Chronic Kidney disease (CKD)

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Take Home Messages

- CKD is classified based on
  - the cause of kidney disease
  - Assessment of glomerular filtration rate (GFR)
  - Extent of albuminuria over at least a 3-month period
- The most common causes of CKD 5D (end-stage renal disease, ESRD) are DM and HTN
- ACEIs and ARBs are primary pharmacologic treatments to delay progression of CKD because of their effects on renal hemodynamics to reduce intraglomerular pressure and proteinuria

Take Home Messages

- Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are emerging as potential agents to prevent progression to later stages of CKD and ESRD
- CKD-mineral and bone disorder (CKD-MBD) includes abnormalities in
  - Parathyroid hormone (PTH)
  - Fibroblast growth factor-23 (FGF-23)
  - Phosphorus, calcium, vitamin D
  - Bone turnover and contributes to soft-tissue and extravascular calcifications

Take Home Messages

- Management of CKD-MBD includes:
  - Dietary phosphorous restriction
  - Phosphate-binding agents
  - Activated vitamin D supplementation
  - Calcimimetic therapy
- Management of anemia:
  - Administration of erythropoiesis-stimulating agents (ESAs): epoetin alfa, epoetin alfa-epbx, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta)
  - Administration of regular iron supplementation to maintain hemoglobin (> 11 g/dL) and prevent the need for blood transfusions

Definition

- CKD is abnormalities in kidney structure or function, present for 3 months or longer
- Lower glomerular filtration rate (GFR) and a higher urinary albumin-to creatinine ratio (uACR) are both independently associated with adverse events
- For decades, kidney disease was primarily considered only when patient's estimated or measured CrCL was reduced to < 50 mL/min
- In 2012, new classification system was incorporated GFR an uACR

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				

CKD

- The prognosis of CKD is dependent on:
  - Cause of kidney disease
  - GFR at time of diagnosis
  - Degree of albuminuria measured by uACR
  - Presence of other comorbid conditions
- Signs
  - Persistent and significant albuminuria (uACR > 1000 mg/g)
  - A marked but nonacute decline in GFR
  - Presence of a nonsurgical cause of hematuria
  - Hypertension refractory to treatment (e.g. ≥ 4 antihypertensive agents)
  - Persistent abnormalities of serum potassium
  - Recurrent or extensive nephrolithiasis
  - GFR < 30 mL/min/1.73 m^2
  - Hereditary kidney disease such as polycystic kidney disease

CKD

- Common Complications of advanced CKD:
  - Hypervolemia
  - Hypertension
  - Hyperkalemia
  - Metabolic acidosis
  - Anemia
  - CKD-related mineral and bone disorder (CKD-MBD)
  - Risk of cardiovascular disease (CVD)
- Other Complications of CKD
  - Hypoglycemic result of decreased degradation of insulin by the kidney
  - GI: nausea, vomiting, anorexia (from uremia), delayed gastric emptying, GERD, GI bleeding
  - Uremic pruritus: may be more severe during or immediately after HD
  - Malnutrition

Etiology of CKD

- **Risk Factors:**
- **Clinical factors:** DM, HTN, OBESITY, Autoimmune diseases, systemic infections, UTI, urinary stones, LUT obstruction, family history, recovery from AKI, reduction in kidney mass, exposure to certain drugs, low birth weight
- **Sociodemographic factors:** older age, Ethnic (African American, American Indian, Hispanic, Asian or Pacific Islander), exposure to certain chemical and environmental conditions

Risk Factors

- DM
  - HbA1c target o approximately 7% has been shown to prevent the surrogate endpoints of microalbuminuria and macroalbuminuria associated with diabetic CKD
- HTN
  - KDIGO guidelines for the management of BP in CKD recommend the goal is to control BP at all categories of CKD regardless of the underlying cause since early treatment of HTN
  - Achievement of target BP have been demonstrated to slow the rate of progression of CKD
- Proteinuria
  - It is a strong independent predictor of accelerated progression of CKD and also a risk factor for CV mortality and mobidity

