L21: Chronic Kidney Disease

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MEDICINE 433

objectives

1. To understand the basic informations on etiology, staging, Diagnosis and treatment.

2. To know complications of CKD and their treatment .

3. To analyze the mechanism and pathophysiology of CKD progression and therapies to slow progression.

Color index: Step up to medicine , slide , Doctor's note , Davidson , Extra Explanation

Pathophysiology of chronic kidney disease

- **CKD is defined as either decreased kidney function (GFR <60 mL/min) or kidney damage (structural or functional abnormalities) for at least 3 months, regardless of cause.**

1. **Loss of nephron mass** → hypertrophy of the remaining nephrons *Compensation *
   - The hypertrophied nephron plasma flow and glomerular pressure increase (vasodilatation of the aff. Arterioles) ➔ basal membrane damage ➔ sclerosis
   - Proximal reab. of NaCl, Fluids and PO_4 ↘
     Collecting ducts secretion of K^+ and H^+ → ***enhanced***
   - These adaptations initially restore hemeostasis
   - But glomerular hyperfiltration → glomerular injury, glomerulosclerosis and further loss of renal function.

2. **Growth factors:**
   - Transforming growth factor-B
   - Platelets derived growth factors
   - Osteopontin, angiotensin-II
   - Endothelin

   → **Interstitial fibrosis**

Normal function of :
1. Proximal tubules : filtrate reabsorption 70%
2. Distal tubules : excrete K and H+

3. An increase in plasma Cr indicates disease progression, whereas a decrease suggests recovery of renal function.
4. Most common in African-American than Caucasian patients.

Diabetes and hypertension are the most common causes of End Stage Renal Disease ESRD.

Etiology of CKD:

Diabetes mellitus (DM)	**40%**
Hypertension	**30%**
Glomerulonephritis	15%
Hereditary cystic and cong. renal disease	4%
Interstitial nephritis/pyelonephritis	4%
Tumours	2%
Miscellaneous	5%

Azotemia refers to the elevation of BUN.
- **Uremia** refers to the signs and symptoms associated with accumulation of nitrogenous wastes due to impaired renal function. It is difficult to predict when uremic symptoms will appear,
but it rarely occurs unless the BUN is >60 mg/dL.

Chronic Kidney Disease-miniral and bone disorder (CKD- MBD)

- Indicates alterations in mineral bone metabolism

- These alterations include :

1- biochemical abnormalities in calcium, phosphorus, PTH, vitamin D and fibroblast growth factor-23.
2- changes in bone morphology : volume, turnover, and mineralization
3- calcification of soft tissue and blood vessels

