Chronic kidney disease (CKD)

Definition of CKD

Structural or functional abnormalities of the kidneys for ≥3 months from early to late-stage disease, **as manifested by either:** Kidney damage, with or without decreased GFR, GFR <60 ml/min/1.73 m2. Estimated glomerular filtration rates (eGFR) range from 90 mL/minute/1.73 m2 in the early stages to 15 mL/minute/1.73 m2 in the late stages of disease is known as end-stage renal disease (ESRD). Patients with ESRD require renal replacement therapy in the form of dialysis or transplantation to sustain life. The prevalence of chronic kidney disease (CKD) increases with age and is greater in females and some ethnic populations. CKD is classified according to severity from 1 to 5, where 5 is the most advanced and 1 the least.

The severity of CKD is classified from 1 to 5 depending upon the level of GFR.

Stage of Renal Disease	Damage	GFR (mL/minute/1.73 m^2)
Stage 1	Kidney damage with normal GFR	≥ 90
Stage 2	Kidney damage with mild decrease in GFR	60–89
Stage 3	Moderate decrease in GFR	30–59
Stage 4	Severe decrease in GFR	15–29
Stage 5	Kidney failure	< 15

Causes of CKD

- Ischemic nephropathy has traditionally Vascular diseases (renal artery disease, hypertension, microangiopathy) been referred to under perfusion of the kidneys
- Diabetes mellitus (Diabetic Kidney Disease) is the most common metabolic disease that leads to CKD, whilst the predominant lesion is glomerular and referred to as diabetic nephropathy.
- All types of chronic glomerulonephritis (GN) or Glomerular diseases (autoimmune diseases, systemic infections, drugs, neoplasia) cause about 15% of cases of advanced CKD.
- Lower urinary tract disease or Tubulointerstitial diseases (urinary tract infection, stones, obstruction, drug toxicity) they represent 5–10% of all cases of CKD.
- Hereditary/congenital diseases / Cystic diseases (polycystic kidney disease) they represent 5% of CKD cases
- CKD to be unknown and this is the case in around 30% of patients who typically present with small kidneys and unremarkable immunological investigations.

Pathophysiology

Most of the renal effects of renin-angiotensin-aldosterone system (RAAS) are through regulating intraglomerular pressures and salt and water balance. First, in patients with CKD, intra-renal pressures are often low and sympathetic overactivity is common; lead to increased renin secretion. This can occur with normal or elevated systemic blood pressure. this promotes production of the mineralocorticoid hormone aldosterone which lead to salt and fluid retention, high intravascular volumes, hypertension and oedema. Vasoconstriction on the efferent glomerular arteriole is mediated by a high density of angiotensin II receptors. When these receptors are ligated by angiotensin II, there is increased intra- glomerular pressures. Whilst this leads to an overall increase in GFR in the short-term, over a longer period glomerular hypertension promotes accelerated glomerular scarring and worsening CKD.

Metabolic and Systemic Consequences of CKD

A- Uraemia

Uraemia results from the accumulation of urea and other nitrogenous toxins. The symptoms of uraemia include anorexia, nausea, vomiting.

B-Cardiovascular Complications

The risk of cardiovascular disease is substantially increased and represent an important cause of death in patients with CKD. Hypertension is the most common complication of CKD. As kidney disease progresses, hypertension due to salt and water retention usually develops. Dyslipidemia may be associated with kidney disease. Patients with CKD are at higher risk for Coronary artery disease and heart failure.

C-Hematologic Complications

1-Anemia: The anemia of CKD is primarily due to decreased erythropoietin production.

2-Coagulopathy: The coagulopathy of CKD is mainly caused by platelet dysfunction. Clinically, patients can have petechiae, purpura, and an increased tendency for bleeding during surgery.

D-Calcium, Phosphorus, and Bone Homeostasis

Declining GFR leads to reduced excretion of phosphate and, thus, **hyperphosphataemia**; which stimulates increased synthesis of parathyroid hormone (PTH). Failing kidneys are not able to convert vitamin D to the active form 1,25-dihydroxycholecalciferol. This will impair intestinal absorption of calcium, thereby **causing hypocalcaemia** which also stimulate PTH production. **Hyperparathyroidism stimulates bone turnover** (**renal osteodystrophy**) (increased bone reabsorption to maintain adequate calcium levels). (Figure-1). The osteodystrophy of renal failure is due to three factors: hyperphosphataemia, vitamin D deficiency and hyperparathyroidism.

