Kidney Disease: Risk Factors and Naturopathic Treatments

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September 12-13, 2026

Conflicts

President NPLEX, unpaid

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No Conflicts in this presentation

No artificial intelligence

Outline

Causes and Staging

Protein

Nutraceuticals

Botanicals

Microbiome

Minerals

Mineralocorticoids

Dialysis

Summary

Cause

Diabetes--- $26x10^6$ have diabetes, > 200,000 in stage 5; glycation damages renal vasculature and filtration system; John Hopkins.2026.

Hypertension--- complication of diabetes, uncontrolled reduces KI filtration mechanisms;

Other one-third--- IgA nephropathy; lupus nephritis; polycystic KI disease; Fabry disease; NatL KI Foundation.2026.

Signs and Sx--- changes in urination– foam, bubbles, nocturia; edema– face, eyes, hands, ankles, feet; fatigue– reduced RBC; GI– nausea-vomit; reduced appetite; metallic taste; skin– dry, itchy, uremic frost; CV– SOB; KI Dz.May Clinic.2026.

Stages

eGFR for staging--- normal 90 mL/min/1.73m^2

Stage 1--- damage with normal function, eGFR $\geq$ 90%

Stage 2--- damage with mild loss of function, eGFR 60-89%

Stage 3--- mild to severe loss of function, eGFR 30-59%

Stage 4--- severe loss of function, eGFR 15-29%

Stage 5--- end stage renal disease (ESRD), or kidney failure, eGFR < 15%

Incidence

CDC.2023.Kidney Disease. Kid Internat Supp.2013;3:368-371. doi.10.1038/kisupp.2013.79.

1 in 7 adults have C KI Dz; 9 in 10 do not know they have it; 1 in 3 have severe and do not know; 36 million USA, 4 million Canada; #8 cause of death;

Diabetes--- 45% of cases

Factors--- African-American; low birth weight; family history

Other Factors--- smoking; use of analgesic/NSAIDS; obesity; hypertension; heavy metals exposure; excessive EtOH; smoking; acute injury; CV Dz; hyperlipidemia; metabolic syndrome; Hep-C; HIV; cancer; lower socioeconomic status;

Cost--- > $120 billion; 25% of Medicare costs;

eGFR *vs* Cystatin C

JAMA.2025;334(21):1912-1926. doi.10.1001/jama.2025.17578.

eGFR and Creatinine---- used to monitor KI Dz patients;

N=821,327 from 23 cohorts; X=59 yo; 49% female; 13.5% diabetes; 40% hypertension

Outcomes---

Hospitalized--- 35% had eGFR 35% lower by at least 30%

Out-patient--- 11% had lower eGFR lower by at least 30%

Lower values of eGFR associated with Sig higher rates of all cause mortality, CV events, KI failure;

Cost--- Cystatin C more expensive lab test;

Cystatin C--- produce at a constant rate by nucleated cells; not resorbed or secreted by renal tubules; nearly complete resorption by proximal tubules; thus serum levels tied to GFR; Clevel Clin J Med.2025;92(9):546-549. doi.10.3949/ccjm.92a25036.

Creatinine--- use in prolonged hospitalized patients, cachexia, amputation, spinal cord injury will overestimate eGFR;

Creatinine--- falsely elevated creatinine in athletes, use of creatine supplements; not so cystatin C;

2021 Chronic KI Dz Epidemiology Collaborative--- use of cystatin C accurately estimated eGFR in diverse patient populations including cancer; it should be a routine test;

2024 KI Dz Global Outcomes--- start with eGFR based on serum creatinine, but if alterations in muscle mass, diet, or other conditions cystatin C equation should be used for greater accuracy and to reduce bias;

Use of cystatin C recommended--- increased or decreased muscle mass; eating disorders; cirrhosis; prolonged hospitalization; amputation; spinal cord injury; antibiotics that decrease extrarenal elimination; BMI > 49 $kg.m^2$; patients with cancer;

Limited value--- malnutrition; thyroid dz; diabetes; smoking, CV Dz; inflammation or increased CRP; solid organ transplant;

Vancomycin--- in a trial, dosing of this antibiotic in the Tx group only 50% received the correct dose *vs* 28% in the control group; Am J Kid Dis.2017;69(5):658-666.doi.10.1053/j.ajkd.2016.11.016.

Cancer--- patients with cancer and chronic KI Dz 3A, 3B, 17% of cancer cohort, at risk of wrong chemotherapy dose; EJIFCC.2021;32(1):41-51.

Lab cost--- creatinine $0.20 to $10.50; cystatin C $20.00 to $160.00 USA;

Cystatin C and KI Function Kidney360.2022;3(10):1807-1814. doi.10.34067/KID.0003202002.

Cystatin C--- produced by all nucleated cells, biomarker of KI function;

Accuracy--- not influenced by muscle mass, age, sex, diet, race;

Cystatin C + Creatinine--- highly precise calculation of GFR in chronic KI Dz;

Cystatin C--- N=0.1 – 0.4 mg/L; elevated = poor KI function; elevated in other conditions– severe obesity, thyroid disorders, glucocorticoid/corticosteroid use, inflammation;

Protein

Protein and Kidney Health J Am Sioc Nephrol.2020;31(8):1667-1679. doi.10.1681/ASN.2020010028.

>60 adults obese or overweight (USA); >12% on GLP-1;

Ideal--- 0.6g/kg ideal wt; recommended is 0.83 g/kg/d; > 1.5 g/kg/d considered high protein diet;

Humans---- hyperfiltration with high protein intake; can increase eGFR after 6 wks; cause loss of KI function in Nurse Health Study after 11 years; 30 trial meta-analysis of short- and long-term trials found protein caused hyperfiltration (changes in eGFR) but not creatinine;

Protein--- KI may enlarge in weight and volume (human, mice) to excrete nitrogenous waste, glucagon, IGF-1, dilated afferent arterioles; evolutionary feedback?

Plant based diet--- reduced acid load; higher acid load may lead to KI Dz over decades;

Hyperphosphatemia--- risk of Cv Dz; elevations in FGF-23 associated with vascular calcifications in patients with chronic KI Dz, L ventricular hypertrophy, and HT failure; ramapril hastens progression of KI Dz compared to those with lower P levels; J Am Soc Nephrol.2011;22:1923-1930.doi.10.1682/ASN.2011020175.

Diet--- legumes in place of 1 red meat meal/wk serving reduced risk of KI Dz 31-62.4%; absorb 40-50% phosphorus from plants *vs* 80% from animal sources; potassium 300-700+ mg in legumes vs 200-400 mg in meat; J Ren Nutr.2017;27:233-242. J Ren Nutr.2017;28:304-312.

Diet Ketogenic--- high in animal fat; highest quartile higher risk of albuminuria vs low lowest quartile; higher risk of GFR decline; diet excludes beneficial fruits, vegetables, legumes, fiber; Am J Kid Dis.2011;547:245-254. Clin J Am Soc Nephrol.2010;5:836-843.

Single kidney--- keep protein $\leq$ 1.2 g/kg/d; Nutrients.2018;512.

Protein Intake and KI Dz JAMA Network Open.2024;7(8):e2426577. doi.10.1001/jamanetworkopen.2024.26577. Ann Intern Med.2012;157(7):471-481.doi.10.7326/0003-4819-157-201210021-00003.

Data--- Nutrition and Frailty in Spain 1, Spain 2, Sweden Study on Aging and Care; ≥ 60 yo; March 2001 – June 2017; follow-up Dec 2021 – January 2024; 10 yr all cause mortality;

N=8543, 14,399 observations; 56.9% female; 78.0 mean age; stage 3-5 KI Dz w/o dialysis;

Diet--- dietary history taken electronically; converted to nutrients; 98 foods and beverages on questionnaire;

Protein--- plant and animal; plant=cereal, legume, nut, vegetable; animal=meat, egg, fish;

KI damage--- Berlin Equation (for adults > 70 yo)= 3736 X Serum creatinine$^{-0.87}$ X Age$^{-0.95}$ X 0.82 (if female); **and** albumin of at least 30 mg/g (3 mg/mmol);

Outcomes

Higher protein → lower mortality if chronic KI Dz; 1-0.80 g/kg/d HR of 0.88; 1.20 vs 0.80 g/kg/d HR 0.79;

Animal vs plant--- animal HR 0.80; plant HR 0.88; p=0.35 for < 75 yo, p=0.32 for > 75 yo;

Absence of KI dz--- HR 0.85, p=0.02; plant protein HR 0.61, p=0.005;

Higher protein → lower mortality if KI Dz, stronger association if **NO** KI Dz;

Plant protein → lower mortality if Ki Dz, stronger association if **NO** KI Dz;

Mortality--- similar btwn animal and plant protein;

N Sig difference male *vs* female

Protein essential to older adult survival;

Similar outcomes--- N=3892 Korea 11 yr; N=356 French > 60 yo, 3 yr; N=259 Japan > 65 yo 4 yr;
Front Nutr.2022;9:850109. doi.10.3389/fnut.2022. Nutrients.2021;13(12):4371.doi.10.3390/nu13124371.
Nutrients.2018;10(11):1744.doi.10.3390/nu10111744.

Low Protein Trial-Italy Clin Kid J.2025;19(1):sfaf341. doi.10.1093/ckj/sfaf341.

N= 110 low protein diet, N=72 normal moderate protein diet; 18-28 months follow-up; mean = 71.2 yo; Bolonga, Italy; stage 4-5 KI Dz;

Diet--- 0.6 – 0.7 g/kg/d; controlled Na, P, energy intake;

Outcomes

Protein intake--- 0.72 g/kg/d *vs* 0.88 g/kg/d, $p<0.001$;

12 months event free survival--- 85.5% *vs* 62.3%;

Dialysis--- lower need in low protein group, $p<0.0001$;

Co-morbidities--- diabetes and cardiovascular dz > 40%;

eGFR--- annual decrease 0.89 mL/min diet *vs* 2.65 mL/min controls, p=0.0004;

Phosphorus--- lower in diet;

N Sig---- calcium, lipid, iron;

Deaths--- 4 in diet; 9 in control; CV Dz in 7, cancer in 6;

Hemoglobin--- higher in low diet with reduced need for erythropoietin tx;

Polycystic Ki Disease and Protein Clin Nutr Open Sci.2023;51:128-135. doi.10.1016/j.nutos.2023.09.003.

