HHP Care Model and Disease Management Webinar Series

Secondary Complications of Chronic Kidney Disease

Thursday, July 8, 2021
5:30pm – 6:30pm

HAWAIʻI PACIFIC HEALTH | HAWAIʻI HEALTH PARTNERS

Moderator – 07/08/21

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  - Due to time constraints, any unanswered questions will be addressed this week and posted on the HHP website
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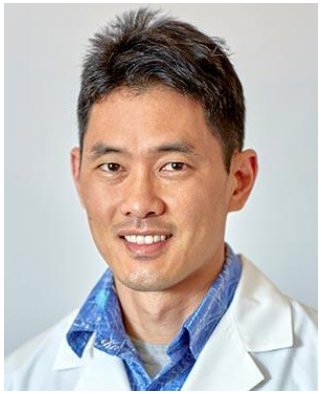
Secondary Complications of Chronic Kidney Disease



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Introduction to Chronic Kidney Disease (CKD)

- Epidemiology of CKD
- Identifying CKD
- Accurately assess kidney function and estimate risk for progression
- Determine cause of CKD
- Take measures to slow down progression of CKD
- **Identify and treat secondary complications of CKD**
- Renal replacement therapy

Summary of Last Presentation

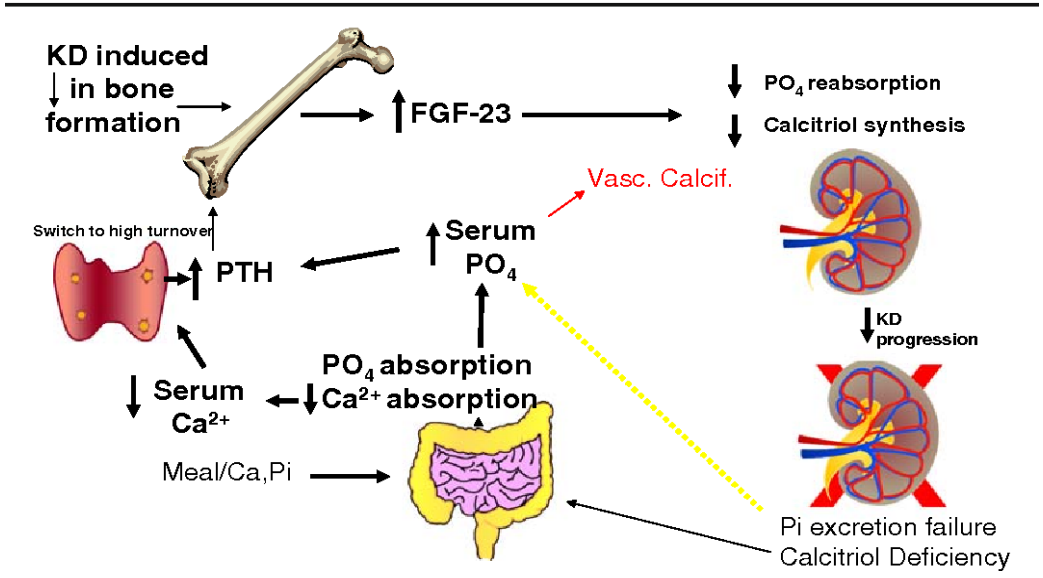
- Target BP and hgba1c values should be individualized but generally <130/80 and <7% to reduce risk of CKD progression
- Use SGLT2 inhibitors in patients with (and without?) diabetes mellitus to prevent CKD progression
- Identify and treat metabolic acidosis with sodium bicarbonate targeting serum bicarbonate >22
- Advise moderate dietary animal protein restriction, increase intake of fruits and vegetables
- Advise weight loss and smoking cessation
- Early nephrology referral for patient's with ADPKD for consideration of Tolvaptan
- Treatment of asymptomatic hyperuricemia for CKD prevention is controversial, but consider if serum uric acid levels are markedly elevated

Secondary Complications of CKD

- Renal bone mineral metabolic disorder
- Anemia and iron management
- Cardiovascular disease in CKD
- Volume overload
- Electrolyte abnormalties
- Uremia