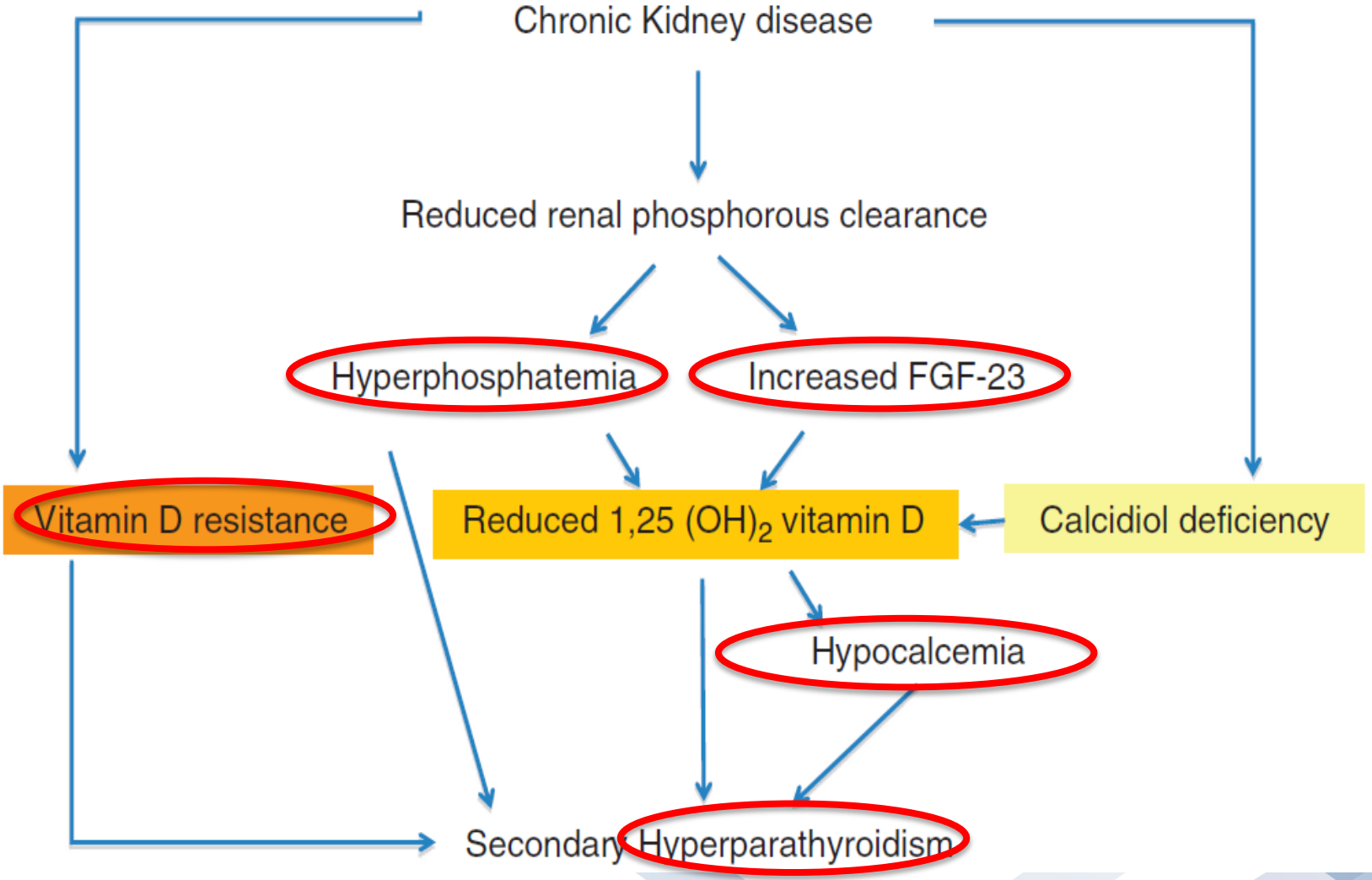
As GFR declines, the excretion of phosphorus is impaired, leading to a tendency to hyperphosphatemia. Hyperphosphatemia is an independent risk factor for the increased morbidity and mortality of stage 5 CKD from cardiovascular events

Recently, *it has been demonstrated that* fibroblast growth factor 23 (*FGF-23*) is stimulated by phosphorus retention *FGF-23* causes *phosphaturia* (via both parathyroid-dependent and independent mechanisms) and maintain 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.

- The classic biochemical abnormalities :

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

Pathogenesis of CKD - MBD



Sndry hyperparathyroidism "only with CKD" : high phosphate and low calcium

- CKD cause MBD "mineral and bone disorder"
- MBD because : excretion of phosphorus is impaired

Risk Factors

ESRD is not defined by BUN or creatinine levels. It is a loss of kidney function that leads to laboratory and clinical findings of uremia.

1. Genetic (family hx of kidney disease)
2. Low socioeconomic status
3. Medical status : e.g. **Diabetes, hypertension***, obesity, cardiovascular disease and smoking.

*Main cause of HTN in CKD are salts and water retention

Chronic Kidney Disease – Stages

5 stages of CKD (evidence of renal damage + GFR)

Stage	Description	GFR Normal GFR = 125 (ml/min/1.73m²)
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	<15 or dialysis

Clinical features

When a patient's renal function is irreversibly compromised but **not** failed, the term **chronic renal insufficiency** is used. It is generally applied to those with a chronic elevation of serum creatinine to 1.5 to 3.0 mg/dL.

Cardiovascular

A. HTN
-Secondary to salt and water retention—decreased GFR stimulates renin–angiotensin system and aldosterone secretion to increase, which leads to an increase in BP.
- Renal failure is the most common cause of secondary HTN.

