CHRONIC KIDNEY DISEASE (CKD)

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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.

Normal Kidney Function

- Fluid balance
- Electrolyte regulation
- Control acid base balance
- Waste removal
- Hormonal function
  - Erythropoietin
  - Renin
  - Prostaglandins
  - Active vitamin 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.

- CKD (CRF) means : chronic progressive irreversible loss of renal function. It is defined as the presence of clinical and/or pathologic evidence of kidney disease for at least 3 months.

- ESRD: advanced CKD (Stage-5) requiring dialysis or kidney transplantation

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%

Risk Factors For CKD

1. Genitic (family hx of kidney disease)
2. Low socioeconomic status
3. Medical status : e.g. diabetes
   hypertension
   obesity
   cardiovascular disease
   smoking

Chronic Kidney Disease - Stages

Stage	Description	GFR (ml/min/1.73m^2)
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

Adapted from Am J Kidney Dis, 2002; 39 (2 Suppl. 1): S46-S75)

Pathophysiology

- Loss of nephron mass → hypertrophy of the remaining nephrons
  - The hypertrophied nephron plasma flow and glomerular pressure increase (vasodilatation of the aff. Arterioles)
  - Proximal reab. of NaCl, Fluids and PO_4 ↘

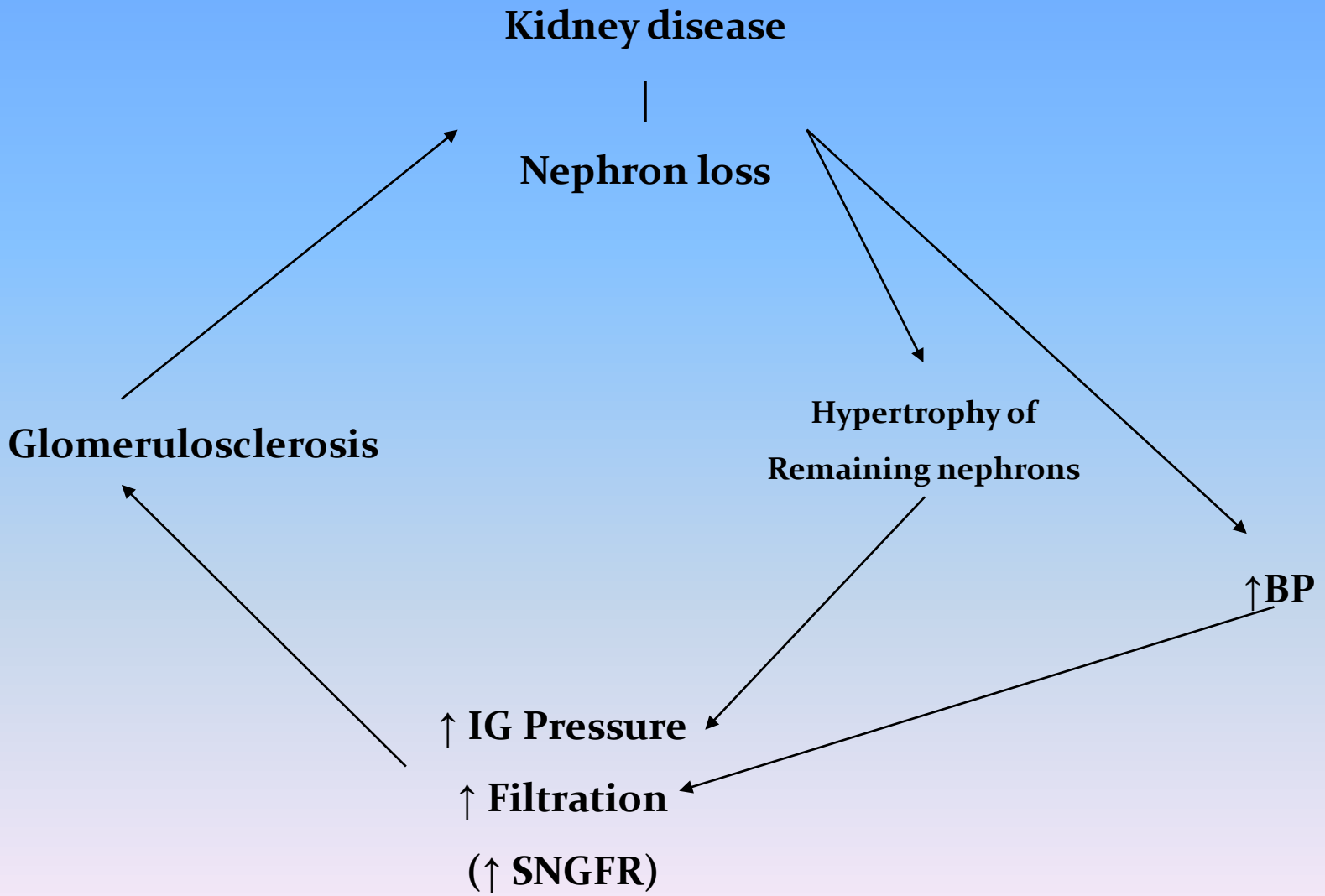
    Collecting ducts secretion of K^+ and H^+ ↗ ***enhanced***
  - These adaptations initially restore hemeostasis
  - But glomerular hyperfiltration → glomerular injury, glomerulosclerosis and further loss of renal function.