CKD-Bone Mineral Disorder

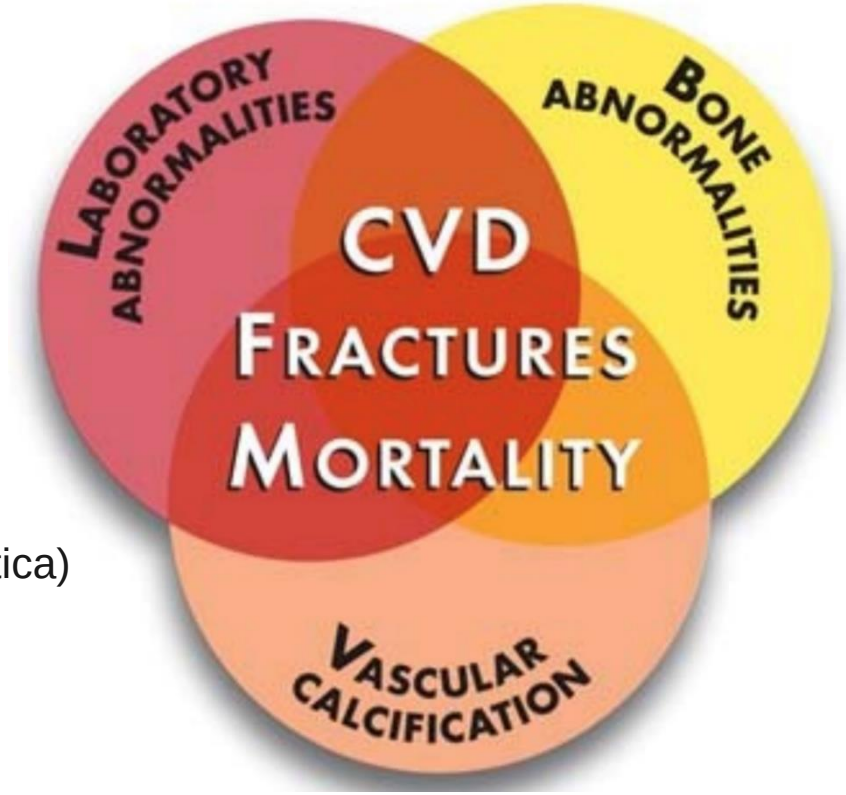
- **Physiology of CKD BMD**
  - **Phosphorus retention leads to hypocalcemia**
  - **25-OH Vitamin D**: Inactive, pre-vitamin D
  - **Calcitriol (active vitamin D)**: Activated by renal 1-a hydroxylase, mineralizes bone
  - **iPTH**: Maintains serum iCa
  - **Uremia**: Causes PTH resistence at level of the bone



AJKD: March 24, 2021 https://doi.org/10.1053/j.ajkd.2020.12.024

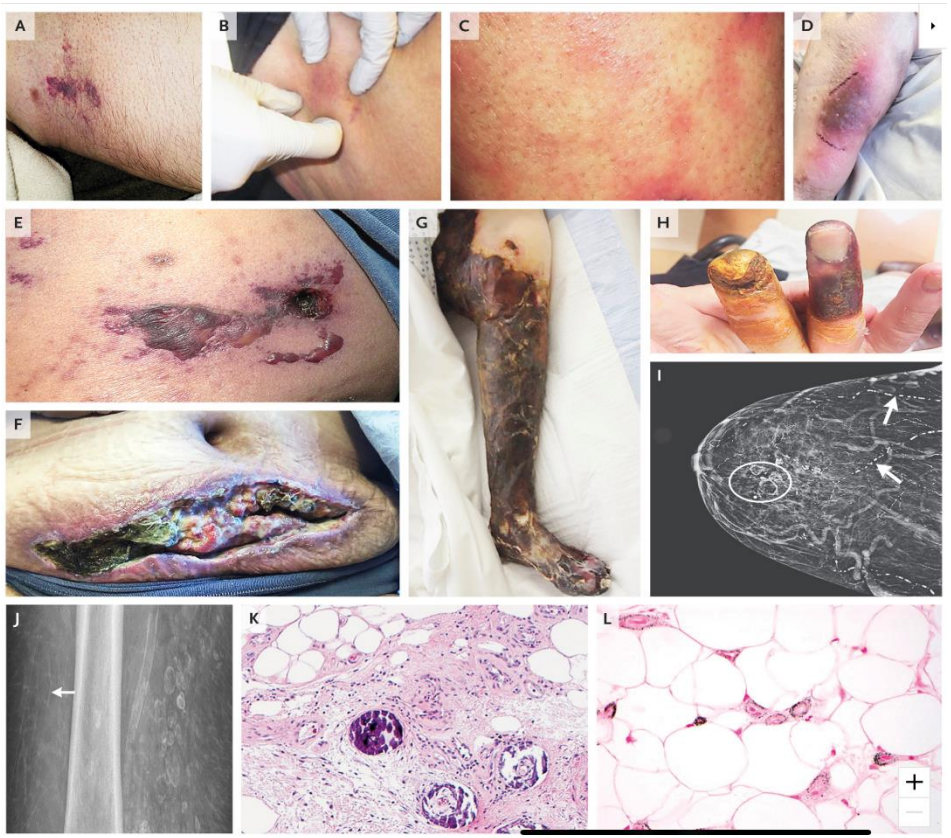
CKD-Bone Mineral Disorder

- A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:
  - Laboratory abnormalities
  - Abnormalities of bone turnover
    - High bone turnover (osteitis fibrosa cystica)
    - Low bone turnover (adynamic bone)
    - Mixed
  - Vascular or soft tissue calcification



