Chronic Kidney Disease

Dr Soraya khajehrezaei

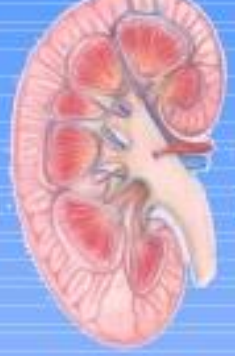
- CKD is defined as abnormalities of kidney structure or function, present for >3 months

- term *end-stage renal disease* represents a stage of CKD where the accumulation of toxins, fluid, and electrolytes normally excreted by the kidneys results in the *uremic syndrome*

Diagnosis

- Bilateral Small size Kidneys
- Lab data
- Previous history (3 months ago)
- Nocturia

- Risk of worsening of kidney function is closely linked to the amount of *albuminuria*
  - CKD staging system according to Scr and albumin excretion
  - marker for the presence of microvascular disease



Renal failure

Differentiation between acute and chronic renal failure

	Acute	*Chronic*
History	Short (days-week)	Long (month-years)
Haemoglobin concentration	Normal	Low
Renal size	Normal	Reduced
Renal osteodystrophy	Absent	Present
Peripheral neuropathy	Absent	Present
Serum Creatinine concentration	Acute reversible increase	Chronic irreversible

Pathophysiology

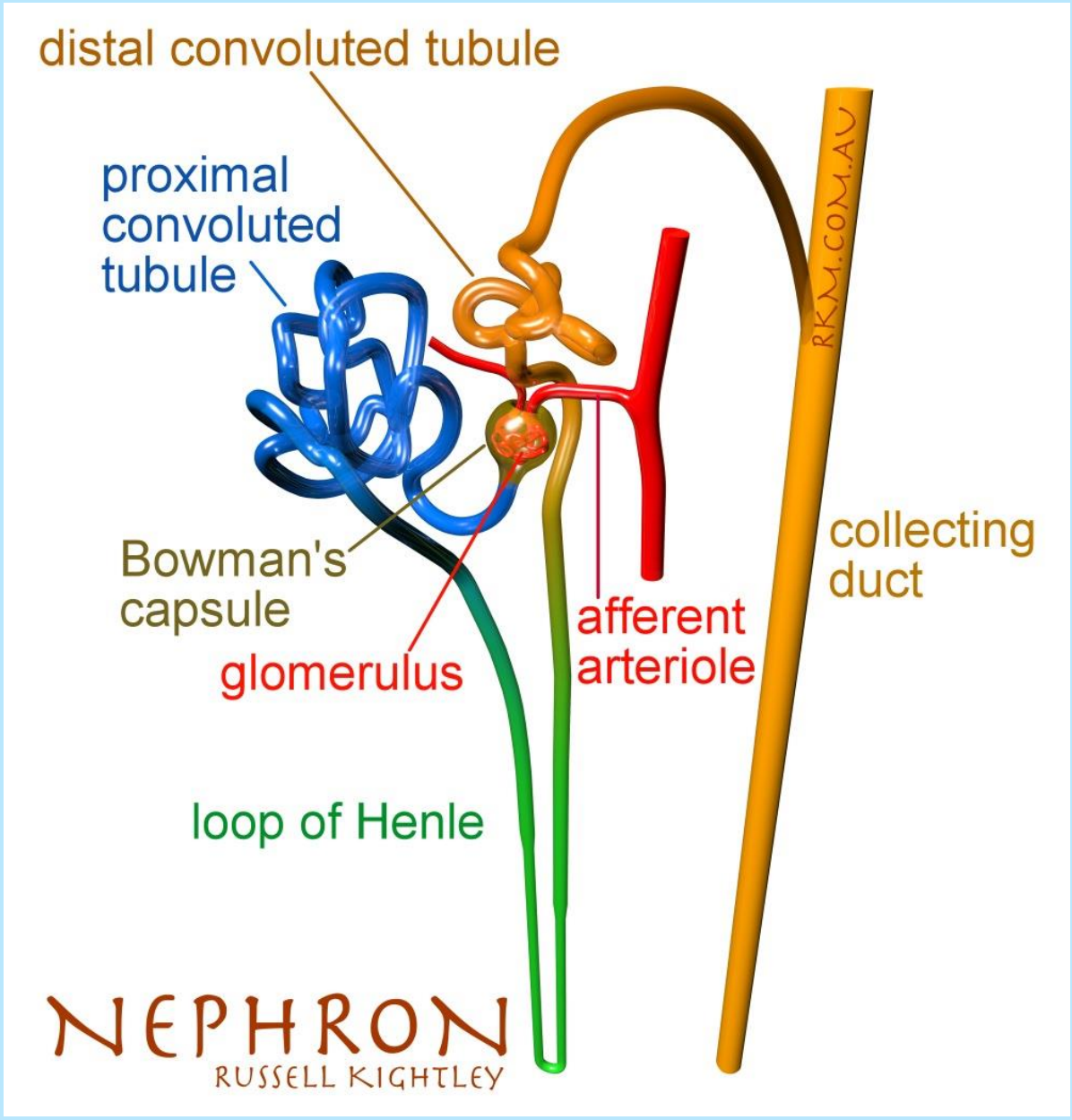
Two mechanisms:

1. initiating mechanisms specific to the underlying etiology
   - genetically determined abnormalities in kidney development or integrity
   - immune complex deposition
   - inflammation in certain types of glomerulonephritis
   - toxin exposure in certain diseases of the renal tubules and interstitium
2. progressive mechanisms involving hyperfiltration and hypertrophy of the remaining viable nephrons:
   - Reduction of renal mass, irrespective of underlying etiology

- **Hyperfiltration**
  - At first: adaptive
  - Final result: maladaptive because increased pressure and flow within the nephron predisposes to
    - distortion of glomerular architecture
    - abnormal podocyte function,
    - disruption of the filtration barrier

- leading to sclerosis and dropout of the remaining nephrons

- At risk patient:
  - Small for gestational age
  - Low birth weight
  - Childhood obesity
  - Hypertension
  - Diabetes mellitus
  - Autoimmune disease
  - Advanced age
  - African ancestry
  - Family history of kidney disease
  - Previous episode of acute kidney injury
  - Presence of proteinuria
  - Abnormal urinary sediment
  - Structural abnormalities of the urinary tract
  - Hereditary disorders: ADPKD, Alport


distal convoluted tubule
proximal convoluted tubule
Bowman's capsule
glomerulus
afferent arteriole
collecting duct
loop of Henle
RKM.COM.AU
NEPHRON
RUSSELL KIGHTLEY

- GFR (~120 mL/min per 1.73 m2)
- After 3rd decade: decline~1 mL/min per year per 1.73 m2
- The equations for estimating GFR are valid only if the patient is in steady state, that is, the serum creatinine is neither rising nor falling over days.
- The mean GFR is lower in women than in men .

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) description and range				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

- Stages 1 & 2: no sign and symptom
- Stages 3 & 4: clinical and laboratory complications of CKD
  - *Anemia and associated easy fatigability*;
  - decreased appetite with progressive malnutrition
  - Ca/P
  - mineral-regulating hormones, such as 1,25(OH)2D3 (calcitriol), PTH, FGF-23
  - Na/K, water, acid-base homeostasis
- Stage 5: ESRD (uremic Syndrome)

