 3b	45–59 mL/min 30–44 mL/min	Moderate reduction in GFR With or without evidence of other kidney disease
4	13–29 mL/min	Severe reduction in GFR
5	<15 mL/min	Kidney failure, use suffix (D) if dialysis

- As CKD progresses, nephron destruction worsens, leading to deterioration in the kidneys' filtration,reabsorption, and endocrine functions.

- Renal function typically does not diminish until about 75% of kidney tissue is damaged. Ultimately, the kidneys become shrunken, fibrotic masses.

❖ PATHOPHYSIOLOGY

✓ **Susceptibility factors** increase the risk for kidney disease but do not directly cause kidney damage. They include advanced age, reduced kidney mass and low birth weight, racial or ethnic minority, family history, low income or education, systemic inflammation, and dyslipidemia.

✓ **Initiation factors** directly result in kidney damage and are modifiable by drug therapy. They include

1 .Diabetic nephropathy

2 .Hypertension

3 .Glomerulonephritis

4 .Polycystic kidney disease

5 .Long-standing vascular disease (e.g., renal artery stenosis)

6 .Long-standing obstructive uropathy (e.g., renal calculi)

7. Exposure to nephrotoxic agents

✓ **Progression factors** hasten the decline in kidney function after initiation of kidney damage. They include glycemia in diabetics, hypertension, proteinuria, hyperlipidemia, obesity, and smoking.

•Most progressive nephropathies share a final common pathway to irreversible renal parenchymal damage and ESRD . Key pathway elements include ***loss of nephron mass, glomerular capillary hypertension, and proteinuria.***

❖ CLINICAL PRESENTATION

- CKD development and progression are insidious. Patients with stage 1 or 2 CKD usually do not have symptoms or metabolic derangements seen with stages 3 to 5,such as

  Anemia, secondary hyperparathyroidism, cardiovascular disease (CVD), malnutrition, and fluid and electrolyte abnormalities that are more common as kidney function deteriorates.

- **Uremic symptoms*(fatigue, weakness, shortness of breath, mental confusion, nausea,vomiting, bleeding, and anorexia)*** are generally absent in stages 1 and 2,

minimal during stages 3 and 4, and common in patients with stage 5 CKD who may also experience itching, cold intolerance, weight gain, and peripheral neuropathies.

- ***End stage renal disease*** is characterized by the requirement of renal replacement therapy to sustain life and it is often accompanied by uraemia, anemia, acidosis, osteodystrophy, and neuropathy and is frequently accompanied by hypertension, fluid retention and susceptibility to infection.

❖ Diagnostic test results

a. Creatinine clearance may range from 0 to 90 mL/min, reflecting renal impairment.

b. Blood tests typically show

1-Elevated BUN and serum creatinine concentration.

2-Reduced arterial pH and bicarbonate concentration.

3- Reduced serum calcium level.

4-Increased serum potassium and phosphate levels.

5-Possible reduction in the serum sodium level.

6-Normochromic, normocytic anemia (hematocrit 20% to 30%).

c. Urinalysis may reveal glycosuria, proteinuria, erythrocytes, leukocytes, and casts. Specific gravity is fixed at 1.010.

d. Radiographic findings. Kidney, ureter, and bladder radiography, IV pyelography, renal scan, renal arteriography, and nephrotomography may be performed. Typically, these tests reveal small kidneys (less than 8 cm in length).

Nuclear medicine investigations

There are two commonly used nuclear medicine investigations,the first uses mercapto acetyl tri-glycerine(MAG3). This isused for assessment of renal perfusion and the identificationof outflow obstruction. The other is a dimercapto succinicacid (DMSA) scan, the purpose of which is to ascertain thepercentage that each kidney contributes to overall function.The similar techniques of CT and MRI provide excellentstructural information about the kidneys and urinary tract.

❖ **Bone disease (renal osteodystrophy)[(1)]**

The osteodystrophy of renal failure is due to three factors:hyperphosphataemia, vitamin D deficiency and hyperparathyroidism

Renal osteodystrophy describes the four types of bone disease associated with CKD:

- secondary hyperparathyroidism

- osteomalacia (reduced mineralization)
- mixed renal osteodystrophy (both hyperparathyroidism and osteomalacia)
    - A dynamic bone disease (reduced bone formation and resorption).

