CKD: Chronic Kidney Disease

429 Medicine Team

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 D_3

> *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*

What is chronic kidney disease (CKD)?

1. Chronic progressive Irreversible loss of renal function and reduction in GFR over a period of months to years
2. ESRD: End Stage Renal Disease (stage-5, staging will be explained later) is considered advanced CKD that requires kidney transplant or dialysis.

Causes (aetiology) of CKD?

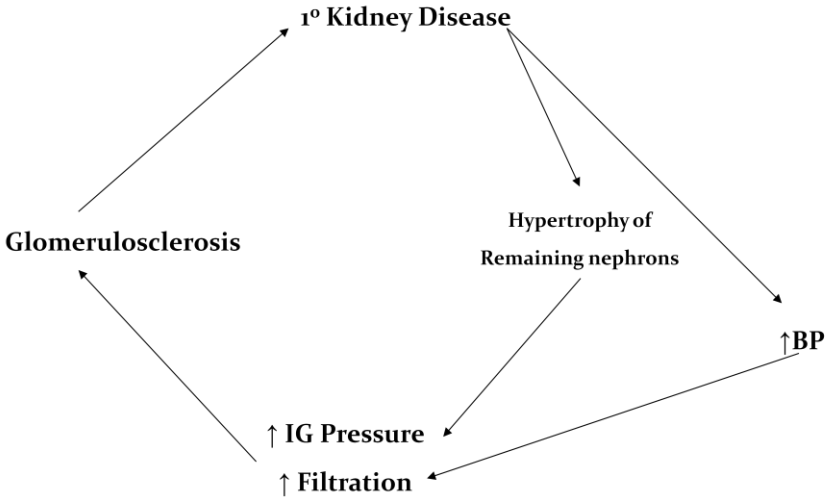
1. Diabetes mellitus (most common cause) 40%
2. Hypertension 30%
3. Chronic glomerulonephritis 15%
4. Hereditary cystic and cong. renal disease 4%
5. Interstitial nephritis/pyelonephritis 4%
6. Tumors 2%
7. Miscellaneous 5%
8. Any of the causes of acute renal failure may lead to chronic renal failure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

Pathophysiology:

1. Because of persistent insult and damage to the kidneys this will cause:
    - Loss of nephron mass → hypertrophy of the remaining nephrones (compensatory mechanism)
    - 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
            - These adaptations initially restore homeostasis, but persistent hyper-perfusion will lead to loss of renal function

2. 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

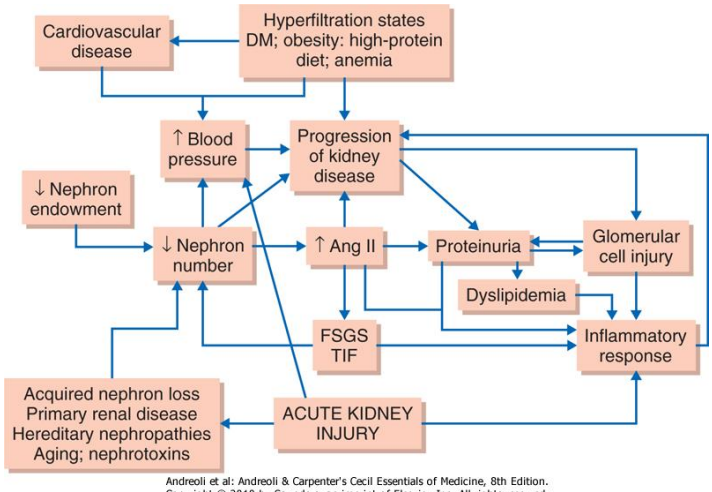
Viscious cycle of CKD that leads to ESRD



3. Diagram explanation: Primary kidney disease (any of the aetiologies)
   - → hypertrophy of nephrones → increase in glomerular pressure
   - → increase in Blood pressure (renal failure is the most common cause of 2ry HTN) → increase filtration
     - → glomerulosclerosis and further nephron damage

Factors contributing to the progression of CKD:

1. Degree of hypertension.
2. Severity of proteinuria.
3. Hyperlipidemia.
4. Drugs (NSAID).
5. High protein diet.
6. Persistent metabolic acidosis.
7. Extent of tubulointerstitial disease.



