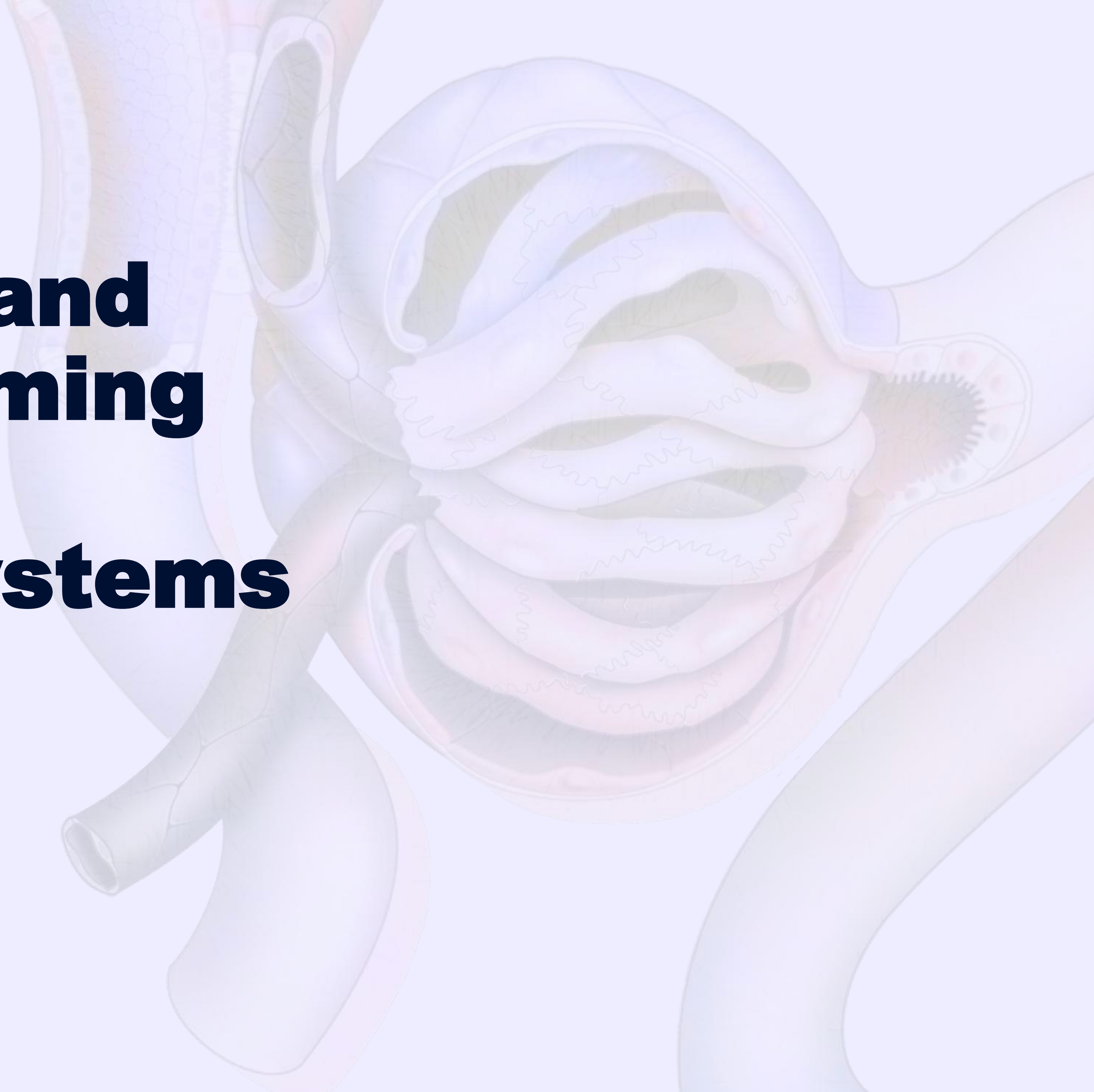
Nutrients, Diet and Lifestyle: Reframing Chronic Kidney Disease as a Systems Disorder



Michael Osiecki

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Conflict of Interest

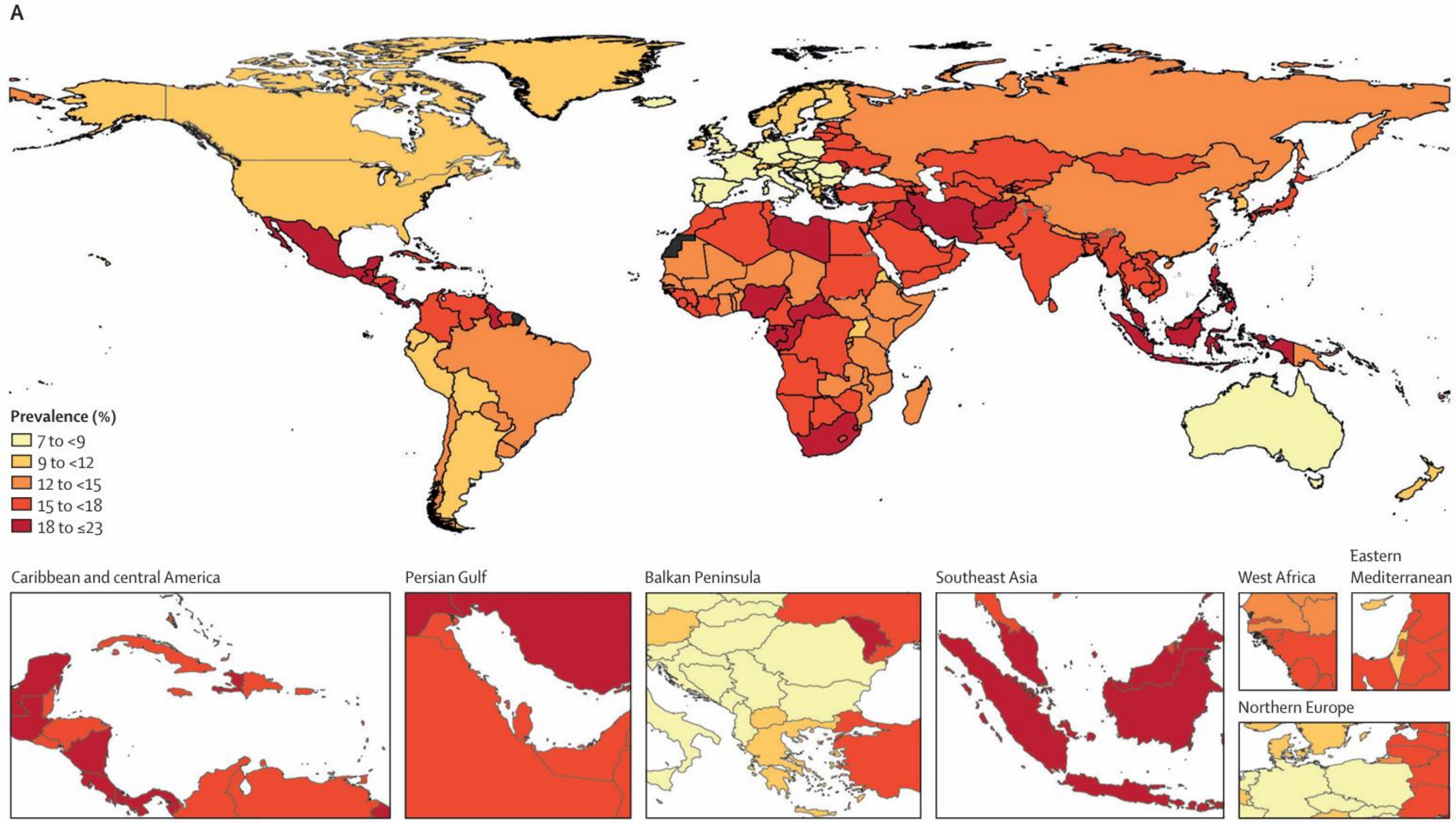
- Dr. Michael Osiecki is the Managing Director and owner of Bio Concepts which sells Nutraceuticals under the brand of Orthoplex.
- Dr. Michael Osiecki is the Vice Chair of Complementary Medicines Australia (CMA), a peak industry body that represents Manufacturers, Sponsors, Suppliers, Retailers and Practitioners in the complementary medicine industry.

