MEDICINE

432 Team

21 Chronic Kidney Disease

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COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

Objectives

1. To understand the basic information 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.

Normal Kidney Function:

- Fluid balance.
- Electrolytes regulation.
- Control acid-base balance.
- Waste removal.
- Hormonal function:
  - Erythropoietin.
  - Renin.
  - Prostaglandins.
  - Active Vitamin D3.

Chronic Kidney Disease (CKD):

Chronic progressive irreversible loss of renal function.

End Stage Renal Disease (ESRD):

Advanced CKD (Stage-5) requiring dialysis or kidney transplantation.

Etiology of CKD:

Diabetes Mellitus.	**40%**
Hypertension.	30%
Glomerulonephritis.	15%
Hereditary cystic and congenital renal disease.	4%
Interstitial nephritis\pyelonephritis	4%
Tumors.	2%
Miscellaneous.	5%

CKD – Stages:

Stage	Description	GFR (ml\min\1.73m²)
1	Kidney damage with normal or ↓ GFR Evidence by lab (e.g. ↑ urea, Creatinine, proteinuria, hematuria…) or by radiology (e.g. cysts, stones, atrophic kidney…) + or normal ↑ GFR.	> 90
2	Mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Sever ↓ GFR	15-29
5	Kidney failure, ENRD	< 15or dialysis

Note: ***from Davidsons's***

Initially, CKD manifest only as biochemical abnormality. Eventually, loss of the excretory, metabolic and endocrine functions of the kidney lead to the clinical symptoms and signs of renal failure which are referred to as uremia.

Pathophysiology of CKD:

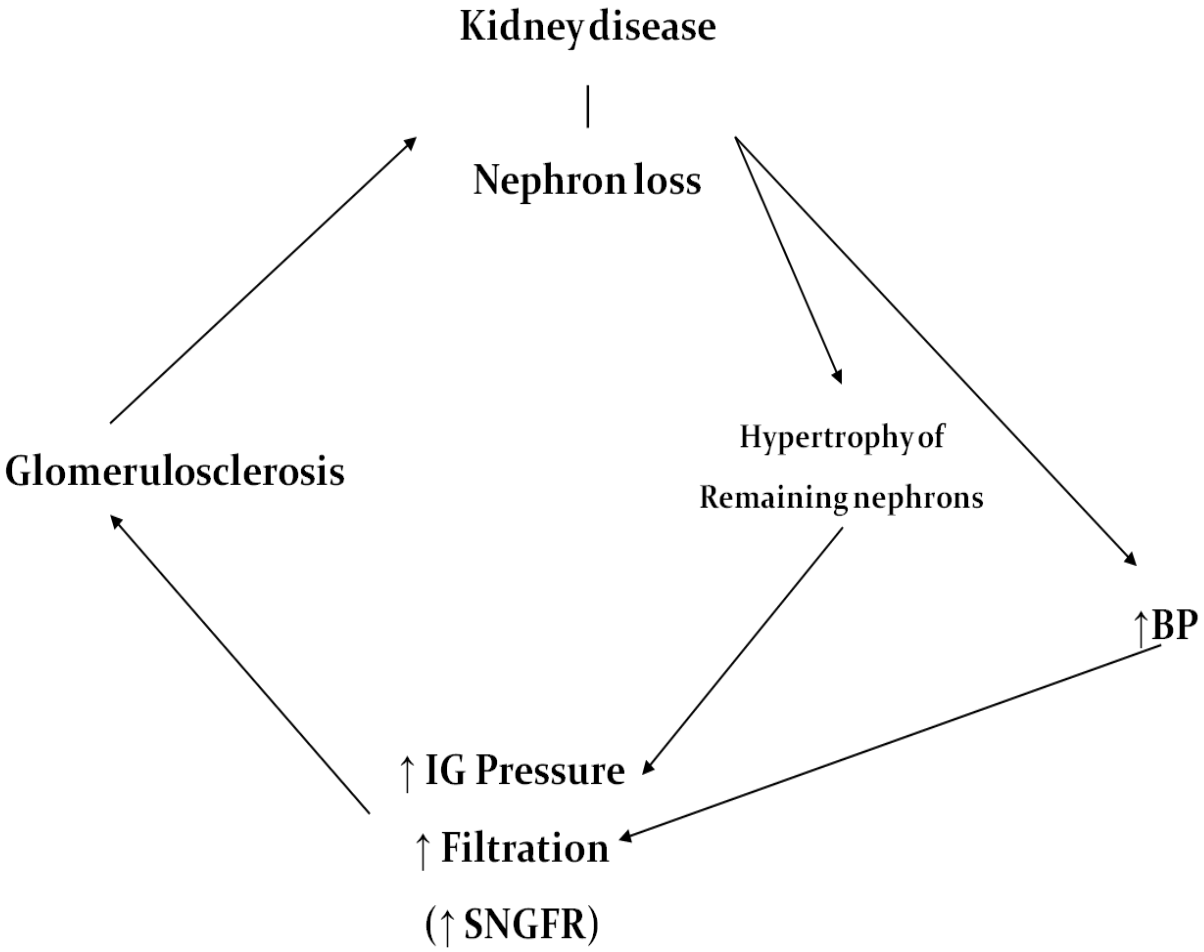
- Loss of nephron mass → hypertrophy of the remaining nephrons
  - The hypertrophied nephron plasma flow and glomerular pressure increase (vasodilatation of the afferent Arterioles)
  - Proximal reabsorption of NaCl, Fluids and PO_4 ↘
  - Collecting ducts secretion of K^+ and H^+ → ***enhanced***
  - These adaptations initially restore hemostasis
  - But glomerular hyperfiltration → glomerular injury, glomerulosclerosis and further loss of renal function

