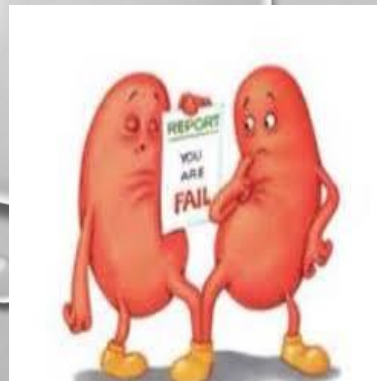
CHRONIC KIDNEY DISEASE

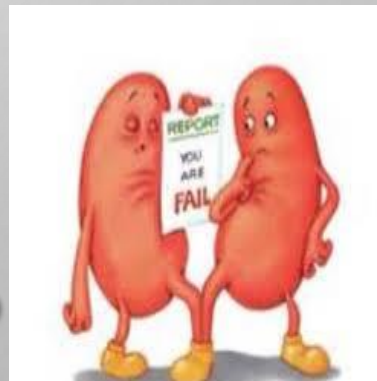
DR SORAYA KHAJEH REZAEI

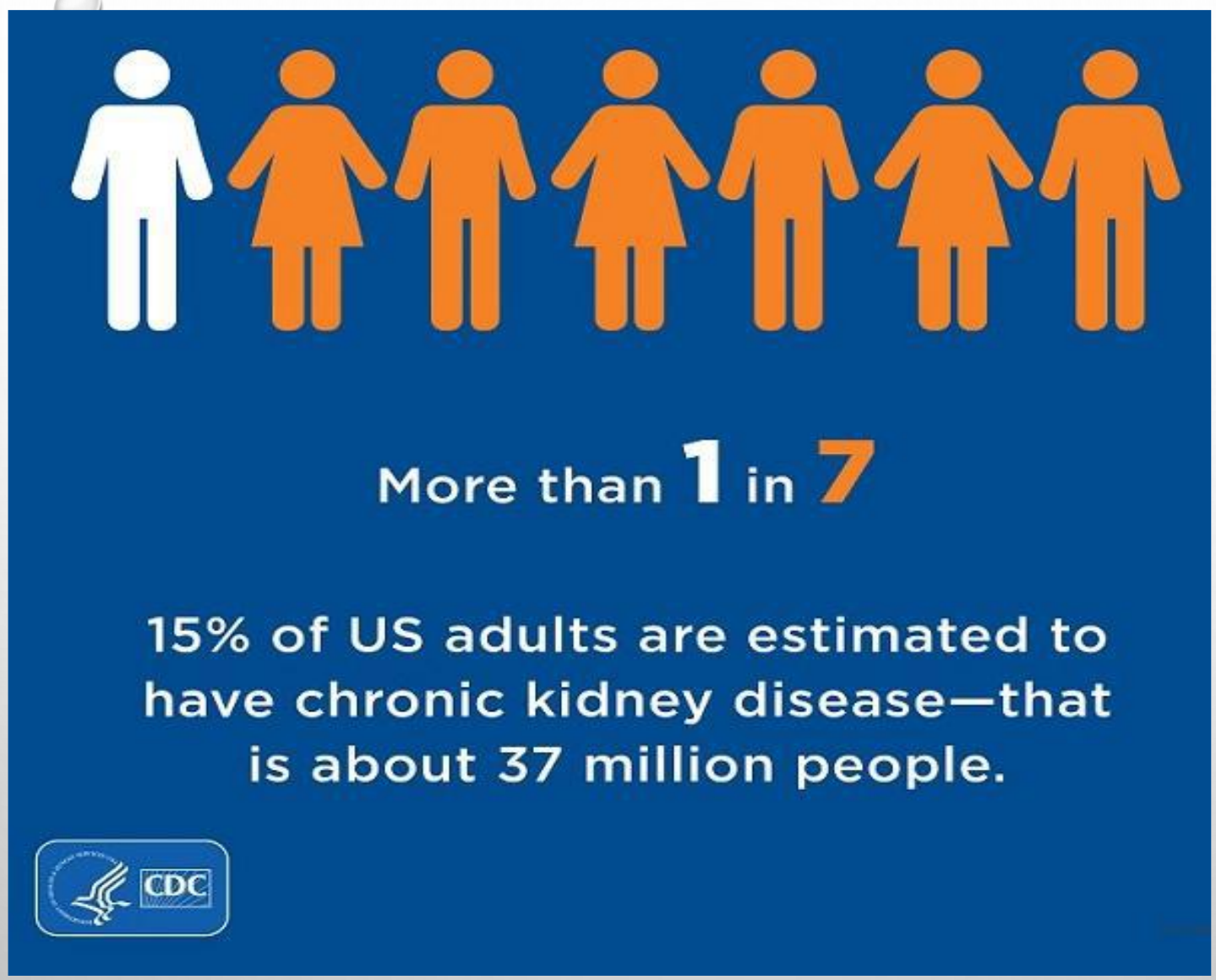


DEFINITION

- 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*

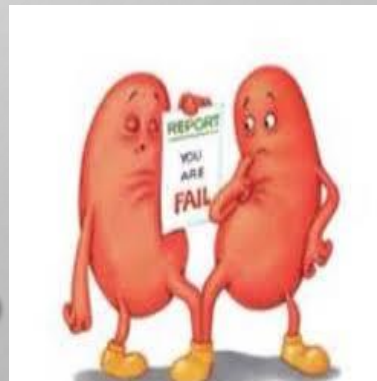



More than 1 in 7
15% of US adults are estimated to have chronic kidney disease—that is about 37 million people.
CDC

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