Outline

- The renal problem and how to identify at risk patients.
- Renal disease as a cause and driver of comorbid conditions
- Exploring Malnutrition and Protein
- Further supplemental support

Global Prevalence

Globally CKD has a prevalence of 7.2% for >30 years of age, rising to 23.4-35.8% for those older than 64 years



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The Silent Disease is on the Rise

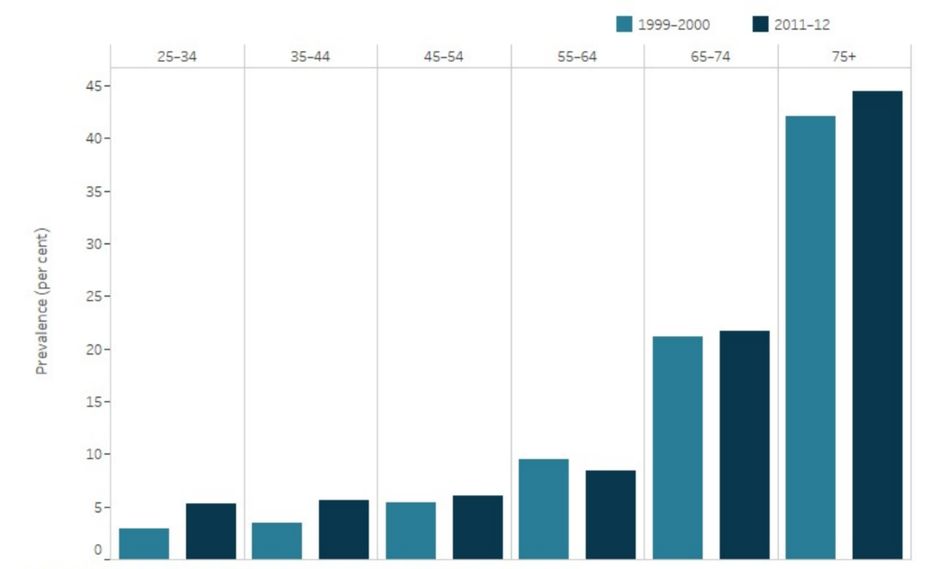
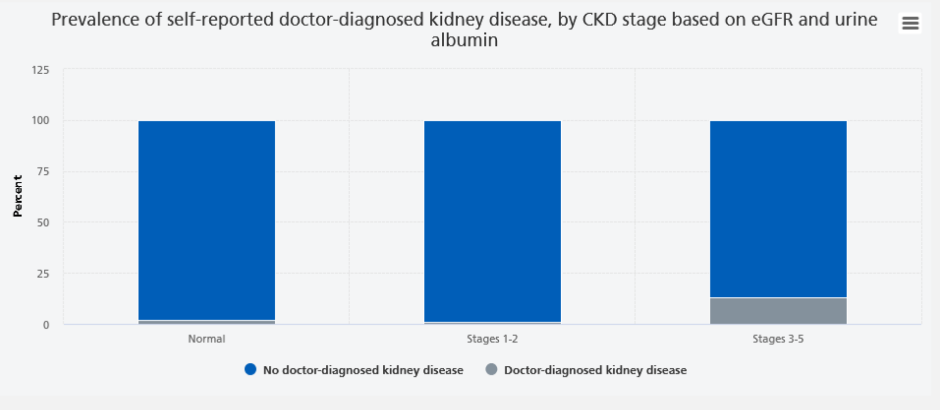


Figure 5: Prevalence of chronic kidney disease by age, 1999–2000 and 2011–12



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Chronic Kidney Disease (CKD)

Increased risk of all forms of death and higher susceptibility to other disease conditions:

- **Cardiovascular disease, at least double that of the general population and major cause of death**
- **Diabetes**
- Cancer
- Infections
- Stroke
- Sarcopenia
- Dementia

Integrative medicine considerations:

- Malnutrition; 40% CKD population is malnourished: Vitamin, mineral (imbalance) and amino acid deficiency (protein wasting) and metabolism (vitamin D)
- **Anaemia**
- **Metabolic acidosis**
- **Secondary hyperparathyroidism (vitamin D3 deficiency, hyperphosphataemia, hypocalcaemia)**
- Increase of ROS and inflammation
- Intestinal hyperpermeability and gut dysbiosis
- AGE and increase RAGE
- NAFLD
- Adipokines and leptin resistance
- Mitochondrial dysfunction (fatigue)
- Arthritis.

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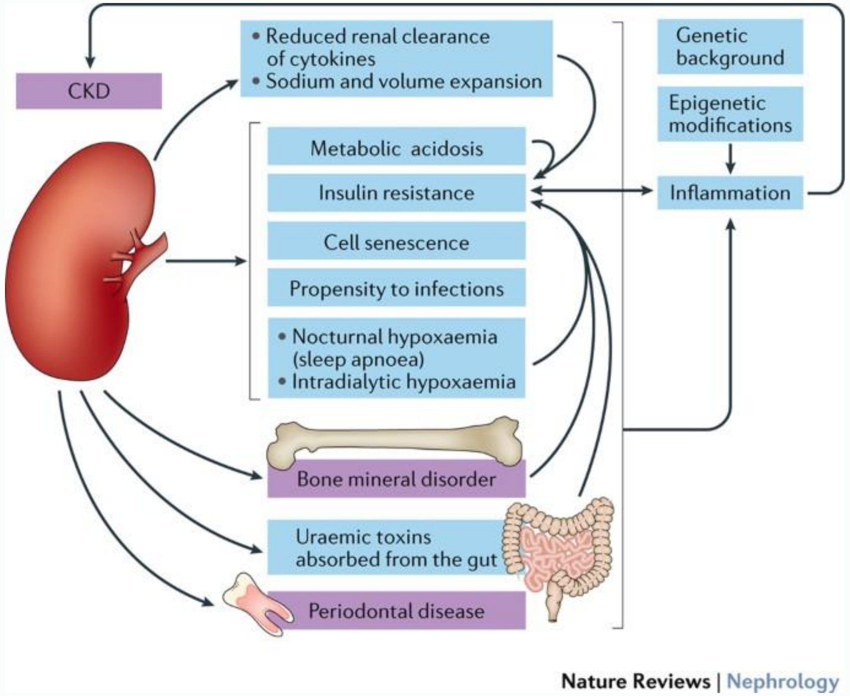
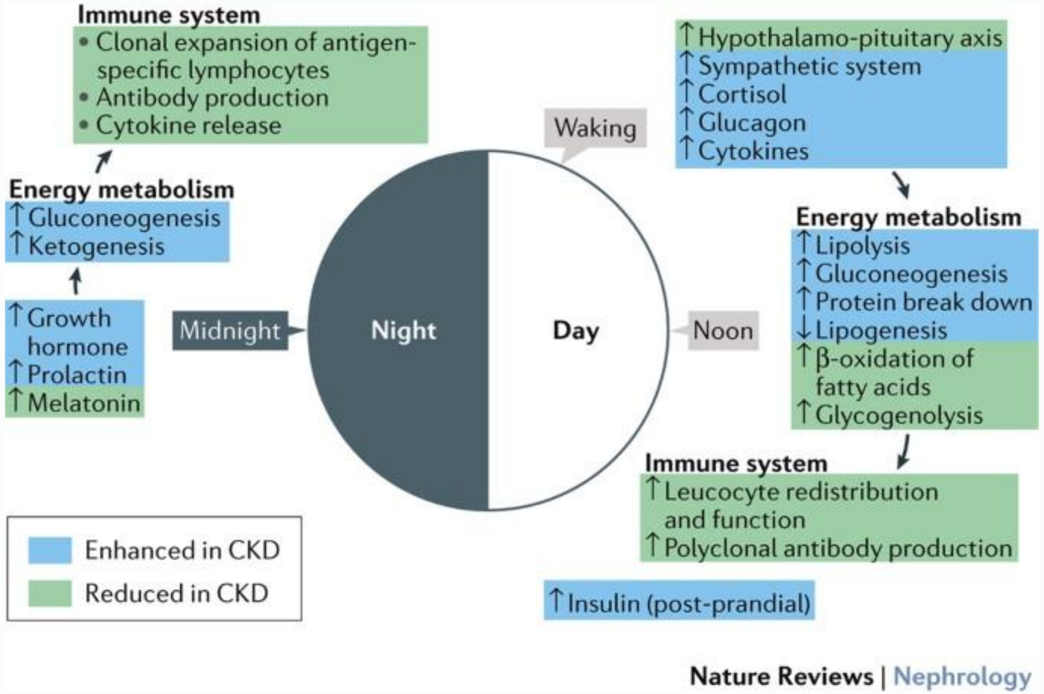
CKD is a Systematic Inflammatory Disease





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Pathology Analytes

Diagnostic Criteria

- Diagnosed by blood: Urea, Creatinine and albumin, GFR/eGFR, proteinuria
- imaging or biopsy.