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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

Classification of chronic kidney disease (stage):

1. 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

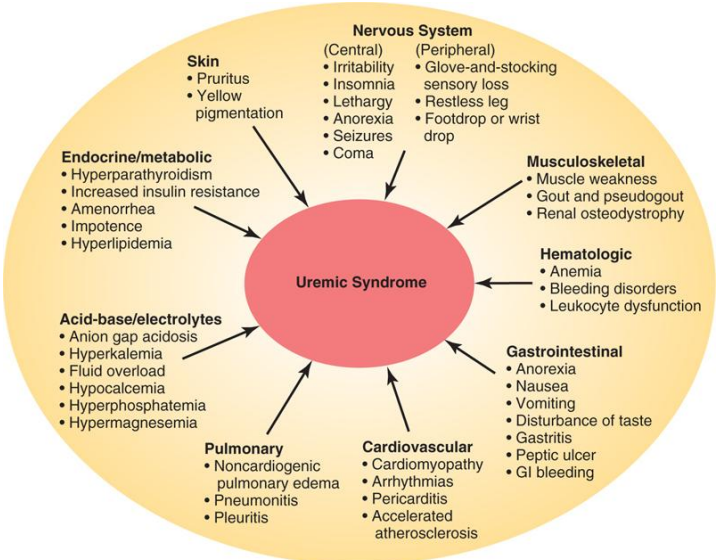
Stage	Description	GFR (ml/min/1.73m2)
1	Kidney damage with normal or ↑ GFR	90
2	Mild ↓ GFR	60 – 90
3	Moderate ↓ GFR	30 - 60
4	Severe ↓ GFR	15 – 29
5	Kidney failure	<15 or dialysis

2. Stage 5 is also known as ESRD

Clinical features:

1. Uremic syndrome:

- 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
    - P_2 microglobulin
    - Hipurate
    - Homocysteine
    - Parathyroid hormone (PTH)
    - Phenoles
    - Phosphate
    - Polyamines
    - Purines
    - 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



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- So keep in mind many of the clinical features of CKD are a result of Uraemia

2. Cardiovascular

- ***Hypertension***
  - Occurs in 90% of patients with ESRD
  - Causes:
    - Salt and water retention (the 1°ry cause)
      - Leads to ↓ in GFR which stimulates rennin-angiotensin and aldestrone secretion → ↑BP
    - Inappropriate secretion of Renin Angiotensin Aldesterone system
    - ↑ sympathetic tone
    - ↑ generation of vasoconstrictors (endothelin)
    - ↓ generation of vasodilators (nitric oxide)
  - Renal failure is the most common cause of secondary hypertension
- ***Cardiomyopathy***
  - Congestive Heart failure (CHF) due to:
    - Volume overload, HTN and anaemia
  - left ventricular hypertrophy (LVH) (could be a result of CHF)
    - Anemia aggravates LVH
  - Coronary artery disease (CAD)
    - About one-half of all hemodialysis patients have significant ischemic heart disease
    - Dyslipidemia, HTN, ↑homocystin, DM, and insulin resistance contribute to atherosclerosis
  - Diastolic dysfunction
  - ***These abnormalities increase 2-5 folds in ESRD.
  - ***Hyperparathyroidism amyloidosis, and iron overload cause also cardiac dysfunction.
- ***Pericarditis and pericardial effusion (due to uremia)***

3. 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.
    - Why do CKD patients have hyperparathyroidism?
  - Decrease in requirements for insulin and OHD in diabetic patients as they develop renal failure
- ***Dyslipidemia :***
  - ↓ HDL cholesterol.
  - ↑ TG and lipoprotein (a).
  - ↓ LDL cholesterol (due to decrease lipoprotein lipase activity)
- ***Fluid and electrolyte:***
  - ↓ GFR and defective tubular function → expansion of plasma and ECF volumes, edema, and hypertension
    - 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
  - hyperkalemia :
    - K^+ elimination in CKD is initially maintained by :

Fluid and electrolyte in summary:

Hyperkalemia!!