- *GFR in many elderly patients is compatible with stage 2 or 3 CKD.*

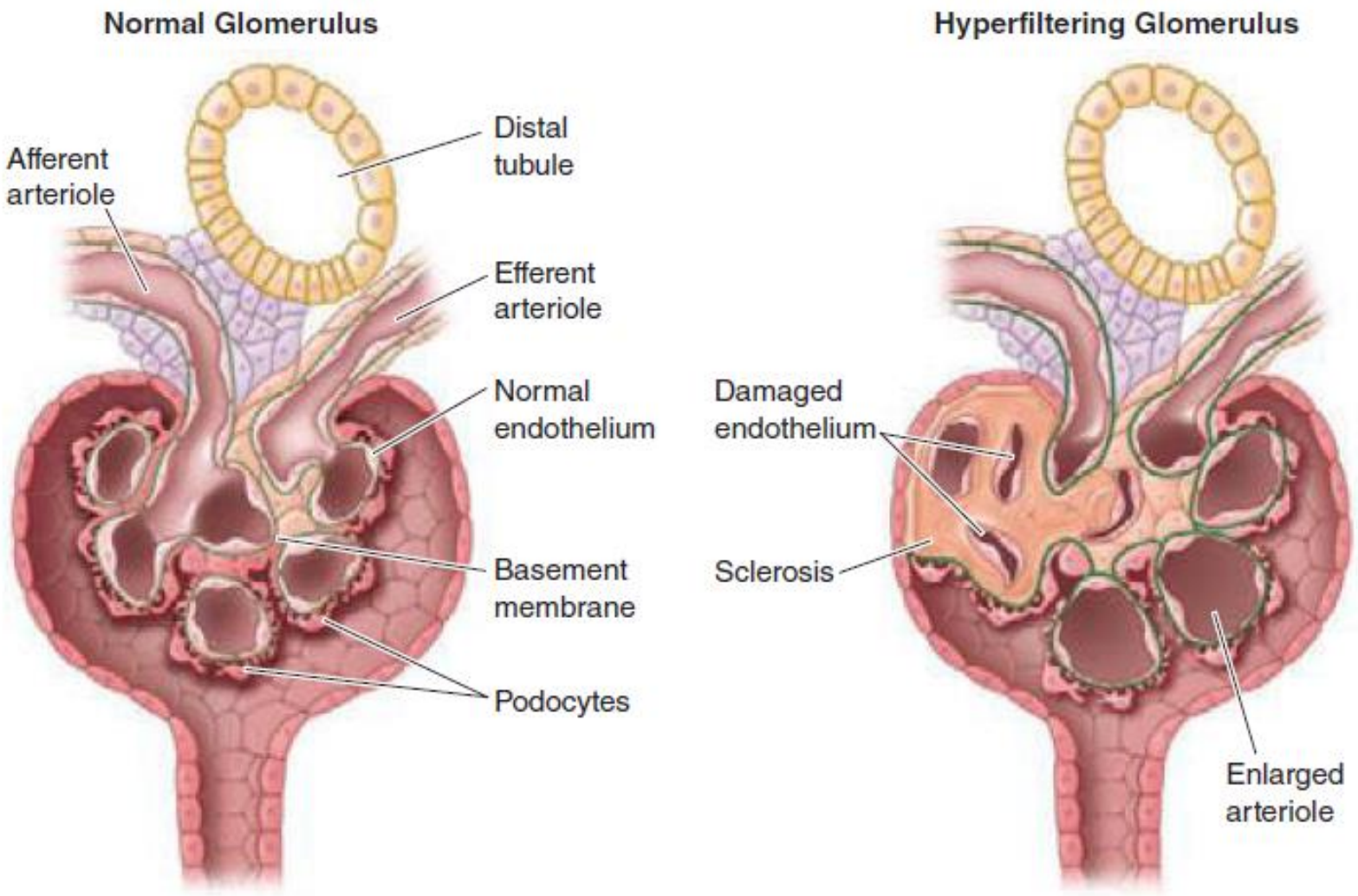

Normal Glomerulus
Afferent arteriole
Distal tubule
Efferent arteriole
Normal endothelium
Basement membrane
Podocytes
Hyperfiltering Glomerulus
Damaged endothelium
Sclerosis
Enlarged arteriole

TABLE 335-1 RECOMMENDED EQUATIONS FOR ESTIMATION OF GLOMERULAR FILTRATION RATE (GFR) USING SERUM CREATININE CONCENTRATION (S_{CR}), AGE, SEX, RACE, AND BODY WEIGHT

1. Equation from the Modification of Diet in Renal Disease study

Estimated GFR (mL/min per 1.73 m^2) = $1.86 \times (S_{Cr})^{-1.154} \times (age)^{-0.203}$

Multiply by 0.742 for women

Multiply by 1.21 for African ancestry

2. CKD-EPI equation

$GFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age}$

Multiply by 1.018 for women

Multiply by 1.159 for African ancestry

where S_{Cr} is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of S_{Cr}/κ or 1, and max indicates the maximum of S_{Cr}/κ or 1.

Leading Categories of Etiologies of CKD (90%)

- Diabetic nephropathy
- Glomerulonephritis
- Hypertension-associated CKD (includes vascular and ischemic kidney disease and primary glomerular disease with associated hypertension)
- Autosomal dominant polycystic kidney disease
- Other cystic and tubulointerstitial nephropathy

Without overt evidence for a primary GN or tubulointerstitial kidney disease:CKD is attributed to HTN.Such individuals can be considered in two categories:

1. silent primary glomerulopathy e.g. FSGS without overt nephrotic or nephritic syndrome.
2. Progressive nephrosclerosis and hypertension is the renal correlate of a systemic vascular disease, such as elderly patients

PATHOPHYSIOLOGY & BIOCHEMISTRY OF UREMIA

- Hundreds of toxins other than urea and Cr (protein)
- A host of metabolic and endocrine functions normally performed by the kidneys is also impaired.
- anemia, malnutrition, and abnormal metabolism of carbohydrates, fats, and proteins
- Accumulation of PTH, FGF-23, insulin, glucagon, steroid hormones including vitamin D and sex hormones, and prolactin change with CKD .
- worsening systemic inflammation:
  - Elevated levels of C-reactive protein
  - Decreased levels of negative acute-phase reactants, such as albumin and fetuin

- Malnutrition-inflammation atherosclerosis/calcification syndrome: acceleration of vascular disease and comorbidity

Summary

1. Accumulation of toxins
2. Loss of kidney functions
3. Progressive kidney inflammation

CLINICAL & LABORATORY MANIFESTATIONS OF CKD AND UREMIA

Water and electrolytes,and acid-base disorders

Sodium and Water Homeostasis

- Total-body content of sodium and water: modestly increased, may not be apparent clinically
- Disruption in urinary excretion
  - Retention
    - HTN
      - Accelerate nephron loss
- Hyponatremia: not commonly
  - Often responds to water restriction

- Overt ECFV expansion:
  - peripheral edema, sometimes hypertension poorly responsive to therapy
  - ✓Salt restriction.
  - ✓loop diuretics, including furosemide, bumetanide, or torsemide
  - ✓loop diuretics (higher doses) with metolazone (DCT)
  - ✓No thiazide
  - ✓Diurtic resistanse: Dialysis

- Inability of kidney in preservation of salt and water
  - Prone to hypovolemia

Potassium Homeostasis

- Augmented potassium excretion in the GI tract:defense mechanism
- *Hyperkalemia causes:*
  - increased dietary potassium intake, protein catabolism, hemolysis, hemorrhage, transfusion of stored red blood cells, and metabolic acidosis.
  - Medications: RAS inhibitors and spironolactone and amiloride, eplerenone, triamterene
  - Hyporeninemic hypoaldosteronism (DM), renal diseases that preferentially affect the distal nephron
    - obstructive uropathy
    - sickle cell nephropathy.