Risk Factors

- Smoking
  - This is associated with kidney damage in general population and in patients with DM and HTN
  - Secondary to nicotine exposure: acute reduction in GFR, increase in urinary albumin excretion, HR, and BP
  - It is also associated with an increase in CV events
- Obesity
  - The risk of CKD 5 was directly related to the magnitude o obesity and remained even after adjustment for DM and HTN
  - Data suggest that weight reduction be included as part of treatment of CKD

Pathophysiology of CKD

- Diabetic CKD is characterized by glomerular mesangial expansion
- Diabetic CKD with Hypertensive nephrosclerosis, the kidneys arterioles have arteriolar hyalinosis (thickening of the arterial walls)
- Polycystic kidney disease is characterized by the development and expansion of renal cysts
- Pathway to ESRD:
  - Loss of nephron mass
  - Glomerular capillary hypertension
  - Proteinuria (direct cellular damage) e.g. albumin, transferrin, immunoglobulins, cytokines, ATII

Anemia of CKD

- The primary cause is a decrease in production of erythropoietin (glycoprotein hormone necessary for erythropoiesis) by interstitial fibroblasts in the renal cortex of the kidney
- This response is lost as kidney disease progresses to CKD 3 and higher
- Iron deficiency anemia is common in individuals with advanced kidney disease (e.g. CKD 4 and 5) due to decreased GI absorption of iron, inflammation, frequent blood testing, blood loss from HD and increased iron demands from erythropoiesis stimulating agent (ESA) therapy
- Additional factors are the decreased red cell life span (120 days → 60 days in CKD 5), the effects of uremic toxins and inflammatory cytokines and B12 & folate deficiencies

CKD-related Mineral and Bone Disorder

- Include abnormalities in PTH, calcium, phosphorus, vitamin D, fibroblast growth factor-23 (FGF-23), bone turnover and soft-tissue calcifications
- Calcium and phosphorus homeostasis is mediated through the effects of PTH, 1.25-dihydroxyvitamin D3, and FGF-23 on bone, GI tract, kidney and parathyroid gland
- As kidney function declines, there is a decrease in serum calcium concentration
- Hypocalcemia is the primary stimulus for secretion of PTH by the parathyroid glands

CKD-related Mineral and Bone Disorder

- Hyperphosphatemia also increases PTH synthesis and release through its direct effects on the parathyroid gland and production of prepro-PTH messenger RNA
- To normalize ionized calcium, PTH increases calcium reabsorption by the distal tubules and decrease phosphate reabsorption in the proximal tubules of the kidney and also increases calcium mobilization from bone
- 1,25-dihydroxyvitamin D3 (calcitriol) promotes increased intestinal absorption of calcium and phosphorus (helps normalize ionized calcium)

CKD-related Mineral and Bone Disorder

- FGF-23 production in bone increases in response to high phosphate levels and increased PTH and promotes phosphate excretion by the kidney
- Calcitriol also works directly on the parathyroid gland to suppress PTH production
- As kidney disease progresses, the concentrations of calcitriol decline due to loss of 1-α hydroxylase activity (enzyme that converses vitamin D precursor to calcitriol in the kidney)
- The vitamin D deficiency leads to reduced intestinal calcium and phosphorus absorption and worsening hyperparathyroidism

CKD-related Mineral and Bone Disorder

- Bone abnormalities are almost universal in dialysis patient and include
  - High bone turnover disease (osteitis fibrosa cystica)
  - Low bone turnover disease (osteomalacia)
  - Adynamic bone disease
- The morbidity and mortality of CKD patients is increased in individuals with both sever hypo-and hyperparathyroidism
- Elevations of serum phosphorus have been associated with increased risk of CV events and/or mortality in patients with CKD 3-5