Pathophysiology

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

→ Interstitial fibrosis

Viscious 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

Uremic syndrome

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

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
- Decrease in requirements for insulin and OHD in diabetic patients as they develop renal failure.

B. dyslipidemia:

- ↓ HDL cholesterol
- ↑ TG and lipoprotein(a)

Metabolic and electrolytes abnormalities in CKD

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 curtailed → hyperkalemia

Metabolic and electrolytes abnormalities in CKD

D. Acid-Base abnormalities – metabolic acidosis

- The body produces about 80 mmol of non-volatile acids from metabolism everyday.
- 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.

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

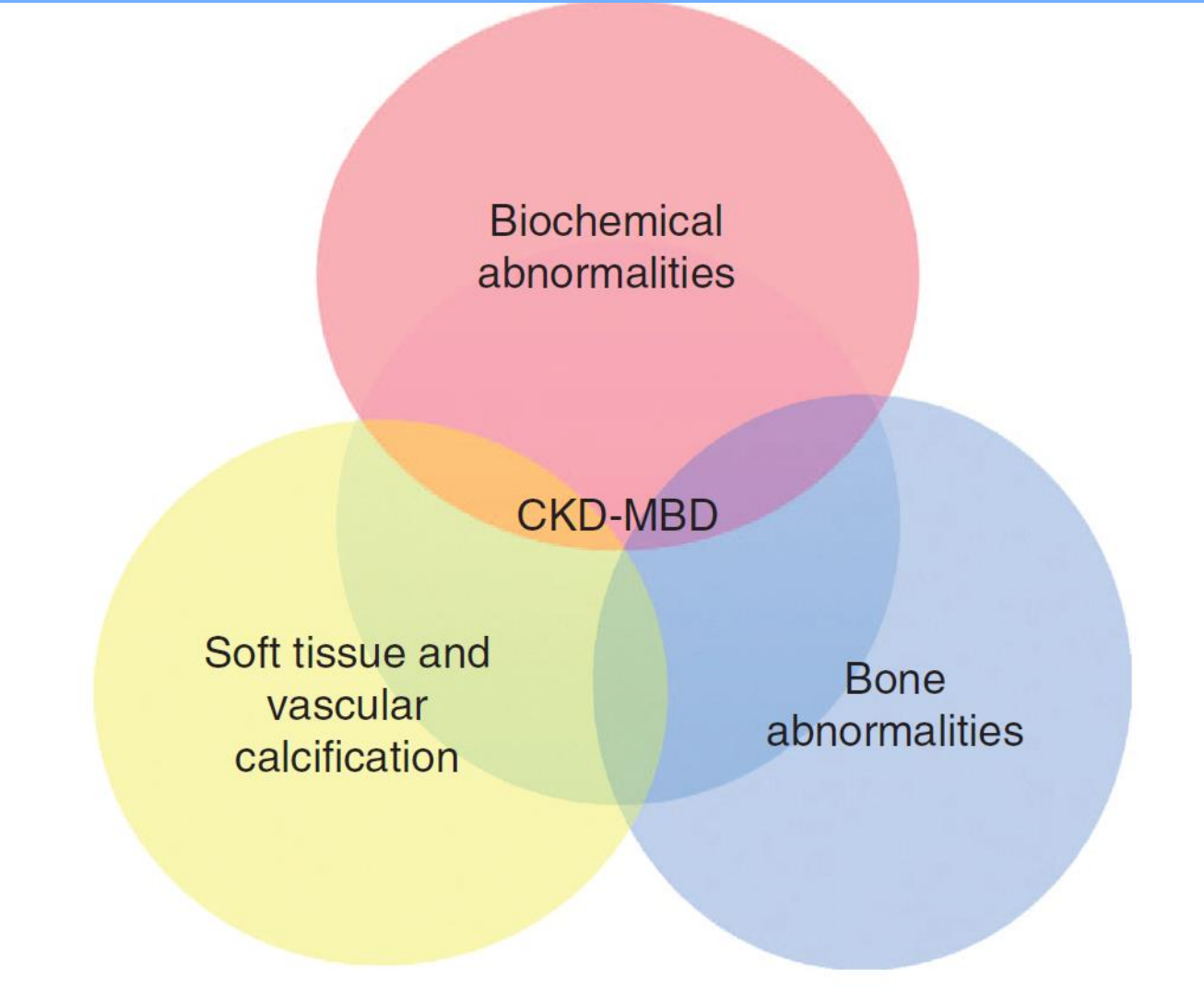
- Indicates alterations in mineral bone metabolism
- These alterations include :