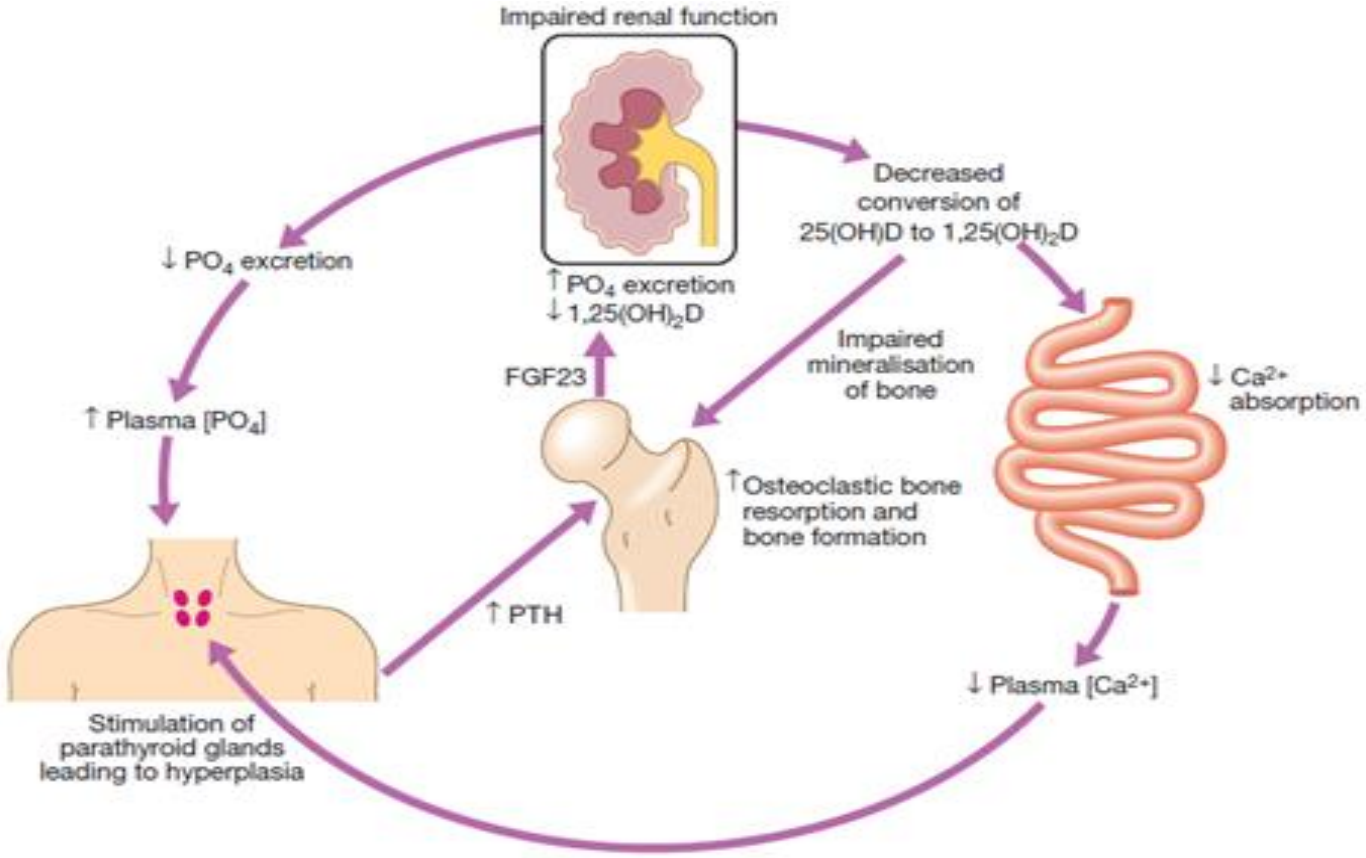

Fig. 1 Pathogenesis of renal osteodystrophy. Low 1,25(OH)2D levels cause calcium malabsorption and this, combined with high phosphate levels, causes hypocalcaemia, which increases PTH production by the parathyroid glands. The raised level of PTH increases osteoclastic bone resorption. Although production of serum fibroblast growth factor 23 (FGF23) from osteocytes also increases, promoting phosphate excretion, this is insufficient to prevent hyperphosphataemia in advanced CKD

E-Electrolyte, and acid-base disorders

Patients with CKD often develop **hyperkalemia** and **metabolic acidosis.**

F-Immune dysfunction

Cellular and humoral immunity is impaired in advanced CKD and there is **increased susceptibility to infections**.