CKD-BMD Complications

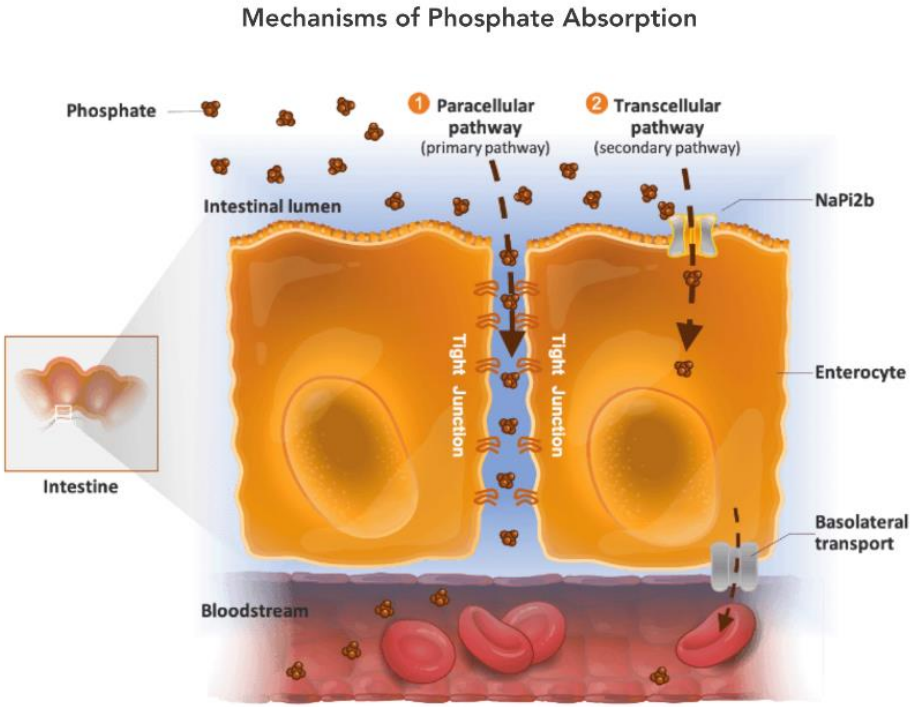
- Fracture
- Worsened anemia
- Calciphylaxes
- Arterial calcification



AJKD: March 24, 2021 https://doi.org/10.1053/j.ajkd.2020.12.024
NEJM: Caliphylaxes. May 2018

Phosphorus Control

- Dietary phosphorus restriction
- Phos binders:
  - Calcium based binders (Phoslo)
  - Sevelamer (Renvela)
  - Iron based binders (Velphoro, Auryxia)
- Paracellular pathway inhibition
  - Tenapanor
- Paracellular pathway inhibitor therapy



Www.ardelyx.com

Oral Phosphate Binders in Kindey Failure. NEJM April 2010

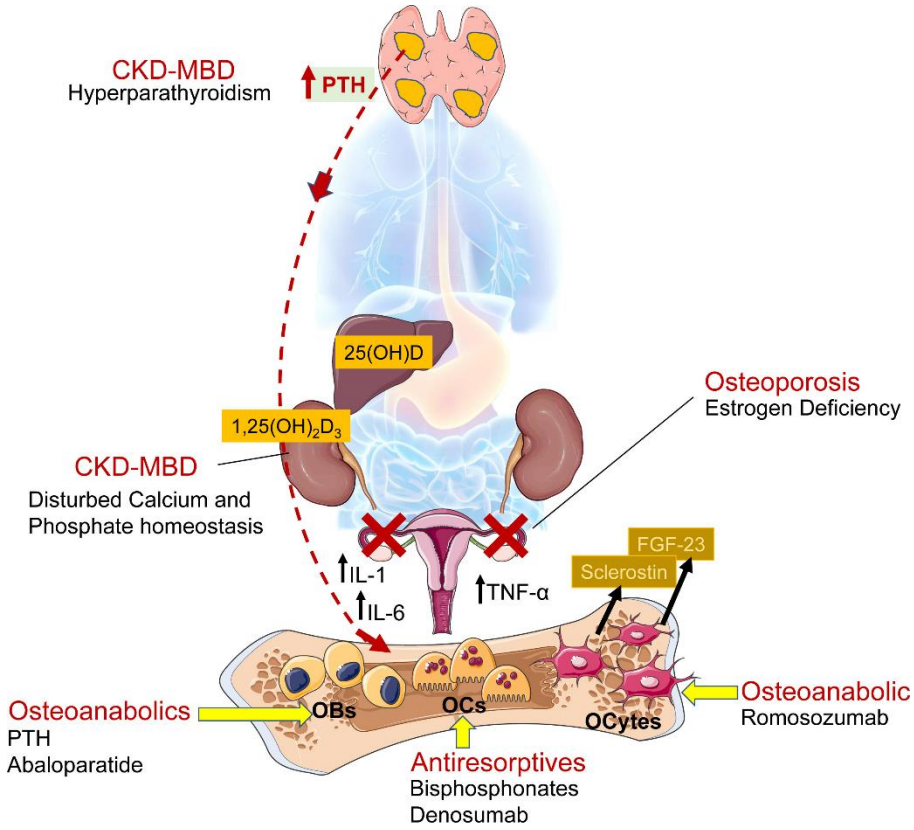
PTH Control

- Vitamin D2 or D3 (both equally efficacious)
  - D2 (ergocalciferol): Plant source
  - D3 (cholecalciferol): Animal source
  - Target vitamin D level >30
- Calctriol
  - Active vitamin D
  - Can cause hypercalcemia
  - Use in CKD patients with secondary hyperparthyroidism(iPTH >150) and replete vitamin D stores
- Calcimemetics (Cinacalcet)
  - Use in hyperparathyroidism with hypercalcemia (off label), need to watch for hypocalcemia