Cysts--- associated with aging, dialysis, medications, hormone changes, genetics;

Autosomal recessive---- infants, children; 1 in 20,000 live births; ~50% die from after birth from respiratory failure due to pulmonary hypoplasia; survivors suffer multiple morbidities and die from hypertension, renal dysfunction, and/or portal hypertension;

Autosomal dominant--- 1 in 500 – 1000; hypertension → CV Dz, cysts in other organs; Tx is supportive, analgesics, antibiotics, blood pressure control;

Review--- N=847, N=6 human studies accepted;

Outcomes

Low protein--- delays progression; improves albuminuria; controls uremia;

Low protein--- < 0.8 g/kg/d; slower progression to end stage KI Dz;

Protein--- causes vasodilation; intraglomerular hyperfiltration; increased vasopressin; changes in glucagon, GLP-1 (semaglutide recognized Tx for KI Dz);

Low protein--- shrinks cysts; reduced expansion of # of cysts; renin in cyst wall may expedite hyperplasia;

Soy protein--- modulates IGF-1 → reduced cyst area; reduces creatinine, phosphorus, triglycerides; trials on soy protein needed;

BCAA (branch chain amino acids)--- leucine, isoleucine, valine; leucine can stimulation cyst lining cell growth via mTOR pathway in autosomal dominant; up to 10% of total protein intake as BCAA likely safe; reduced BCAA accumulation reduced mTORC1/cAMP and mitochondria energetics;

Plant Based Diet: Chronic Renal Insufficiency Study Am J Kidney Dis.2023;83(5):624-635. doi.1053/j.ajkd.2023.09.020.

N=2539 chronic KI Dz; 21-74 yo; mild to moderate KI Dz, eGFR 20-70 mL/min/1.73 m^2; 2002-2008; observed to end of 2018;

Diet--- assessed National Cancer Institute Diet History Questionnaire; scored as to healthy plant-based, unhealthy plant-based, animal based using 17 food groups;

Outcomes---

KI Dz progression--- defined as $\geq$ 50% eGFR rate decline from baseline or dialysis or transplant or all cause mortality;

KI Dz progression--- 977 cases in 7 years; 836 deaths in 12 years; lower in plant-based diet-healthy, $p<0.001$; highest rate in plant-based- unhealthy; each 10-point higher score plant base-unhealthy associated with a higher risk of KI Dz progression (HR 1.14) and all-cause mortality (HR 1.11);

Concern--- self-reported diet(s) may be subject to errors;

KI Dz and Albuminuria J Endocrinol Metab.2022;107:1247-1256. id int Suppl.2012;3:1-150. Biomed.2021;9:385. Diabetologia.2008;51:S98. Diabetologia.2009;52:208-212. Diabetologia.2010;52:1506-1516.

Diabetes--- albuminuria strongest risk factor for progression;

Factors--- poor glycemic control; obesity; metabolic acidosis; anemia; CV Dz; infection and inflammation; cognitive decline; reduced physical exercise threshold; malnutrition;

KI Dz International-– albuminuria divided into 3 stages;

- A1 <30 mg/g
- A2 30-300 mg/g
- A3 > 300 mg/g

Nutraceuticals

Thiamine and KI Dz Alt Med Rev.2011;16:12-20.

Thiamine excretion--- associated with eGFR decline; accumulation of soluble vascular cell adhesion molecule-1 and von Willebrand factor; markers of inflammation; endothelial cell damage; precedes microalbuminuria;

Thiamine deficiency--- weakens enzyme defenses against glycation; metabolic stress;

Pharmaceutical that alter Thiamine metabolism--- aminoglycosides; cephalosporins; fluoroquinolones; loop diuretics; penicillins; phenytoin; sulfonamide derivatives; tetracycline derivatives; trimethoprim; Alt Med Rev.2011;16:12-20.

Riboflavin and KI Dz

Riboflavin--- absorbed in proximal jejunum; transforms B2 to FMN and FAD and then excreted in urine (yellow); flavoenzymes in oxidation-reduction reactions for metabolism of CHO, amino acids, lipids; Adv Nutr.2016;7:973-975. Curr Opin Chem Biol.2007;11:195-202. Molecules.2018;23:1957.

Mice--- riboflavin in diabetic mice reduced oxidative stress and DNA damage → improved urea, creatinine, and KI antioxidants status; Arch Biochem Biophys.20156;584:10-19.

Riboflavin--- improved glutathione reductase; reduced lipid peroxidation, sulfhydryl levels in KI; Transplant Proc.2007;39:249-252. Protein J.2010;29;250-256.

Pharmaceuticals that interfere with riboflavin--- anticholinergics, tetracyclines, probenecid inhibit absorption; doxorubicin deactivates and depletes; tricyclic antidepressants, phenothiazines, phenytoin, methotrexate inhibits; thiazide diuretics increase urinary excretion; probenecid decreases excretion; Adv Nutr.2016;7:973-975.

Niacin and KI Dz

Niacin supplementation--- restricts phophorous absorption; could lower serum phosphate in KI Dz; Nephrol Dial Transplant.2017;32:870-879.

Niacin--- essential for synthesis of B6 (pyridoxine); methyl folate; Int J Fod Sci Nutr.2020;2020;71:738-749. Adv Food Nutr Res.2018;83:83-149.

Pyridoxine and KI Dz

Smoking--- reduces pyridoxine; Br HJ Nutr.2014;112:1065-1072.

Protein--- inverse correlation to dietary protein intake; Clin Nutr.2020;39:2824-2831.

Pyridoxine--- levels decrease with age; women lower than men; Clin Nutr.2020;39:2824-2831.

Pharmaceuticals--- cycloserine, ethionamide, isoniazid, penicillamine, theophylline interfere with metabolism; interacts with levodopa; JAMA.1971;218:1924-1927.

T2D--- commonly deficient *vs* non-diabetic controls; nephropathy, endothelial dysfunction, and inflammation; Nutrients.2021;13:3229.

Deficiency--- reduced granulocytes, lymphocytes, lymphocytic maturation; decreased antibody production; Endocr Metab Immune Disord.2019;19:1100-1115.

Oxalate--- deficiency contributes to increased serum oxalate levels, oxalate crystal formation; ascorbic acid deficiency also a factor in oxalate crystal formation; Biochem Biophys Acta.2016;1862:1055-1062.

Biotin and KI Dz

Microbiome--- antibiotics reduce organisms that produce biotin; Academic Press;New York.NY.2022.

Pharmaceuticals--- carbamazepine and primidone (anticonvulsants) long term reduce absorption at intestinal brush border; Am J Clin Nutr.1989;49:127-131.

Diabetes--- biotin stimulates pancreatic islet glucokinase activity and expression; increase insulin secretion; induce insulin receptor synthesis; Front Nutr.2022;9:2682.

Kidney--- deficiency correlated to severity of KI Dz; J Nutr Biochem.2013;24:169-177.

Folate and KI Dz

Pharmaceuticals that inhibit folate and its conjugates--- methotrexate; antacids; bile acid sequestrants; carbamazepine; H2 receptor antagonists; NSAIDS; PPI; sulfasalazine; triamterene (diuretic); Biochemn Soc Trans.2020;48:559-567.

Insulin--- folate deficiency decreases insulin levels; Plos One.2018;13e0202910.

Elevated homocysteine--- inhibits insulin receptor tyrosine kinase activity; decreases phosphatidylinositol 3-kinase activity; J Mol Endocrinol.2005;34:119-126.

Cobalamin and KI Dz JAMA Open.2022;5e2146124. Int Immunopharm.2025:152:114454.

Deficiency--- leads to absence of demethylation of methyltetrahydrofolate → folate deficiency;

Diabetics--- deficiency → oxidative stress outside of hyperhomo- cysteinemia pathway in Ki Dz;

Pharmaceuticals that reduce cobalamin – anticonvulsants; bile acid sequestrants; chemotherapy; colchicine; H2-antagonists; metformin; PPI;

Fructose and KI Dz Biomed.2023;11(4):1153.

Fructose metabolism--- increase uric acid in proximal tubules → injury and release of inflammatory mediators; this in turn leads to urate crystalluria, dysuria, and passage of sandy urine;

KI injury--- high fructose drinks; NSAIDS; heavy metals; pesticides; this in turns leads to def K+, renal vasoconstriction, chronic tubulointerstitial injury;

Carnitine and KI Dz

Carnitine--- dietary intake– red meat, fish, whole milk, avocado; endogenous synthesis-– 25% from LV, KI, brain; Mol Aspects Med.2004;25:455-473.

Hydroxylation of gamma-butyrobetaine to carnitine catalyzed by BBOX1; elevated expression in KI tissues; decreased KI function downregulated BBOX1 → reduced carnitine biosynthesis; Nat Commun.2025;16:1543.

KI Dz--- chronic inflammation; oxidative stress; protein restriction may reduce precursors (lysine, methionine) and limit cofactors (Vit C, niacin, B6, Fe) required for carnitine synthesis; Ann rev Nutr.1998;18:39-61.

Trimethylamine--- microbiome forms this from carnitine; oxidized in LV to TMAO (trimethylamine-N-oxide); Am J Kid Dis.2003;41:S116-S122.

Dysbiosis of KI Dz promotes carnitine to TMA → Carnitine deficiency, a marker of KI Dz progression;

Carnitine--- 90% of carnitine is reabsorbed in renal tubular cells but renal damage significantly lowers reabsorption;

CoQ10 and KI Dz

Diabetes--- lower levels of CoQ10 and even lower if chronic KI Dz; Int J Mol Sci.2020;21:7870.

CoQ10--- biosynthesis pathway tied to enzymes that are associated with glomerular phenotypes and CoQ10 deficiency linked to proteinuria and progressive KI Dz; Ren Fail.a2011;33:819-823. Adv Pharm Bull.2016;6:509-=514.