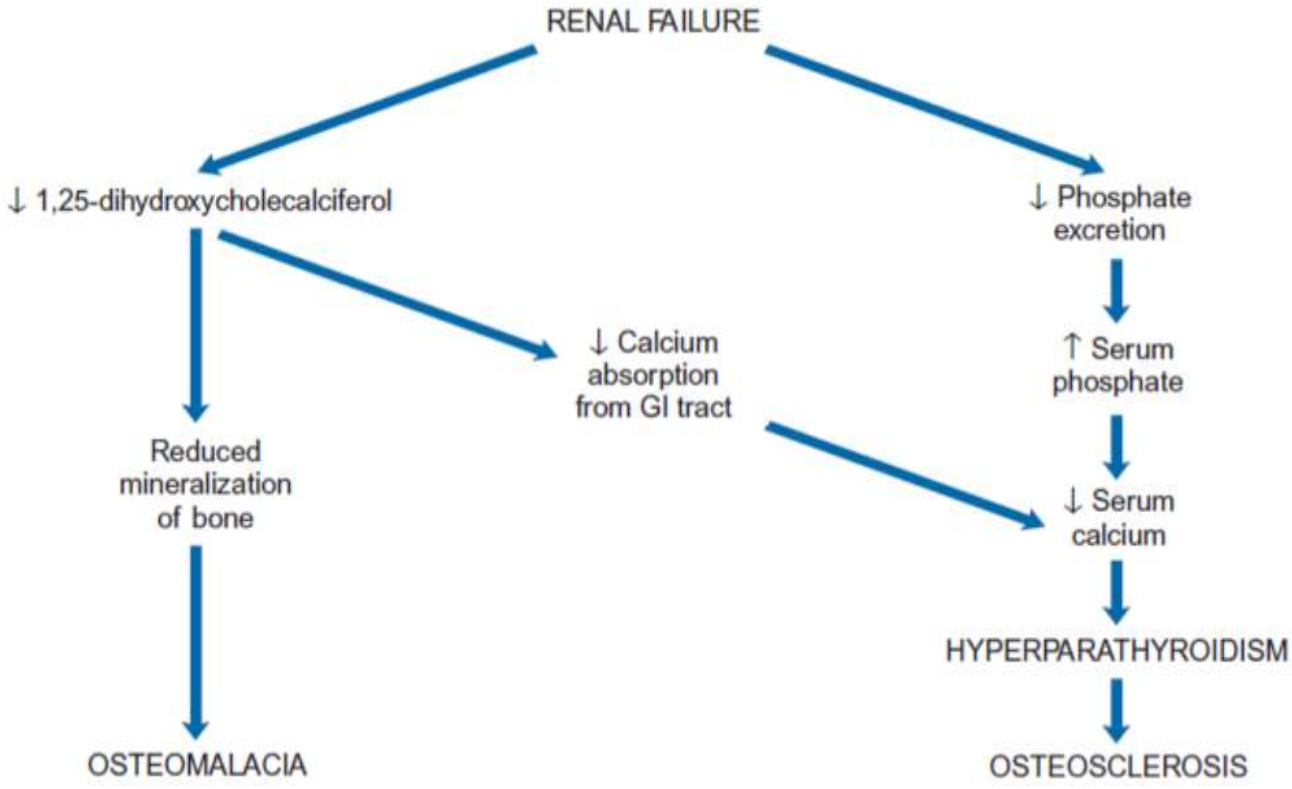


Fig. 18.8 Disturbance of calcium and phosphate balance in chronic renal failure.

❖ Treatment objectives

The aims of the treatment of CKD can be summarized as follows:

•Reverse or arrest the process causing the renal damage this may not be possible

•Avoid conditions that might worsen renal failure

•Treat the secondary complications of CKD (renal anemia and bone disease)

•Relieve symptoms

•Implement regular dialysis treatment and/ortransplantation at the most appropriate time

- Correct body chemistry abnormalities.