KDIGO 2017 CKD-MBD Guidelines

Osteoporosis in CKD

- **GFR >30mL/min**
  - Treat CKD BMD
  - Calcium/vit D supplementation
  - Use anti-resorbtive therapy if low BMD or fragility fracture
- **GFR 15-30mL/min**
  - Treat CKD BMD
  - Lower dose Ca/vit D supplementation (Ca 1200mg/d, vit D 800u/day)
  - Can consider anti-resrobtive therapy if no CKD MBD and if there is fragility fracure
- **GFR <15mL/min**
  - Treat CKD MBD
  - Can consider denosumab if fracture and no adynaic bone or BMD
- Do not use osteoporosis drugs in patients with adynamic bone disease!
- Bisphosphonates contraindicated with eGFR <35mL/min
- **Denosumab** (monoclonal ab, prevents osteoclast formation-> decreased bone resorption and increased bone mass)
  - Not cleared by kidneys, okay to use with eGFR <30mL/min. Hypocalcemia.



Management of Osteoporosis in CJKD. CJASN June 2018

Anemia and Iron Management

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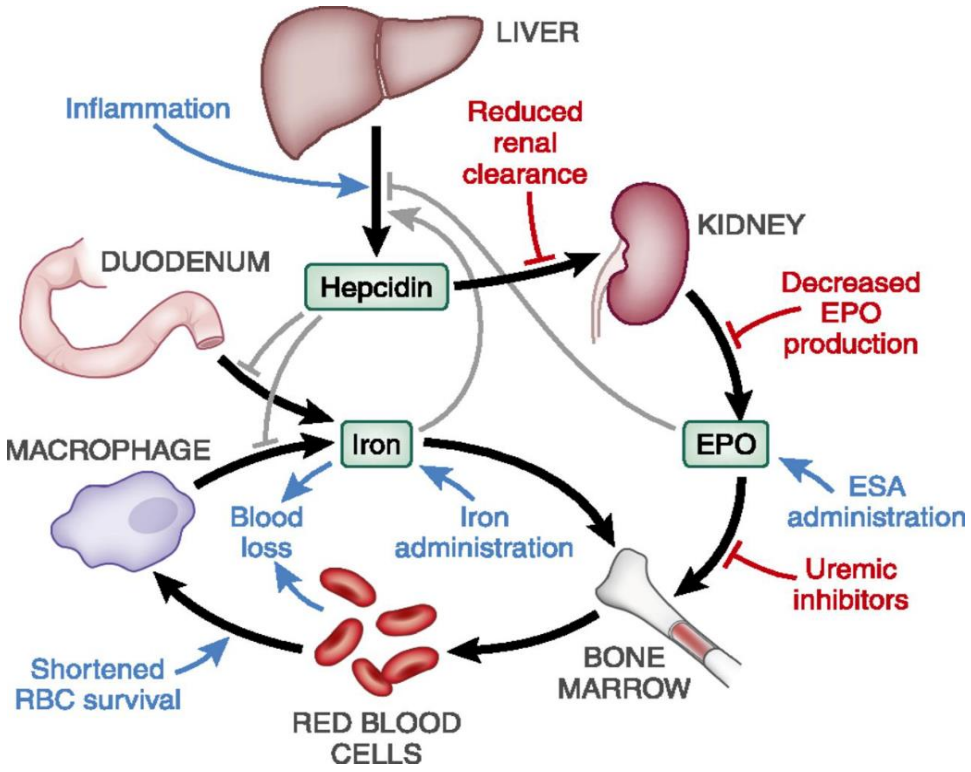
Physiology: Anemia of CKD

