Medicine

430

# Chronic Kidney Disease

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**This lecture has not been edited**

# Chronic kidney disease

## Normal kidney function:

1. Fluid balance.
2. Electrolyte regulation.
3. Control acid base balance.
4. Waste removal.
5. Hormonal function.
   - Erythropoietin
     - Promotes the formation of RBC's > when kidney is damaged anaemia might be present
   - Renin
   - Prostaglandin
   - Active Vit 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*

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## Chronic Kidney Disease (CKD):

- Chronic progressive Irreversible loss of renal function and reduction in GFR over a period of months to years
- ESRD(End Stage Renal Disease) : is considered advanced CKD that requires kidney transplant or dialysis.

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## Classification of chronic kidney disease (stage):

- To establish CKD two main elements must be present:
  - Evidence of kidney damage by pathological studies, lab results or imaging modules ( specially for stage 1&2)
  - decrease in the GFR
  - if GFR = 100 but there's no other signs → normal kidney
  - high creatinine level + high urea level → damaged kidney

| STAGES | DESCRIPTION | GFR |
|---|---|---|
| **1** | Kidney damage with normal or increased GFR | > 90 |
| **2** | Mild decrease in GFR | 60 – 90 |
| **3** | Moderate decrease in GFR | 30 - 60 |
| **4** | Severe decrease in GFR | 15 – 29 |
| **5 (ESRD)** | Kidney failure | < 15 or dialysis |

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## Pathophysiology:

❖ Because of persistent insult and damage to the kidneys this will cause:

- Loss of nephron mass (nephrones damaged) → hypertrophy of the remaining nephrones inorder to maintain function( as a compensatory mechanism) → increase GFR pressure → + increase in filtration due to high BP → rupture of basement membrane

- Hypertrophy leads to:
  - increase nephron plasma flow → increase in glomerular pressure → vasodilatation of the afferent blood vessels ( even more hyper perfusion)
  - This persistent hyper-perfusion of the glomerulus → glomerular injury (glomerulosclerosis and further loss of renal function)
- This compensatory mechanism leads to:
  - Enhanced reabsorption of of NaCl, Fluids and $PO_4$ in the proximal duct
  - Enhanced secretion of $K_+$ and $H_+$ in the collecting duct

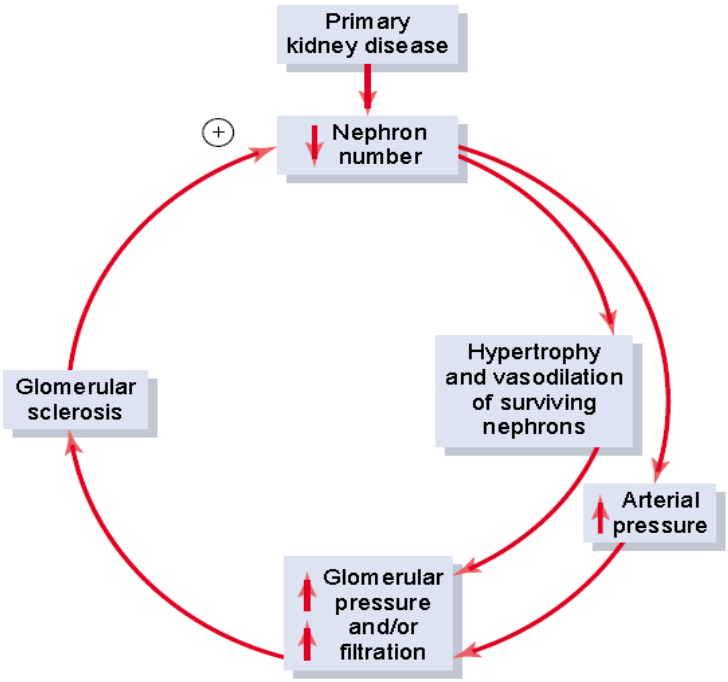
o These adaptations initially restore homeostasis, but persistent hyper-perfusion will lead to loss of renal function