Diagnostic Considerations for Anemia of CKD

- Signs and symptoms
  - Fatigue, shortness of breath, cold intolerance, chest pain, tingling in the extremities, tachycardia, headaches and general malaise
- Laboratories
  - Hb, TSat (serum iron/total iron-binding capacity [TIBC]) x 100), Transferrin, serum ferritin, RBC indices, WBC, differential and platelet count, absolute reticulocyte count
- Other causes evaluations
  - Blood loss, deficiencies in vitamin B12 or folate or other disease states that contribute to anemia including HIV infection and malignancies

Diagnostic Considerations for CKD-MBD

- Signs and symptoms
  - Are often not evident until significant skeletal damage has developed e.g. bone pain and skeletal fractures
- Laboratories
  - Serum phosphorus, calcium, PTH, 25(OH)D, 1,25$(OH)_2D_3$ or calcitriol and FGF-23
- Others
  - Bone architecture (gold standard test is a bone biopsy for histologic analysis)

Treatment of CKD

- **Desired Outcome**
  - To delay or prevent progression of the disease while minimizing the development or severity of associated complications
  - Planning for RRT (transplantation, HD or PD) should begin for patients deemed high risk for progression to ESRD (CKD 4)
  - With CKD 5D, the primary goal is to sustain and improve the patient's quality of life and prevent adverse outcomes by aggressively managing complications
- **General Approach**
  - Evaluated frequently to assess the risk of progression of CKD, identify the presence and causes of 2nd complications and comorbid conditions
  - To receive treatment for complications prior to development of CKD 5D

Recommendations

- **Nonpharmacologic**
  - Exercise 30 mins, five times per week
  - Weight loss if BMI > 25 kg/m²
  - Smoking cessation
  - Alcohol: 2 standard drinks per day for men, 1 for women
  - If hypertension: low-sodium diet (< 2 g/day)
- **Pharmacologic**
  - Adjust medication doses for kidney function
  - Seek pharmacist or medical advice fore using OTC medicine or nutritional protein supplements
  - Herbal medicines are not recommended
  - Temporarily discontinue potentially nephrotoxic/renally excreted drugs if eGFR < 60 mL/min/1.73m² in patients or hypovolemic

Recommendations

- **Vaccines**
  - Influenza yearly
  - Pneumococcal vaccine if eGFR < 30 mL/min/1.73m², nephrotic syndrome, DM or receiving immunosuppression. Single booster dose at year 5
  - Hepatitis B vaccine if eGFR < 30 mL/min/1.73m² and risk of progression of CKD
  - Aspirin suggested for patients who have had atherosclerotic events
  - Avoid oral phosphate-containing bowel preparation in people with a GFR < 60 mL/min/1.73m² or in those known to be at risk of phosphate nephropathy

Proteinuria: ACEIs and ARBs

- A meta-analysis has shown that the effects of ACEIs or ARBs such as doubling of serum creatinine and prevention of progression of albuminuria are equivalent and can be used interchangeably
- ACEI or ARB should be used as first-line therapy if urine albumin excretion in ≥ A2 (uACR > 30 mg/g)
- Specific dosing recommendations for ACEIs and ARBs for treatment of proteinuria should be initiated at the lowest recommended dose.
- The dose is usually increased until albuminuria is reduced by 30-50% or side effects occur (eGFR decreased > 30% or elevation in serum potassium

Proteinuria vs ACEIs and ARBs

- The lack of response to ACEI or ARB therapy may be due to aldosterone escape from RAAS blockade
- Combination therapy with an ACEI plus and ARB or direct renin inhibitor (aliskiren) results in a greater reduction in macroalbuminuria (but no longer recommended!!!)
- Combination therapy was also associated with increased risks of hyperkalemia and acute kidney injury

DCKD vs SGLT-2

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DCKD vs SGLT-2

- **SGLT-2** reduce glucose and sodium reabsorption in the proximal tubule of the kidney, these agents decrease glomerular hyperfiltration and reduce glomerular hypertension
  - The US FDA approved *canagliflozin* for treatment of DCKD to reduce the risk of renal events, cardiovascular mortality, and hospitalization for heart failure
- **Aldosterone antagonists (Spironolactone)** significantly reduced proteinuria and blood pressure, but doubled the risk of hyperkalemia and significantly increased the risk of gynecomastia
  - It is unknown whether adding spironolactone to ACEI or ARB (or both) will reduce the risk of major CV events or ESRD