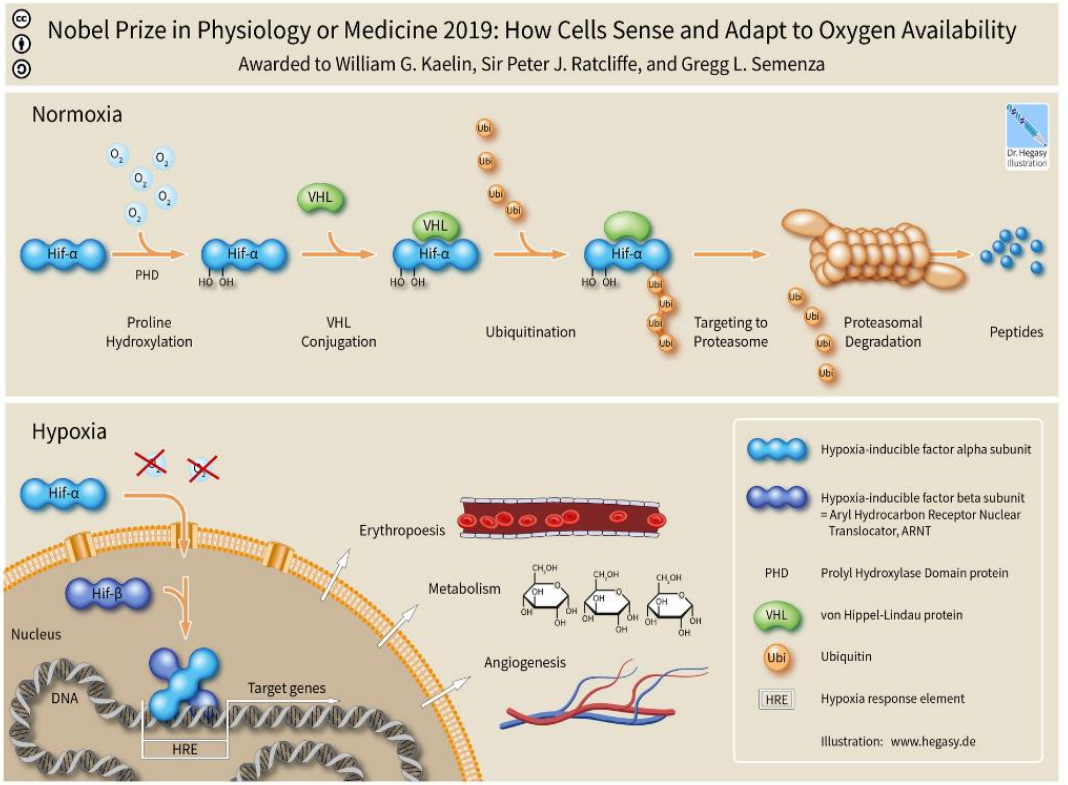
- Erythropoetin is produced by renal tubular cells and stimulates bone marrow production of RBCs
- EPO decreases as GFR declines, due to reduce renal mass
- Hypoxia inducible factor-2 (HIF2)



JASN October 2012. https://doi.org/10.1681/ASN.2011111078

Hypoxia Inducible Factor

- HIF promotes erythropoesis
- HIF is degraded by **HIF-Propyl-hydroxylaseb** (HIF-PHI)
- HIF-PHI is stimulated in normoxia
- HIF-PHI is degraded in hypoxia stabilizing HIF activity and erythropoiesis



The role of hypoxia inducible factors in metabolic disease. Nature Reviews. October 2018

Erythropoesis Stimulating Agents (ESAs)

- Erythropoetin
  - **Epoetin** (Procrit, Epogen)
  - **Darbepoetin alpha** (Aranesp)
  - **Methoxy polyethylene glycol-epoetin beta** (Mircera)

- Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs)
  - New class of once daily oral ESA

HIF-PHI Inhibitors

- Vadadustat (NEJM April 2021)
  - Vadadustat vs darbepoetin
  - Target hgb 10-11
  - Vadadustat non-inferior to darbepoetin
  - Higher rate of major adverse cardiovascular events in Vadadustat group (HR 1.17, 95%CI 1.01-1.36)
- Roxadustat (JASN Feb 2021)
  - Roxadustat vs placebo
  - Higher all-cause mortality (21 vs 18%), CV events (23 vs 21%) and serious adverse events (57 vs 54%) in Roxadustat treated patients

Erythropoesis Stimulating Agents (ESAs)-**Safety**

- **CHOIR Trial**(NEJM 11/2006): High (hgb 13.5) versus low (11.3) hgb target. No benefit in QOL but increased adverse events (stroke, HF, MI, death) in high group

- **CREATE Trial** (NEJM 11/2006): High (13-15) versus sub-normal (10.5 to 11.5). Dialysis start, HA and HTN increased in high hgb group, no difference in CV outcomes. Improved QOL in high hgb group

- **TREAT Trial** (NEJM 11/2009): Darbipoetin vs pacebo, reduced transfusion but increased stroke risk (HR 1.92), HTN and malignancy associated mortality

Iron

- Target ferritin >200, TSAT >20%
- Oral Iron
  - Goal elemental iron intake of 200mg/day in up to 3 divided doses
  - I use ferrous sulfate 325mg (65mg of elemental iron)
  - Use ferric citrate (Auryxia) if there is elevated phos and low iron stores
- IV iron
  - **FIND-CKD trial** (Neph Dial Trans. Sept 2017): Ferric carboxymaltose infusion vs. Oral iron did not increase risk of infections or CV related side effects vs. eGFRs stable
  - I use Ferumoxytol 510mg x 2 doses at least 1 week apart

Erythropoesis Stimulating Agents (ESAs)

- Principles of ESA prescribing
  - Minimize use of ESAs due to increased HTN, CVA risk
  - Treat iron deficiency first (ferritin >200, TSAT >20%)
  - Ensure B12 and folate stores are replete
  - Don‘t normalize the hgb, reasonable target is 10-11
  - There is increased risk of stroke, vascular access thrombosis, hypertension and cancer associated mortality/progression in CKD patients treated with ESA