CoQ10 in Nephrotic Syndrome Kid Internat.2022;102:604-612.doi.10.1016/jkint.2022.04029.

N=116; CoQ10 deficiency due to COQ2 (N=32), COQ6 (N=24), or COQBB (N=60) genes; European Rare Kidney Disease Network, European Pediatric Nephrology

Tx--- ubiquinone or ubiquinol; 3 – 60 mg/kg/d in 2-3 divided doses; 60% started at full dose;

Outcomes

Median follow-up--- 1.3 yr (0.6 – 3.6 yr); most < 10 yo at initial Tx;

CoQ10 in leukocytes--- deficient in >25%; increased 208%, 223%, 238%;

Proteinuria--- decreased by 88% by 1 year, p<0.0001; remained at ~40% for at least 5 yr of follow-up; complete remission in 23%

Remission--- 25%; 34% when 2 genes; 35% for 3 genes; 5 yr survival 62% *vs* 19% in untreated, p<0.005; highest remission in COQ6 gene;

Progression--- severe encephalopathy; epilepsy; headache with phonophobia and photophobia; sensorineural deafness; CoQ0 reduced these symptoms in some of the children;

Other medications in 40--- ACE inhibitors; angiotensin receptor blockers; 4 able to discontinue medications;

CoQ10--- more that half received CopQ10 when progressed to end-stage;

Adverse events--- GI upset; <2% discontinued Tx;

Conclusions--- CoQ10 can slow or prevent KI Dz progression; early diagnostics are key to effective therapy;

CoQ10 and Nicotinamide Riboside (NR) in KI Dz J Cl Insight.2023;8(11)e.167274. doi,10.1172jcl.insight.167274.

N=25; DB, PC, R, Crossover with eGFR < 60mL/min/1.73m^2; 61 ± 11.6 yo; 40% female; X = eGFR 36.9 ± 9.2 mL/min; 167% diabetes; 30-79 yo;

Tx--- CoQ10 1200 mg/d; placebo; NR 1000 mg/d;

Outcomes---

NS--- physical endurance, cardiorespiratory fitness; cycling ergometry; slightly > in CoQ10; exercise efficiency > NR;

CoQ10--- plasma increased and triglycerides decreased, $p<0.05$;

NR--- altered NAD and TCA cycle; decreased triglycerides, $p<0.05$;

CoQ10, NR--- both well tolerated; no serious side effects compared to placebo;

CoQ10--- positive impact on beta-oxidation; positive impact on triglycerides that increase as KI Dz worsens; ketones decreased 41% (fatty acid oxidation), $p<0.07$;

NR--- improved systemic mitochondrial metabolism; NAD^+ is depleted in KI Dz; in mice increased NR genes turned on and HT ejection fraction improved; reduced ceramides (sphingolipid) which case adverse health effects;

Concerns--- partially at start of COVID-19 → lifestyle changes in subjects;

CoQ10 and KI Dz Review Internatl Urol Neph.2022.54(1):173-184.doi.10.1007/s11255-021-02838-2.

N=12 studies; 6 with CV outcomes;

Outcomes---

Malonaldehyde--- Sig reduced

hsCRP--- Sig reduced

HbA1c--- Sig reduced

Quantitative Insulin Sensitivity Check Index (QUICKI)--- Sig reduced;

NS--- total cholesterol; LDL; HDL; triglycerides;

Omega 3:Omega 6 Ratio in KI Dz

Dialysis--- w3 and w6 are most often low;

W3--- benefits to CV protection; immune modulation; anti-inflammatory; dry skin; improved hydration of arms and face; Adv Pharm Bull.2016;6:509-516.

Omega 3 and Dialysis CV Dz NEJM.2025; doi.10.1056/NEJMoa2513032.

Leading cause of death in patients receiving hemodialysis is CV Dz;

N= 1228; Canada and Australia, 26 sites, Nov 2013 to July 2019; N=610 fish oil; N=618 placebo;

Tx--- EPA 1.6 g, DHA 0.8 g/d; placebo corn oil;

Outcomes---

Lower CV events in Tx--- 0.31 *vs* 0.61 per 1000 patient days, $p<0.001$;

w3 group--- lower non-cardiac deaths; lower cardiac death and non-fatal MI; lower peripheral vascular dz leading to amputation; lower fatal and non-fatal strokes; first CV event or death from any cause;

N Sig--- adherence; adverse events;

Vit K and KI Dz Foods.2024.13(11):1646. Kid Internat.2021;100:1023-1036.doi.10.1016/j.kint.2021.06.037.

Vit K 1--- synthesized by plants; green leafy vegetables;

Vit K2--- a family of 13 subtypes; originate from bacterial synthesis; *Lactococcus lactis* synthesize MK5 to MK9 , e.g. yogurt, cheese, sauerkraut; natto from soy >1000 ug/100 g (MK7);

- K2-MK4– menaquinone-4
- K2-MK7– menaquinone-7

Vit K3--- menadione; animal nutrition; anti-cancer, cytostatic;

Therapeutic potential--- Cv Dz; KI Dz; Neurodegenerative Dz; Diabetes; Cancer;

Menaquinones--- produced in large intestine, but poorly absorbed so do not prevent vit K deficiency;

Osteocalcin--- associated with bone loss in KI Dz;

Uncarboxylated osteocalcin--- increased in 60% of KI Dz stage 3-5 patients; even higher in dialysis patients; partially tied to recommendations to reduce K and P intake, i.e. reduce leafy greens and diary intake; in 85 dialysis patients K2-MK4 not K1 was low; thus higher incidence of bone fractures;

Restrictions in KI Dz--- limit K+ to <3 g/d; limit P to 800-1000 mg/d;

KI Dz--- increased CV calcification linked to altered K2 metabolism and supply; vit K intake above the recommendations reduced CV Dz and all-cause mortality; Clin Nutr.2015;34:235-240.

Statins--- decrease K2-MK4 by inhibition of the conversion enzyme UBIAD1 and in vascular walls, lipophilic statins > hydrophilic statins;

- Lipophilic–- atorvastatin, simvastatin, lovastatin, fluvastatin, pitavastatin
- Hydrophilic– rosuvastatin, pravastatin;
- Lipophilic--- double risk for dementia; AANP.2026. Alz Dement.2025;11(1):e70039. doi.10.1002/trc2.70039.

K2MK toxicity--- 20,000 ug has no known human toxicity in Japanese pregnant women trials;

Vit K3 (menadione)--- in large doses allergic reactions; hemolytic anemia; cytotoxicity to LV cells;

K2-MK7--- reduced aortic valve calcification 57% compared to placebo; vascular calcification reductions seen at >4 wks across 27 trials; trials doses of 135 ug – 2000 ug in hemodialysis patients;

Vit C and KI Dz Am J Clin Nutr.2025;doi.10.1016/j.ajcnut.2025.09.008.

N=62 dialysis 3/wk; N=41 Ki Dz stage 4-5; N=42 KI transplant recipients; N=447 KI donors; N=385 healthy KI controls; Netherlands; 47-70 yo;

Assessments--- dietary intake, supplements allowed in healthy;

Outcomes---

Plasma C--- highest in the healthy, 14% deficient; then KI donors, 22% deficient; deficient in KI transplant, 48% deficient; KI Dz, 56% deficient; KI dialysis, 26% deficient due to supplementation;

Dialysis removed--- 27 – 123 mg in conventional dialysis; 97-156 mg in nocturnal dialysis;

eGFR--- in healthy positively associated with plasma vit C independent of potential confounders, $p<0.001$;

KI Dz--- inadequate intake of Vit C;

Vit C--- should be monitor in KI Dz patients; dysfunctional resorption in the proximal tubule; preferred threshold $\geq$ 50 umol/L;

PPI and/or ASA use--- decreased plasma Vit C in any group, $p=0.06$

Potassium--- intake positively associated with vit C intake, $p<0.001$; intake not associated with plasma potassium;

Benzoic acid--- normally excreted by KI; accumulates as KI function declines; benzoic acid in food reacts with vit C → benzene formation, further depleting vit C;

Potassium--- restrictions in KI Dz may contribute to vit C deficiency; potassium restrictions do not match plasma findings, this restriction is backed by weak data; fruits and vegetables have multiple benefits; restriction after transplantation should be dropped;

Depletion of vit C--- ASA; loop diuretics; PPI; corticosteroids;

NAC and KI Dz Kid Int Rep.2024;9:2883-2903. doi.10.1016/j.ekir.2024.07.020.

NAC-deacetylating acylase--- highest activity in KI; second highest is in LV;

KI Dz--- impaired synthesis and depletion of GSH (glutathione) associated with KI Dz; worsens as KI Dz progresses; Nrf2 regulates the enzymes of GSH metabolism; Nrf2 expression and targets altered in acute and chronic KI Dz;

Methylglyoxal--- important uremic toxin; NAC and metformin are methylglyoxal scavenges;

Aldosterone--- induces vasoconstriction in diabetes; NAC counteracted this (4 g IV over 1 h) and increased renal blood flow;

KI Dz progression--- NAC reduced cellular dysfunction and progression of chronic KI Dz;

Absorption--- 600 mg oral is 8.3% bioavailable; 1200 mg is 11.6% bioavailable; 600 mg BID for 6 days yielded a significant increase in plasma, greater over 10 days;

Dialysis patients--- plasma concentrations from oral were higher than in healthy subjects; 600 mg BID for 8 wks increased NAC in plasma from 2.6 to 24.8 umol/L;

Dialysis patients--- NAC concentration steady state after 4th dose of 2g NAC during the first 3 h post-hemodialysis (3 sessions/wk); from 86 – 104 umol/L;

Half life--- 6 h in healthy subjects; excreted in K within 36 h;

Dialysis patients--- up to 90% reduction in clearance; nonrenal clearance also impaired; terminal half-life 35-51 h;

Renal benefits--- renal mass reduction, obstruction, and cytotoxicity; reduced increased creatinine, BUN, proteinuria; protective on glomerular filtration rate; reduced glycation end products; reduced renal ROS; prevent mitochondrial dysfunction;