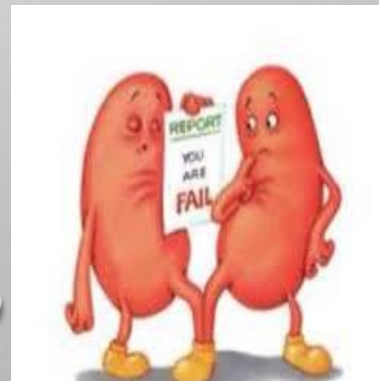
PATHOPHYSIOLOGY

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 etiolog

- **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

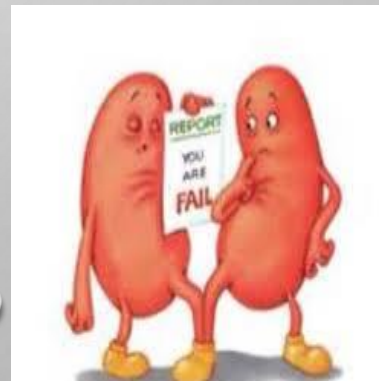
- leading to sclerosis and dropout of the remaining nephrons



AT RISK PATIENT

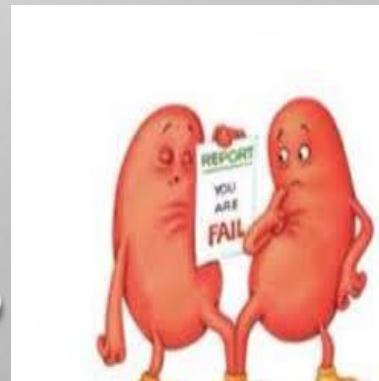
:

- 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



KIDNEY FUNCTION

- 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 .