G-Neurological and muscle function

Muscle symptoms are probably caused by general nutritional deficiencies and electrolyte disturbances (especially hypocalcaemia). **Muscle cramps** are common. The '**restless leg syndrome**', in which the patient's legs are jumpy during the night, may be troublesome. The neurological changes are non-specific and include **inability to concentrate**, **memory impairment**, and **irritability** probably caused by uraemic toxins.

Diagnostic test:

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

b. Blood tests typically show elevated BUN and serum creatinine concentration, reduced serum calcium level, increased serum potassium and phosphate levels and normochromic, normocytic anemia (hematocrit 20% to 30%).

c. Urinalysis may reveal glycosuria, proteinuria, erythrocytes, leukocytes, and casts.

d. Radiographic findings. Kidney, ureter, and bladder radiography. Typically, these tests reveal small kidneys (less than 8 cm in length).

Treatment

The goal is to delay the progression of CKD, minimizing the development or severity of complications.

Nonpharmacologic Therapy

- Reduction in dietary protein intake has been shown to slow the progression of kidney disease. Protein intake should be lowered to 0.8 g/kg/day in adults with diabetes or people with a GFR less than 30 ml/min/1.73 m2 who are not on dialysis. However, protein restriction must be balanced with the risk of malnutrition in patients with CKD. In particular, patients on dialysis are at risk for nutritional abnormalities, which can lead to increased rates of hospitalization and death. Patients receiving dialysis should maintain protein intake of 1.2 g/kg/day.

- Limiting salt intake to less than 2 g of sodium per day (equivalent to 5 g sodium chloride) will help to control blood pressure and reduce water retention in CKD.

- **Fluid restriction is generally not required** in CKD patients and, if excessive, may lead to volume depletion and hypernatremia. Restriction is appropriate in patients with dilutional hyponatremia.

- **Potassium should be restricted** to 60 mEq/d in individuals with hyperkalemia. Tomato-based products, bananas, potatoes, and citrus drinks are high in potassium and should be avoided in these patients.

- **Dietary phosphate restriction** should be to 800-1000 mg/d. Dairy products, dark colas, and nuts should be avoided in hyperphosphataemia . **Dialysis** removes various amounts of phosphorus; however, by itself it is insufficient to maintain phosphorus balances in most patients.

- Patients with CKD should be encouraged to **increase physical activity**, with a goal of at least 30 minutes five times per week, to achieve a healthy weight, with a goal BMI of 20 to 25.

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 Hypertension

Optimum control of blood pressure is one of the most important therapeutic measures since hypertension causes damage to the intrarenal vasculature resulting in thickening of the walls of arterioles and small vessels. This damage effectively reduces renal perfusion, contributing to stimulation of the RAAS. Arteriolar vasoconstriction, sodium and water retention result, which in turn exacerbates the hypertension. Antihypertensive therapy with certain agents might produce a transient reduction in GFR over the first 3 months of treatment as the systemic and glomerular blood pressure drop; this is mainly seen with ACE inhibitors/angiotensin receptor blockers (ARBs). However, it is possible to ultimately halt or slow the decline in many cases.

Calcium channel blockers

For patients without proteinuria, calcium channel blockers (CCBs) are the agents of choice. They produce vasodilatation principally by reducing Ca2+ influx into vascular muscle cells. Calcium-channel blockers, including amlodipine and felodipine have similar effects and may be used instead of ACE inhibitors.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

The role of ACE inhibitors in hypertensive patients with renal insufficiency is complicated, the current evidence base supports the principle that all diabetic patients with albuminuria and CKD should be treated with ACE inhibitors or ARBs regardless of blood pressure. There is also evidence that in non-diabetic patients with proteinuria, the use of these drugs can reduce proteinuria and thus reduce progression of CKD. ACE inhibitors reduce circulating angiotensin II and ARBs block binding to the angiotensin II receptor, which results in vasodilatation and reduced sodium retention. For long-term management, it is usually preferable to use an agent with a duration of action that permits once-daily dosing. ACE inhibitors are potassium sparing and therefore serum potassium should be monitored carefully. A low-potassium diet may be necessary. ARBs have properties similar to ACE inhibitors with the advantage that, since they do not inhibit the breakdown of kinins such as bradykinin, they do not cause the dry cough associated with the ACE inhibitors.