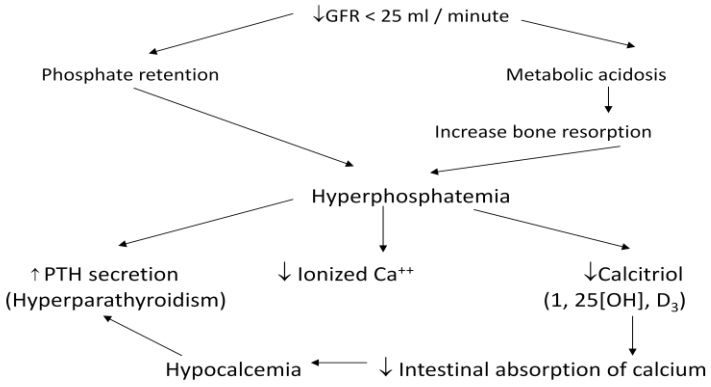
Hyponatremia

Volume overload

Hyperphosphatemia

Hypermagnesiumia

        - 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.
        - ↑ 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 resulting from abnormalities of mineral ions (Ca, pon, Mg), PTH and Vit.D metabolism in the presence of factors related to the uremic state.
- Spectrum of ***bone abnormalities in ROD***:
    1. **Osteitis fibrosa cystica** (high bone turnover) due to :
        - ↑ PTH.

- ↑ activity of both osteoclast and osteoblast.

2. **Osteomalacia.**
3. **Adynamic bone disease** (low bone turnover).
    - Risk factors :
        i. Advanced age.
        ii. CAPD.
        iii. Diabetes mellitus.
        iv. Calcitriol therapy.
        v. Parathyroidectomy.
        vi. Flouride and iron intoxication.
    - Mechanism: Defect in osteoplast development or activity caused by factors related to the uremic state.
4. **Combination of the above**

5. Neuromuscular abnormalities:

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

6. Haematological:

- ***Anaemia***
    1. Decreased production of erythropoietin causes:
    2. Normocytic, normochromic anemia
    3. Develops as serum creatinine increases > 180 mcm/L and GFR declines to < 30 ml/minute
- ***Platelet dysfunction: due to uremia***
    1. Bruising, ecchymoses, bleeding from mm.(mucus membrane)
    2. Platelets dysfunction (count is normal): ↓VWF (van wildebrand factor), which facilitate the interaction between platelets and endothelium through its binding to platelet glycoprotein (IIb, IIIa) receptors

7. GI (due to uraemia):

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

8. Dermatologic:

- ***Uremic pruritus*** is related to:
    1. Calcium and phosph deposition (2^{o} ↑ PTH)
    2. Hypercalcemia
    3. Peripheral neuropathy
    4. Dry skin
    5. Anemia
    6. Inadequate dialysis

Evaluation of patients with CKD:

a. The history should document the presence of uremic symptoms and possible etiology from: Diabetes Mellitus, Hypertension, congestive Heart Failure, MM, NSAID
b. Family history can suggest PCKD (poly cystic kidney disease) or hereditary nephritis
c. Measure Cr clearance to estimate GFR
d. Volume depletion and obstructive nephropathy should be identified and treated promptly
e. Ultrasound – small, shrunken kidneys
    - Normal kidney size with CKD: DM, amyloid, MM

Management of patients with CKD

- ***Fluid and electrolyte disorder:***
    - Salt intake restriction – daily Na+ < 100 meq
    - Loop diuretics
    - Hyponatremia – fluid restriction 1 – 1.5 L/day.
    - Hyperkalemia:
        - 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.
        - Treatment of hyperkalemia :
            - IV calcium gluconate 10 cc of 10%.
            - Followed by 25 ml of 50% dextrose solution with 5-10 units regular insulin.
            - B2-adrenergic agonist nebulizer (salbutamol).
            - NaHCO3 IV/oral
- ***Hyperphosphatemia and secondary hyperparathyroidism :***
    - Reduce phosphate intake to < 10 mg/kg/day.
    - Phosphate binders: Calcium carbonate.
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: <u>parcicalcitrol</u> (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).**
    - *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.

Extra note: life threatening complications in CKD are:

1. Hyperkalemia which causes cardio toxicity and arrhythmias
2. Pulmonary oedema secondary to volume overload
3. Infection