CKD and Cardiovascular Disease

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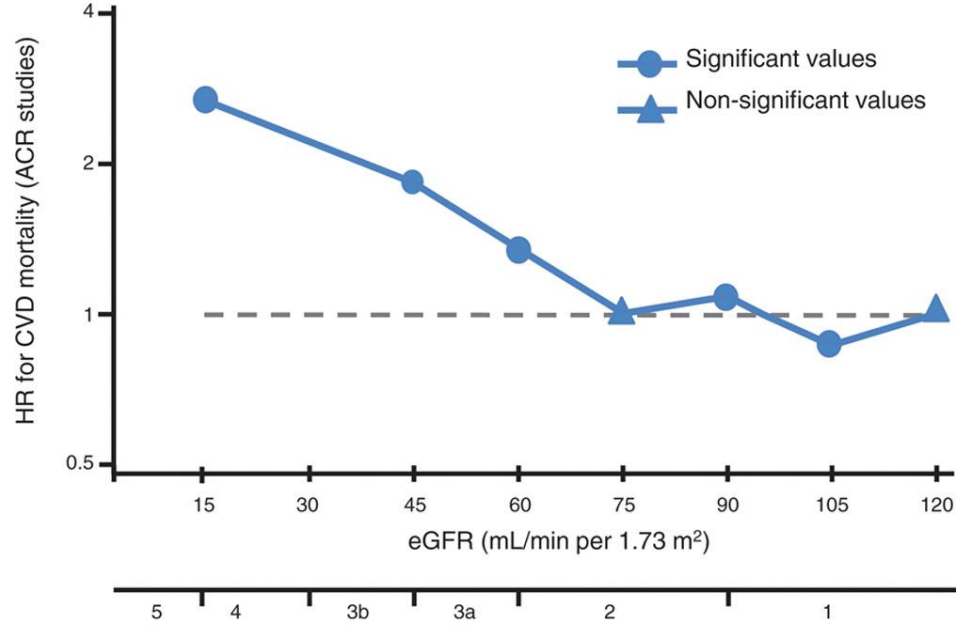
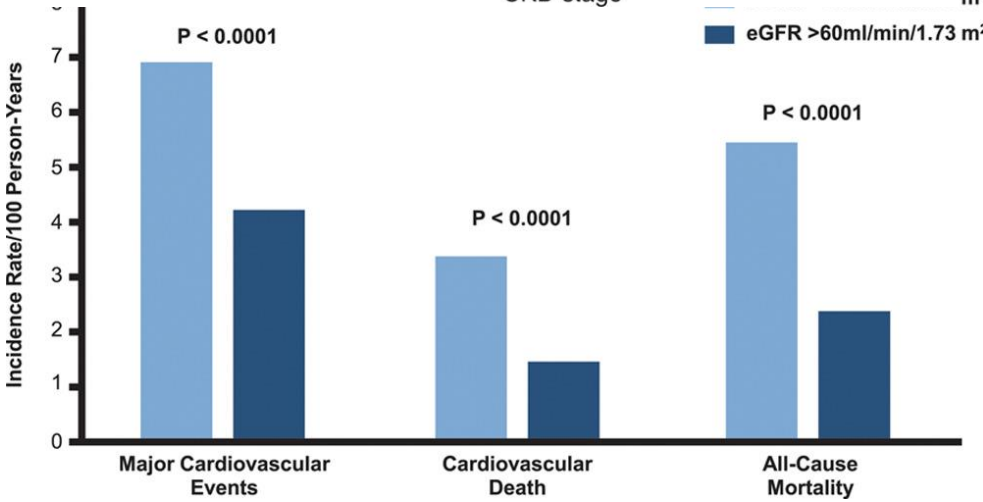
CV Disease in CKD

- Patients with CKD have substantially increased CV risk
- CKD is a coronary risk equivalent
- Uremic toxins increase vascular stiffness, endothelial function, pro-inflammatory and promote vascular calcifications





Circulation: March 2021

CV Risk Factors in CKD

Traditional risk factors (more prominent in earlier stage CKD)	Non-traditional risk factors (more prominent in later stage CKD)
Hypertension	Uremic toxins
Diabetes mellitus	Increased calcium load → arterial (medial) calcification
Dyslipidemia	Abnormalites in bone mineral metabolism
Older age	Increased systemic inflammatory/poor nutritional catabolic state
Smoking	Albuminuria

IV Iron and Heat Failure

- Iron deficiency common in heart failure and CKD
- Low iron stores strongly associated with risk for heart failure hospitalization in patients with CKD (CJASN April 2021)

- Evidence:
  - **FAIR-HF Trial** (NEJM 12/2009): 459 patients with class 2-3 HF randomized to IV iron vs placebo. Significant improvement in symptoms, functional capacity and QOL
  - **CONFIRM-HF** (Eur Heart Jr. 03/2015): 61% reduction in HF associated hospitalization