Further Considerations

Markers are in the range or trending outside the ranges.

- eGFR – calculated with creatinine or cystatin C. Values between 60 and 90 ml/min/1.75 m^2 need to be investigated with urinalysis. Rate of decline is important here.
- eGFR based on creatinine overestimates function, especially >60 ml/min/1.75 m^2

- Difference between eGFR (Cys C) – eGFR (Creat) (diff<-10) has a higher mortality and renal failure.
- Cystatin C- reciprocal (1/Cys C) may be more sensitive to renal decline than creatinine levels (0.5-1 mg/L)
- Bicarbonate – low (22-29 umol/L)
- Anion Gap – high (8-16 mmol/L)
- Urea – high (2.5-7.8 mmol/L)
- Creatinine – high (M: 59-104 umol/L, W: 45-84 umol/L)
- Uric acid/urate – high (M: 0.2-0.45 mmol/L, F: 0.15-0.4 mmol/L)
- Phosphate and potassium
- Low/decreasing lymphocytes

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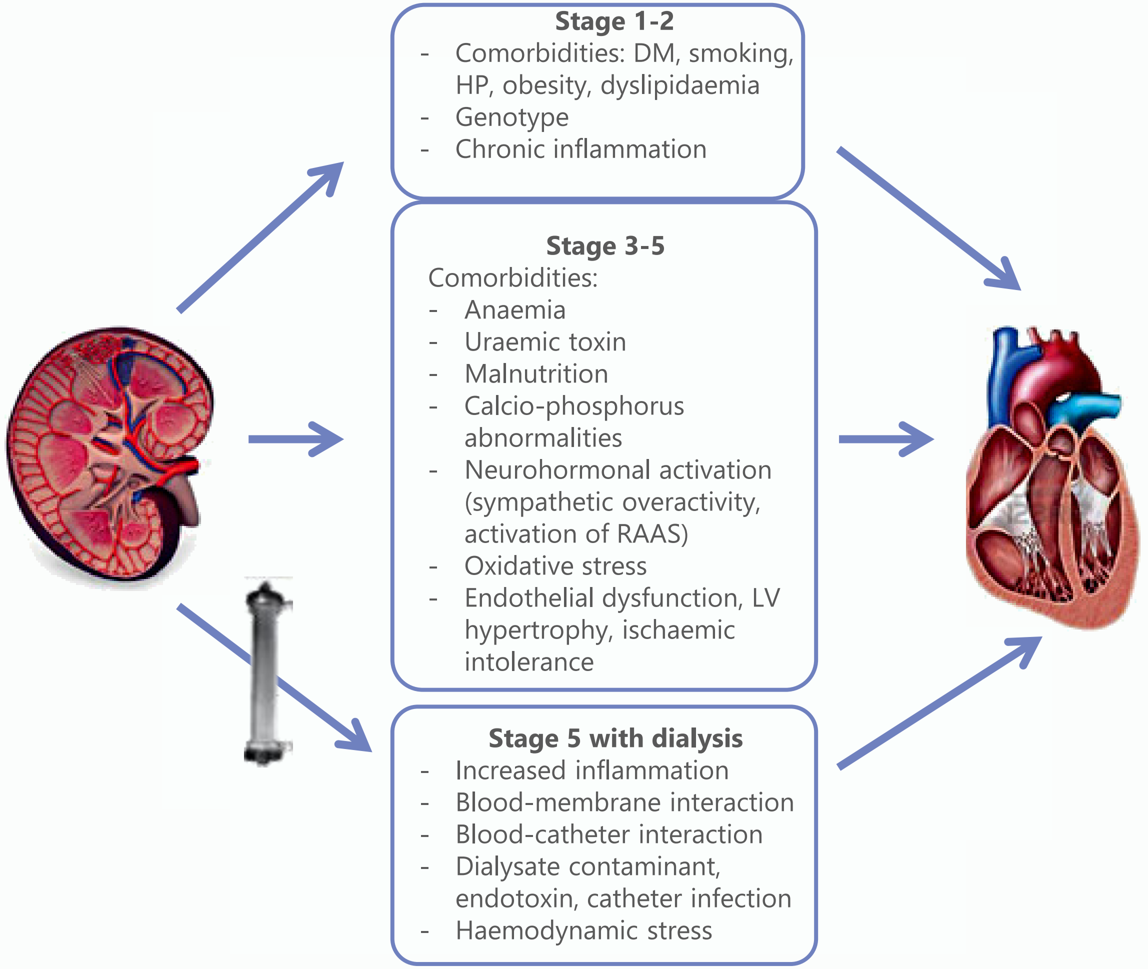
Stages of Renal Failure and Comorbidities and Contraindications

		Albuminuria Stage		
		Normal (urine ACR mg/mmol)	Microalbuminuria (urine ACR mg/mmol)	Macroalbuminuria (urine ACR mg/mmol)
CKD stage	GFR	Male: <2.5 Female : <3.5	Male: 2.5 - 25 Female 3.5 - 35	Male: >25 Female : >35
1	≥90	Low risk	Moderately increased risk	Very high risk
2	60-89	Low risk	Moderately increased risk	Very high risk
3a	45-59	Moderately increased risk	High risk	Very high risk
3b	30-44	High risk	High risk	Very high risk
4	15-29	Very high risk	Very high risk	Very high risk
5	<15 or on dialysis	Very high risk	Very high risk	Very high risk

Figure 2: Stages of chronic kidney disease and risk of progression, by GFR and albuminuria

Note: For 'low risk' categories, CKD is not present unless haematuria, structural or pathological abnormalities are present.



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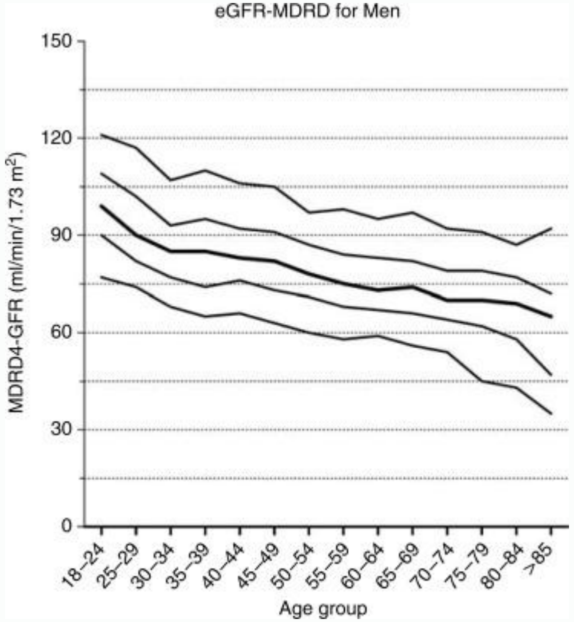
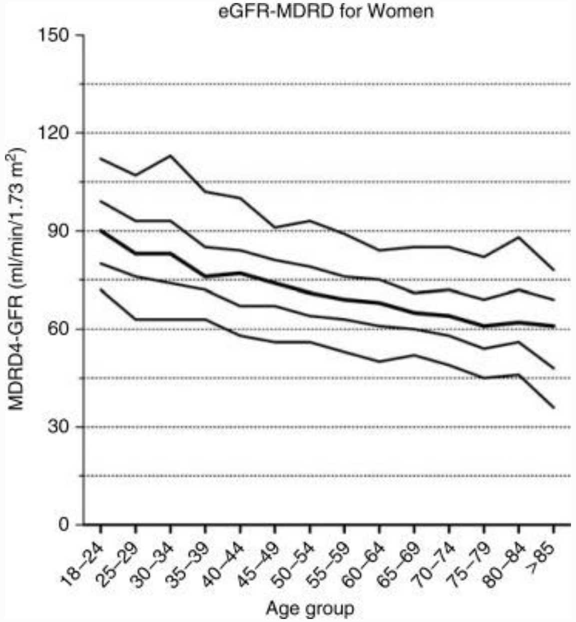
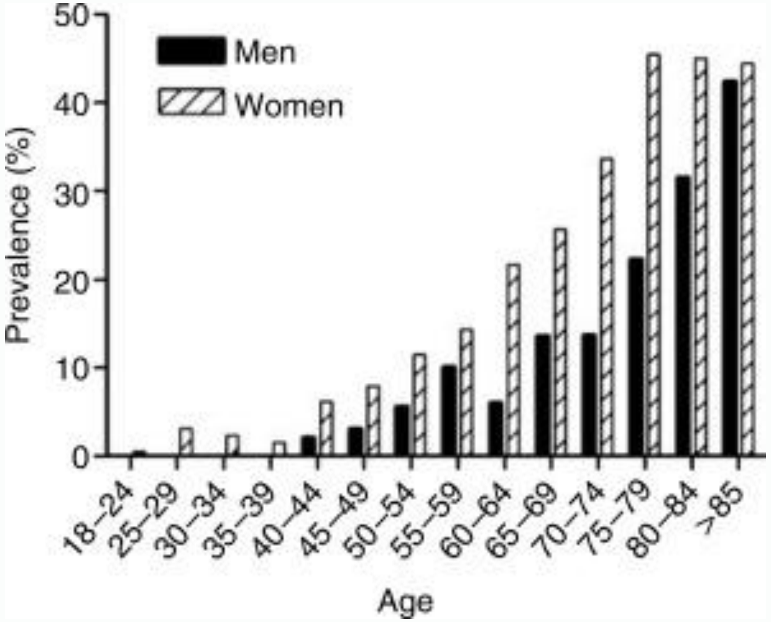
eGFR and Age