Note: ***from*** ***http://emedicine.medscape.com/article/238798-overview#aw2aab6b2b2***

Plasma levels of substances such as urea and creatinine start to show measurable increases only after total GFR has decreased to 50%.

- Growth factors:
  - Transforming growth factor-B
  - Platelets derived growth factors → Interstitial Fibrosis.
  - Osteopontin, angiotensin-II
  - Endothelin

Viscous cycle of CKD that leads to ESRD



Factors contributing to the Progression of CKD:

- Degree of hypertension.
- Severity of proteinuria.
- Hyperlipidemia.
- Drugs (NSAID).
- High protein diet.
- Persistent metabolic acidosis.
- Extent of tubulointerstitial disease.

Note:

Managing these risk factors will help the patient to live without dialysis for as long as possible.

Uremic syndrome:

Uremia results from retention of end products of protein metabolism

* Administration of urea causes only mild symptoms.

*Other potential uremic toxins:

-Guanidine	- Phenoles
- P2 microglobulin	- Phosphate
- Hipurate	- Polyamines
- Homocysteine	- Purines
- Parathyroid hormone (PTH)	-Dimethyl arginine

Note: *from* *http://emedicine.medscape.com/article/245296-clinical*

Signs of uremia include: pruritus (itching) nausea, vomiting, fatigue, muscle cramps, skin color changes, thirst, mental status changes, weight loss & visual disturbances.

Metabolic and electrolytes abnormalities in CKD:

A. 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.

- Decreased insulin and OHD requirements in diabetic patients as they develop renal failure. Otherwise, they might develop hypoglycemia as they have decrease in insulin clearance.

B. Dyslipidemia:

- ↓ HDL cholesterol.
- ↑ TG and lipoprotein (α).

C. Fluid and Electrolytes:

- ↓ 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**
- Patient with salt lossing nephropathy require stepwise increases
  - in Nacl and fluid intake
- K+ elimination in CKD is initially maintained by:
  - Enhanced K+ secretion in surviving nephrons

- Colonic K+ secretion (from aldosterone stimulated by hyperkalemia and metabolic acidosis)

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

D. Acid-Base abnormalities – metabolic acidosis "imp"

- The body produces about 80 mmol of non-volatile acids from metabolism everyday.
- These acids accumulate as renal failure progresses.
- Production of ammonia NH3 (in distal and CD cells) decreases →