B . CHF—due to volume overload, HTN, and anemia
C . Pericarditis (uremic)
-Bloody pericarditis with pericardial rub is one of the indication of dialysis

Fluid and electrolyte problems

- Volume overload—watch for pulmonary edema
- Hyperkalemia—due to decreased urinary secretion
- Hypermagnesemia—occurs secondary to reduced urinary loss
- Hyperphosphatemia—see above
- Metabolic acidosis—due to loss of renal mass (and thus decreased ammonia production) and the kidney's inability to excrete H+

-In CKD Na level depends in intake while K level is high " hyperkalemia"
-In CKD Colon start to excrete k as compensation
-In CKD we have acidosis with high anion gap in most time

Neurologic

a. Symptoms include lethargy, somnolence, confusion, peripheral neuropathy, and uremic sezures .physical findings include weakness, asterixis and hyperreflexia. Patients may show "restless legs"—neuropathic pain in the legs that is only relieved with movement.

b. Hypocalcemia can cause lethargy, confusion, and tetany.
-Hiccups is one of the CNS abnormalities in CKD
-flapping tremor " indicate encephalopathy" is one of the indication of dialysis

GI

- usually due to uremia

a. Nausea, vomiting
b. Loss of appetite (anorexia)

- ↑ Gastrin in CKD

Hematologic

- **Normocytic normochromic anemia (secondary to deficiency of erythropoietin)—**may be severe
- Bleeding* secondary to platelet dysfunction (due to uremia). Platelets do not degranulate in uremic environment.

*Von-Willebrand factor deficiency lead to platelet dysfunction and increase bleeding time

Immunologic

uremia inhibits cellular and humoral immunity

Clinical features

Hypocalcemia leads to secondary hyperparathyroidism, which removes calcium from bones, making them weak and susceptible to fracture.

Endocrine/metabolic

a. Calcium–phosphorus disturbances

1. Decreased renal clearance of phosphate leads to **hyperphosphatemia**, which results in decreased renal production of 1,25-dihydroxy vitamin D. This leads to **hypocalcemia**, which causes secondary hyperparathyroidism.
2. So, **hypo**calcemia and **hyper**phosphatemia are usually seen, but long-standing secondary hyperparathyroidism and calcium-based phosphate binders may sometimes cause **hypercalcemia.**
3. Secondary hyperparathyroidism causes **renal osteodystrophy,** which causes weakening of bones and possibly fractures.
4. Hyperphosphatemia may cause calcium and phosphate to precipitate, which causes vascular calcifications that may result in necrotic skin lesions. This is called **calciphylaxis.**

B. Sexual/reproductive symptoms due to hypothalamic–pituitary disturbances and gonadal response to sex hormones: in men, decreased testosterone; in women amenorrhea, infertility, and hyperprolactinemia

C. Pruritus (multifactorial etiology)—common and difficult to treat. Dialysis and ultraviolet light.

-CKD patients have high tendency to develop bone fractures " spine and hip "

Uremic syndrome

Uremia results from retention of end products of protein metabolism

* Administration of urea causes only mild symptoms

Dyslipidemia

- ↓ HDL cholesterol
- ↑ TG and lipoprotein

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.

Dermatologic

Uremic pruritus is related to:

- Calcium and phosph deposition (2° ↑ PTH)
- Hypercalcemia
- Peripheral neuropathy
- Dry skin
- Anemia
- Inadequate dialysis

How To Diagnose

Life-threatening complications in CKD
- Hyperkalemia—obtain an ECG (be aware that potassium levels can be high without ECG changes).
- Pulmonary edema secondary to volume overload—look for recent weight gain.
- Infection (e.g., pneumonia, UTI, sepsis)

❖ **Natural Hx of CKD**

- **Early** : usually asymptomatic in its early stages
- **Late** : symptoms and signs usually related to
  - *sodium and water retention (HTN, Odema)
  - *metabolic and hormonal complications (anemia , vit –D deficiency,PTH)
  - * increased incidence of CVD, infection, and impaired physical function.

Investigation

Urinalysis	Cr clearance	CBC	Serum electrolytes	Renal ultrasound
• examine sediment	• Measure Cr clearance to estimate GFR	• anemia, • thrombocytopenia	• K+ • Ca2+ • PO43 • serum protein	• **evaluate size of kidneys/rule out obstruction** 1. **Small kidneys* are suggestive of chronic renal insufficiency with little chance of recovery.** 2. **Presence of normal-sized or large kidneys does not exclude CKD.** 3. **Renal biopsy—in select cases to determine specific etiology**

Except in: DM , amyloidosis , polycystic kidney disease

Management

Transplantation is the only cure.

In a patient with CKD, symptomatic volume overload and severe hyperkalemia are the most common complications that require urgent intervention.