CKD and volume overload

- Subtle volume over load, salt sensitive hypertension and impaired response to large sodium load can occur at higher levels of GFR.
- Gross volume overload more common once eGFR <10 to 15mL/min

- Diuretics
  - Comparative strength of loop diuretics Lasix 40mg = Bumetanide 1mg = Torsemide 20mg
  - Thiazide diuretics more effective at higher levels of eGFR (>30mL/min) for BP lowering but can be added to loop diuretics in refractory volume overload

CKD and Volume Overload

- There is no benefit with mechaincal ultrafiltration in acute decompensated HF and cardio-renal syndrome
  - 188 patients with ADHF and worsened renal function, randomized to stepped pharmacoloic therapy versus mechanical ultrafiltration
  - Similiar weight loss between two groups but higher incidence of serious adverse events in UF group (72% vs. 57%). Better renal outcomes in diuretic group.
  - Reserve mechanical UF or dialysis for patients who fail diuretic therapy

CARRESS HF. NEJM Nov 2012

Electrolyte and Acid Base Disorders

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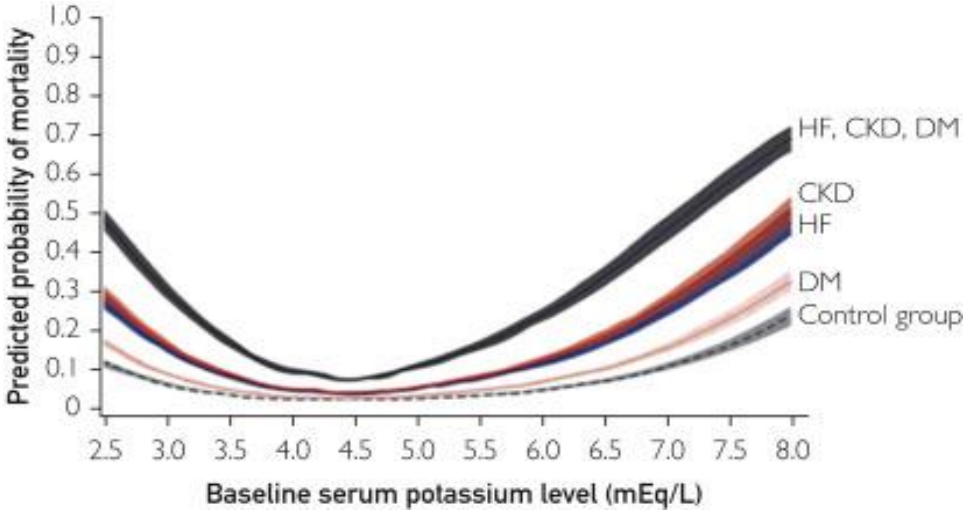
Electrolyte Abnormalities - **Hyperkalemia**

- Causes:
  - Deceased GFR
  - ACE/ARB therapy
  - Metabolic acidosis
  - Hypo-renin-hypoaldosteronism
- J-shaped mortality



Clinical Management of Hyperkalemia. Mayo Clinic Procedings. March 2021

- Chronic management:
  - Low K diet (<3 grams, <70mEq/d)
  - Avoiding/adjusting hyperkalemic medication
  - Correct metabolic acidosis
  - Diuretics
  - Potassium binders:
    - Patiromer (Veltassa)
    - Zirconium cyclosilicate (Lokelma)
    - SPS (Kayexylate)

Potassium Binding Agents

TABLE 2. Selected Characteristics of K^+-Binding Agents for Hyperkalemia

Characteristic	SPS	Patiromer	SZC
Approval date	1958	US, 2015; EU, 2017	US, 2018; EU, 2018
Mechanism of action	K^+ binding in exchange for Na^+ in GI tract (↑ fecal excretion)	K^+ binding in exchange for Ca^{2+} in GI tract (↑ fecal excretion)	K^+ binding in exchange for H^+ and Na^+ in GI tract (↑ fecal excretion)
Site of action	Colon	Colon	Small and large intestines
Selectivity for K^+	Nonselective; also binds Ca^{2+} and Mg^{2+}	Nonselective; also binds Na^+ and Mg^{2+}	Highly selective; also binds $NH4^+$
Onset of action	Variable; several hours	7 h	1 h
Na^+ content	1500 mg per 15-mg dose	None	400 mg per 5-g dose
Ca^{2+} content	None	1.6 g per 8.4-g dose	None
Sorbitol content	20,000 mg per 15-g dose	4000 mg per 8.4-g dose	No sorbitol content
Dosing	15 g 1-4 times (oral); 30-50 g 1-2 times (rectal)	8.4 g QD (oral), titrate up to 16.8 g or 25.2 g QD	10 g TID (oral) for initial correction of hyperkalemia (for ≤48 h), then 5 g QOD to 15 g QD for maintenance
Serious AEs	Cases of fatal GI injury reported	None reported	None reported
Most common AEs	GI disorders (constipation, diarrhea, nausea, vomiting, gastric irritation), hypomagnesemia, hypokalemia, hypocalcemia, systemic alkalosis	GI disorders (abdominal discomfort, constipation, diarrhea, nausea, flatulence), hypomagnesemia	GI disorders (constipation, diarrhea, nausea, vomiting), mild to moderate edema

AE = adverse event; Ca^{2+} = calcium; EU = European Union; GI = gastrointestinal; H^+ = hydrogen ion; K^+ = potassium; Mg^{2+} = magnesium; Na^+ = sodium; $NH4^+$ = ammonium; QD = once daily; QOD = every other day; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate; TID = three times daily; US = United States; ↑ = increased.