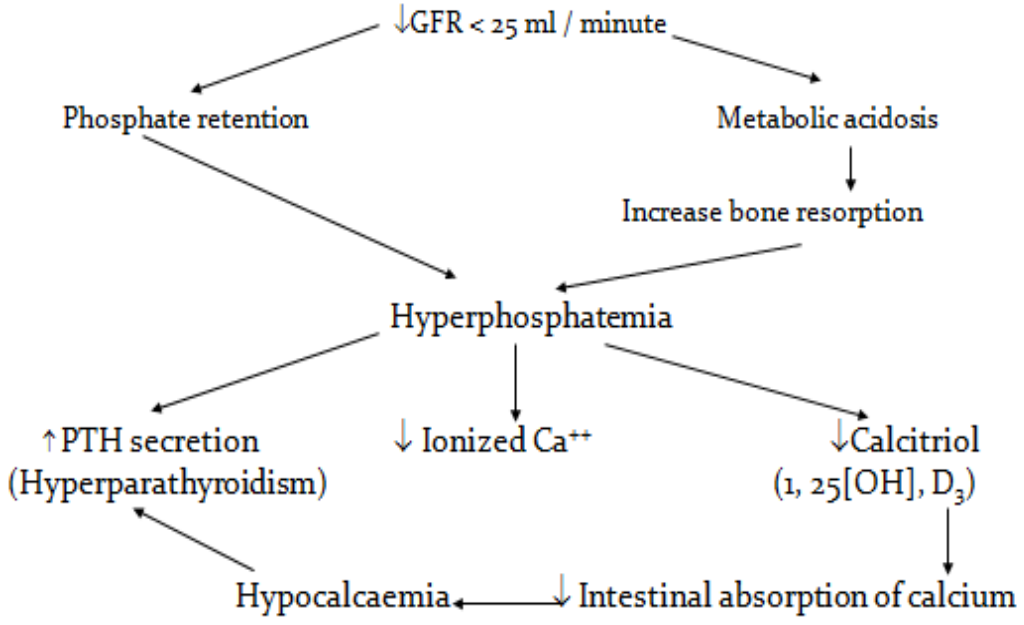
  Limits distal tubular H+ trapping as NH4 and hence, decreases renal bicarbonate regeneration.
- Additionally, there may be proximal HCO_3 wasting or reduced distal H+ secretion.

So, the phosphate retention and metabolic acidosis will cause hyperphosphatemia, which will result in hypocalcaemia, so the result will be hyperparathyroidism.

Eventually, there will spontaneous release of PTH later in the disease, so we will get both hypercalcemia and hyperphosphatemia.

Metabolic acidosis = secretion of HCO_3.

E. Calcium and phosphate abnormalities:



F. Hyperphosphatemia:

- *Independent risk factor in the increased morbidity and mortality of stage-5 CKD from cardiovascular events.*
- Hyperphosphatemia, ↑ ca * po4 product (>55 mg/dl), and ↑ calcium load (dietary + dialysate) predict coronary artery calcifications (> 50% of stage 5 CKD patients) as evaluated by electron beam computed tomography.

G. Renal Osteodystrophy (ROD):

Bone disorders in uremeic patients resulting from *mineral ion abnormalities*, PTH & Vit-D metabolism. They include: Osteitis fibrosa cystica, Adynamic bone disease, Osteomalacia or a combination of them.

Osteitis fibrosa cystica (high bone turnover): *due to the increased level of PTH* and increased activity of both osteoclast and osteoblast.

Adynamic bone disease (low bone tumor):
A *defect in osteoblast development* or activity caused by factors related to the uremic state

Risk factors:

- Advanced age
- CAPD
- Diabetes mellitus
- Calcitriol therapy
- Parathyroidectomy
- Flouride and iron intoxication

Cardiovascular abnormalities of ESRD (CKD-5):"important"

1. Hypertension:
   - Occurs in 90% of patients with ESRD
   - Causes:
     - Salt and water retention (the primary cause)
     - Inappropriate secretion of RAA system.
     - ↑ Sympathetic tone.
     - ↑ Generation of vasoconstrictors (endothelin).
     - ↓ Generation of vasodilators (nitric oxide).