NAC--- focused effects on renal mitochondrial bioenergetics; mitochondrial complexes I and III protection associated with NAC renal protection; induces removal if damaged mitochondria; prevent lipid accumulation and lipid toxicity in the KI;

Potential--- reduce cardiovascular complications in KI Dz; prevent atherogenesis in KI Dz;

Key factors--- time of administration in relation to damaging factor(s); route of administration; characteristics of the patient population;

Hepatorenal syndrome--- NAC 150 mg/kg over 2 h, then 100 mg/kg over 5 days; improved KI function (urine output, Na output, improved glomerular filtration rate);

Acute KI injury in 2% of acetaminophen poisonings; NAC prevents severe LV injury and subsequent KI injury;

Cardiac surgery--- may decrease KI function; oral and IV NAC show benefit in existing KI Dz;

KI Dz 3-4--- NAC 600 mg BID for 7 days preceding Fe infusion reduced oxidative stress, but not reduce Fe induced KI toxicity;

Cisplatin nephrotoxicity--- IV NAC as KI rescue therapy improved KI function;

Iodinated contrast media--- 1-2% in normal to 30% in reduce KI function have proteinuria and tubular damage (mild? transient?); NAC before and after was beneficial;

Concerns--- oral administration prior to contrast beneficial; continuous infusions likely better than bolus administrations; albuminuria may be a better predictor for the individual patient;

Residual KI function--- 1200 mg BID for 4 wk in hemodialysis and peritoneal dialysis patients; Peri Dial Int.2011;31:545-550. doi.10.3747/pdi.2009.00263. Hemodial Int.2012;16:512-516. doi.10.1111/j.1542-4758.2012.00702.x.

Plasma homocysteine--- 1200 mg BID for 4wk reduced levels in KI Dz stage 5, $p<0.07$; mechanism was greater metabolism of homocysteine;

Glutathione (GSH) in KI Dz Tocicol Appl Pharm.2005;204(3):329-342. doi.10.1016/j.taap.2004.10.004. Renal Fail.1992;14(3):311-319.doi.10.3109/08860229209106635.

GSH--- critical to KI function; multiple carriers are known;

GSH--- rapid turnover in tubule cells; glycine rather then GSH modulates the sensitivity of tubules to KI insults;

Botanicals

KI Dz and Botanical Considerations J Evid-Bas Integr Med.2022;27:1-16. doi.10.1177/2515690x221079688.

KI Dz--- inflammation; fibrosis; oxidative stress;

Review--- clinical and pre-clinical trials; at least 40 plant species identified; 19 trialed in humans;

Outcomes examples---

Rheum officinale, R. palmatum--- 350 mg reduced glucose, urine protein, lipoprotein, apolipoprotein; improved Signs & Sx in KI Dz patients;

Astragalus membranaceus--- 15 g; reduced creatinine, BUN, albumin; remission of proteinuria; improved quality of life in KI Dz;

Tripterygium wilfordi--- 2 mg reduced excretion of proteins, podocytes; decreased CTCG, TGF-beta1;

Vitis vinifera--- 350 mg seed increased GFR; decreased proteinuria, triglycerides, anemia;

Cordyceps sinensis--- 2 g reduced glomerulosclerosis, renal interstitial fibrosis, triglycerides, lipoproteins; renal protective in KI Dz;

Silybum marianum--- 350 mg restored thiol imbalance in end stage diabetic nephropathy;

Beta vulgaris--- 300 mg reduced systolic, diastolic, and mean arterial pressures; reduced renal resistive index;

Curcuma longa--- 600 – 1500 mg reduced diabetic, nondiabetic proteinuria;

Boswellia serrata--- 516 mg decreased PGE2, inflammation in KI Dz;

Bupleurum falcatum, B. chinensis--- reduced protein excretion, hematuria, normalized proteinuria;

Zingiber officinale--- 1 g reduced fasting glucose in KI Dz patients;

Glycyrrhiza glabra--- 500 mg decrease pre-dialysis K^+;

Herbal combinations--- also effective;

Caution--- herbal remedies potentially implicated in up to 35% of acute KI injury in Africa; *Callilepis laureola, Aloe capensis, Catha edulis, Dioscorea quartiniana, Securidacea longependunculata, Irvingia gabonensis, Euphorbia paralias,* J Neph Renal Ther.2016;doi.10.24966/NRT-7313/100008.

Polyphenols and KI Dz Foods.2022;11:1060. doi.10.3390/foods11071060.

Resveratrol--- reduced injury in acute KI Dz; reduced TNF-alpha, IL-1beta; reduced protein injury; reduced septic injury in rats; protective of KI function in diabetes; reduced glycation end- product formation; inhibited LPS glomerular damage; with ramapril reversed glomerulosclerosis in early-stage KI Dz;

EGCG (epigallocatechin-3-gallate)--- reduced reactive oxygen species, damage by iron overload, oxidative stress, nitrosative stress; prevented renal tubular damage; reduce macrophage infiltration, renal fibrosis;

Ellagic acid--- reduced renal ischemia/reperfusion injury;

Honokiol--- reduced sepsis acute KI injury; reduced oxidative stress and inflammatory cytokine production;

Quercetin--- prevent KI damage; improved renal function; targets miR-499-5p/APC axis to improve renal function; reduced oxidative stress and renal inflammation;

Oleuropein--- reduce weight, KI injury, decreased inflammation, decreased oxidative stress;

Cisplatin KI Injury---

- Resveratrol-- reduced nephrotoxicity; decreased its accumulation in the KI;
- Quercetin– reduced elevation in creatinine, BUN;
- Myricitrin-- reduced ROS, creatinine, BUN;
- EGCG-- nephroprotective; decreased MDA; restored glutathione;
- ECG-- prevented oxidative stress and apoptosis by down regulation of the MAPK pathway → improved renal function;
- Tannic acid-– countered acted nephrotoxicity and DNA damage;
- Honokiol--- counteracted renal cell damage;

Gentamicin--- resveratrol prevented nephrotoxicity; curcumin reduced renal toxicity via modulation of redox pathway and mitochondrial alterations;

Polyphenol absorption--- absorbed in SI and in the LV undergoes Phase I and II metabolism; back to SI and into systemic circulation; excretion in urine leads to effects seen in the renal system; KI cells have a role in metabolism through Phase I and II biotransformation reactions;

Polyphenol metabolites--- 34 have been identified in urine; intestinal dysbiosis can affect bioavailability of polyphenols and their metabolites and their measurement;

HTD1801 and KI Dz NEJM.2026;5(7).doi.10.1056/EVIDoa2500317.

HTD1801--- berberine ursodeoxycholate; berberine + ursodeoxycholic acid (UDCA) into a single ionic salt for oral administration; tested in T2D, MASH (metabolic dysfunction associated steatohepatitis); Shenzhen High Tide Therapeutics, Inc. Hong Kong;

Kidney--- Phase 3 trial; increased eGFR 3.08 mL/min/1.73m^2 at 52 wks; no evidence of hyperfiltration or fluid retention; reduced NF-kB; dose dependent improvement in renal architecture; reduced tubular injury scores, renal inflammation, fibrotic changes; decreased 24 h albuminuria;

HDT1801--- 1000 mg BID Tx N= 365; Placebo N=184; all on metformin ≥ 8 wks;

Outcomes---

HbA1c--- from 8.5% baseline to 7.8% at 24 wks, p<0.0001; placebo no change;

Adverse events--- diarrhea 23.8% *vs* 1.1% placebo; 3 were severe; no severe hypoglycemia;

UDCA--- hydrophilic bile acid that dissolves cholesterol gallstones; chronic cholestatic LV Dz; primary biliary cholangitis;

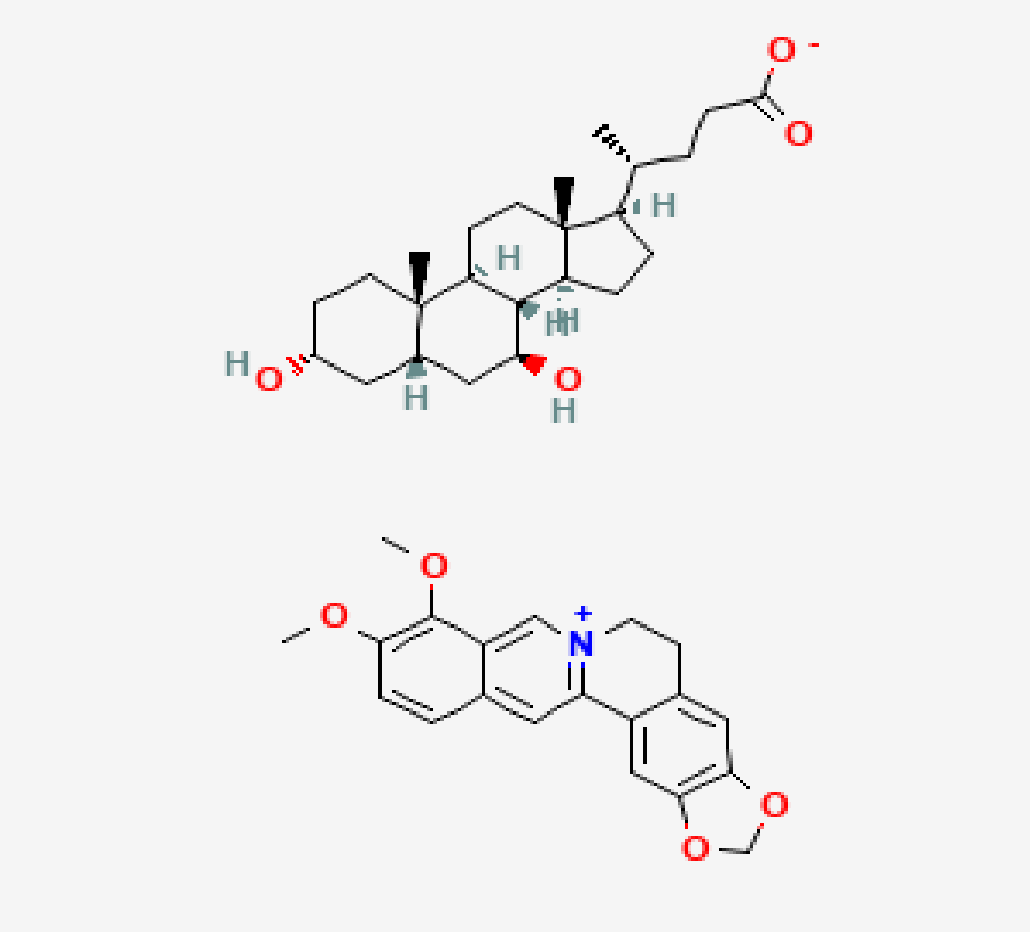
UDCA--- use for centuries for LV Dz; used in TCM; used in intrahepatic cholestasis of pregnancy; NLM.2023.PMID 31424887.