❖ Growth factors:

- All of these following factors lead to increase interstitial fibrosis and loss of function:
  - Transforming growth factor-B
  - Platelets derived growth factors
  - Osteopontin, angiotensin-II
  - Endothelin

## Vicious Circle of Chronic Renal Failure Leading to End-Stage Renal Disease

In many cases, an initial insult to the kidney leads to progressive deterioration of kidney function and further loss of nephrons to the point where the person must be placed on dialysis treatment or transplanted with a functional kidney to survive. This condition is referred to as *end-stage renal disease.* Studies in laboratory animals have shown that surgical removal of large portions of the kidney initially causes adaptive changes in the remaining nephrons that lead to increased blood flow, increased GFR, and increased urine output in the surviving nephrons. The exact mechanisms responsible for these changes are not well understood but involve hypertrophy (growth of the various structures of the surviving nephrons) as well as functional changes that decrease vascular resistance and tubular reabsorption in the surviving nephrons. These adaptive changes permit a person to excrete normal amounts of water and solutes even when kidney mass is reduced to 20 to 25 per cent of normal. Over a period of several years, however, the renal functional changes may lead to further injury of the remaining nephrons, particularly to the glomeruli of these nephrons.




The cause of this additional injury is not known, but some investigators believe that it may be related in part to increased pressure or stretch of the remaining glomeruli, which occurs as a result of functional vasodilation or increased blood pressure; the chronic increase in pressure and stretch of the small arterioles and glomeruli are believed to cause sclerosis of these vessels (replacement of normal tissue with connective tissue). These sclerotic lesions can eventually obliterate the glomerulus, leading to further reduction in kidney function, further adaptive changes in the remaining nephrons, and a slowly progressing vicious circle that eventually terminates in end-stage renal disease

## Factors contributing to the progression of CKD:

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

A simplified depiction of risk factors interacting with pathophysiologic mechanisms to accelerate chronic kidney disease progression. DM, diabetes mellitus; FSGS, focal segmental glomerulosclerosis; TIF, tubulointerstitial fibrosis

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## Causes (aetiology) of CKD?

1. Diabetes mellitus ( most common cause) 40%
2. Hypertension 30%
3. Chronic glomerulonephritis 15%
4. Hereditary cystic and cong. renal disease 4%
5. Interstitial nephritis/pyelonephritis 4%
6. Tumors 2%
7. Miscellaneous 5%
8. Any of the causes of acute renal failure may lead to chronic renal failure if prolonged and the treatment is delayed

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## Clinical features:

1. Uremic syndrome: ( due to toxic product accumulation)
   - First what is ***Uremia?*** Refers to signs and symptoms associated with accumulation of nitrogenous wastes due to impaired renal function
   - Uremia results from ***retention of end products of protein metabolism***.
     - Administration of urea causes only mild symptoms.
     - Other potential uremic toxins :
       - Guanidine - Phenoles
       - $P_2$ microglobulin - Phosphate
       - Hipurate - Polyamines
       - Homocysteine - Purines
       - Parathyroid hormone (PTH) - Dimethyl arginine
   - *Uremia* is a syndrome that affects every organ system. Uremic syndrome is likely the consequence of a combination of factors, including retained molecules, deficiencies of important hormones, and metabolic factors, rather than the effect of a single uremic toxin
2. Metabolic and electrolytes abnormalities
   - ***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

(pt will suffer from hypoglycemia →treat with increase insulin dosage)

** Why do CKD patients have hyperparathyroidism?

HPT secondary to CKD is an overproduction of PTH caused by several changes that occur in bone and mineral metabolism as a result of decreased kidney function. The first changes that usually occur with declining kidney function involve the deficiency of activated vitamin D and an increase in phosphorus excretion by the remaining functional nephrons. Both of these changes stimulate an increase in PTH synthesis and secretion.