Diet	ACE inhibitors	BP control	Glycemic control	Correction of electrolyte abnormalities
A. **Low protein—to 0.7 to 0.8 g/kg body weight per day** B. **Use a low-salt diet if HTN, CHF, or oliguria are present.** C. **Restrict potassium, phosphate, and magnesium intake.**	**Dilate efferent arteriole of glomerulus** a. If used early on, they reduce the risk of progression to ESRD because they b. slow the progression of proteinuria. b. Use with great caution because they can cause hyperkalemia.	a. **ACE inhibitors** are the preferred agents. Multiple drugs, including diuretics.	**prevents worsening of proteinuria.**	**a. Correct hyperphosphatemia with calcium** citrate (a phosphate binder). b. Patients with chronic renal disease are generally treated with **long-term oral calcium and vitamin D** in an effort to prevent secondary hyperparathyroidism and uremic osteodystrophy. **c. Acidosis—**treat the underlying cause (renal failure). Patients may require oral bicarbonate replacement. -Don't give Vit D if there is Hyperphosphatemia
Anemia Target for Hb is 10-12	**Pulmonary edema**	**Pruritus**	**Smoking**	**Hyperlipidemia**
Treat with erythropoietin -erythropoietin is less effective in the presence of iron drficiency	**Arrange for dialysis if the condition is unresponsive to diuresis.**	**Try capsaicin cream or cholestyramine and UV light.**	**Smoking cessation**	the goal is to keep **low density lipoprotein cholesterol < 100** mg/dl by diet control and statin group.

Management

Dialysis

Specific indications for dialysis

1. Nonemergent indications

a. Cr and BUN levels are **not** absolute indications for dialysis.

b. Symptoms of uremia

- Nausea and vomiting
- Lethargy/deterioration in mental status, encephalopathy, seizures
- Pericarditis

2. Emergent indications (usually in the setting of renal failure)

a. Life-threatening manifestations of volume overload

- Pulmonary edema
- Hypertensive emergency refractory to antihypertensive agents

b. Severe, refractory electrolyte disturbances, for example, hyperkalemia, hypermagnesemia

c. Severe metabolic acidosis

d. Drug toxicity/ingestions (particularly in patients with renal failure): methanol, ethylene glycol, lithium, aspirin

Absolute indications for dialysis

- **A**cidosis—significant, intractable metabolic acidosis
- **E**lectrolytes—severe, persistent hyperkalemia
- **I**ntoxications—methanol, ethylene glycol, lithium, aspirin
- **O**verload—hypervolemia not managed by other means
- **U**remia (severe)—based on clinical presentation, not laboratory values (e.g., uremic pericarditis is an absolute indication for dialysis)

Creatinine level is not an absolute indication for dialysis.

The differences between AKI and CKD

TABLE 7-4 Differentiation of AKI Versus CKD

Favors Chronic	Favors Acute
History of kidney disease, HTN, abnormal urinalysis, edema	—
Small kidney size on renal ultrasound	—
—	Return of renal function to normal with time
Hyperkalemia, acidemia, hyperphosphatemia, anemia	Hyperkalemia, acidemia, hyperphosphatemia, anemia
—	Urine output <500 mL/day without uremic symptoms
Urinalysis with broad casts (i.e., more than two to three WBCs in diameter)	—

Adapted from Schrier RW, ed. *Diseases of the Kidney and Urinary Tract.* Vol II. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2001:1098, Figure 41-5.

MCQs

1. **Most common cause of end-stage renal disease is:**
   a) Amyloidosis
   b) Diabetes Mellitus
   c) Hypertension
   d) Polycystic kidney disease

2. **Patients with progressive chronic renal failure, typically will develop:**
   a) Hemolytic anemia
   b) Aplastic anemia
   c) Hypochromic, microcytic anemia
   d) Normochromic normocytic anemia

3. **Impaired metabolic processes such as Hyperkalemia, Acidosis, Hyperlipidemia, Hyperuricemia, and malnutrition are some effects of:**
   a) Hematuria
   b) Oliguria
   c) Uremia
   d) Nephrotoxins

4. **In chronic kidney disease, kidney appear atrophied and lost except in which one of the following :**
   a) Diabetes
   b) Polycystic kidney disease
   c) Amyloidosis
   d) All Above

5. **High urea in blood called:**
   a) Azotemia
   b) Uremia*
   c) hematuria

6. **Which is the treatment of choice for many patient with end-stage renal disease?**
   a) Hemodialysis
   b) Peritoneal dialysis
   c) Kidney transplant

7. **Main cause of HTN in Chronic kidney disease :**
   a) stimulation of renin- angiotensin system
   b) Na+ Reatention
   c) hight urea in blood

Answers : 1-b 2-d 3-c 4-d 5-a 6-c 7-b

*uremia : Azotemia + symptoms of elevated blood urea

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Medicine is a science of uncertainty and an art of probability

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