Mechanism--- multiple; inhibits absorption of cholesterol in intestine and its secretion in bile; preserves cell structure, including plasma membranes and mitochondria; induces secretion of bile acids;

Dose--- 8-10 mg/kg/d in 3-4 doses; up to 25 mg/kg have been used in trials; 300 mg BID to prevent gallstones;

Adverse events--- diarrhea 2-9%; microbiome?; exacerbation of pruritis but can also relieve it;

Ursodeoxycholic Acid + Berberine



Microbiome

KI Dz and Microbiome Am J Physiol Renal Physiol.2019;316:F1211-F1217. doil1152/ajprenal.00298.2018.

Bacteroides fragilis--- polysaccharide A cultivates beneficial T helper cells (Th1/Th20); migration to lymph tissues/organs encourage Th1 differentiation;

Renal failure--- increased urea in blood; urea converts to ammonia; favors bacteria that contain urase; increases in Actinobacteria, Firmicutes, Proteobacteria compared to healthy controls; reductions in *Bifidobacterium catenulatum, B. longum, B. bifidum, Lactobacillus plantarum, L. paracasei, Klebsiella pneumoniae;*

Diet--- high salt decreases some bacteria species, esp. *Lactobacillus;* alters frequency of Th17 lymphocytes;

Uremic toxins--- indoxyl sulfate; p-cresyl-sulfate; levels are increase 10-50 fold in KI Dz compared to 100% binding and excretion in healthy KI; damage renal tubular cells; cause coagulation disturbances; endothelial dysfunction; leukocyte activation; cardiac fibrosis; hypertrophy; insulin resistance; coronary artery disease;

Resistant starches--- derived from vegetables, fruits, wheat, corn, nuts; restriction of K+ foods limits these beneficial starches that protect the colon wall, provide epithelial integrity;

Epithelium--- claudin-1, occludin (tight junctions), zonula occludens-1 depleted in rats with KI Dz → reduced colon mucosa integrity; tight junction disruption allows endotoxins and microbial fragments to further disrupt the endothelial barrier → increased infections in KI Dz patients;

Crohn's Dz--- fecal microbiome has some parallels in KI Dz;

AST-120--- oral adsorbent of porous carbon micro-spheres adsorbs uremic toxins in rats with reduced renal function; little to no benefit in a human trial; pre- and pro-biotics reduce p-cresyl sulfate and improved the microbiome;

B. longum--- reduced serum indoxyl sulfate

Sevelamer hydrochloride--- phosphate binders bind uremic indoles and p-cresol in rats and humans, but not in patients on dialysis;

Rats--- resistant starches slowed KI Dz progression; reduced interstitial fibrosis, renal tubular damage, activation of proinflammatory molecules;

Humans--- dietary fibre lowers indoxyl sulfate during hemodialysis; acarbose had similar benefit;

Further research is needed

Microbiome for KI Dz J Agri Food chem.2021;69(26):doi.10.1021.acs.jafc.1c1547.

Dysbiosis--- gut dysbiosis is a major contributor to chronic KI Dz;

Mice--- 0.2% adenine induced KI Dz;

Tx--- *Lactobacillus paracasei, Lactobacillyus plantarum;*

Outcomes---

KI function--- significantly improved; reduced KI injury; reduced fibrotic proteins;

Other KI--- decreased oxidative stress, proinflammatory reactions, elevated immune response;

Gut dysbiosis--- reversed; commensal bacteria restored, esp. short-chain fatty acid producers → improved intestinal barrier;

Probiotics--- could be a preventive approach against chronic KI Dz; *L spp.* reduce uremic compounds;

Probiotic Research Review Cureus.2026;18(1):3102520.doi.10.7759/cureus.102520.

Nephrologists N=60; trials N=18 from 2003 – 2024;

Outcomes---

Waste--- uremic toxins ammonia/urea, uric acid; bacteria metabolites indoxy sulfate, p-cresyl sulfate, trimethylamine N-oxide (TMAO), indole-3-acetic acid; poorly eliminated in KI Dz; epithelial tight junctions compromised → systemic circulation, CV Dz, KI Dz;

Diet--- reduced fiber, protein, carbohydrates; lack of fermentable fibre for *Bifidobacteria, Lactobacilli;*

Beneficial bacteria--- produce short-chain fatty acids (SCFA), acetate, propionate, butyrate that preserve gut health; decrease SCFA → leaky gut; medications reduce beneficial bacteria diminishing microbiome diversity; phosphate binders and ion exchange resins alter microbiome, decrease transit time;

Beneficial--- *Streptococcus thermophilus; Lactobacillus acidophilus, Bifidobacterium longum, Bacillus coagulans;*

S. thermophilus.--- reduces BUN, uric acid, p-cresol;

L. acidophilus.--- reduces uremic toxins; reduces pathogenic bacteria in SI;

B. longum.---- removes putrefactive bacteria, phenolic and indole metabolites;

B. coagulans--- alters intestinal permeability to prevent toxin translocation;

Dose--- best benefit > 15 billion in multiple strains 6 months; safety and good benefits seen at 180 billion for 2 months, 90 billion for 6 months; 45 billion BID for 6 months;

Caution--- KI transplant as immune suppressants reduce ability to fight infections;

Minerals

Trace Minerals in KI Dz Annl Transla Med.2022;100(24):1400.doi.10.20137/atm-22/5969.

Trace minerals--- Fe, Zn, Se, Cu, I, Mn;

Iron--- erythropoietin (EPO) def in KI Dz; RBC life shorter in KI Dz, 50-75 d; reduced Fe absorption from diet; ferritin an acute phase reactant that is elevated as an inflammatory response regardless of Fe deficiency; several biomarker tested, but all confounded by KI inflammation so assessment of Fe status in KI Dz is challenging;

Fe--- supplement or infusion → microbial proliferation; secondary infections, esp. bolus doses; *Staphylococcus epidermidis* benefits from Fe!

Ferritin--- elevated ferritin associated with increased risk of infections;

Ferroptosis– non-apoptotic form of programmed cell death due to over accumulation of iron dependent membrane lipid peroxides; probable mechanism to progression of KI Dz, esp. diabetic nephropathy;

Ferroptosis prevention– vit C; vit E, tocotrienols > tocopherols as antioxidants; P-5-P (B6); Vit A; vit D; vit K2; goal is to restore GSH and glutathione peroxidase 4 (GPX4); Antioxc.2024;13:1571. doii.10.3390/antiox13121571.

Iron guidelines--- assess oral before IV infusions; consider in dialysis

Zinc--- serum decreased in KI Dz; decreased absorption; decreased intake; higher urinary excretion; redistribution of Zn; def Zn leads to brittle, fragile RBC membrane; in KI Dz the KI produce insufficient erythropoietin to stimulate erythropoiesis;

Zinc--- 34 mg/d improved anemia

Zinc deficiency--- associated with cardiovascular dz in KI Dz; stiff vascular walls; Zinc supplementation suppresses NF-kB pathway;

Zinc supplementation--- improved HDL; lower CRP and IL-6 (mice);

Fibrosis--- significant in KI Dz; maladaptive repair of KI, HT, CV system and other organs; Zinc protective of LV and LU; Zinc reduced fibrosis and oxidative stress in myocardial tissue;

Excess zinc--- erythropoietin resistant anemia; can elevated blood pressure and induce Cupper deficiency; ratio 15:1 ?:

Selenium--- found in grains, vegetables, seafood, meat, diary, and nuts; critical to glutathione; highest in KI and thyroid;

KI Dz--- deficiency from low dietary intake; impaired intestinal absorption; decrease Se-binding proteins; increased urinary output; lost in dialysis; when low risk of death from infections;

Se + CoQ10--- improved KI function, improved GFR; renal tubules and podocytes contain large concentration of mitochondria that require Se; 200 mcg/d for 3 mo in T2D with KI Dz increased GSH, KI perfusion, and GFT;

Se--- important for T-cell and B-cell production and activity;

Fibrosis--- renal cells lost and replaced by an extracellular matrix that leads to fibrosis;

Dose--- 200 mcg/d safe and effective in KI Dz; 400-450 mcg/d may be used but caution for toxicity, Se can replace Sulfur thus affecting amino acids and the proteins they are metabolized to; nail clippings considered the most accurate assessment of Se status

Copper--- #3 trace mineral after Zn and Fe; in KI Dz increased Cu and decreased Zn; if deficient oral or IV Cu gluconate, sulfate or chloride;

Cu--- may catalyze to ROS and decreased GSH; toxic effect of Cu can cause acute or chronic renal failure; Zn can increase serum Zn and decrease Cu accumulation; Cu in the KI decreases after transplantation due to inflammation and immunosuppressant medications;

Diabetes--- high risk for KI Dz as are obesity and hyperlipidemia; excess fatty acids damage KI, promote ROS, lipid peroxidation;

Wilson’s Dz--- classic model of chronic Cu poisoning; affects LV, CNS; deposits in cornea, KI, and bones; mitochondrial dysfunction → apoptosis and activation of AMPK-mTOR pathway in the hypothalamus;

Iodine--- from marine fish, seafood, dairy and fortified salt; 90% eliminated in urine; WHO recommends 150 mcg/d, 250 mcg/d if pregnant; Am J Kid Dis.2001;38:S80-S84.