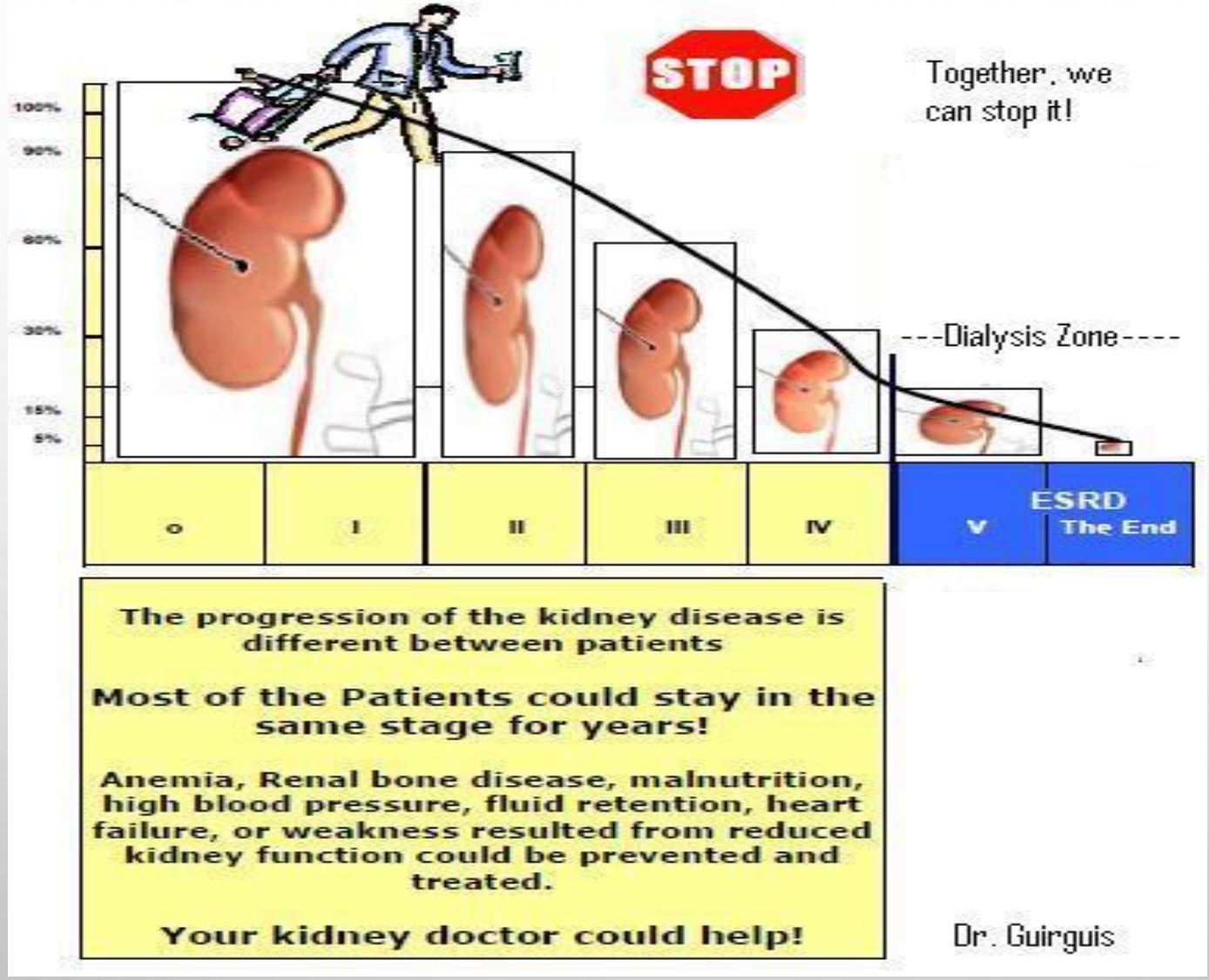


Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

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			

- 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.*


STOP
Together, we can stop it!
100%
90%
60%
30%
15%
5%
---Dialysis Zone----
o
I
II
III
IV
V
ESRD
The End
The progression of the kidney disease is different between patients
Most of the Patients could stay in the same stage for years!
Anemia, Renal bone disease, malnutrition, high blood pressure, fluid retention, heart failure, or weakness resulted from reduced kidney function could be prevented and treated.
Your kidney doctor could help!
Dr. Guirguis