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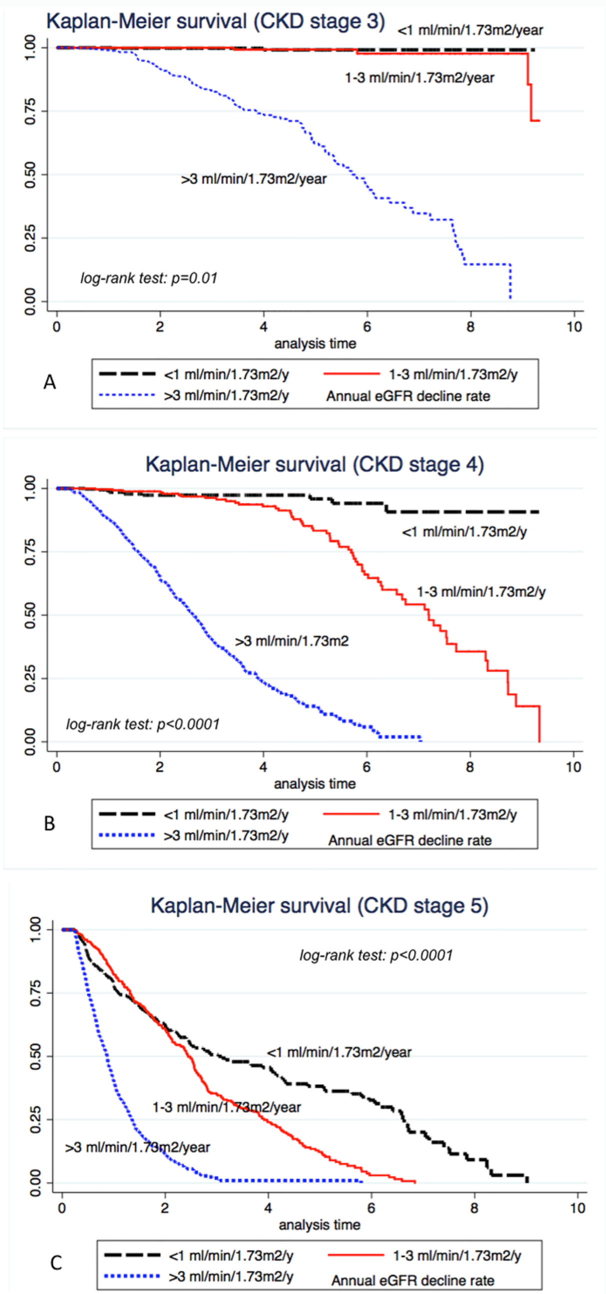
eGFR Rate of Decline - Key Diagnostic

- Not everyone with CKD will progress to end stage renal disease. However, patients who have a drop of >3 ml/min/1.73 m^2/year are extremely likely to be on dialysis within 10 years.
- Healthy people on average lose 0.4 ml/min/1.73m^2/year.
- Patients with this rate of decline are a priority for intervention.



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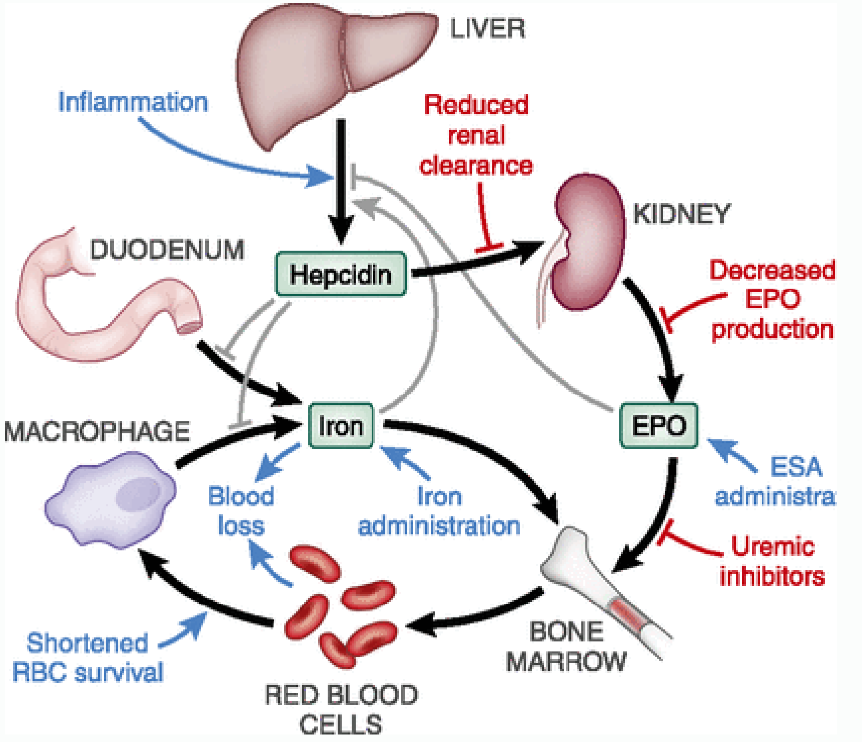
CKD and Anaemia

- Erythropoietin is mostly made in the kidney. When damaged, the production decreases.
- Along with a loss of protein and iron, red blood cell production decreases.
- Elevated urea & uraemic toxins (indoxyl sulfate and p-cresyl sulphate) inhibit EPO signalling & is a bigger driver of anaemia.
- Inflammation induces hepcidin, reducing circulating free iron and hypoferraemia. Inducing degradation of ferroportin in the enterocytes.
- Anaemia is a major driver of renal disease progression due to subsequent hypoxia in all organs. Therefore, a feedforward process of further damaging the kidneys and leading to heart failure.