- *Hypokalemia:*
  - is not common
  - reduced dietary potassium intake, especially in association with:
    - excessive diuretic therapy
    - concurrent GI losses

Metabolic Acidosis

- Daily proton production: 50-100 meq
- common in advanced CKD
  - less ammonia production as urinary buffer.
  - Hyperkalemia further depresses ammonia production
- *Hyperkalemia and hyperchloremic metabolic acidosis is often present ,even at earlier stages of CKD.*
  - *In more advanced disease:*
    - high anion gap (Limited urinary excretion of acid)
- In most patients
  - Metabolic acidosis is mild
  - pH is rarely < *7.32*
  - *corrected with oral sodium bicarbonate supplementation*

- Compensatory mechanisms:
  - Increased amoniagenesis in intact nephrons
  - Bone buffering system
- when the serum bicarbonate concentration falls below 20–23:
  - may be associated with the development of protein catabolism
  - Alkali supplementation may attenuate the catabolic state and possibly slow CKD progression

Treatment:

- Salt restriction,loop diuretics
- Water restriction in hyponatremia
- Dietary restriction of potassium
- Dose reduction or avoidance of potassium retaining medication
- Potassium binding resins
- Dialysis
- Sodium bicarbonate

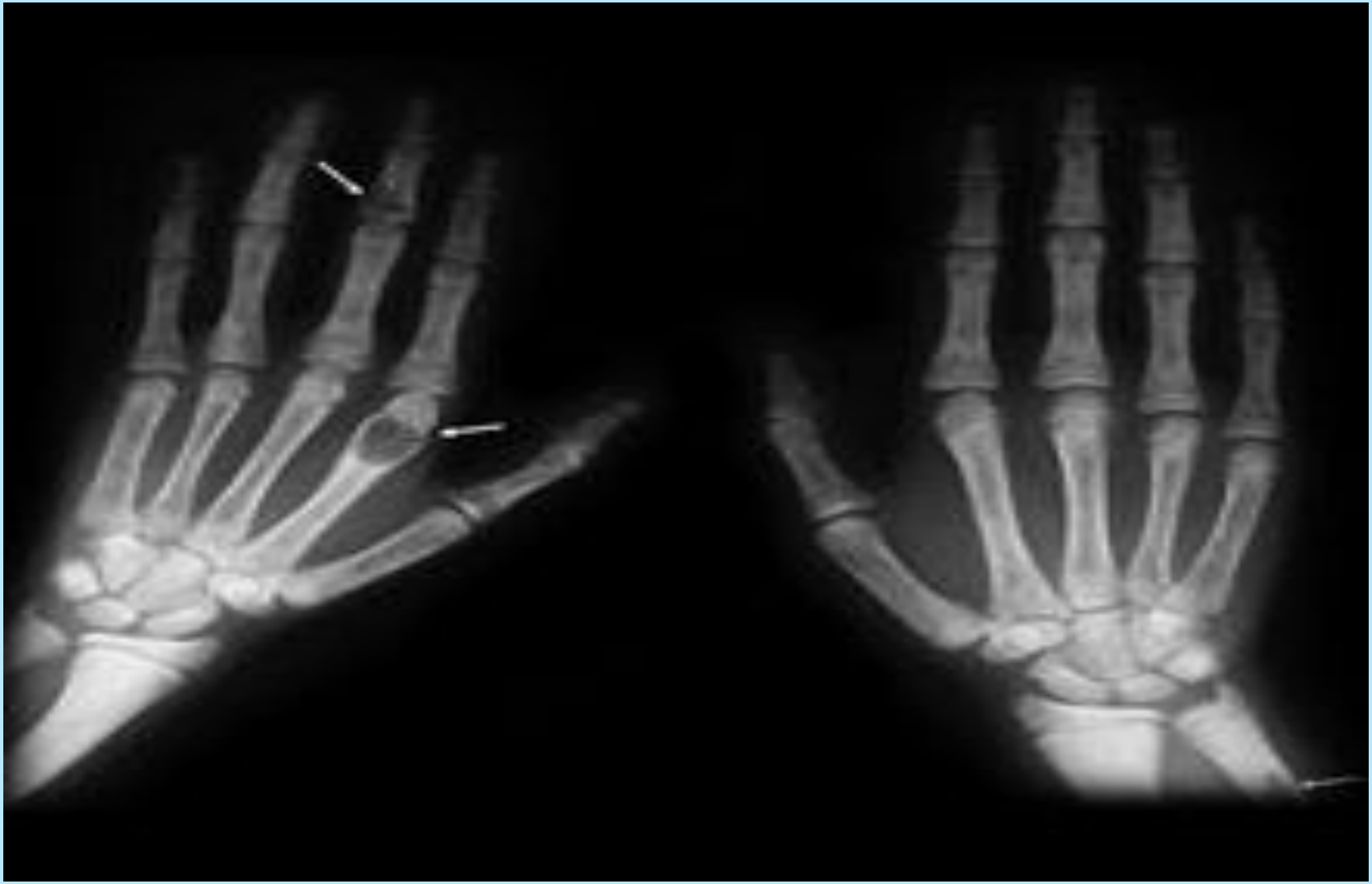
DISORDERS OF CALCIUM AND PHOSPHATE METABOLISM

Bone Manifestations of CKD

- high bone turnover with increased iPTH levels
  - osteitis fibrosa cystica
  - classic lesion of secondary hyperparathyroidism
  - bone pain and fragility, brown tumors, compression syndromes, and erythropoietin resistance
  - PTH as uremic toxin (muscle weakness, fibrosis of cardiac muscle, and nonspecific constitutional symptoms)

Osteitis fibrosa cystica

Brown tumor



- low bone turnover with low or normal PTH levels:
  1. adynamic bone disease
     - Risk factor: diabetics and the elderly
     - reduced bone volume and mineralization may result from: excessive suppression of PTH production, chronic inflammation, or both.
     - Suppression of PTH: use of vitamin D preparations or from excessive calcium exposure in the form of calcium-containing phosphate binders or high calcium dialysis solution
     - Complications: increased incidence of fracture and bone pain and an association with increased vascular and cardiac calcification or soft tissue calcification (tumoral calcinosis")
  2. Osteomalacia: AL overload, vit D deficiency

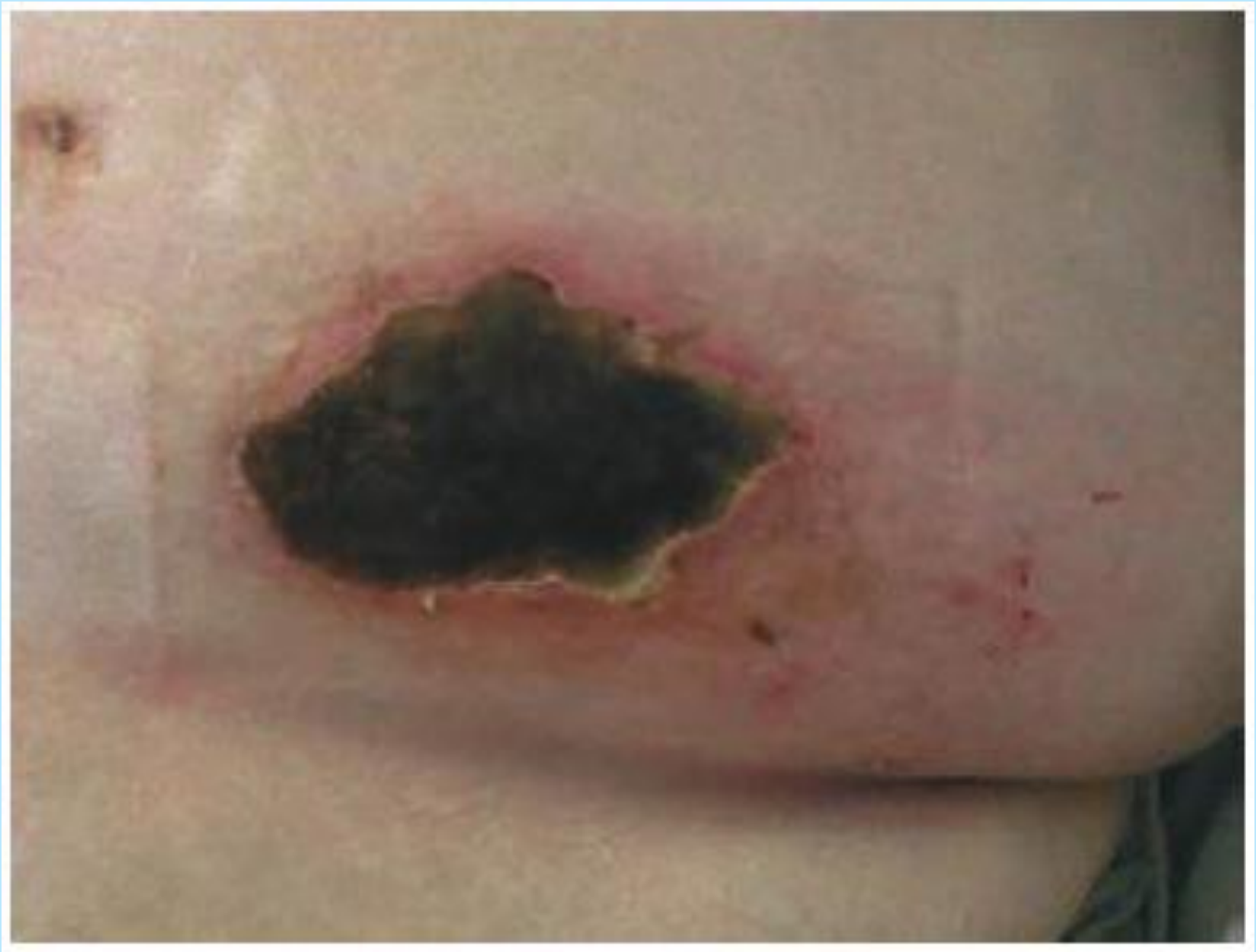
These changes start to occur when the GFR falls below