Diuretics

Diuretics are of use in patients with salt and volume overload, which is usually indicated by the presence of oedema. This type of hypertension may be particularly difficult to treat. The choice

of agent is generally limited to a **loop diuretic**. **Potassium sparing diuretics** are usually contraindicated owing to the risks of developing hyperkalaemia, and **thiazides** become ineffective as renal failure progresses.
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. Patients who do not respond to oral loop diuretic therapy alone may benefit from concomitant administration of metolazone, which acts synergistically to produce a profound diuresis. Alternatively, the loop diuretic may be given intravenously.

B-Blockers

B-Blockers are commonly used in the treatment of hypertension in CKD. They exhibit a range of actions including a reduction of renin production. It is advisable to use the more cardioselective B-blockers atenolol or metoprolol. Atenolol is excreted renally and consequently should require dosage adjustment in renal failure. In practice, however, atenolol is effective and tolerated well by renal patients at standard doses. However, metoprolol is theoretically a better choice since it is cleared by the liver and needs no dosage adjustment, although small initial doses are advised in renal failure since there may be increased sensitivity to its hypotensive effects.

2-CKD–Mineral and Bone Disorder (CKD-MBD)

The first step in treatment of metabolic bone disease is control of hyperphosphatemia. The management of hyperphosphatemia depends initially upon restricting dietary phosphate. This can be difficult to achieve effectively, even with the aid of a specialist dietician, because phosphate is found in many palatable foods such as dairy products, eggs, chocolate and nuts followed by the administration of oral phosphorus binders if targets are not achieved.

Phosphate-Binding Agents:

Phosphate binding agents are used to bind dietary phosphate in the GI tract to form an insoluble complex that is excreted in the feces. These agents should be administered with each meal. Calcium-based phosphate binders, including calcium carbonate and calcium acetate, are effective in decreasing serum phosphate levels, as well as in increasing serum calcium levels. (For patients with hypocalcemia, calcium carbonate or calcium acetate may also be given as a calcium supplement taken between meals to promote calcium absorption).

Calcium acetate binds more phosphorus than the carbonate salt, making it a more potent agent for binding dietary phosphate. The calcium-containing phosphate binders also aid in the correction of metabolic acidosis, another complication of kidney failure. Calcium-based phosphate binders should not be used if serum calcium levels are near the upper end of the normal range or are elevated. The dose of calcium-based phosphate binders should not provide more than 1500 mg of elemental calcium per day, and the total elemental calcium intake per day

should not exceed 2000 mg, including medication and dietary intake. The most common adverse effects of calcium-containing phosphate binders are constipation and hypercalcemia.

Sevelamer, lanthanum, and iron-based phosphate binders do not contain calcium, magnesium, or aluminum. These agents are particularly useful in patients with hyperphosphatemia who have elevated serum calcium levels or who have vascular or soft tissue calcifications.

Sevelamer is a cationic polymer that is not systemically absorbed and binds to phosphate in the GI tract, and it prevents absorption and promotes excretion of phosphate through the GI tract via the feces.

3- Hyperlipidemia Treatment

Hyperlipidemia plays a role in the development of cardiovascular disease (CVD) in patients with CKD. The KDIGO guidelines recommend starting statins for all patients with non-dialysis dependent CKD aged 50 years and older, regardless of GFR category. Statins should also be used for patients aged 18 to 49 years who have known coronary artery disease, DM, prior ischemic stroke and myocardial infarction. However, because of the lack of efficacy in reducing cardiovascular events and the risk of adverse effects associated with statins in patients with ESKD, statins should not be initiated in patients on dialysis, unless they were receiving statins prior to starting dialysis.

4- Anemia of CKD

Pharmacologic therapy for anemia of CKD includes iron supplementation to prevent and correct iron deficiency and erythropoiesis-stimulating agent (ESA) therapy to correct erythropoietin deficiency. Iron supplementation is first-line therapy for anemia of CKD if iron deficiency is present, and for some patients the target Hb may be achieved without concomitant ESA therapy. For most individuals with advanced CKD, however, combined therapy with iron and an ESA will be necessary to achieve the target Hb. Oral iron supplements are generally the first-line treatment for iron supplementation for patients with CKD not receiving hemodialysis. When oral iron is not effective to increase iron stores or for patients receiving hemodialysis, IV iron should be administered.
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 iron products include sodium ferric gluconate and iron sucrose, which are better tolerated and 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 rate of infusion depends on the preparation used.