REPORT
YOU ARE
FAIL

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

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

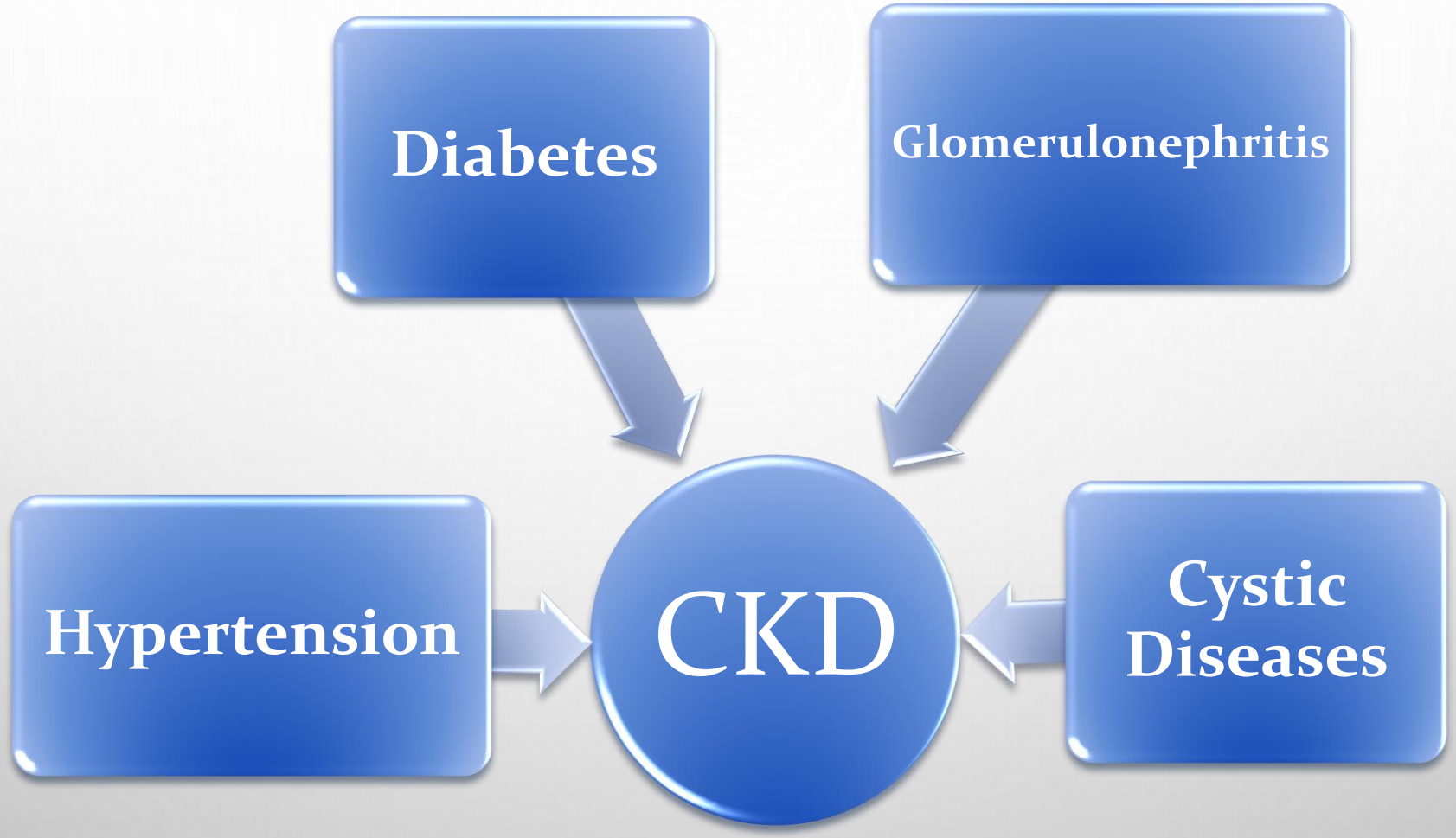
Multiply by 1.018 for women

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.

ETIOLOGIES OF CKD

- 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


Diabetes
Glomerulonephritis
Hypertension
CKD
Cystic Diseases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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

CLINICAL & LABORATORY MANIFESTATIONS OF CKD AND UREMIA

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.
  - ✓ diuretics (higher doses) with metolazone (DCT)
  - ✓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

ELECTROLYTES,AND ACID-BASE DISORDERS 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

K/DOQI™ Clinical Practice Guidelines on Bone Metabolism Target Levels

	CKD Stage 3	CKD Stage 4	CKD Stage 5 (on dialysis)
P (mg/dL)	2.7 - 4.6	2.7 - 4.6	3.5 - 5.5*
Ca (mg/dL)	"Normal"	"Normal"	8.4 - 9.5; Hypercalcemia = >10.2
Intact PTH (pg/mL)	35 - 70	70 - 110	150 - 300*