60 mL/min

- FGF-23: phosphatonins that promotes renal phosphate excretion.
  - increase early in the course of CKD,
  - even before phosphate retention and hyperphosphatemia.
- FGF-23:
  - increased renal phosphate excretion
  - stimulation of PTH, which also increases renal phosphate excretion
  - suppression of the formation of 1,25(OH)2D3
- independent risk factor for LVH and mortality
- Elevated levels of FGF-23 may indicate the need for therapeutic intervention:
  - phosphate restriction or lowering agents

- Strong association between hyperphosphatemia and increased cardiovascular mortality rate
- Vascular and heart valve calcification
  - age
  - hyperphosphatemia
  - low PTH levels
- Hyperphosphatemia: vascular cells to an osteoblast-like profile, leading to vascular:
  - Calcification
  - Ossification

- Calciphylaxis:
  - livedoreticularis and advances to patches of ischemic necrosis, especially on the legs, thighs, abdomen, and breasts
  - vascular occlusion in association with extensive vascular and soft tissue calcification
- Matrix GLA protein: preventing vascular calcification
- Warfarin: decrease regeneration of matrix GLA protein



Treatment

- Hyperphosphatemia:low phosphate dite,phosphate-binding agent(calcium-containing or non-calcium-containing)
- Hyperparathyroidism:calcitriol,cinacalcet

CARDIOVASCULAR ABNORMALITIES

- Cardiovascular disease: occlusion coronary, cerebrovascular, and peripheral vascular disease
- compared to the age- and sex-matched general population ranges from ***10- to 200-fold***, depending on the stage of CKD
- Between 30 and 45% of those patients who do reach stage 5 CKD have advanced cardiovascular comlication
- ***Risk factors****:*

1. Traditional (“classic”):hypertension, hypervolemia, dyslipidemia, sympathetic overactivity, and hyperhomocysteinemia
2. nontraditional (CKD-related): anemia, hyperphosphatemia, hyperparathyroidism, increased FGF-23, sleep apnea, and generalized inflammation

- The inflammatory state:
  - accelerate vascular occlusive disease
  - low levels of fetuin: more rapid vascular calcification

- AugmentMI :LVH, microvascular disease, recurrent hypotension in HD patients
- Cardiac troponin levels are elevated in CKD without evidence of MI.Serial measurements may be needed
- HF:secondary to MI,LVH,diastolic dysfunction,CMP,salt and water retention,anemia,sleep apnea

- Low pressure Plural Effusion:With increased permeability of alveolar capillary membrane