Data from references 12, 59, 60, and 79 to 81.

Clinical Management of Hyperkalemia. Mayo Clinic Procedings. March 2021

Electrolyte Abnormalities - **Hyponatremia**

- Hyponatremia more common in CKD
  - Causes:
    - Decreased ability to clear free water (isosthenuria)
    - Diuretics
    - Dietary sodium restriction
    - Coexisting medical conditions (cirrhosis, CHF)

Electrolyte Abnormalites - **Metabolic Acidosis**

- Progressive CKD leads to impaired renal hydrogen ion excretion and worsening metabolic acidosis
- Initially non-gap metabolic acidosis develops then transition to anion gap metabolic acidosis as uremic toxins accumulate
- Metabolic acidosis accelerates CKD progression and can cause muscle wasting, malnutrition, bone mineral loss and impaired growth (in children)
- Treatment of metabolic acidosis with sodium bicarbonate can slow CKD progression (6.6 vs 17%), lower risk for RRT (6.9 vs 12.3%) and lower all cause mortality (3.1 vs. 6.8%), without increase in BP, body weight or hospitalizations

J. Nephrol. Oct 2019;32(6):989

Uremia

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Uremic Toxins

- Blood urea nitrogen (BUN) accumulates in renal failure but is not the main uremic toxin
  - Rapid reduction in urea during dialysis can cause dialysis dysequilibrium syndrome
- Uremic symptoms can develop once the eGFR is <15mL/min
- Uremic fetor (amines): Smell test
- Uremic toxins affect endothialial function, vascular stiffness and are pro-inflammatory

Uremia. NEJM Sept 2007

Table 1. Uremic Solutes.*

Solute Group	Example	Source	Characteristics
Peptides and small proteins	$Beta_2$-microglobulin	Shed from MHC	Poorly dialyzed because of large size
Guanidines	Guanidinosuccinic acid	Arginine	Increased production in uremia
Phenols	p-Cresol sulfate	Phenylalanine, tyrosine	Protein bound, produced by gut bacteria
Indoles	Indican	Tryptophan	Protein bound, produced by gut bacteria
Aliphatic amines	Dimethylamine	Choline	Large volume of distribution, produced by gut bacteria
Furans	CMPF	Unknown	Tightly protein bound
Polyols	Myoinositol	Dietary intake, cell synthesis from glucose	Normally degraded by the kidney rather than excreted
Nucleosides	Pseudouridine	tRNA	Most prominent of several altered RNA species
Dicarboxylic acids	Oxalate	Ascorbic acid	Formation of crystal deposits
Carbonyls	Glyoxal	Glycolytic intermediates	Reaction with proteins to form advanced glycation end products

* Uremic solutes may have multiple sources, although only one is listed. MHC denotes major histocompatibility complex, and CMPF 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid.

Symptoms/Consequences of Uremia

- **Malnutrition**: Causes- proteinuria, catabolism, uremic inflammation, low protein diet, uremic anorexia
- **Percarditis**: Suspect with pleuritic chest pain, fever and pericardial friction rub. There is no diffuse ST segment elevation. Absolute indication to start dialysis.
- **Uremic bleeding**: Due to platelet dysfunction. Treat with DDAVP or dialysis.
- **Uremic pruritis**: Difelikefalin (kappa opioid receptor angonist)
- **Uremic neuropathy**: Encephalopathy, seizures, coma, polyneuropathy, restless leg

Uremia. NEJM Sept 2007
Nutritonal Management of CKD. NEJM Nov 2017

Conclusions

- Bone disease in CKD is more then just about bone protection. Identify low versus high bone turnover state. Prevent metabolic complications from progressing early on, before they become severe.
- Treat anemia of CKD cautiously due to increased stroke and malignancy risk. Target hgb 10-11. HIF-PHI inhibitor are an oral ESA but are not better or safer then traditional EPO.
- CKD is a CV risk equivalent
- IV iron therapy with HF and CKD shows improved HF outcomes
- New K binders are safer then SPS and can allow continuation of evidence based medications like ACE-I/ARBS and spironolactone
- Symptoms of uremia can start to occur when the eGFR is <15mL/min

Q&A

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Next Webinar:

HHP Care Model and Disease Management Webinar Series

Heart Failure webinar #3 – Dr. Carol Lai

Thursday, July 29, 2021

5:30pm – 6:30 pm

Thank you!

- A recording of the meeting will be available afterwards.
- Unanswered question?
  - Contact us at info@hawaiihealthpartners.org

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