  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

Chronic kidney disease–mineral and bone disorder



CKD - MBD: Pathogenesis

As GFR declines, the excretion of phosphorus is impaired, leading to a tendency to hyperphosphatemia.

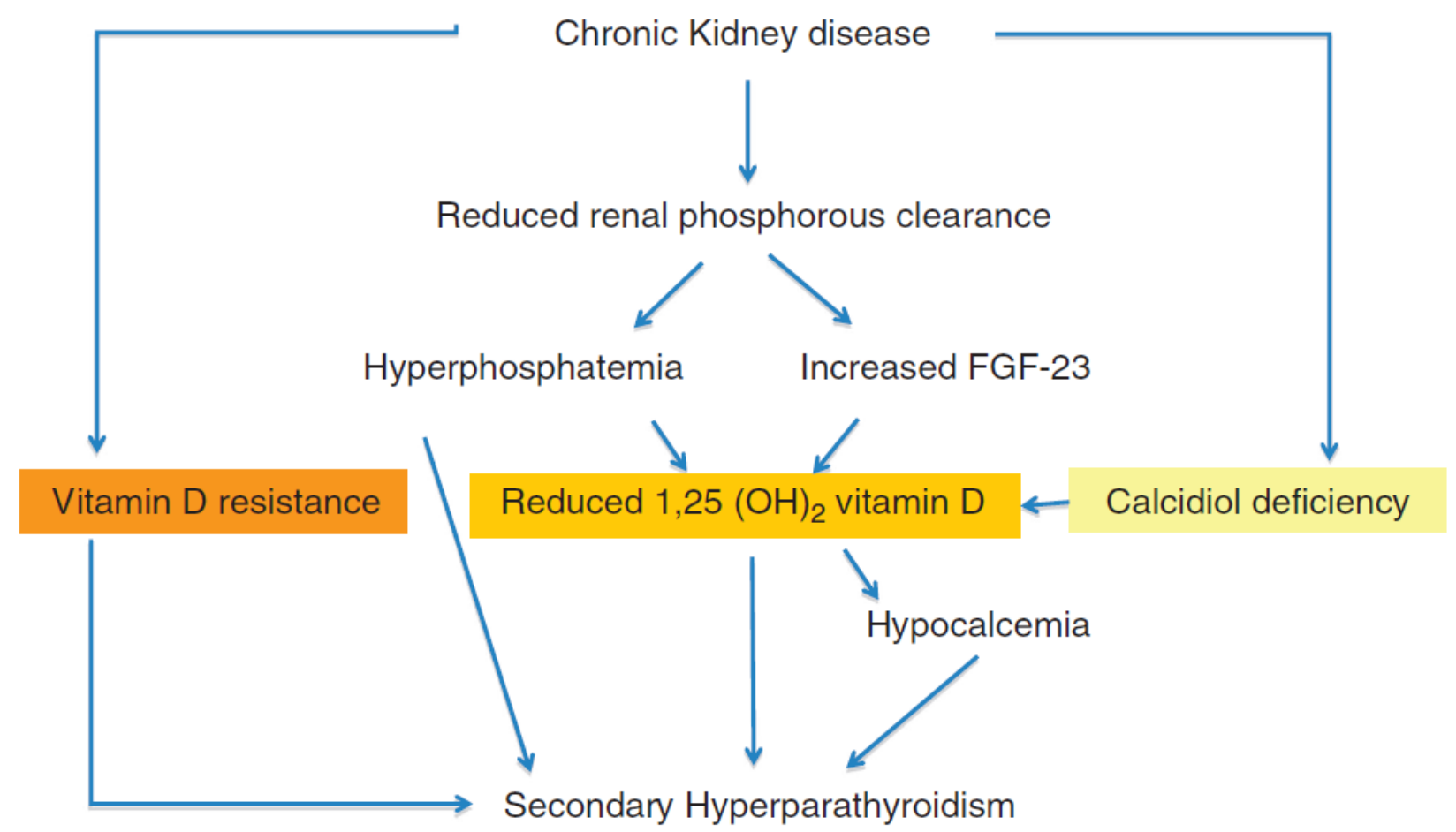
Hyperphosphatemia is an independent risk factor for the increased morbidity and mortality of stage 5 CKD from cardiovascular events

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.

Pathogenesis of CKD - MBD



Reasons for altered vitamin D metabolism in CKD

Calcidiol deficiency	Reduced sun exposure, reduced skin synthesis, reduced ingestion of foods rich in vitamin D, loss of DBP with proteinuria
Calcitriol deficiency	Reduced calcidiol availability, reduced renal 1-α hydroxylase availability, down regulation of renal 1-α hydroxylase from hyperphosphatemia and FGF-23, reduced endocytotic uptake by megalin, increased degradation of calcitriol by PTH and FGF-23
Calcitriol resistance	Loss of VDR in parathyroid glands, impaired binding of active vitamin D to VDR and impaired binding of vitamin D–VDR complex to the VDR element

Adpated with permission from Nigwekar *et al.*[25]

CKD - MBD

- The classic biochemical abnormalities :

  hypocalcemia
  hyperphosphatemia
  hyperparathyroidism
  hypovitaminosis D
  elevated FGF-23

Bone abnormalities = Renal Osteodystrophy (ROD)

is a complex disorders of bones in uremic patient resulting from abnormalities of mineral ions (Ca, po4, Mg) ,PTH , Vit-D and FGF23 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: a. *↑PTH*
     b. *↑activity of both osteoclast and osteoblast*
  2. *Adynamic bone disease (low bone tumour)*
  3. *Osteomalacia (low turnover accompanied by undermineralized bone tissue)*
  4. *Combination of the above*

- *Patients with these bone abnormalities may be asymptomatic or may develop symptoms related to* ***bone pain*** *or* ***fractures.***

  ESRD patients on dialysis have > 3-4 times increased risk of vertebral and hip fractures compared to general population even after adjustment for age, gender and race.