KI Dz--- elevated in KI Dz due to decreased excretion; this can lead to thyroid enlargement; many dialysis patients have enlarged thyroid glands/goiters; Am J Kid Dis.2001;38:S80-S84.

Medical Imaging--- iodinated contract can cause contrast induce nephropathy in patients with KI Dz; IV saline prophylaxis is indicated for GFR < 30 L/min/1.73m^2; prevention should be considered for GFR of 30-44 L/min/1.73m$^{2;}$ Clin Exp Nephrol.2020;24:1-44.

Manganese--- mainly from plant sources, nuts, seeds, vegetables; excreted in stool via bile secretions; inversely related to Fe absorption as share same transporters in SI; roles in energy metabolism, immune function, serum glucose regulation, and antioxidant;

KI Dz--- findings vary, elevated, decreased; deposits seen in basal ganglia; tied to Fe status in KI Dz?

Mn--- cofactor in Mn superoxide dismutase (MnSOD); detoxifies free radicals in mitochondria, glomerular, tubules

Resveratrol--- improves oxidative stress and normalizes MnSOD;

Mn toxicity--- concentrated effects seen in CNS → neurobehavioral disorders, extrapyramidal damage including the basal ganglia, similar to Parkinson's Dz; KI seems resistant to its toxicity; CK isoenzymes often elevated; may accumulate in HT → acute cardiac depression and hypotension;

Dose--- long term low dose may change LV structure; high dose affects LV structure and function, and inhibits of antioxidant genes; risk of cirrhosis and fibrosis;

Dose--- 1.8 – 2.3 mg/d ?; Canada-– upt to 11 mg/d in diet; higher intake associate with lower KI Dz risk, China (CLHLS), USA (NHANES); Renal Fail.2025;47(1):2512049. doi.10.1080/0886022X.2025.2512049.

Potassium and KI Dz renal Dieticians BC.2023.

Elevated K^+--- may cause tingling in toes, fingers, muscle weakness, arrythmia;

Diet--- fresh fruit, vegetables, whole grains, proteins have less potassium available *vs* processed foods; moderate protein; limit or avoid additives; fibre help with K elimination; boiling and draining reduces K intake

K--- KI regulates K; distal tubule monitor/sense K and then modify the NaCl transporter; KI failure often has low K; human diet historically was high in K and low in Na, reverse today;

Low K diet--- hypokalemia; lower intracellular K, lower body weight, higher KI weight; intracellular acidosis; over expression of IGF-1-BP (binding protein); intrarenal generation of angiotensin II despite suppression of the renin-angiotensin system; impaired KI angiogenesis; in hypokalemic nephropathy normalization of plasma K does/can reverse NaCl sensitivity, permanent KI damage?; K deficient diet + bicarbonate or endothelin A or B antagonists can prevent KI damage;

Low K in children--- can it cause KI injury? risk of increased renin up to 6x; K supplementation decreased BP (13 yo); DASH diet beneficial;

Race--- African ancestry lose more K in stool and sweat; genetic difference in handling K and lower Na pump activity;

Children--- KI Dz and hypertension tied to obesity; diet high in Na, protein, calories and low K;

Sex--- female rats, mice have lower plasma K set point; estrogen has role; female mice on low K prone to nephrogenic diabetes; human Gitelman Syn (SLC12A3) KI cannot resorb NaCl → low K, low Mg, low Ca, metabolic alkalosis; Sx—high thirst, nocturia, crave salty foods; need more K during pregnancy; role of sex and K poorly understood in humans;

Diet--- low K increases risk for hypertension, CV morbidity and mortality and adverse KI outcomes; low K increases phosphorylation and NaCl transporter in distal tubule → increased Na resorption which helps to conserve K; if a high NaCl diet then → to NaCl hypertension;

Children--- hypertension related to dietary K not NaCl intake;

Salt Substitution trial --- N=2376; Nat Med.2020;26:374-378.

Outcomes---

BP--- reduce by 51%

K--- Sig excretion increased, Na unchanged;

Second Salt Substitution Trial --- N=20,995; NEJM.2021;385:1067-1077.

Outcomes---

Reduced--- Sig BP, stroke, CV events, death;

K--- excretion Sig increased; Na excretion decreased;

Potassium ~ 600 + mg; avocado 700 mg;

KI Dz--- salt substitution simple, beneficial in KI Dz patients; CV deaths outweigh risk of hyperkalemia deaths;

Short-Term K^+ in KI Dz JASN.2022;22:1779-1789. doi,10.1681/ASN.2022020147.

N=191; KI Dz G3b-4; 83% on renin-angiotensin inhibitors; 38% diabetic;

Tx--- KCl 40 mmol/d = 3000 mg/d;

Outcomes---

Sig--- increased urinary K excretion, plasma K (0.4 mmol/L), plasma aldosterone; reduced plasma bicarbonate, urine pH;

N Sig--- urinary Na excretion; plasma renin, BP, eGFR, albuminuria; urinary ammonium excretion;

Hyperkalemia--- 11% developed K > 5.9 mmol/L, were older;

Sodium in KI Dz Int J Mol Sci.2020;21:4744. doi.10.3390/ijms2113744.

WHO--- recommends <2.3 g Na/d or 5.8g/d NaCl;

Na--- 24 h urine is the gold standard; single point in time testing inaccurate; trends best method;

KI Dz--- interrelated to hypertension; >75%; BP 120-139/80-89 mmHg 25% higher risk of KI Dz; hypertension often resistant in KI Dz → worse CV Dz prognosis; early hypertension indicates extracellular volume expansion; intrarenal production of angiotensin II → proinflammatory cytokines, IL-6, VEGF, already present in KI dz; arterial stiffness, endothelial dysfunction;

NaCl intake--- < 3g/d forecasts CV risk; salt suggests a U-shaped mortality curve; low NaCl often associated with low protein intake;

KI Dz--- NaCl intake leads to increased BP; Na sensitivity seen in early Ki Dz; later L Ventricular hypertrophy; Na stored in skin reduced after a single dialysis session, mechanism unclear;

NaCl restriction--- reduces proteinuria; lowers BP and L ventricular hypertrophy; personalized NaCl intake may have better outcomes;

Low NaCl intake--- ~2.5 g/d malnourished; reduced lean body mass; lower calorie and protein intake;

DASH Diet NLM.2025.PMID:29494120.

DASH--- Dietary Approaches to Stop Hypertension;

Foods---

- Vegetables, fruits, whole grains;
- Low fat/fat free dairy; fish; poultry; legumes; nuts/seeds; vegetable oils;
- Limit saturated fats such a meat; full-fat dairy, tropical oils;
- Limit sugar sweetened beverages; sweets;
- Na 2300 mg/d; 1500 mg/d lowered BP further;
- 2000 calories/day;

Trials--- early 1990s to lower NaCl intake; NEJM.2001;344(1):3-10.

Calcium and KI Dz

Curr Osteopor Rept.2017;15:214-221. doi.10.1007/s11914-0147-0368-x.

KI--- regulate calcium and produce active form of D3; KI Dz reduces or blocks active Vit D production → low Ca;

KI Dz--- Ca disturbances begin in the earliest stages of KI dz and worsen its progression; elevated fibroblast growth factor FGF-23; elevated parathyroid hormone (PTH); decreased 1,25 D; elevated phosphate; decreased Ca; dialysis disrupts Ca balance → fluxes in Ca balance in soft tissue and bone, thus steady state never achieved;

Ca status--- steady state ~6 d on a controlled diet in healthy adults; therefore, wait at least 1 wk to assess dietary changes;

Ca--- 99% in bones and teeth as hydroxyapatite, a calcium phosphate crystal lattice; mediated by intestines (90% SI, 10% LI), kidney, bone; 2 hormones are D3 and parathyroid; parathyroid raises ionized Ca by causing KI proximal tubules to increase renal absorption of Ca, stimulate osteoclasts to increase bone resorption, increase CYP27B1 to convert 25-hydroxyvitamin D (25D) to active 1,25D;

Ca--- high intake suppresses PTH and D25 to 1,25D conversion; adequate intake; low intake takes Ca from bone to maintain balance;

KI Dz--- risk of Ca low absorption due to decreased 1,25D; intestinal epithelium tight junctions altered affecting paracellular transport;

Ca Balance Studies--- healthy and KI dz 800-1000 mg elemental Ca; adding Ca carbonate produce a positive Ca balance; Ca output in urine low in KI Dz patients; Kidney Int.2012;8(11):1116-1122. Kidney Int.2013;83(5):959-966.

KDOQI--- guidelines recommend Ca 2000 mg/d from diet; restrict calcium-phosphate binders; KDIGO recommends 800-1000 mg/d not to exceed 1500 – 2000 mg/d to avoid vascular calcification; the latter (KDOQI) is considered too high; supplement only if diet under 1000 mg/d;

Question--- how much Ca is patient consuming in diet?

Phosphorus in KI Dz Adv Nutr.2014;5:98-103.doi.10.3945/an.113004655.

KI Dz--- as KI function decline P concentrations rise; risk of pharthyroid hyperplasia → 2nd hyperparathyroidism, bone disease, elevated bone turnover, fractures; Caucasian females with stages 3-4 have 2.5-fold risk of nonvertebral fractures, 2.0- fold risk in Black women; hyperphosphatemia → soft tissue calcification esp. vascular tissue even in young patients;

FGF23--- increase in early KI Dz; risk factor for death → HT failure, stroke, L ventricle mass changes, even if KI function is preserved; mechanism not fully understood;

P--- elevation a risk for developing end stage KI Dz; seen in >100,000 patients of multi-ethnic origins; impaired endothelial function seen in L ventricle in 227 non-diabetic patients;

P--- higher dietary content associated with increased cancer risk; in mice increase LU cancer;

P--- higher in western diet due to foods processed with phosphate additives;

Lab--- P undergoes significant circadian variation in 24 h; fasting serum P is considered a poor indicator of dietary P intake;

P--- data bases to estimate P is inaccurate, often underestimating; bioavailability varies, low in cereals and higher in meats;

Protein--- some restriction is beneficial, but is it the protein, or the P, or both?