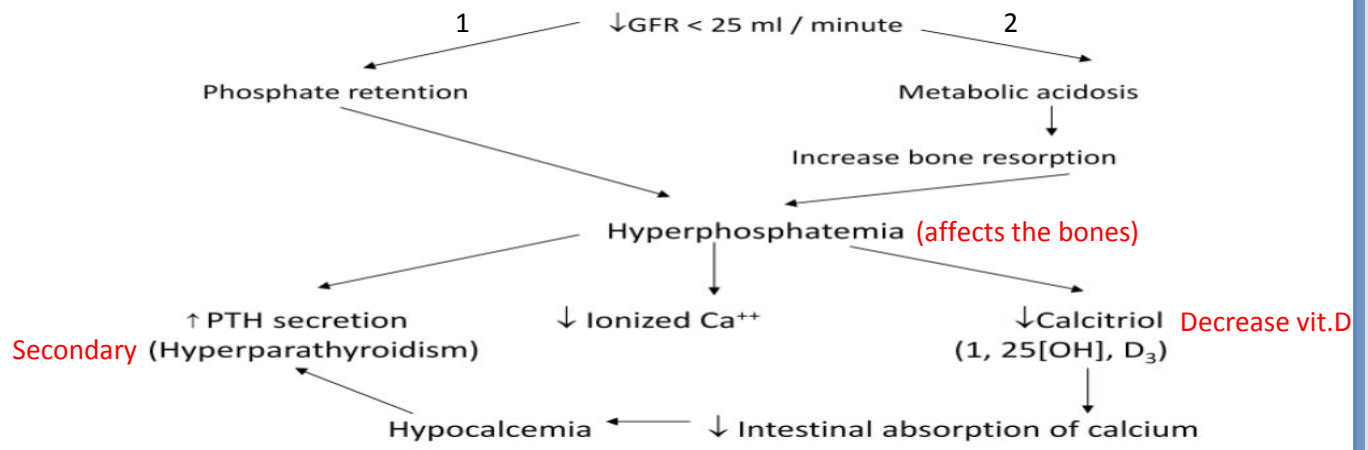
- ***Dyslipidemia :***
  - Decrease HDL cholesterol.
  - Increase TG and lipoprotein.
  - Decrease LDL cholesterol (due to decrease lipoprotein lipase activity)
- ***Fluid and electrolyte:***
  - Decrease GFR and defective tubular function → expansion of plasma and ECF volumes, edema, and hypertension(due to fluid retention)
    - Hypertension is common unless $Na^+$ intake is restricted to 100 meq/day
  - Hyponatremia: can result from failure to excrete free water when intakes exceed 1.5 L/day
    - Patient with salt losing nephropathy require stepwise increases in NaCl and fluid intake

OR

  - hyperkalemia :
    - $k^+$ 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 curtailed ⍰ hyperkalemia

- **Volume overload: watch out for pulmonary edema**
  - ***Acid-Base: Metabolic acidosis***
    - The body produces about 80 mmol of non-volatile acids from metabolism every day, These acids accumulates as renal failure progresses
    - Production of ammonia $NH_3$ (in distal and CD cells) decreases ⍰ limits distal tubular $H^+$ trapping as $NH_4$ and hence, decreases renal bicarbonate regeneration.
    - Additionally, there may be proximal $HCO_3$ wasting or reduced distal $H^+$ secretion.
- ***Calcium- phosphate disturbances: V.IMP! read carefully:***
  - Decreased renal clearance of phosphate will lead to: Hyperphosphatemia:
    - This will result in decrease production of Vit D → hypocalcaemia
    - This hypocalcaemia will cause secondary hyperparathyroidism
      - So because there is no Vit D the body will not be able to absorb calcium from the intestine, so it will release PTH in order to try and compensate for the calcium loss
      -
    - So we will see **1.**hypocalcaemia
      - Long standing 2ry hyperparathyroidism may cause hypocalcaemia
    - And **2.** secondary hyperparathyroidism
      - Will cause renal osteodystrophy
  - Decreased renal clearance leads to metabolic acidosis → increase bone resorption → hyperphosphatemia ( phosphate released from bone)
  - Hyperphosphatemia:
    - Independent risk factor in the increased morbidity and mortality of stage-5 CKD from cardiovascular events.
    - Increase Ca * $PO_4$ product (>55 mg/dl), and increase calcium load (dietary + dialysate)

- Predict coronary artery calcifications (> 50% of stage 5 CKD patients) as evaluated by electron beam computed tomography.