2. Cardiomyopathy:
   - Left ventricular hypertrophy (LVH).
   - Coronary artery disease (CAD).
   - 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
✓ Anemia aggravates LVH
✓ Hyperparathyroidism amyloidosis, and iron overload cause also cardiac dysfunction.

3. Pericarditis and pericardial effusion "indication of hemodialysis".

Neuromuscular abnormalities:

❖ CNS dysfunction:

- Decreased attention, agitation, confusion, insomnia, and impaired memory.
- May develop also: depression, hallucinations, delusions, hiccups, cramps, flapping tremor "sign of encephalopathy and indication of hemodialysis", myocloms, fasciculation, and seizures.

❖Peripheral neuropathy:

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

Hematologic abnormalities:

a. Anemia

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

b. Platelet Dysfunction "check the bleeding time"

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

Gastrointestinal abnormalities:

- Anorexia, nausea, and vomiting.
- Uremic fetor "urine odor on the breath", stomatitis, esophagitis, gastritis, and peptic ulcer disease.
- ↑ Gastrin in CKD.

Dermatologic abnormalities:

Uremic pruritus is related to:

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

Evaluation of Patients with CKD:

In the ultrasound we will see: small, shrunken kidneys.

Normal kidney size with CKD: diabetes mellitus, amyloid, and multiple myeloma.

The history should document the presence of **uremic symptoms,** and possible etiology from: **diabetes mellitus, hypertension, congestive heart failure, multiple myeloma, and NSAID.** Family history can suggest **polycystic kidney disease "PCKD"** or hereditary nephritis.

Volume depletion and obstructive nephropathy should be identified and treated promptly.

Management of patients with CKD

From Uptodate.com: The general management of a patient with chronic kidney disease (CKD) involves the following issues:

- Treatment of reversible causes of renal failure.
- Preventing or slowing the progression of renal disease.
- Treatment of the complications of renal failure.
- Adjusting drug doses when appropriate for the level of estimated glomerular filtration rate (eGFR).
- Identification and adequate preparation of the patient in whom renal replacement therapy will be required.

http://www.uptodate.com/contents/overview-of-the-management-of-chronic-kidney-disease-in-adults?source=machineLearning&search=chronic+kidney+disease&selectedTitle=1%7E150&sectionRank=1&anchor=H6#

1. **Fluids and electrolytes disorders.**
2. **Hyperphosphatemia and secondary hyperparathyroidism.**
3. **Hyperlipidemia.**
4. **Anemia.**

1. Fluid and electrolytes disorders

- ✓ Salt intake restriction – daily Na^+ **< 100 meq.**
- ✓ Loop diuretics.
- ✓ Hypernatremia – fluid restriction **1-1.5 L/day.**
- ✓ **Hyperkalemia:**
  - Exogenous sources of K^+: dates, dried fruits, citrus fruits, banana, chocolate, and salt substitute.
  - Medications that increase the level of K^+: ACE inhibitors, angiotensin receptor blockers, NSIADs, K^+ sparing diuretics, beta-blockers, and heparin.
  - Treatment of hyperkalemia:
    - IV calcium gluconate **10 cc of 10%.**
    - Followed by **25 ml of 50%** **dextrose solution with 5-10 units regular insulin.**
    - Beta2-adrenergic agonist nebulizer **(Salbutamol).**
    - **$NaHCO_2$ IV/oral.**

2. Hyperphosphatemia and secondary hyperparathyroidism

a. Reduce phosphate intake to **< 10 mg/kg/day.**
b. Phosphate binders: **calcium carbonate, sevelamer (Renagel), and lanthanum carbonate.**
c. Vitamin D (Clacitirol) **0.125 meq/day.**
   - Must be withheld until serum phosphate concentration have been controlled to **<6 mg/dl because it may cause sever soft tissue calcification.**
   - Vitamin D compounds can cause hypercalcemia and hyperphosphatemia, **which may increase coronary calcification, so Parcicalcitrol (Zemplar) is an analogue that inhibits PHT synthesis without elevation of calcium/phos.**
d. Indication for parathyroidectomy: **PHT > 800 pg/ml with symptoms of bone disease (myopathy, bone pain) persistent hyperphosphatemia soft tissue calcification.**