*Evidence

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)


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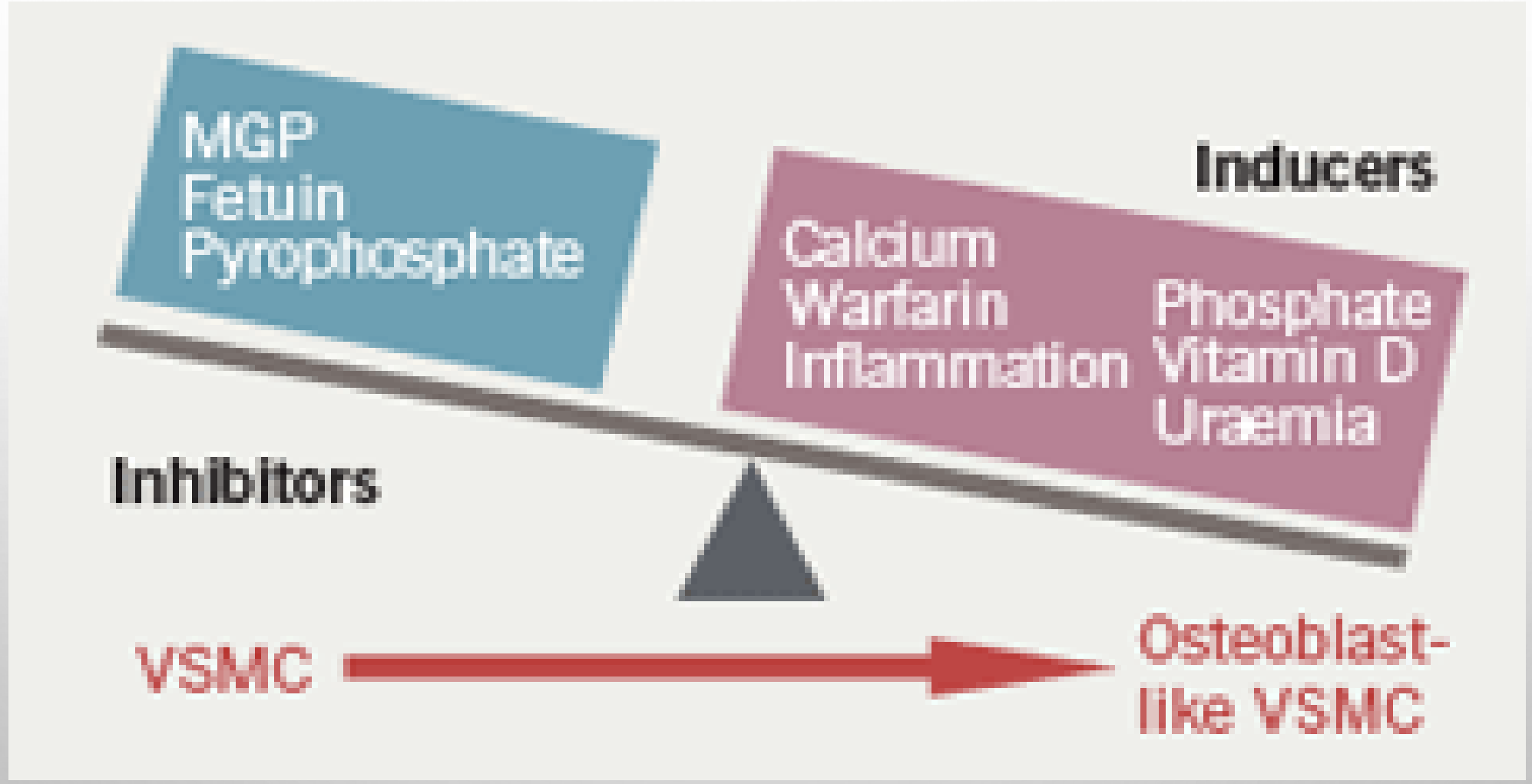
- low bone turnover with low or normal PTH levels:
  1. adynamic bone disease
     - Risk factor: diabetics and the elderly
     - reduced bone volume and mineralization may result from: excessive suppression of PTH production, chronic inflammation, or both.
     - Suppression of PTH: use of vitamin 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