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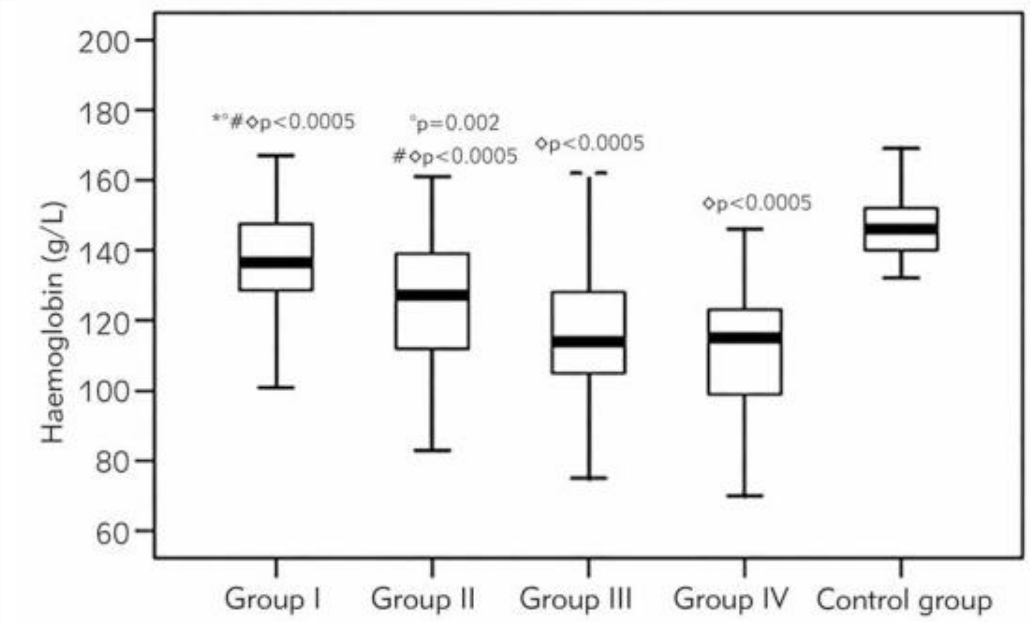
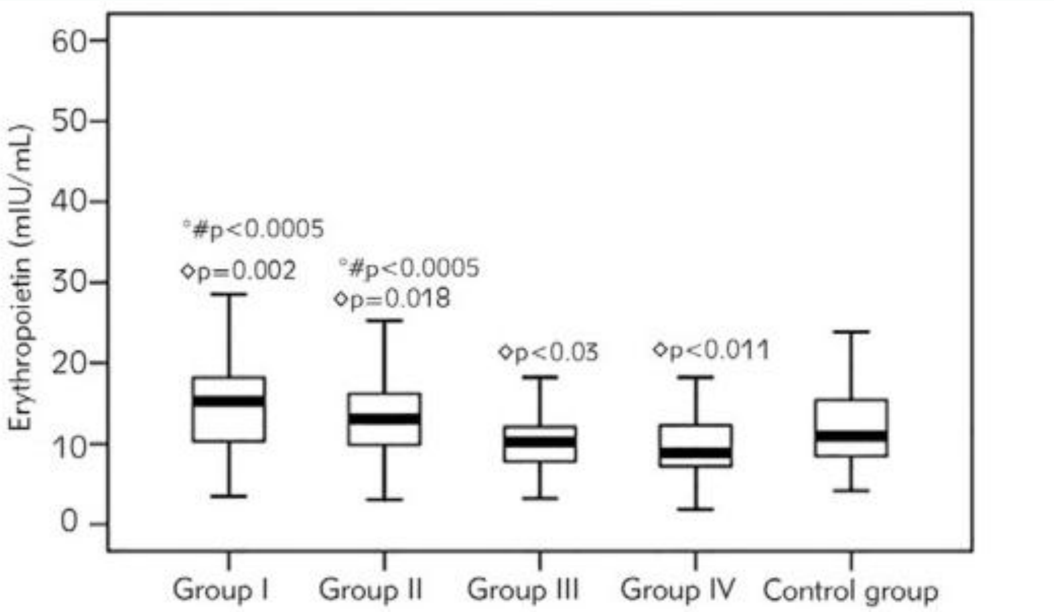
Renal Function Correlates with Haemoglobin and EPO Levels





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Endocrine Disruption in Renal disease

The etiology of selected endocrine abnormalities in chronic kidney disease

Type of defect	Example
Abnormalities of hormone catabolism Decreased metabolic clearance	Insulin, PTH, leptin, adiponectin, gastrin
Abnormalities of hormone production	
Reduced hormone production in endocrine organs	testosterone, estrogens
Reduced hormone production by the kidney	$1,25(OH)_2D_3$, erythropoietin
Reactive hypersecretion of hormone to reestablish homeostasis	PTH, FGF 23, erythropoietin
Inappropriate hypersecretion due to disturbed feedback	ACTH, LH, prolactin
Abnormal secretion pattern (pulsatility; circadian rhythm)	GH, LH
Abnormalities of hormone activity	
Increased isoforms with potentially less bioactivity (because of posttranscriptional modifications)	LH
Increased serum hormone binding proteins concentration resulting in the reduced availability of free hormone	IGF
Decreased serum hormone binding proteins concentration resulting in the increased availability of free hormone	leptin
Changed receptor quantity and/or structure	vitamin D receptor
Altered postreceptor cellular signaling	insulin, GH
Altered activation of prohormones	proinsulin, thyroxin (T_4)

Hypothalamic-pituitary-gonadal axis disturbances in chronic kidney disease

	Female	Male
FSH	N	↑
LH	↑	↑
Prolactin	↑	↑
Estradiol	↓	N
Progesterone	↓	—
Testosterone	—	↓

Hypothalamic–pituitary–thyroid axis alterations in chronic kidney disease, chronic nonthyroidal, nonkidney illness and primary hypothyroidism

	TSH	T_4	T_3	rT_3
Chronic kidney disease	N	N, ↓	↓	N
Chronic nonthyroidal, nonkidney illness	N	N, ↓	↓	↑
Primary hypothyroidism	↑	↓	↓	N

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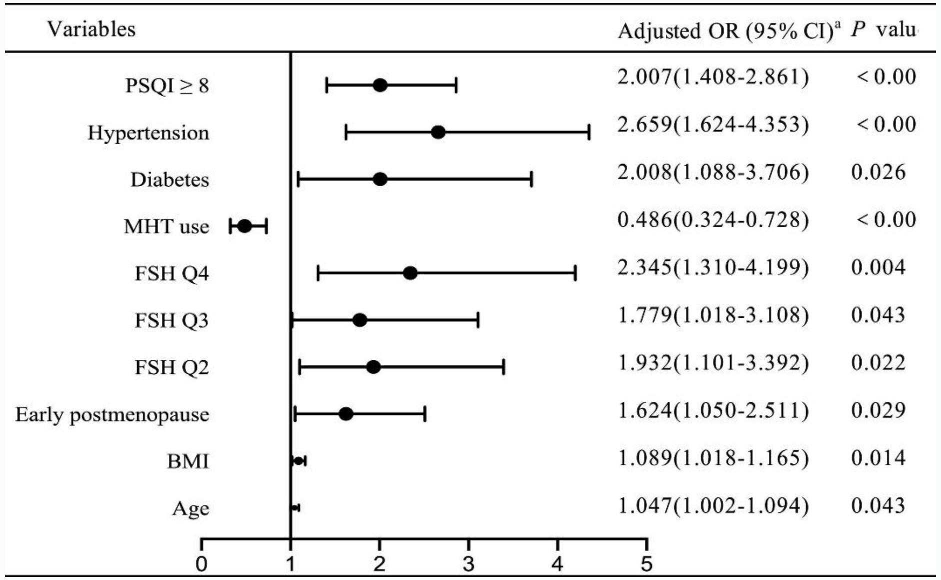
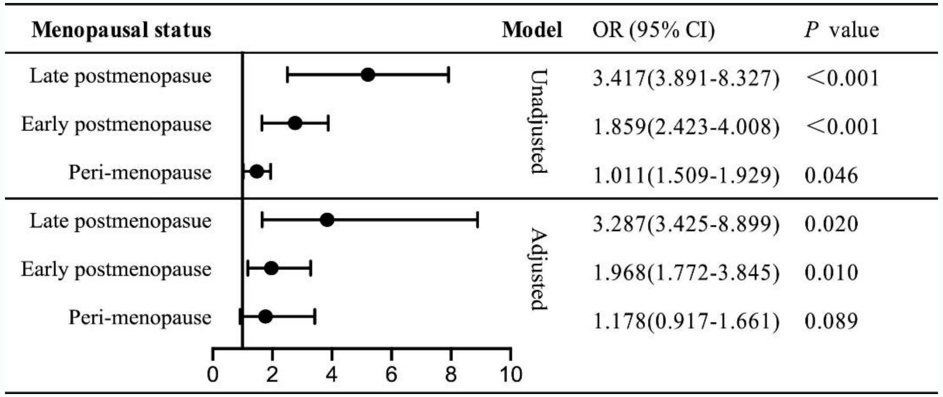
Menopause: An Initiator of Renal Function Decline

- The hormonal changes in menopause result in increased prevalence of hypertension, diabetes and dyslipidaemia that increases the risk of cardiovascular disease and CKD.
- The changes in mineral balance of calcium (bone loss) and increasing sensitivity to sodium due to the drop in oestrogen puts pressure on the kidneys.
- Oestrogen decreases angiotensin 1 receptors in the kidney (vasoconstriction pathway), as well as ACE and increases AGT.
- Poor sleep compounds the effects
- We see renal function decline in at-risk women at menopausal age.