Erythropoiesis-stimulating agents (ESAs):

Initiate therapy for hemoglobin less than 10 g/dL. The hemoglobin concentration should be maintained within the range 10–12 g/100 ml. Epoetin alfa 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 hematocrit is 33% to 35%. Maintenance doses are titrated based on hematocrit after this level is reached. Epoetin alfa therapy should be temporarily stopped if hematocrit exceeds 36%. Side effects include hypertension in up to 25% of patients. Headache and malaise have been reported.
Darbepoetin is an epoetin alfa analogue. Its advantage is a prolonged plasma half-life, thus allowing it to be administered once weekly or twice weekly.

Vitamin D deficiency and hyperparathyroidism

Vitamin D deficiency may be treated with the synthetic vitamin D analogues 1-hydroxycholecalciferol **(alfacalcidol)** at 0.25–1 μcg/day or 1,25-dihydroxycholecalciferol **(calcitriol)** at 1–2 μcg/day. The serum calcium level should be monitored, and the dose of alfacalcidol or calcitriol adjusted accordingly. The rise in 1,25-dihydroxycholecalciferol and calcium levels that result from starting vitamin D therapy usually suppresses the production of PTH by the parathyroids. If vitamin D therapy does not correct PTH levels then **parathyroidectomy**, to remove part or most of the parathyroid glands, may be needed. This surgical procedure was once commonly performed on CKD patients, but is now less frequent owing to effective vitamin D supplementation.
Cinacalcet is a calcimimetic which increases the sensitivity of calcium sensing receptors to extracellular calcium ion, this results in reduced PTH production. The benefit of this treatment is the suppression of PTH without resultant hypercalcaemia. It is recommended for use as an alternative to parathyroidectomy for patients who are not fit enough to undergo this procedure.

Treatment of GI disturbances

Nausea and vomiting may persist after starting a low protein diet. Metoclopramide is useful to treat this, but sometimes accumulation of the drug and its metabolites may occur, leading to extrapyramidal side effects. Patients should be started on a low dose, which should then be increased slowly. Prochlorperazine or cyclizine may also be useful. The 5-HT3 antagonists such as ondansetron have also been shown to be effective. The anaemic patient often becomes less nauseated when treated with an erythropoiesis stimulating agent.

Constipation is a common problem in patients with renal disease, partly as a result of fluid restriction and anorexia and partly as a consequence of drug therapy with agents such as phosphate binders. It is particularly important that patients managed with peritoneal dialysis do

not become constipated, as this can reduce the efficacy of dialysis. Conventional laxative therapy may be used, such as bulk-forming laxatives or increased dietary fibre for **less severe constipation.**
Alternatively, a stimulant such as senna with enemas or glycerine suppositories may be used for **severe constipation**. Higher doses of senna, typically 2–4 tablets at night, may be required. It should be noted that certain brands of laxatives that contain ispaghula husk may also contain significant quantities of potassium, and should be avoided in renal failure because of the risk of hyperkalaemia. Sterculia preparations are an effective alternative.

Treatment of skin problems.

The exact mechanism responsible for the itching is not clear and several possibilities have been suggested including: xerosis (dry skin), skin micro-precipitation of divalent ions, elevated PTH levels and increased dermal mast cell activity.
Sometimes correction of serum phosphate or calcium levels improves the condition. Conventionally, oral antihistamines are used to treat pruritus. Non-sedating antihistamines such as loratadine are generally less effective than sedating. Antihistamines such as chlorphenamine which may be useful, particularly at night. Topical crotamiton lotion and creams may also be useful in some patients.

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 for end-stage renal disease.
However, up to 60% of patients on dialysis programs are not fit enough to be put on the transplant list. The average transplant recipient lives two or three times as long as a dialysis patient who does not receive a renal transplant but remains on dialysis treatment. In addition, a transplant patient is less likely to be hospitalized and has a better quality of life than a dialysis patient. The secondary complications of CKD such as anemia and bone disease resolve in many patients who are successfully transplanted.