- HTN: accelerated nephron loss

Treatment

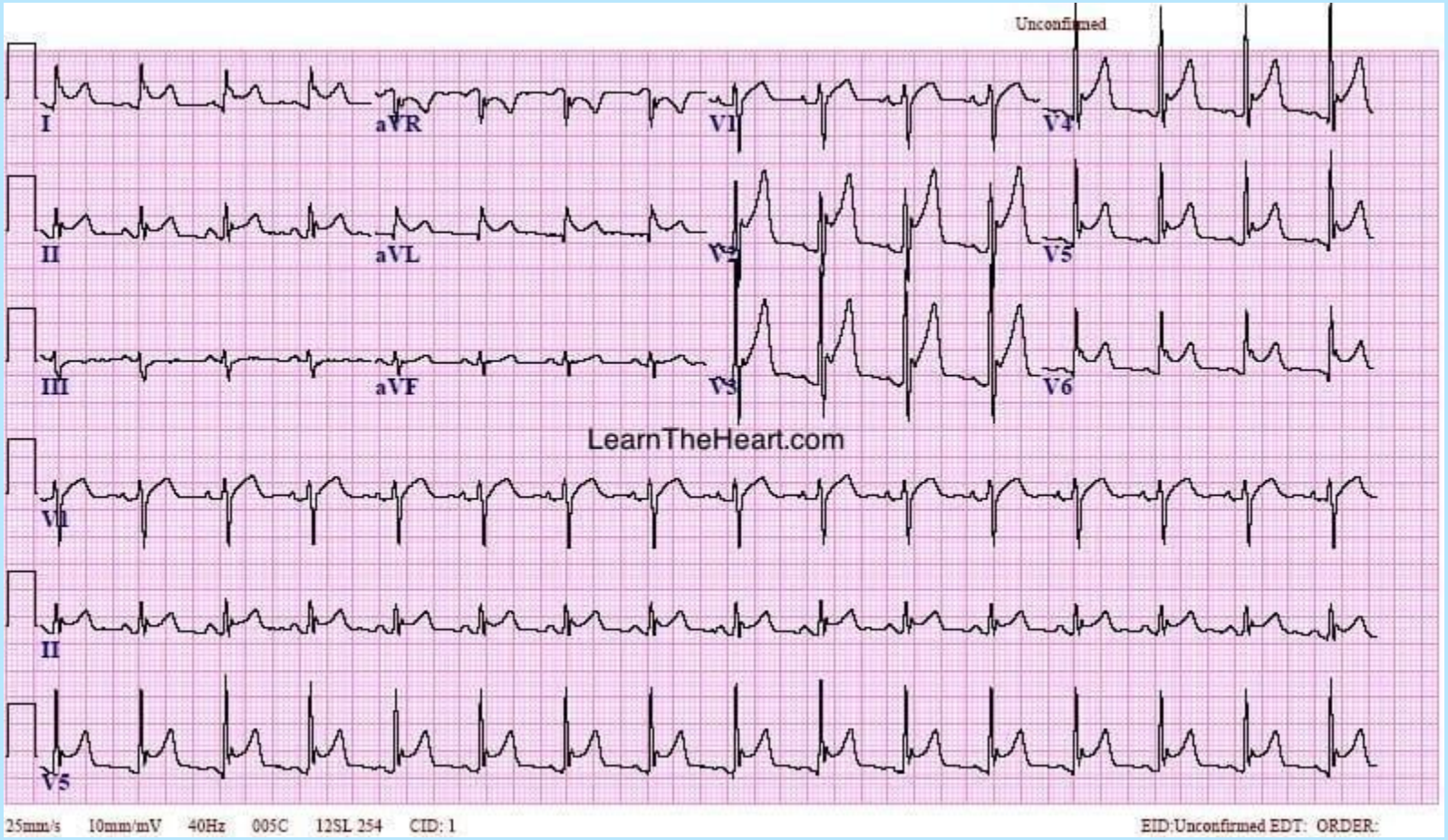
- CKD with diabetes or proteinuria >1gr per 24h,BP should be reduced to <130/80mmHg.
- Salt restriction first line
- ACEinh/ARB:<30% Reduction of GFR can be tolerated
- Cardiovascular risk factors;Traditional and non-traditional

Pericardial Disease

- PE -/+ pericarditis
- Often in underdialyzed,non-adherent
- Diagnostic of pericarditis:
  - Chest pain with respiratory accentuation,
  - Friction rub
  - Pericardial effusion
  - Rarely tamponade
- Classic electrocardiographic abnormalities include PR-interval depression and diffuse

  ST-segment elevation

  Treatment:urgent dialysis,intensification of the dialysis,pericardial drainage in impending tamponad


Unconfirmed
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
LearnTheHeart.com
V1
II
V5
25mm/s 10mm/mV 40Hz 005C 12SL 254 CID: 1
EID:Unconfirmed EDT: ORDER:

HEMATOLOGIC ABNORMALITIES

Anemia

- A normocytic, normochromic anemia:
  - stage 3 CKD
  - almost universal by stage 4

- Adverse effects:
  1. decreased tissue oxygen delivery
  2. increased cardiac output
  3. ventricular dilation
  4. ventricular hypertrophy.

Clinical manifestation:

- Fatigue
- Diminished exercise tolerance
- Angina
- Heart failure
- Decreased cognition and mental acuity
- Impaired host defense against infection
- In children with CKD: growth restriction

TABLE 335-3 CAUSES OF ANEMIA IN CKD

- Relative deficiency of erythropoietin
- Diminished red blood cell survival
- Bleeding diathesis
- Iron deficiency
- Hyperparathyroidism/bone marrow fibrosis
- Chronic inflammation
- Folate or vitamin B_{12} deficiency
- Hemoglobinopathy
- Comorbid conditions: hypo-/hyperthyroidism, pregnancy, HIV-associated disease, autoimmune disease, immunosuppressive drugs

Treatment

- ESA:obviated the need for regular blood transfusion
- Iron(po for CKD and PD patients,IV for hemodialysis patients)
- VitB12 and folate
- Anemia resistant causes: inflammation,inadequate dialysis,severe hyperparathyroidism,chronic blood loss,hemolysis,chronic infection or malignancy
- Target hemoglobin: 100-115g/l

Abnormal Hemostasis

- prolonged bleeding time
- decreased activity of platelet factor III
- abnormal platelet aggregation and adhesiveness
- impaired prothrombin consumption
- Decreased vwf
- Susceptibility to VTE

Treatment:

- DDAVP
- Cryoprecipitate
- IV conjugated estrogens
- Blood transfusions
- ESA therapy
- Optimal dialysis

NEUROMUSCULAR ABNORMALITIES

- Neuropathy
  1. CNS:
     - Mild disturbance:memory and concentration and sleep disturbance
     - Hiccup,cramps and twiching
     - In advanced untreated kidney failure:asterixis, myoclonus, seizures, and coma
  2. PNS: stage4 CKD
     - sensory nerves > motor
     - lower extremities > upper
     - distal parts of the extremities > proximal
  3. Autonomic
- Myopathy
- Subtle clinical manifestations of uremic neuromuscular disease usually become evident at stage 3 CKD

- “restless leg syndrome”: ill-defined sensations of sometimes debilitating discomfort in the legs and feet relieved by frequent leg movement.
- If dialysis is not instituted soon after onset of sensory abnormalities, motor involvement follows, including muscle weakness
- Many of the these complications will resolve with dialysis

GASTROINTESTINAL AND NUTRITIONAL ABNORMALITIES

- Uremic fetor:
  - a urine-like odor on the breath
  - Breakdown of urea to ammonia in saliva
  - often associated with an unpleasant metallic taste (dysgeusia). Gastritis, peptic disease, and mucosal ulcerations at any level of the GI tract
- prone to constipation: worsened by of calcium and iron supplements.
- Retention of uremic toxins: anorexia, nausea, vomiting
- Protein restriction may put patient at risk for malnutrition that is indicaton for RRT

- Metabolic acidosis and the activation of inflammatory cytokines can promote protein catabolism

- Assessment:
  - dietary history, including food diary
  - subjective global assessment; edema-free body weight
  - measurement of urinary protein nitrogen appearance.
  - Adjunctive tools: skinfold thickness, mid-arm muscle circumference
  - additional laboratory tests: such as serum pre-albumin and cholesterol levels
  - Dual-energy X-ray absorbtiometry:estimate lean body mass

ENDOCRINE-METABOLIC DISTURBANCES

- Glucose metabolism:

1. Slower decline in blood glucose after a glucose load.
2. FBS: normal or only slightly elevated
3. slight to moderate elevation in insulin levels both in the fasting and postprandial states.

- Progressive reduction in insulin requirement
- Oral anti-hyperglycemic agent:dose reduction or avoidance
- SGLT2inh(empagliflosin):reduction in kidney function decline and cardiovascular event

- In women:

1. estrogen levels are low
2. Menstrual abnormalities
3. Infertility
4. inability to carry pregnancies to term
5. GFR ~40 mL/min:
   - high rate of spontaneous abortion
   - only ~20% of pregnancies leading to live births,

- In men:

1. reduced plasma testosterone
2. sexual dysfunction
3. oligospermia

- Adolescent children: delayed sexual maturation

DERMATOLOGIC ABNORMALITIES

- Pigmentation: deposition of retained pigmented metabolites, or *urochromes* in CKD or ESRD
- Pruritus: often tenacious even after dialysis
  - R/o scabies, and hyperphosphatemia
  - Local moisturizers
  - mild topical glucocorticoids
  - oral antihistamines
  - ultraviolet radiation

- Nephrogenic fibrosing dermopathy:unique to CKD
  1. progressive subcutaneous induration, especially on the arms and legs.
  2. very rarely in patients with CKD who have been exposed to gadolinium
- Current recommendations:
  - CKD stage 3 (GFR 30–59 mL/min): minimized exposure to Gad
  - CKD stages 4–5 (GFR <30 mL/min): avoid the use of gadolinium agents
- rapid removal of gadolinium by hemodialysis (CKD or ESRD) shortly after the procedure may mitigate this complication

Management of patients with CKD

- History(PMH,FH,DH,GYN) and P/E:often subtle(BP,organ damage,funduscopy in DM,edema,..)
- Laboratory investigation:Search for underlying disease (Viral marker,vasculite marker,pro electrophoresis),CKD consequences(iron study,ca,cr vitD,PTH,VitB12,folate,urine pr…)
- Imaging studies:sono(presence of two kidneys,size,symmetry,mass,obstraction,length),CT, MRI,Nuclear medicine,VCUG(reflux nephropathy),radiographic contrast(precausion)

Kidney biopsy:not advised in CKD(likelihood of bleeding,scarring,time of specific therapy has passed)contraindication include HTN,active UTI,bleeding diathesis,severe obesity
If indicated:desmopressin,dialysis prior to bx

CKD Treatment

- Superimpose processes: ECFV depletion,uncontrolled HTN,UTI,nephrotoxic,obstructive urophathy,flare of original disease
- Slowing the progression of CKD: decline glomerular HTN and Proteinuria with ACEinh or ARB,NDHP CCB(diltiazem,verapamil).Target BP:130/80
- Dose adjustment:may not be needed for agents >70% excretion nonrenal.some drugs should be avoided
- RRT:Dialysis,TX
- Patient education,social support