❖ <u>NONPHARMACOLOGIC THERAPY</u>

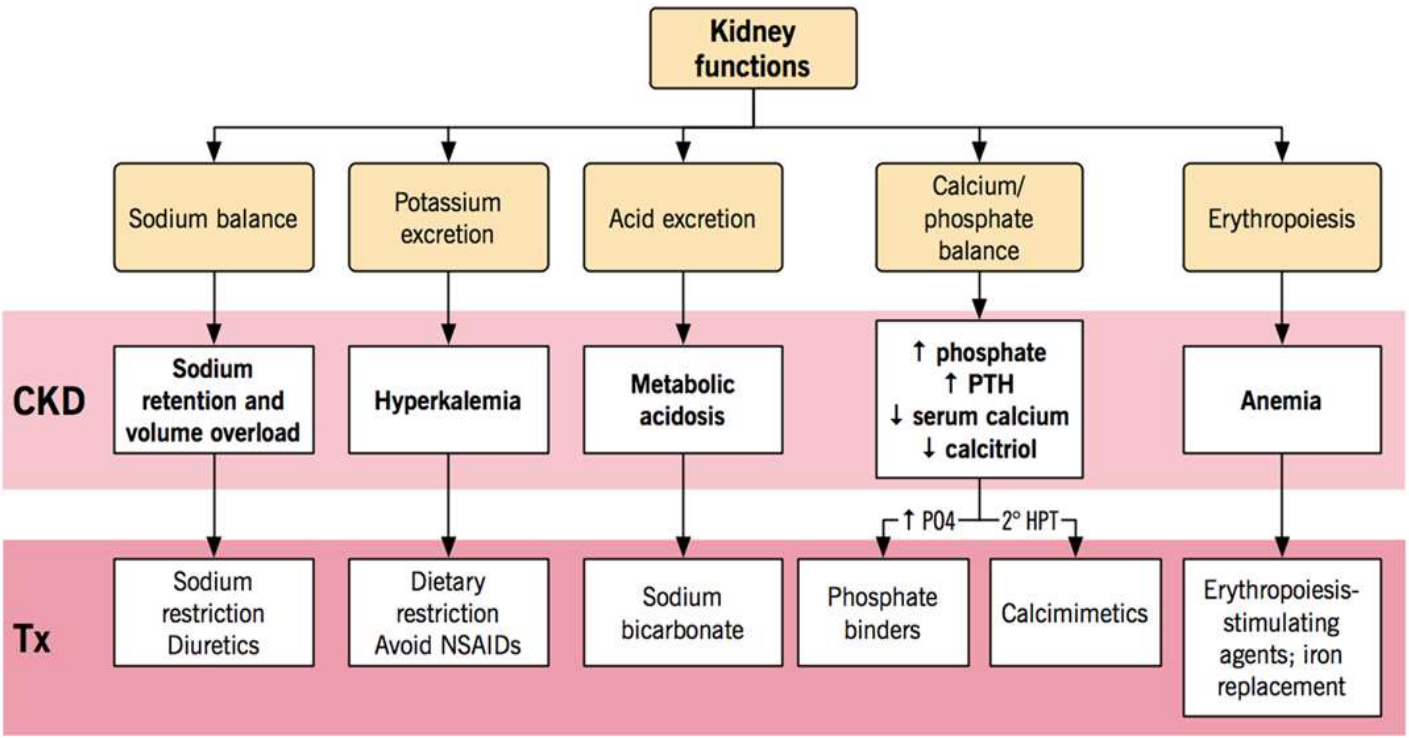
•Restrict protein to 0.8 g/kg/day if GFR is less than 30 mL/min/1.73 m2.???

- Sodium and fluid restriction to reduce the risk of fluid overload, potassium restriction to reduce the risk of hyperkalaemia and vitamin supplementation.

•Encourage smoking cessation to slow progression of CKD and reduce the risk ofCVD.

•Encourage exercise at least 30 minutes five times per week and achievement of a bodymass index (BMI) of 20 to 25 kg/m2.

Complications of CKD



❖ **PHARMACOLOGIC THERAPY**

Management of the CKD patient is generally conservative. Dietary measures and fluid restriction relieve some symptoms of CKD and may increase patient comfort and prolong life until dialysis or renal transplantation is required or available.

1 .Treatment of edema. Angiotensin-converting enzyme (ACE) inhibitors and diuretics may be given to manage edema and CHF and to increase urine output.

a. ACE inhibitors—are widely used to delay progression of CKD because they help preserve renal function and typically cause fewer adverse effects than other antihypertensive agents. They also decrease proteinuria and nephrotic syndrome.

b. Diuretics. An osmotic diuretic, a loop diuretic, or a thiazide-like diuretic may be given.

✓ Osmotic and loop diuretics together can be used.
✓ As loop diuretics need to be filtered to exert an action, progressively higher doses are required as CKD worsens. Doses of more than **250 mg/day** of furosemide may be required in advanced renal failure.
✓ Potassium sparing diuretics are usually contraindicated owing to the risks of developing hyperkalaemia, and thiazides become ineffective as renal failure progresses.

- ✓ Thiazide-like diuretics. Metolazone (Zaroxolyn®) is the most commonly used thiazide diuretic in CKD.
- ✓ Furosemide and metolazone act synergistically. Combination use is common, and metolazone should be administered 30 min before furosemide to achieve the optimal diuretic effect.