Fluid and electrolyte in summary:
Hyperkalemia, Hyponatremia, Volume overload ,Hyperphosphatemia and Hypermagnesiumia

**3. 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.

**4. Renal osteodystrophy:**

- It is a complex disorders of bones in uremic patient <u>resulting from abnormalities of mineral ions (Ca, pon, Mg), PTH and Vit.D metabolism</u> in the presence of factors related to the uremic state.
- Spectrum of ***bone abnormalities in ROD***:

**a. Osteitis fibrosa cystica** (high bone turnover) due to:
  - ↑PTH.
  - ⍰ activity of both osteoclast and osteoblast.

**b. Osteomalacia.( due to accumulation of minerals)**

**c. Adynamic bone disease** (low bone turnover).
  - Risk factors :
    - Advanced age.
    - CAPD.
    - Diabetes mellitus.
    - Calcitriol therapy.
    - Parathyroidectomy.
    - Flouride and iron intoxication.
  - Mechanism: Defect in osteoplast development or activity caused by factors related to the uremic state.

**d. Combination of the above**

**5. Cardiovascular abnormalities of ESRD (CKD-5)**

- **Hypertension**
  - Occurs in 90% of patients with ESRD (common)
  - Causes: * Salt and water retention (the 1omy cause)

– Inappropriate secretion of RAA system
– ↑ sympathetic tone
– ↑ generation of vasoconstrictors (endothelin)
– ↓ generation of vasodilators (nitric oxide)

- **Cardiomyopathy**
  - left ventricular hypertrophy (LVH)
  - Coronary artery disease (CAD)
  - Congestive heart failure (CHF)
  - Diastolic dysfunction

✓ These abnormalities increase 2-5 folds in ESRD (very common)
✓ 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.

- Pericarditis-fluid retention-and pericardial effusion-bloody- (due to uremia)

**6. Neuromuscular abnormalities:**

- ***CNS dysfunction***
  - Decreased attention, agitation, confusion, insomnia, and impaired memory May develop
  - Also: depression, hallucinations, delusions, hiccups, cramps, flapping tremor, myocloms, fasciculation, and seizures.
- ***Peripheral neuropathy***
  - usually symmetric, lower limbs
  - Sensory precedes motor dysfunction
  - Restless leg syndrome and burning feet, relieved by movement
  - Postural hypotension (autonomic dysfunction)
- ***Hypocalcemia*** can cause lethargy, confusion and tetany

Note!
Hiccups are very common + it's an indication for dialysis
Flapping tremor always indicate failure (renal failure, respiratory failure or liver failure)

**7. heamatological:**

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

Compensation doesn't work … start dialysis

- Platelet Dysfunction
  - Bruising, ecchymoses, bleeding from mm
  - Platelets dysfunction (count is normal, function is abnormal): ↓VWF (will cause platelet dysfunction that will lead to bleeding → we do bleeding test tendency) van wildebrand factor, which facilitate the interaction between platelets and endothelium through its binding to platelet glycoprotein (IIb, IIIa) receptors.