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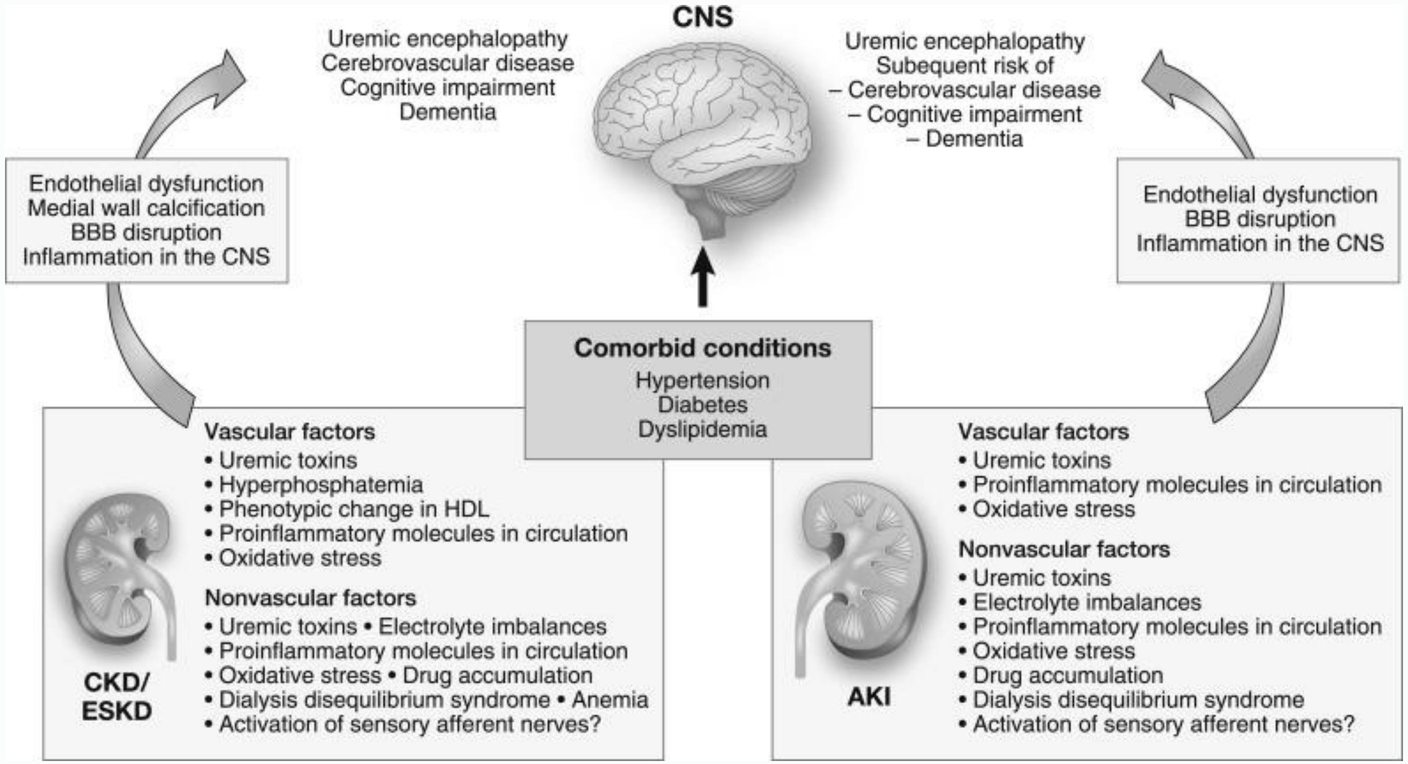
How CKD or AKI Damages the Central Nervous System

The Brain-Kidney Axis



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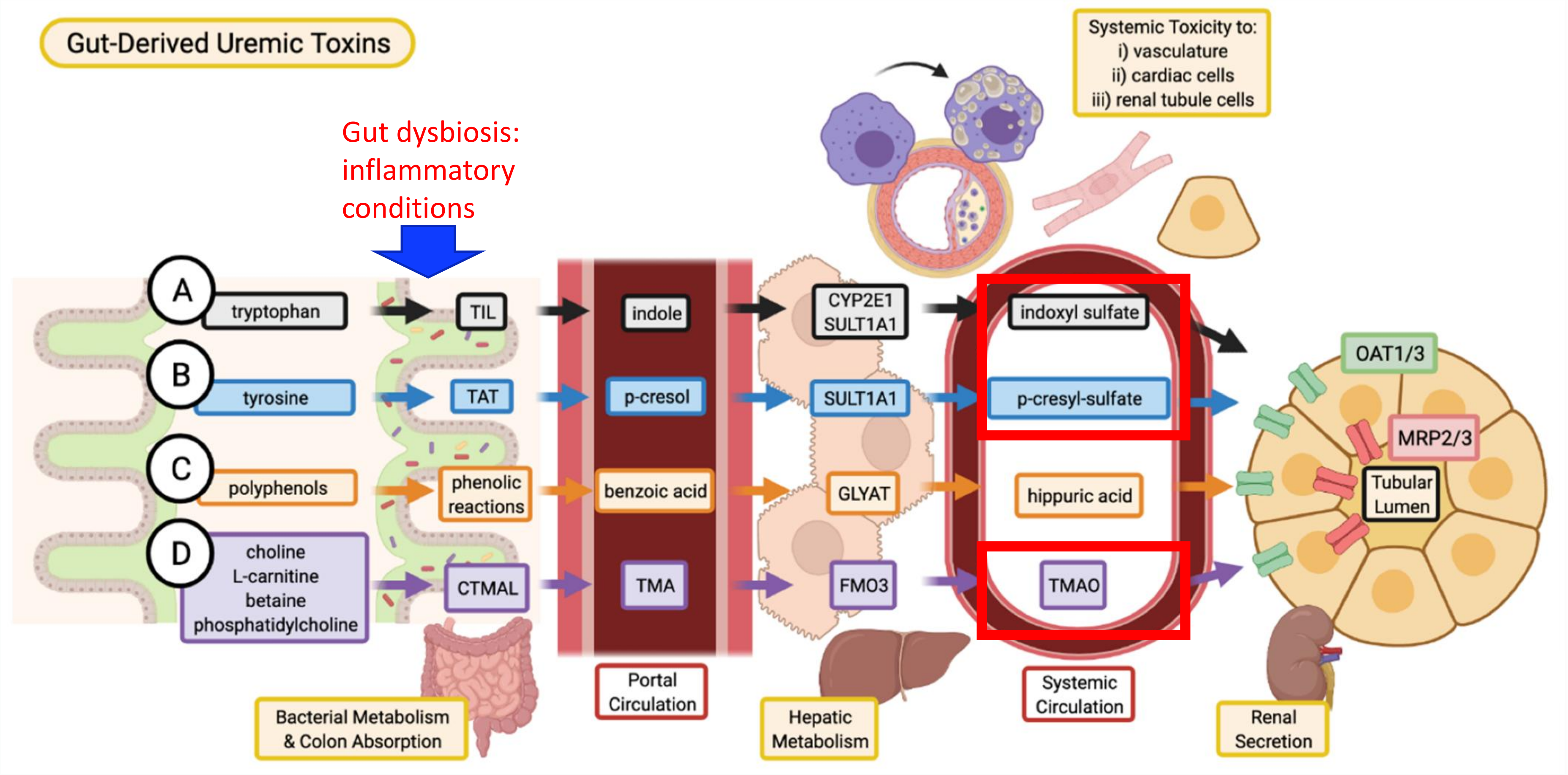
Uremic Toxins: The Gut Kidney Axis



Renal disease leads to a build-up of uremic toxins, driving inflammation which feeds back to gut dysbiosis and disrupting protein post translational modifications

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The Gut-Kidney Axis

- CKD results in disruption to the intestinal barrier as well as changes to the microbiome. Through influx of circulating urea to the gut lumen and dietary restriction that reduces food containing fibre to avoid hyperkalaemia and hyperphosphataemia.
- These factors promote systemic inflammation and cardiovascular morbidity by mediating microbial dysbiosis, disruption of the intestinal epithelial barrier, and translocation of endotoxin, bacterial fragments, and uraemic toxins across the “leaky gut” into the bloodstream.
- This can lead to further immunosuppression.
- Uraemic toxins and gut issues cause disruption in nutrient absorption and microbiome production of vitamins like thiamine leading to functional deficiencies.
- Constipation is common in CKD patients and can increase the production of uraemic toxins like p-cresyl sulphate.
- Low protein diets can alter the microbiome and reduce uraemic toxin production.
- Prebiotics can reduce serum urea −2.23 mmol/L, 95% CI −3.83 to −0.64, P = 0.006.