- 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


MGP
Fetuin
Pyrophosphate
Inhibitors
Inducers
Calcium
Warfarin
Inflammation
Phosphate
Vitamin D
Uraemia
VSMC
Osteoblast-
like VSMC

- 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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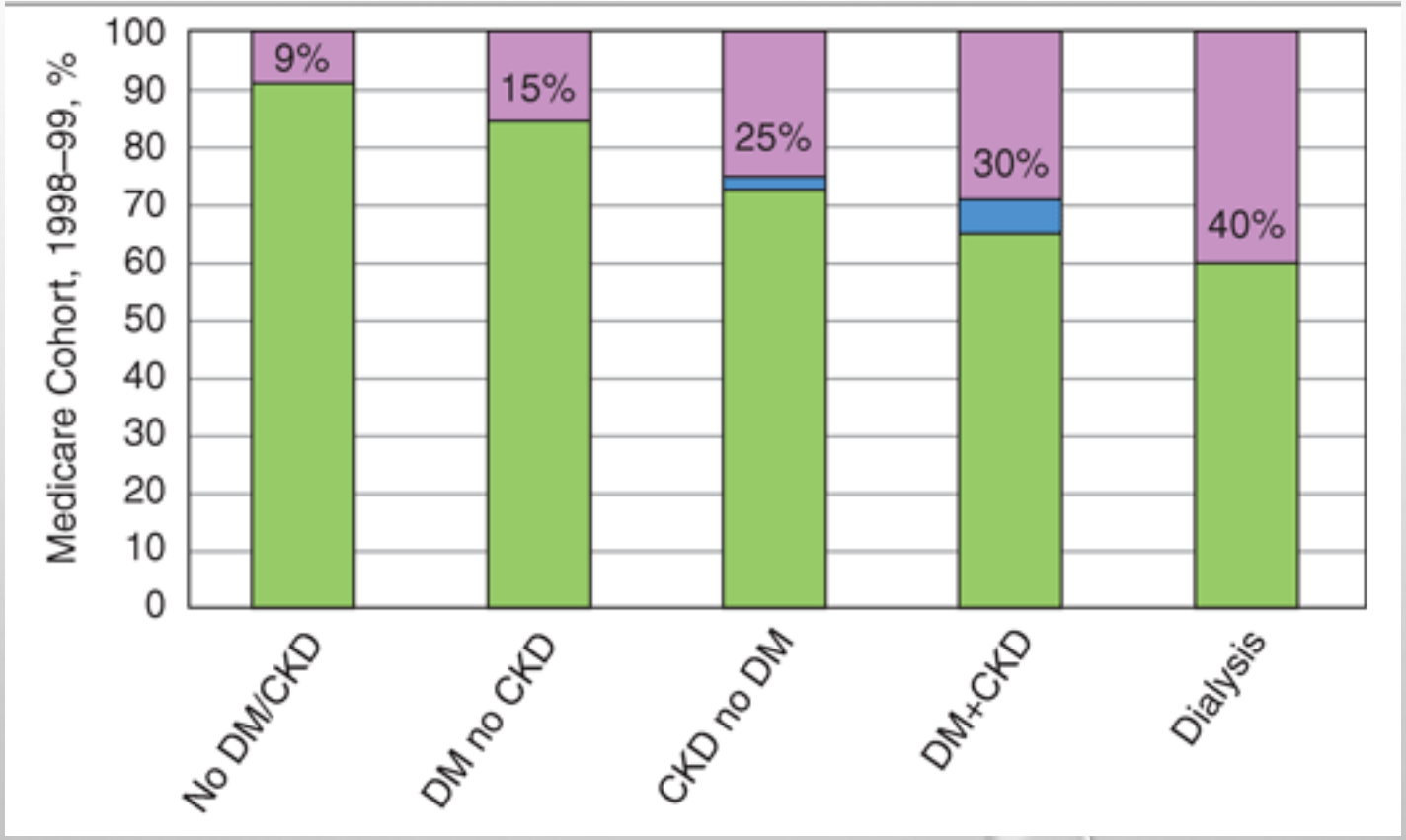
CKD MBD TREATMEN