- Adynamic bone disease
  - Risk factors:
    - Advanced age
    - CAPD
    - Diabetes mellitus
    - Calcitriol therapy
    - Parathyroidectomy
    - Flouride and iron intoxication
  - Mechanism:
    - Defect in osteoblast development or activity caused by factors related to the uremic state

Cardiovascular abnormalities of ESRD (CKD-5)

1. Hypertension
   - Occurs in 90% of patients with ESRD
   - Causes:
     - Salt and water retention (the 1°my 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
3. Pericarditis and pericardial effusion

- ✓ 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.

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
  - Postural hypotention (autonomic dysfunction)

Hematologic abnormalities

a. 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

b. Platelet Dysfunction

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

Dermatologic abnormalities

Uremic pruritus is related to:

- Calcium and phosph deposition (2^{o} ↑ PTH)
- Hypercalcemia
- Peripheral neuropathy
- Dry skin
- Anemia
- Inadequate dialysis

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

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

- All patients with CKD should have a basic evaluation including : CBC, urinalysis, U&E, LFTs, Ca, P, magnesium, PTH, Vit-D, urine pro/cr ratio.
- Further evaluations will depend on initial findings and likely diagnostic possibilities.

Management of Patients with CKD

1. Nutrition:

   restriction intake of

   * protein; not less than 0.8mg/kg/day

   * phosphate

   * sodium

   *potassium

Management of Patients with CKD

2. **Salt and water retention:**
   - Salt intake restriction – daily Na^+ < 100 meq
   - fluid restriction 1 – 1.5 L/day
   - Loop diuretics
   - RAS inhibition(ACEi, ARB) if HTN w proteinuria
3. **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)
     - $NaHCO_3$ IV/oral

4. Hyperphosphatemia and secondary hyperparathyroidism:

a. Reduce phosphate intake to < 10 mg/kg/day
b. Phosphate binders: Calcium carbonate
Sevelamer (Renagel)
Lanthanum carbonate
c. Vitamin D (Calcitriol) 0.125 mcq/day
- Must be withheld until s. phosphate concentration have 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.
d. Indication for parathyroidectomy:
PTH > 800 pg/ml with symptoms of bone disease (myopathy, bone pain) persistent hyperphosphatemia soft tissue calcifications

5. **Hyperlipidemia**

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

6. **Anemia**

* **Target Hb/Hct:**

- K DOQI → Hb 11-12
  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 stores
- 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)

A. 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

B. IV iron

- 1 gr of iron saccharate (ferrosac) divided into 10 doses of 100 mg given with each dialysis session.

Treatment Guidelines (Anemia)

C. **Recombinant Erythropoeitin – epoeitin alfa (eprex)**

- *patients on* : starting dose 120 – 180 IU/kg/week, IV
- *pre-dialysis patients and PD patients*: 80-120 IU/kg/week subcutaneously weekly dose
- *Hb/Hct monitoring* every 4 weeks
- *the most common side effects*: headache, HTN, arthralgia, and diarrhea
- *resistance to epoeitin:*

1. inadequate Epo dose
2. anemia of chronic disease (infection, inflammation)
3. functional iron deficiency
4. secondary to hyperparathyroidism
5. carnitine deficiency
6. hemoglobinopathies
7. aluminum toxicity
8. B_{12}/folate deficiency
9. malnutrition

D. Darbepoetin Alfa (Aranesp)

- Recombinant Epo
- Half-life: threefold longer IV and twofold longer S/C than that of epoetin
- Recommended starting dose 0.45 mcg/kg S/C weekly or double the dose every 2 weeks.

Exercise

- Aerobic exercise and resistance training have been shown to:

- decrease inflammation, oxidative stress, endothelial dysfunction and insulin resistance.
- reduce blood pressure
- improve hyperlipidemia, proteinuria, and obesity
- decrease CV mortality/morbidity
- may decrease the rate of progression of CKD

Johansen & Painter,2012; Leehey et al 2009; Moinuddin & Leehey 2008 , 2010; Tentori 2008

Thank You!