2-Treatment of hypertension.

- **Antihypertensive agents** may be needed if blood pressure becomes dangerously high as a result of edema and the high renin levels that occur in CKD. Antihypertensive therapy should be initiated in the lowest effective dose and titrated according to the patient's needs.

a. ACE inhibitors—captopril, enalapril, lisinopril, fosinopril
ACE inhibitors and ARBs can be used safely in most patients with CKD.

- ACE inhibitors and ARBs should be used at moderate to high doses, as used in clinical trials.

- ACE inhibitors and ARBs should be used as alternatives to each other, if the preferred class cannot be used.

- ACE inhibitors and ARBs can be used in combination to lower blood pressure or reduce proteinuria.

- Patients treated with ACE inhibitors or ARBs should be monitored for ***hypotension, decreased GFR, and hyperkalemia***.

- In most patients, the ACE inhibitor or ARB can be continued if:
- - GFR decline over 4 months is <30% from baseline value or Serum potassium is ≤5.5 mEq/L.

b. Dihydropyridine calcium-channel blockers, including amlodipine (Norvasc®) and felodipine (Plendil®), have similar effects and may be used instead of ACE inhibitors.

C.β-Blockers

B-Blockers are commonly used in the treatment of hypertensionin CKD.
It is advisable to use the more cardioselective β-blockers**atenolol** or **metoprolol**.
Atenolol is excreted renally and consequentlyshould require dosage adjustment in renal failure.In practice, however, atenolol is effective and tolerated wellby renal

patients at standard doses. However, metoprolol istheoretically a better choice since it is cleared by the liver andneeds no dosage adjustment, although small initial doses areadvised in renal failure since there may be increased sensitivityto its hypotensive effects.

d. Other antihypertensive agents are sometimes used in the treatment of CKD, including -adrenergic drugs, **clonidine (Catapres®)**, and vasodilators, such as **hydralazine(Apresoline®)**.

3-Treatment of hyperphosphatemia

Involves administration of a phosphate binder, such as aluminum hydroxide, calcium carbonate ora combination of calcium- andnon–calcium-containing products (e.g., sevelamer HCL and lanthanum carbonate).

•Adverse effects of all phosphate binders are generally limited to GI effects, includingconstipation, diarrhea, nausea, vomiting, and abdominal pain.

4-Treatment of hypocalcemia

a. Oral calcium salts

b. Vitamin D

- **Mechanism of action and therapeutic effect**. Vitamin D promotes intestinal calcium and phosphate absorption and utilization and, thus, increases the serum calcium concentration.

- **Choice of agent**. For the treatment of hypocalcemia in CKD and other renal disorders, **calcitriol (Rocaltrol®)** (vitamin D3, the active form of vitamin D) is the preferred vitamin D supplement because of its greater efficacy and relatively short duration of action. **Administration and dosage**. Calcitriol is given orally or via IV; the dose is titrated to the patient's needs (0.5 to 1.0 mg/day may be effective).????

- **Precautions and monitoring effects**

(a) Vitamin D administration may be dangerous in patients with renal failure and must be used with extreme caution.

(b) Vitamin D toxicity may cause a wide range of signs and symptoms, including headache, dizziness, ataxia, convulsions, psychosis, soft tissue calcification, conjunctivitis, photophobia, tinnitus, nausea, diarrhea, pruritus, and muscle and bone pain.

(c) Vitamin D has a narrow therapeutic index, necessitating frequent measurement of BUN and serum urine calcium and potassium levels.

❖ Treatment of Hyperlipidemia

•The prevalence of hyperlipidemia increases as renal function declines.

•National guidelines differ on how aggressively dyslipidemia should be managed inpatients with CKD. kidney disease improving global outcomes (KDIGO guidelines) recommend treatment with a statin (e.g., atorvastatin20mg, fluvastatin 80 mg, rosuvastatin 10 mg, simvastatin 20 mg) in adultsaged 50 and older with stage 1 to 5 CKD not on dialysis.

•In patients with ESRD, lipid profile should be reassessed at least annually and 2 to 3months after changing treatment.

❖ Treatment of anemia

- Renal anemia is common when the glomerular filtrationrate (GFR) falls below 30 mL/min but can be corrected by erythropoietin in 90–95% of cases by administration of iron (e.g., ferrous sulfate), folate supplements, and epoetin alfa.

1-Severe anemia may warrant transfusion with **packed red blood cells**.