3. Hyperlipidemia

The goal is to **keep low-density lipoprotein cholesterol < 100 mg/dl by diet control and statin group.**

4. Anemia

- **Target Hb/Hct:**
  - **KDOQI "Kidney Disease Outcomes Quality Initiative":**
    Our target level of Hb = 11-12, Hct = 33-36%
  - **Anemia will cause:**
    Increased left ventricular hypertrophy **"LVH",** decreased quality of life, and reduces survival in patients on hemodialysis **"HD".**
  - **Conversely:**
    Hb > 13 and Hct > 42 are associated with more coronary events and increased mortality as evidenced by CHOIR (USA) and CREATE (Europe) studies.

- **Target iron levels:**
  - Percent transferrin saturation **(T-SAT)** reflects iron available for erythropoiesis.
  - Serum ferritin reflects overall iron stores.
  - **In CKD, target T-SAT (20-50), target serum ferritin > 100 ng/ml.**
  - **Iron supply should be withheld if T-SAT >50, serum ferritin > 800 ng/ml.**

SUMMARY

1. CKD is the progressive irreversible loss of kidney function
2. Mainly caused by diabetes, hypertension & glomerulonephritis
3. Loss of nephron mass leads to hyperfiltration in the remaining healthy nephrons, which in turn causes glomerular injury and eventual glomerulosclerosis.
4. CKD causes many abnormalities:
    a. Decreased insulin requirements
    b. Dyslipidemia
    c. Hyperkalemia
    d. Hypertension
    e. Metabolic acidosis
    f. Hyperphosphatemia
    g. Renal osteodystrophy
        i. Osteitis fibrosa cystica due to hyperparathyroidism
        ii. Adynamic bone disease due to uremia
    h. Cardiomyopathies, pericarditis & pericardial effusion
    i. Neuromuscular abnormalities (confusion, flapping tremor, postural hypotension & peripheral neuropathy, usually symmetrical)
    j. Hematologic abnormalities: anemia & platelet dysfunction
    k. Uremic signs
5. Ultrasound reveals shrunken kidneys (normal in diabetics, multiple myeloma & amyloid)
6. Family history may suggest polycystic kidney disease
7. Manage fluid & electrolyte disorders by:
    a. Salt & fluid restriction (Na<100meq, H2O1-1.5L/day)
    b. Loop diuretics
    c. Treat hyperkalemia with calcium gluconate & insulin. Salbutamol & NaHCO2 can also be used
    d. Statins for hyperlipidemia
8. Hyperphosphatemia & hyperparathyroidism:
    a. Reduce phosphate intake
    b. Phosphate binders: calcium carbonate, lanthanum carbonate & sevelamer
    c. Parathyroidectomy is indicated when PHT>800pg/ml with bone disease symptoms
9. Anemia: raise Hb levels to 11-12 & Hct between 33-36%
    a. Target iron levels:
        i. T-SAT 20-50, serum ferritin>100ng/ml
        ii. Do not administer supplement if T-SAT>50 or serum ferritin>800ng/ml

Questions

1) Which of the following is due to hyperparathyroidism in CKD?
   a. Osteomalacia
   b. Adynamic bone disease
   c. Osteitis fibrosa cystica
   d. Osteo-sarcoma

2) CKD patient with GFR of 68. Which stage is he at?
   a. Stage 1
   b. Stage 2
   c. Stage 3
   d. Stage 4

3) CKD causes:
   a. Decreased TG levels
   b. Decreased HDL levels
   c. Increased glucose levels
   d. Increased PH levels

4) Insulin is used in CKD to:
   a. Manage hypokalemia
   b. Manage hypophosphatemia
   c. Manage hyperphosphatemia
   d. Manage hyperkalemia

432 Medicine Team Leaders

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Answers:

1st Questions: c

2nd Questions: b

3rd Questions: b

4th Questions: d