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

- Hyperparathyroidism:calcitriol,cinacalcet

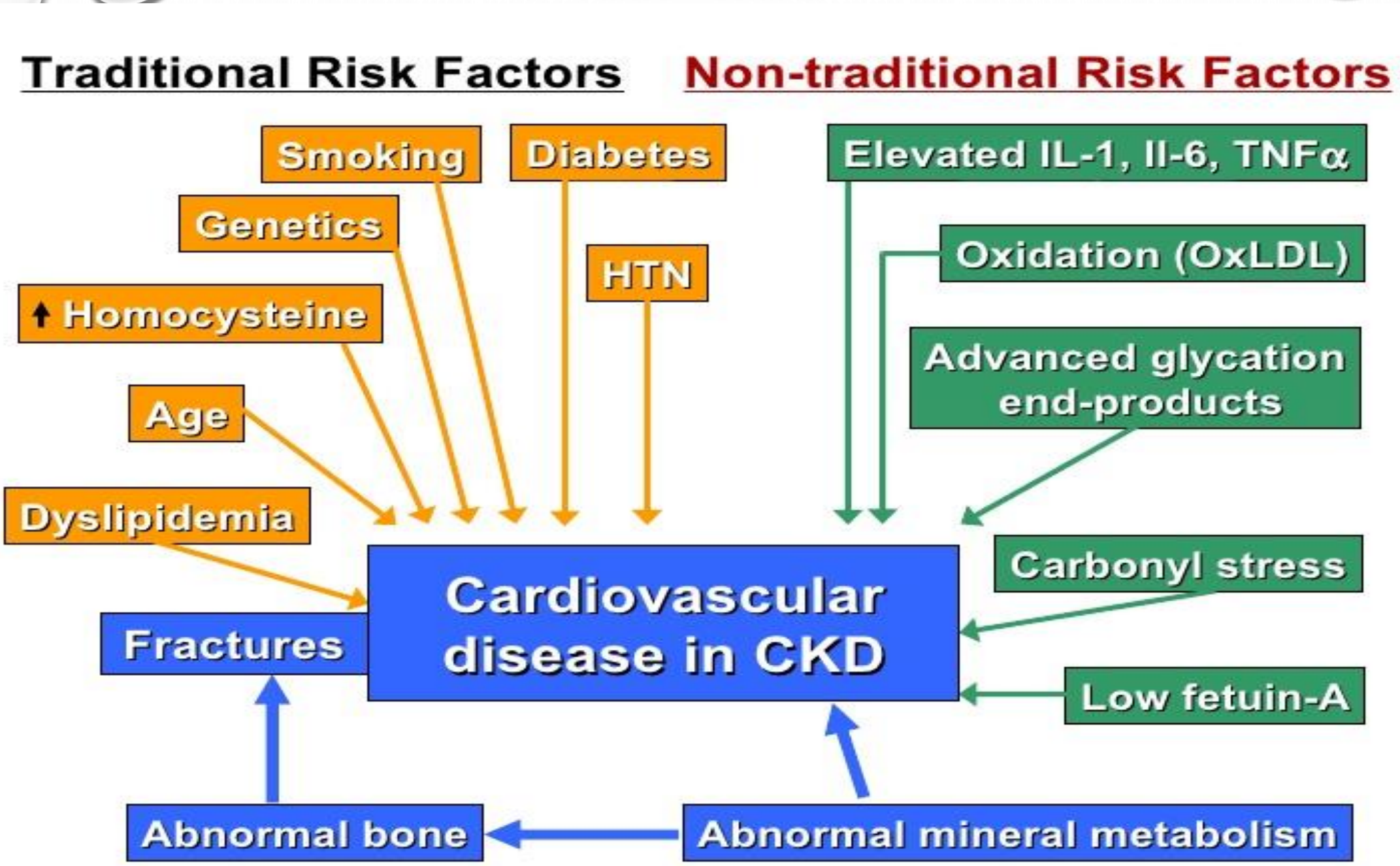
CARDIOVASCULAR ABNORMALITIES



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


Traditional Risk Factors
Non-traditional Risk Factors
Smoking
Diabetes
Genetics
HTN
Homocysteine
Age
Dyslipidemia
Fractures
Cardiovascular disease in CKD
Abnormal bone
Abnormal mineral metabolism
Elevated IL-1, Il-6, TNFα
Oxidation (OxLDL)
Advanced glycation end-products
Carbonyl stress
Low fetuin-A