2-Epoetin alfa (Procrit®, Epogen®) stimulates the production of red cell progenitors and the production of hemoglobin. It also accelerates the release of reticulocytes from the bone marrow.

- An initial dose of epoetin alfa is 50 to 100 U/kg intravenously or subcutaneously three times a week. The dose may be adjusted upward to elicit the desired response.
- Epoetin alfa works best in patients with a hematocrit below 30%. During the initial treatment, the hematocrit increases 1.0% to 3.5% in a 2-week period.
- The target hematocritis 33% to 35%. Maintenance doses are titrated based on hematocrit after thislevel is reached.
- Epoetin alfa therapy should be temporarily stopped if hematocrit exceeds 36%.
- Additional side effects include hypertension in up to 25% of patients. Headache and malaise have been reported.

3-Darbepoetin (Aranesp®) is an epoetin alfa analogue. Its advantage is a prolonged plasma half-life, thus allowing it to be administered once weekly or biweekly.

4-Intravenous iron products may be given to replete iron stores. This route is preferred to oral supplementation due to low oral bioavailability and GI intolerance. Iron dextran is commonly used; however, it is associated with hypotension and anaphylaxis. Newer ironproducts include **sodium ferric gluconate** and **iron sucrose**, which are better toleratedand can be infused more rapidly compared to iron dextran. Patients with ***severe iron deficiency*** may receive up to a total of **1 g** of an iron preparation over several days. The rateof infusion depends on the preparation used.

❖ Treatment of GI disturbances

1-Antiemetics help control nausea and vomiting.

2-Docusate sodium or methylcellulose may be used to prevent constipation.

3-Enemas may be given to remove blood from the GI tract.

❖ **Treatment of skin problems**.

The exact mechanismresponsible for the itching is not clear and several possibilitieshave been suggested including: xerosis (dry skin), skinmicro-precipitation of divalent ions, elevated PTH levels andincreased dermal mast cell activity. Generally, however, nounderlying cause is found and it is likely that a multifactorialprocess is responsible.

Sometimes correction of serum phosphate or calcium levels improves the condition, as by parathyroidectomy.

Conventionally, oral antihistamines are used to treat pruritus. Non-sedating antihistamines such as loratidineare generally less effective than sedating antihistaminessuch as chlorphenamine which may be useful,particularly at night.

Topical crotamiton lotion and creamsmay also be useful in some patients. Other non-drug therapiesinclude either warming or cooling the skin using baths,three times weekly, UVB phototherapy and modified electricalacupuncture..

❖ Treatment of acidosis

Since the kidney is the main route for excreting H+ ions, CKD may result in a metabolic acidosis. This will cause a reduction in serum bicarbonate that may be treated readily with oral doses of sodium bicarbonate of 1–6 g/day. As the dose of bicarbonate is not critical, it is easy to experiment with different dosage forms and strengths to suit individual patients. If acidosis is severe and persistent then dialysis may be required. Correction of acidosis may slow the decline in renal function.

❖ Renal transplantation

Renal transplantation remains the treatment of choice forend-stage renal disease. However, up to 60% of patientson dialysis programs are not fit enough to be put on thetransplant list.

The average transplant recipient lives two orthree times as long as a matched dialysis patients who doesnot receive a renal transplant but remains on dialysis treatment.In addition, a transplant patient is less likely to behospitalized and has a better quality of life than a dialysispatient. The secondary complications of CKD such as anemiaand bone disease resolve in many patients who are successfullytransplanted. Furthermore,

there are major healtheconomic benefits to renal transplantation compared todialysis. Transplantation is a far less expensive treatmentthan dialysis, particularly after the first year, when the largemajority of the costs are limited to payment for the immunosuppressivedrugs.

References:-

1- Roger walker,Cate Whittlesea.Clinical Pharmacy and Therapeutics. Elsevier Ltd .Fifth edition 2012.
2-Barbara G wells,Joseph T Dipiro,etal.Pharmacoterapy Handbook. The McGraw-Hill .ninth edition 2015.
3-MARIE A. CHISHOLM-BURNS,BARBARA G.WELLS,et al.PHARMACOTHERAPYPRINCIPLES &PRACTICE.Third edition.2015
4-Brian K. Alldredge,Robin L. Corelli,et al.Applied Therapeutics The Clinical Use of Drugs.Tenth Edition.2013.
5-Leon Shargel, Alan H. Mutnick.et al.Comprehensive Pharmacy Review.Eighth Edition.2013.