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Dialysis treatment for one year has a 10-15% mortality rate

5-year survival rate of 40-50%

Can drop further with co-morbid conditions like diabetes and CVD, 5-year survival rate is 25%

Highest risk is in the first 3 months

While transplant survival is 80% after 5 years

CKD is a disease of malnutrition

Sarcopenia and CKD

- Prevalence of sarcopenia in CKD patients 9-65% higher than age matched populations. This is more on the higher side when the patient is on dialysis at 25-75%.
- Older (>75 years) patients on dialysis have a far higher rate of sarcopenia than less senior (65-74 years) patients, 55% v 12.5%.
- Muscle degradation is more of a factor in CKD, with higher levels of inflammation, insulin resistance, metabolic acidosis, vitamin D deficiency and oxidative stress.
- Overall malnutrition leads to higher mortality for CKD patients.

	CKD-related sarcopenia	Ageing-related sarcopenia
Muscle protein degradation	Increased	No change/increased
Muscle protein synthesis	Decreased	Decreased
Resting energy expenditure	Increased/unchanged	Unchanged
Inflammation	Increased	Increased or unchanged
Insulin resistance	Present	Present
Body fat	Unchanged, increased or decreased	Normally increased
Muscle fiber change	Atrophy in type I and II fibers	Preferential loss of type II fibers

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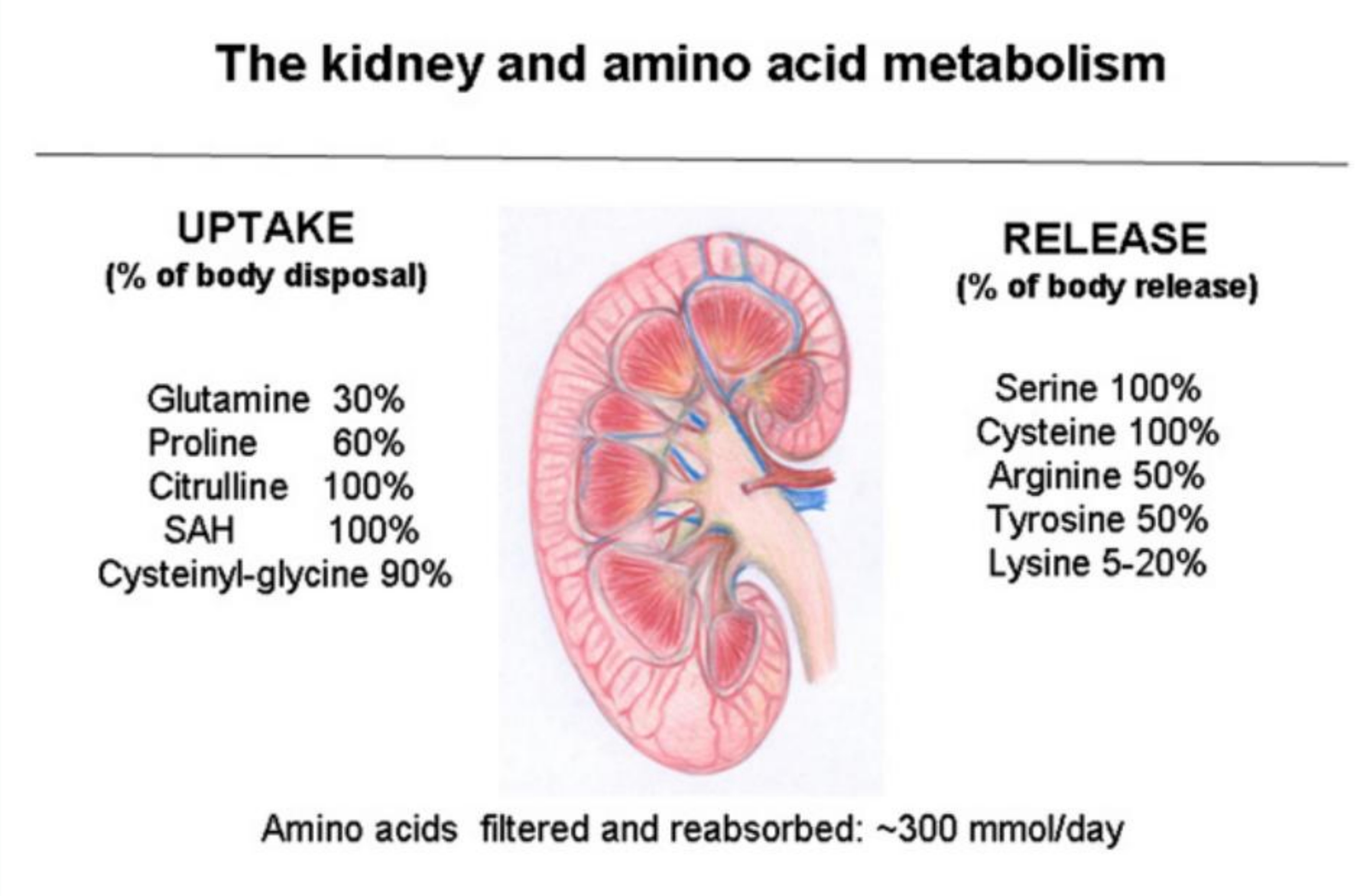
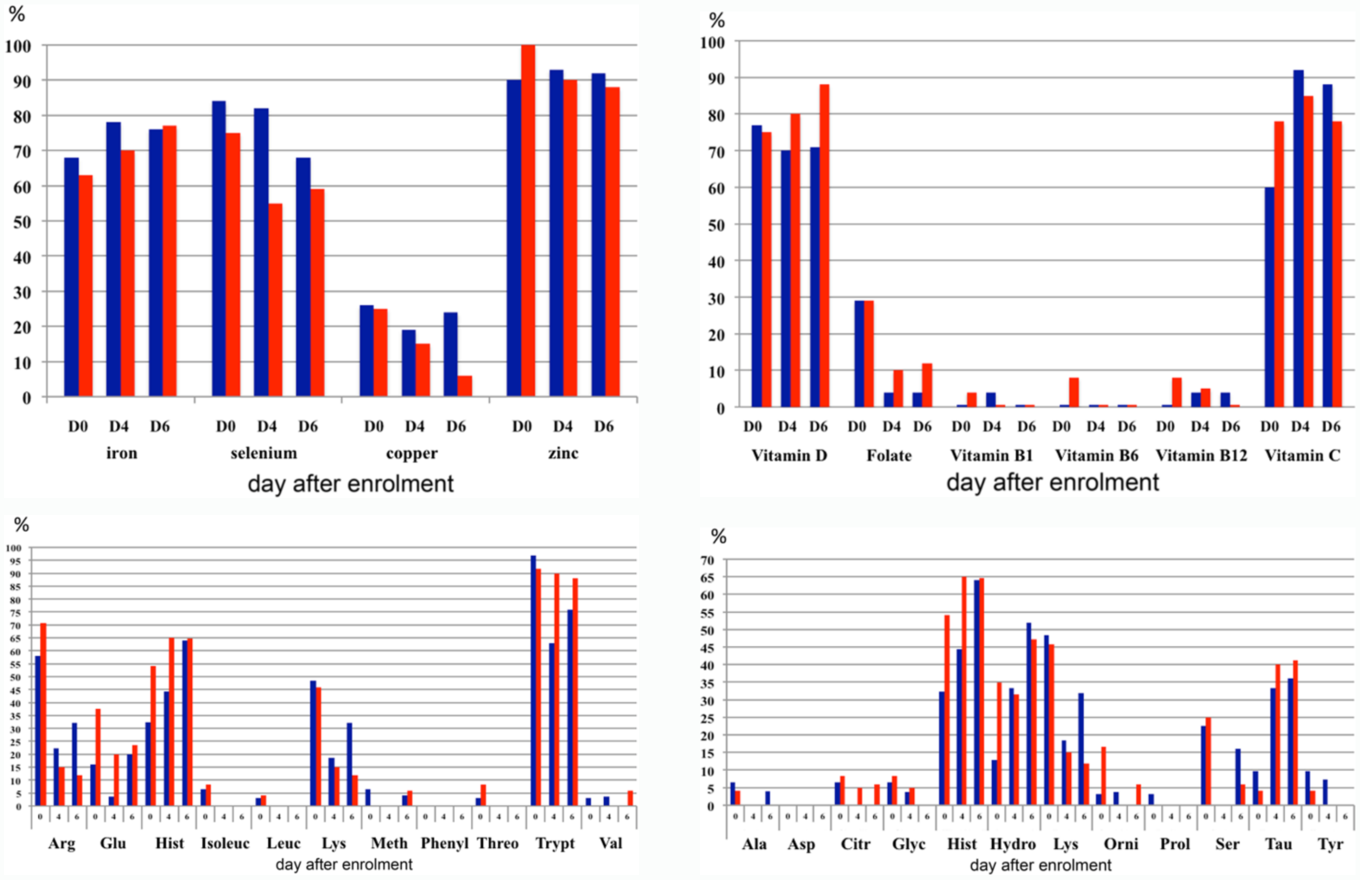
Kidney and Amino Acid Metabolism