- 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

CVD 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

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

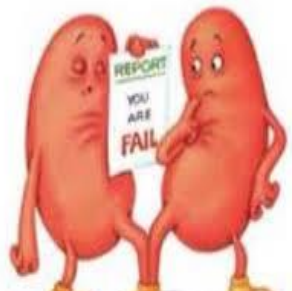
Hyperparathyroidism/bone marrow fibrosis

Chronic inflammation

Folate or vitamin B_{12} deficiency

Hemoglobinopathy

Comorbid conditions: hypo-/hyperthyroidism, pregnancy, HIV-associated disease, autoimmune disease, immunosuppressive drugs



ANEMIA 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

Neurological disorder	Prevalence	Clinical features	Management
Cognitive dysfunction	30–40% of patients on dialysis	Impairments in memory and executive function	Most effective: renal transplantation Other option: erythropoietin
Restless legs syndrome	15–20% of patients with CKD	Subjective urge to move the legs, worse nocturnally; symptoms exacerbated by inactivity and relieved by movement	Most effective: dopaminergic agonists; levodopa Other option: advice regarding sleep hygiene
Length-dependent uremic neuropathy	90% of patients with CKD	Sensory loss, weakness and wasting, maximal distally; absence of ankle jerks; lower limbs more severely affected than upper limbs	Most effective: transplantation, adequate dialysis (increase frequency or use high-flux dialysis); neuropathic pain therapy Other options: vitamin supplementation; strict potassium restriction; erythropoietin; exercise program
Autonomic neuropathy	~60% of patients with CKD	Impotence; postural hypotension; cardiac arrhythmia; symptomatic intradialytic hypotension	Most effective: transplantation; adequate dialysis; sildenafil to treat impotence Other option: midodrine to treat intradialytic hypotension
Carpal tunnel syndrome	5–30% of patients with CKD	Hand paresthesia and numbness; weak thumb abduction	Most effective: splinting; local steroid injection; surgical decompression
Ischemic monomelic neuropathy	Rare in CKD	Diffuse weakness and sensory loss distal to an arteriovenous fistula	Immediate fistula banding or ligation
Uremic myopathy	50% of patients with CKD	Proximal weakness of the lower limbs	Most effective: adequate dialysis; exercise program; adequate nutrition Other options: erythropoietin; L-carnitine

Abbreviation: CKD, chronic kidney disease.

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

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

Antihyperlipidemic therapy

- Statins slow the rate of decline in renal function
- Statins have antiproteinuric activity
- Improve cardiovascular outcomes in patients with CKD
- Antiinflammatory effect
- Target: LDL-C < 100 mg/dL

SLOWING THE PROGRESSION

- Control of Blood Glucose
- Control of intraglomerular hypertension
- Antihypertensive therapy
- Antihyperlipidemic therapy

CONTROL OF INTRAGLOMERULAR HYPERTENSION

- Use of ACEI or ARBs
  - In diabetic nephropathy and nondiabetic chronic kidney diseases
  - The greatest benefit in patients with higher degrees of proteinuria

Potential Reno protective Effects of Angiotensin-Converting Enzyme Inhibitors

- Inhibit tubule sodium resorption
- Decrease arterial pressure
- Decrease aldosterone production
- Decrease proteinuria
- Improve altered lipid profiles
- Decrease renal vascular resistance
- Reduce scarring and fibrosis
- Attenuate oxidative stress and free radicals

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) ،SGLT2 inh.Target BP:130/80
- Other targets for renal protection:Protein restriction Smoking cessation.Treatment of chronic metabolic acidosis with supplemental bicarbonate may slow the progression to end-stage kidney disease. Glycemic control
- Dose adjustment:may not be needed for agents >70% excretion nonrenal.some drugs should be avoided
- RRT:Dialysis,TX
- Patient education,social support