Mineralocorticoids

Aldosterone and KI Dz Am J Transl Res.2024;16(8):4246-4255. doi.10.62347/NRGG6465. Circ Res.2020;127(3). Doi,.10.1161/CIRRESAHA.120.317424.

Aldosterone--- systemic or local has significant role in KI Dz; hyperactivation of mineralocorticoid receptor (MR) in distal tubules, collecting ducts → endothelial dysfunction, fibrinolytic disorders, oxidative stress, cardiovascular fibrosis, renal fibrosis;

Aldosterone--- identified 1950; from adrenal cortex: zona glomerulosa; fluid balance, Na resorption, K excretion; synthesis and secretion controlled by renin-angiotensin system; renin synthesized by granular cells in glomerular parietal apparatus and influenced by reduce renal blood flow, renal hemorrhage, dehydration, NaCl intake; also produced by HT, blood vessels, brain, adipocytes;

Stimulation of aldosterone release--- low plasma NaCl; high K; hypovolemia; hypoglycemia; atrial natriuretic peptide; activated genomic and non-genomic pathways; ACTH secretion → aldosterone production;

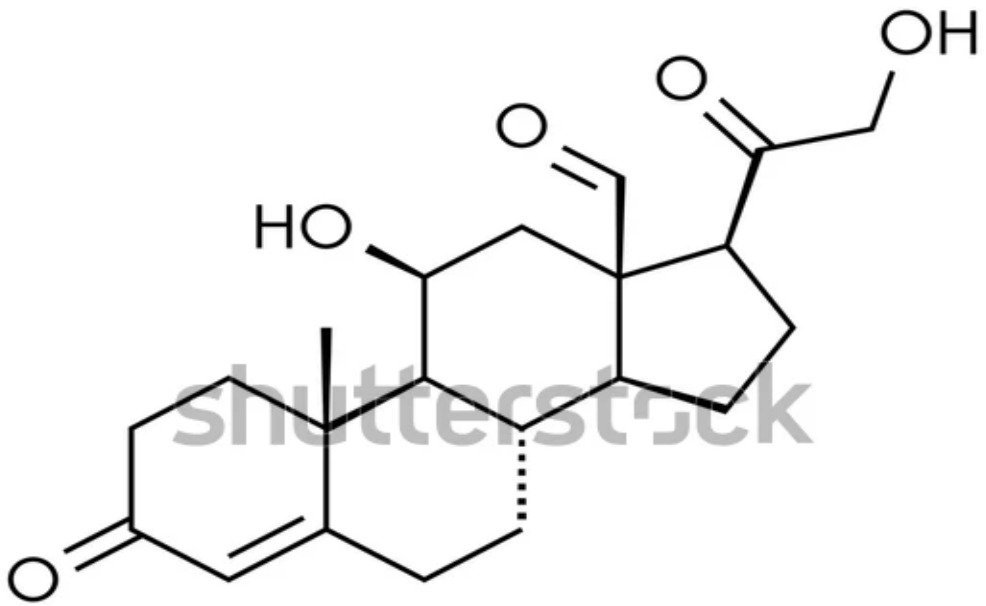
Mineralocorticoid receptors for aldosterone--- KI distal tubules, collecting ducts; colon; salivary glands; sweat glands; heart, vascular walls; brain, hippocampus; brown adipose tissue;

Serum aldosterone and KI Dz--- some trials show correlation, others do not; larger sample sizes (10,000+) required; control for confounders also required;

Primary aldosteronism--- correlation to KI Dz, KI damage;

Hypertension--- abnormal glucose metabolism, diabetes and not primary aldosteronism correlated to KI Dz;

Aldosterone antagonism--- increased risk of hyperkalemia, mastocytosis; similar results with spironolactone, elevated K+, reduced protein in urine;



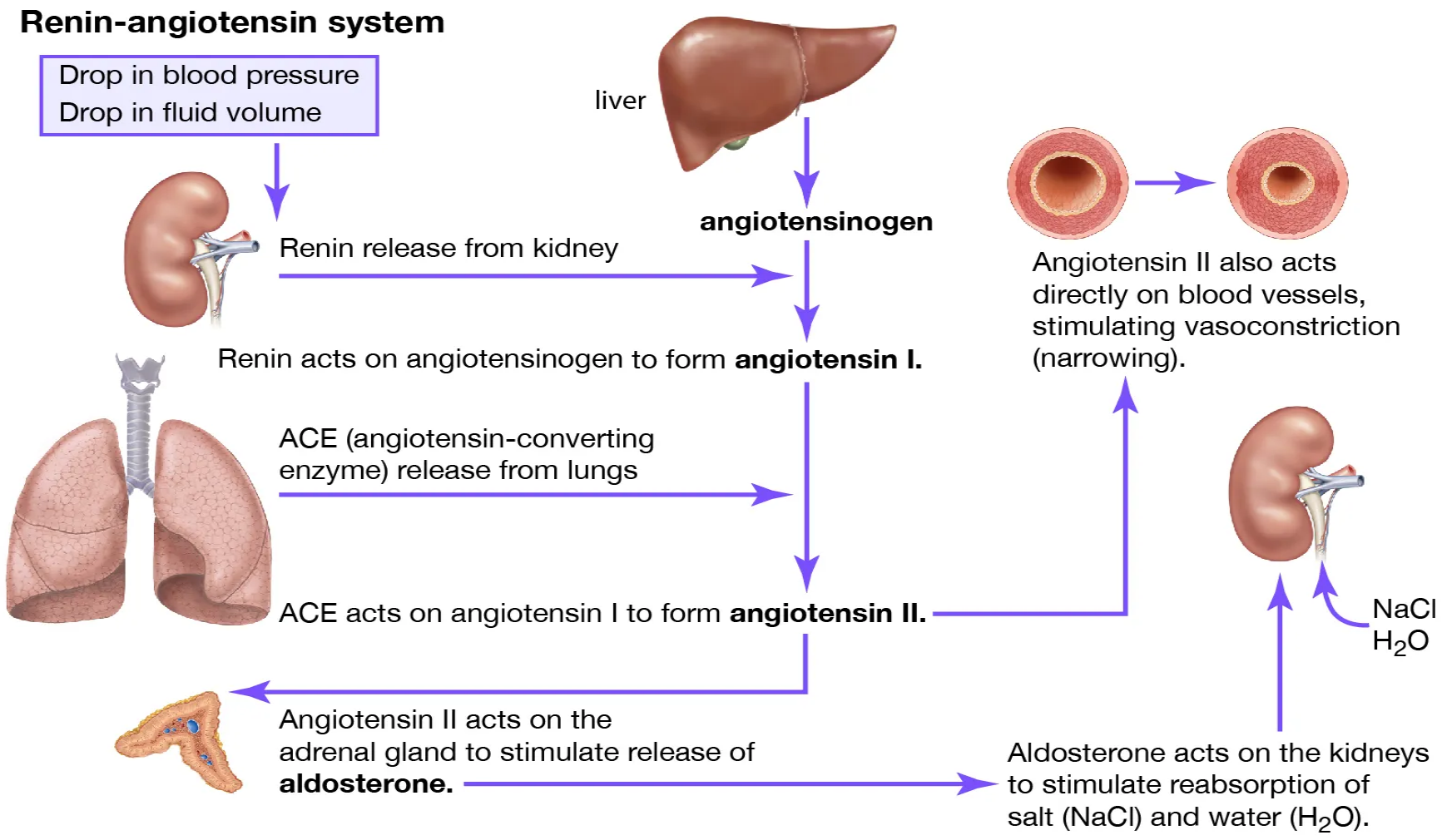
aldosterone

Renin and KI Dz Primary Aldoster.2025.NLM.PMID:30969601. Am J Med.2004;116(4):263-272. doi.10.1016/j.amjmed.2003.09.034.

Renin--- converts angiotensin (from LV) to angiotensin I; then converted to angiotensin II by ACE in the LU;

Angiotensin II--- vasoconstrictor and triggers release of aldosterone → leading to retention of NaCl and water → elevated blood pressure;

Renin--- elevation could be arterial stenosis, dehydration, hemorrhage, Addison's Dz (adrenal insufficiency); low renin could be primary Conn's Dz (hyperaldosteronism), excess NaCl intake, medications, *Glycyrrhiza* spp., corticosteroids, BCP, thiazide diuretics, spironolactone, fludrocortisone, MAOI, SNRI;



Angiotensin and KI Dz Expt Ther Med;2023:25.153. Cir Res.2020;127:606-609. doi.10.1161/circresaha.120.317624.

KI--- excretory; metabolic; endocrine; highest blood flow per gram of organ tissue; blood flow is 20-25% of resting cardiac output;

Sympathetic stimulation--- vasoconstriction of afferent arteriole → reduce glomerular blood flow, reduced hydrostatic pressure, reduced GFR (normal 125 mL/min); elevated BP over time → KI Dz;

Increased angiotensin II--- from renin activation → hypertension; inflammation; atherosclerosis;

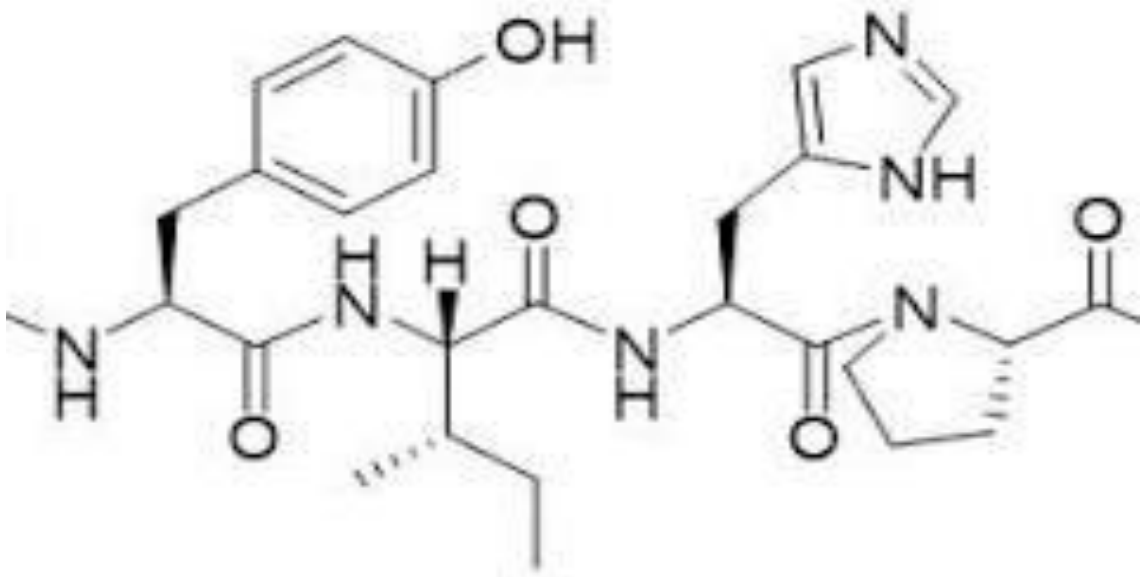
KI--- can often recover from acute injury, but not from chronic injury; KI Dz is eGFR < 60 mL/min/1.73m^2; renal cells replaced by extracellular matrix in glomeruli and other renal tissues;