**8. Gastrointestinal abnormalities**

- Anorexia, nausia, and vomiting
- Uremic faetor, stomatitis, esophagitis, gatritis, and peptic ulcer disease
- ↑ Gastrin in CKD

**9. Dermatologic abnormalities**

- Uremic pruritus is related to:
  - Calcium and phosph deposition ($2^o$ ↑ PTH)
  - Hypercalcemia
  - Peripheral neuropathy
  - Dry skin
  - Anemia
  - Inadequate dialysis

## Evaluation of Patients with CKD:

- The 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
- Volume depletion and obstructive nephropathy should be identified and treated promptly
- Ultrasound – small, shrunken kidneys
  - Normal kidney size with CKD: DM, amyloid, MM

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## Management of Patients with CKD

- ***Fluid and electrolyte disorder:***
- Salt intake restriction – daily Na+ < 100 meq
- Loop diuretics ( to decrease fluid retention)
- Hyponatremia – fluid restriction 1 – 1.5 L/day.
- Hyperkalemia: ( must be treated first,it's a life threatening condition)
  - Exogenous sources of K+: dates, dried fruits, citrus fruits, banana, chocolate, salt substitute.

- Medications that ⍰ K+: ACEI, ARB, NSAID, K+, sparing diuretics, B-Blockers, and heparin. ( given under supervision )
- Treatment of hyperkalemia :
  - IV calcium gluconate 10 cc of 10%. ( to stabilize the heart muscle and prevent it from arrest)
  - Followed by 25 ml of 50% dextrose solution with 5-10 units regular insulin. (shift $k^+$ to extracellular fluid)
  - B2-adrenergic agonist nebulizer (salbutamol). (shift $k^+$ to extracellular fluid)
  - NaHCO3 IV/oral (not given with edema pts)

- ***Hyperphosphatemia and secondary hyperparathyroidism :***
  - Reduce phosphate intake to < 10 mg/kg/day.
  - Phosphate binders: Calcium carbonate. (given with food cause it binds with $PO_4$ in food and then get execrated with stool )
    - Sevelamer (Renagel).
    - Lanthanum carbonate.
  - Vitamin D (Calcitriol) 0.125 mcq/day.
    - Must be withheld until s. phosphate concentration has 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/phos.
  - Indication for parathyroidectomy : PTH > 800 pg/ml with symptoms of bone disease ( myopathy, bone Pain ), persistent hyperphosphatemia soft tissue calcifications.
- ***Hyperlipidemia :***
  - The goal is to keep low density lipoprotein cholesterol < 100 mg/dl by diet control and statrim group.
- ***Anemia :***
  - **Target Hb/Hct :**

- K DOQI → Hb 11-12. ( Hb must stay in this narrow range)
  Hct 33-36%.
- Anemia: ↑ LVH
  ↓ quality of life
  reduces survival in patients on HD
- Conversely: Hb > 13
  Hct > 42

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 erythopoiesis.
  - Serum ferritin reflects overall iron stones.
  - In CKD, target T-Sat > 20 (20 – 50). target S. ferritin > 100 ng/ml.
  - Iron supp. should be withheld, if T-sat > 50. S. ferritin > 800 ng/ml.

- **Treatment Guidelines (Anemia) :**
  - **Oral iron :**
    - In non-dialysis patients (CKD 1-4):
      - 100-200 mg elemental iron should be given daily in 2-3 days, either one hour before meals or two hours post. (1 tab Ferrous fumerate, 200 mg contains 66 mg elemental iron).
    - In dialysis patients (CKD 5) :
      - IV iron should be given as on-going iron losses tends to be higher.
  - **IV iron :**
    - 1 gm of iron saccharate (ferrosac) divided into 10 doses of 100 mg given with each dialysis session.
  - **Recombinant: Erythropoietin – epoeitin Alfa (eprex).** Long acting erythropoietin
    - *Patients on HD: starting dose 120 – 180 IU/kg/week, IV.*
    - *Pre-dialysis patients and PD patients: 80-120 IU/kg/week subcutaneously weekly doses.*
    - *Hb/Hct monitoring every 4 weeks.*
    - *The most common side effects: headache, HTN, arthralgia, and diarrhea.*
    - *Resistance to epoeitin :*
      - Inadequate Epo dose.
      - Anemia of chronic disease (infection, inflammation).
      - Functional iron deficiency.