DCKD vs SGLT-2

- **Dihydropyridine calcium channel blockers (CCBs)** do not appear to have any beneficial effects beyond those attributable to reducing blood pressure.
- **Non-dihydropyridine agents (*diltiazem and verapamil*)** have yielded beneficial effects on proteinuria.
  - The postulated mechanisms for this decrease in kidney injury include suppression of glomerular hypertrophy, inhibition of platelet aggregation and a decrease in salt accumulation.
  - These agents have been used to reduce proteinuria in combination with and ACEI or ARB.
  - In general, these agents should be considered second-or third-line antiproteinuric drugs when an ACEI or ARB is contraindicated or not treated.

Hypertension

Urine albumin excretion > 30 mg/24 hours

- Low dose ACEI or ARB
  - Use caution if eGFR < 30 mL/min/1.73m^2 or BP< 110/70 mmHg
  - Repeat eGFR in 2-4 weeks, repeat ACR & BP in 4-6 weeks
  - Alternatives to decrease proteinuria if ACEI or ARB contraindicated:
    - Non-dihydropyridine CCB (diltiazem, verapamil). Not recommended if patient on β-blocker
    - Aldosterone antagonists (spironolactone, eplerenone) but associated with increase risk of hyperkalemia
  - Hold if patient has severe vomiting, diarrhea, or intravascular volume depletion as increase risk of prerenal AKI

Hypertension

Urine albumin excretion > 30 mg/24 hours

- If BP > 130/80 mmHg:
  - increase dose of ACEI or ARB
  - Increase dose of ACEI or ARB and/or add thiazide diuretic or dihydropyridine CCB
    - Use loop diuretic if edema present
  - if required, add other antihypertensives such as aldosterone antagonists (especially if hypokalemic), β-blocker or α-blocker to achieve BP target)
  - If BP still not ≤ 130/80 mmHg, then add clonidine, hydralazine or minoxidil

Urine albumin excretion < 30 mg/24 hours

- If BP ≤ 130/80 mmHg: check BP every 3 months

Diabetes

- Should be screened annually for CKD starting at the time of diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes (serum creatinine, eGFR, a uACR)
- The management of diabetes in patients with CKD includes reduction of proteinuria and achievement of desired blood pressure and HbA1c (should be 7%)
- Patients with CKD 3 and 4 are at higher risk of developing hypoglycemia because of the reduction in metabolism of insulin by the kidney as GFR declines
- These patients may require reduced doses of oral or injectable hypoglycemic agents

Diabetes

- ***Metformin*** is considered a first-line agent in individuals with type 2 diabetes and CKD.
  - Can be initiated and/or continued in patients with an eGFR ≥ 45 mL/min/1.73m^2
  - Contraindicated in patients with an eGFR < 30 mL/min/1.73m^2
  - Should be temporarily discontinued before administering iodinated contrast agents for imaging studies.
- SGLT-2 inhibitors may be used in patients with an eGFR > 25 to 30 mL/min/1.73m^2

Anemia

- The desired outcomes of anemia management are to increase oxygen-carrying capacity, decrease signs and symptoms of anemia, and decrease the need for blood transfusions.
- Hb is preferred monitoring parameter for RBC production.
- FDA and KDIGO recommended ESAs and Iron to initiate therapy in anemia of CKD.
- The risk of mortality and CV events is higher in CKD patients treated to higher Hb target values with an ESA.
- Start an ESA when Hb is 9-10 g/dL in CKD 5
- Do not use ESAs to intentionally increase Hb> 13 g/Dl
- Iron initiation when Tsat is ≤ 30% and ferritin is ≤ 500 ng/mL