Angiotensin II--- 1000 times higher in KI than circulating in other tissues; causes Na and water retention, cellular hypertrophy, oxidative stress, podocyte impairment via AT1 receptor activation;

Mechanism--- angiotensin II acts like a cytokine with proinflammatory and profibrotic outcomes; increases transforming growth factor-beta (TGF-beta) and platelet derived growth factor; renin and aldosterone also increase TGF-beta;

TGF-beta--- induces oxidative stress; stimulates extracellular matrix synthesis and inhibits proteases that degrade extracellular matrix; renal fibrosis results → increased fibrogenesis and collagen deposits in extracellular matrix;

Angiotensin I



Dialysis

Dialysis and KI Dz NIH.Hemodialysis.2018. NCT06270134.

Dialysis--- waste removal from the blood; e.g. urea (nitrogen), muscle waster (creatinine), acids;

Incidence--- > 30,000 in Canada; thousands in monitoring; 77% in-centre hemodialysis; ~600,000 USA; 7556 dialysis centers; ~$1000/ session; 200,000 KI transplant; USA highest in the world; >2 million world-wide;

Hemodialysis--- dialysis machine removes blood from a vein (arm), filters in a dialyzer, returns blood to body via an artery in arm; usually 3 d/wk, 3-4 h per session; enlarged blood vessels; grafted fistula (arm) can take 6 mo the heal;

Peritoneal--- uses the lining of the abdomen (peritoneum) to filter the patient's blood; dialysate into the peritoneal cavity make the process possible; solution drains into a bag outside the body;

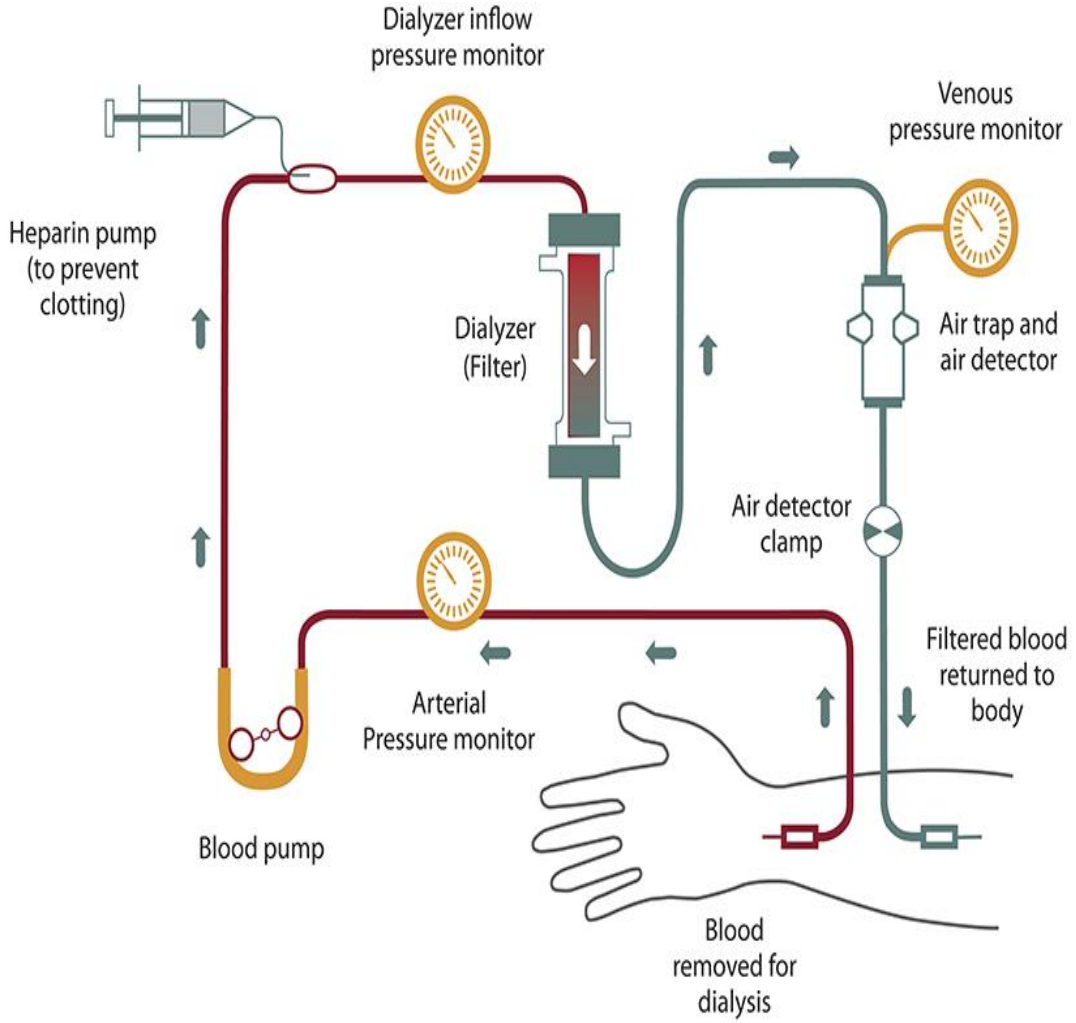
Peritoneal continuous ambulatory dialysis--- a bag above the should lets dialysate flow with gravity into the abdomen; this take ~30-4- min, is done 3-5/day;'

Peritoneal automated dialysis--- a machine automatically adds dialysate to the peritoneum, 3-5 exchanges per session; often performed while the patient sleeps; 8-12 h procedure; must be done daily;

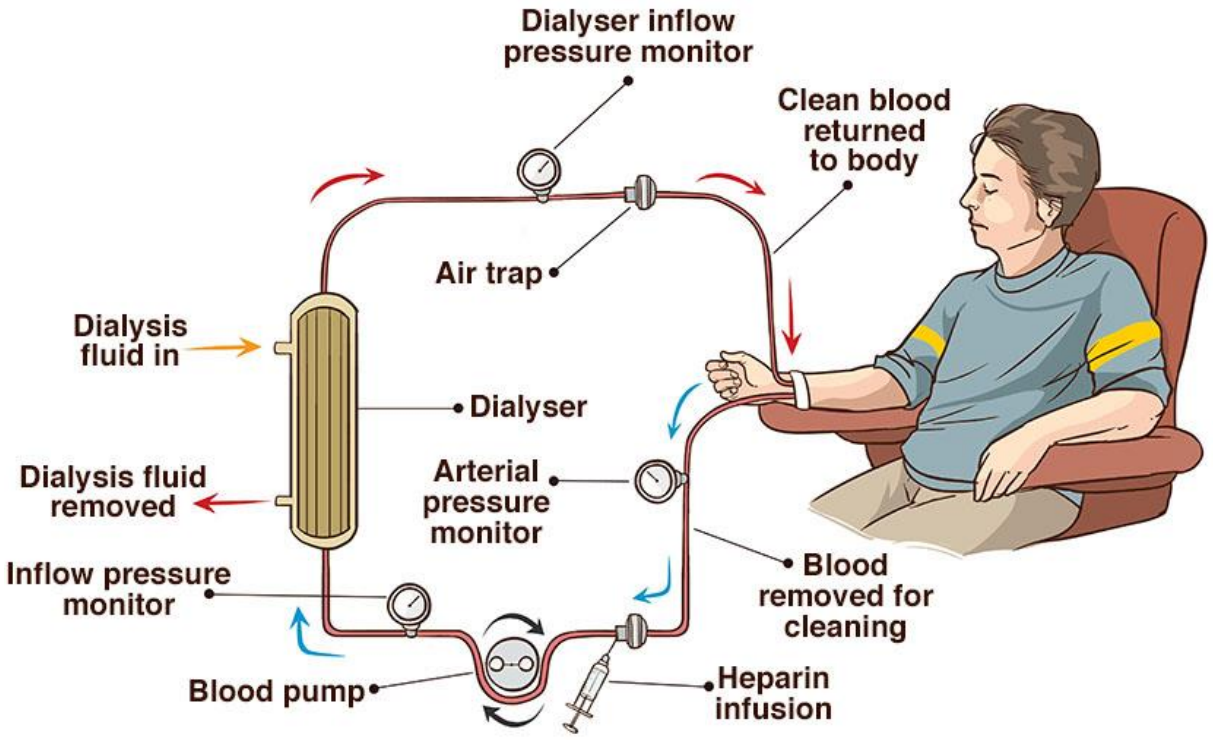
Risks--- infection; scar tissue; blood clots (heparin required); inflammation (peritonitis); abdominal hernia;

Dialysate--- solution of NA, K, Ca, Mg, Cl; bicarbonate to prevent metabolic acidosis; dextrose for peritoneal dialysis to draw out excess water;

Dialysate Trial--- 32 mmol/L vs 39 mmol/L, Ontario; assesses hospitalizations, mortality, fractures;



Haemodialysis



Summary

Causes and Staging

Protein

Nutraceuticals

Botanicals

Microbiome

Minerals

Mineralocorticoids

Dialysis

Thank You

Questions?

Discussion?