Garibotto Giacomo G, Sofia A, Saffioti S, Bonanni A, Mannucci I, Verzola D. *Clin Nutr*. 2010;29(4):424-433. doi:10.1016/j.clnu.2010.02.005
Knol, M. G. E., Wulfmeyer, V. C., Müller, R.-U., & Rinschen, M. M. (2024). Nature Reviews Nephrology, 20(12), 771–788. https://doi.org/10.1038/s41581-024-00872-8

Malnutrition in Acute Kidney Injury



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Amino Acid Metabolomic Profiling between CKD and ESKD

Table 2. Plasma concentrations of amino acids and amines in nondialyzed patients with CKD stages 2–5 and hemodialyzed patients (micromoles per liter)

Variables	CKD2–5 (*n*=52)	Hemodialysis (*n*=25)	*P* Value
Total amino acid	2558.3±441.7	2162.9±615.4	0.01[a]
Total essential amino acid	989.8±237.9	762.1±284.0	<0.001[a]
Total nonessential amino acid	1568.5±272.4	1400.8±379.8	0.06
Total branched chain amino acid	405.4±138.1	314.7±127.2	0.01[a]
Alanine	320.9±102.8	232.7±90.4	<0.001[a]
Arginine	91.0±29.9	68.0±29.6	<0.001[a]
Asparagine	40.9±10.0	40.5±14.6	0.58
Aspartate	5.8±19.5	15.7±23.1	0.01[a]
Citrulline	49.9±24.2	67.5±26.1	0.01[a]
Glutamine	526.6±70.3	473.2±117.8	0.04[a]
Glutamate	84.9±83.4	58.3±49.0	0.09
Glycine	187.6±62.2	166.8±54.0	0.27
Histidine	76.4±14.9	67.8±25.6	0.03[a]
Isoleucine	75.9±28.6	61.5±25.4	0.03[a]
Leucine	114.0±50.0	87.3±47.6	0.02[a]
Lysine	189.6±45.1	150.3±62.9	0.001[a]
Methionine	37.5±11.4	26.8±12.0	<0.001[a]
Ornithine	60.9±22.9	56.1±19.3	0.39
Phenylalanine	67.0±15.8	59.2±18.0	0.06
Proline	228.9±70.5	279.7±108.7	0.04[a]
Serine	82.0±19.3	65.9±27.6	0.003[a]
Threonine	100.6±29.9	75.8±36.5	0.01[a]
Tryptophan	48.4±14.4	24.0±14.1	<0.001[a]
Tyrosine	65.0±22.7	43.5±17.8	<0.001[a]
Valine	215.4±69.0	165.9±62.1	0.003[a]
Asymmetric dimethylarginine	0.81±0.4	1.79±0.6	<0.001[a]
Symmetric dimethylarginine	1.17±2.4	0.64±0.4	0.03[a]
Hydroxykynurenine	2.07±1.2	5.50±1.8	<0.001[a]

All values are mean ± SD.
[a]$P<0.05$.

Table 3. Plasma concentrations (micromoles per liter) and urinary excretion (micromoles per mole creatinine) of amino acids and amines in nondialyzed CKD patients

Variables	Plasma Concentration			Urinary Excretion		
	CKD2–3	CKD4–5	*P* Value	CKD2–3	CKD4–5	*P* Value
Total AA	2512.4±411.0	2597.7±470.2	0.49	246.5±107.1	324.8±303.2	0.90
Total essential AA	1006.0±234.1	975.9±244.5	0.68	71.8±35.4	104.7±101.4	0.80
Total nonessential AA	1506.4±249.4	1621.8±284.4	0.13	200.1±126.8	220.1±204.5	0.56
Total branched chain AA	421.4±133.5	391.6±142.9	0.41	6.1±7.2	7.1±15.8	0.18
Alanine	305.3±100.0	334.3±105.0	0.32	23.8±21.5	30.7±29.2	0.54
Arginine	88.5±25.7	93.1±33.3	0.58	7.8±6.6	8.2±6.0	0.42
Asparagine	38.6±10.4	43.0±9.2	0.11	7.2±3.3	14.7±14.7	0.07
Aspartate	6.1±23.4	5.6±15.9	0.56	12.7±15.0	9.0±22.4	0.08
Citrulline	35.9±16.3	61.8±23.6	<0.001[a]	1.0±1.2	7.1±14.3	<0.001[a]
Glutamine	514.8±68.3	536.6±71.6	0.27	25.0±15.8	31.4±44.2	0.40
Glutamate	72.1±45.3	96.0±105.4	0.83	29.8±61.5	19.3±25.1	0.50
Glycine	185.3±48.1	189.5±73.1	0.71	69.9±44.8	67.6±69.6	0.32
Histidine	74.9±11.2	77.7±17.5	0.61	34.9±23.4	30.0±26.0	0.30
Isoleucine	76.7±26.9	75.2±30.4	0.80	0.9±1.9	0.6±2.9	0.11
Leucine	124.8±45.1	104.9±53.0	0.12	2.2±3.5	2.2±5.9	0.23
Lysine	186.3±45.7	192.4±45.2	0.53	10.4±10.3	26.5±30.7	0.11
Methionine	36.6±11.8	38.3±11.2	0.59	1.2±1.1	1.3±1.9	0.50
Ornithine	53.9±22.6	66.9±21.8	0.01[a]	15.4±57.1	1.8±5.1	0.33
Phenylalanine	62.9±12.0	70.5±17.9	0.15	4.9±2.9	6.7±7.1	0.94
Proline	212.4±71.8	243.0±67.5	0.12	2.6±2.6	13.8±18.5	<0.001[a]
Serine	83.4±20.7	80.7±18.1	0.62	21.3±10.2	25.4±19.7	0.73
Threonine	101.6±31.9	99.8±28.6	0.92	11.1±10.5	20.9±29.1	0.43
Tryptophan	55.5±12.3	42.3±13.4	<0.001[a]	4.5±2.5	4.8±3.9	0.88
Tyrosine	66.9±22.8	63.3±22.9	0.59	6.5±3.9	7.5±6.9	0.94
Valine	219.9±64.6	211.6±73.6	0.69	3.0±2.6	4.3±7.9	0.54
ADMA	0.57±0.29	1.02±0.48	<0.001[a]	2.37±0.93	1.51±1.43	<0.001[a]
SDMA	1.54±3.48	0.85±0.58	0.69	2.85±0.93	2.89±2.91	0.06
Hydroxykynurenine	1.19±0.39	2.82±1.22	<0.001[a]	0.13±0.10	0.45±0.90	0.15

All values are mean ± SD. CKD2–3, CKD stages 2 and 3; CKD4–5, CKD stages 4 and 5; AA, amino acid; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine.
[a]$P<0.05$.

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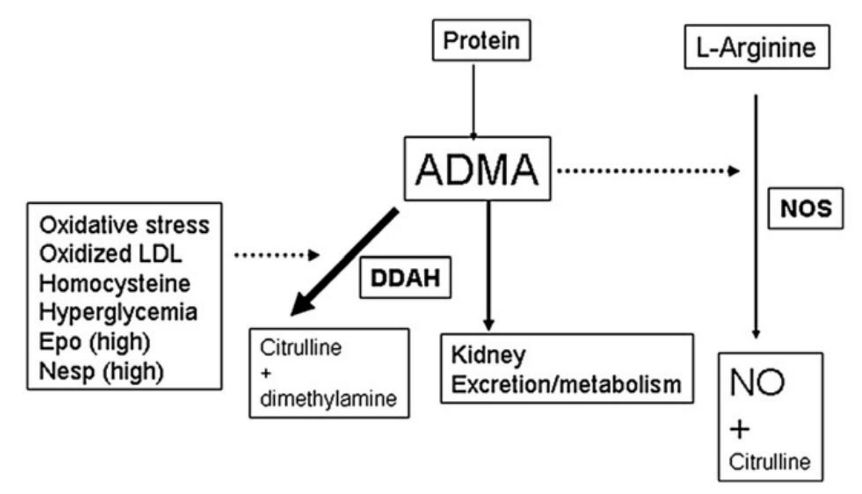
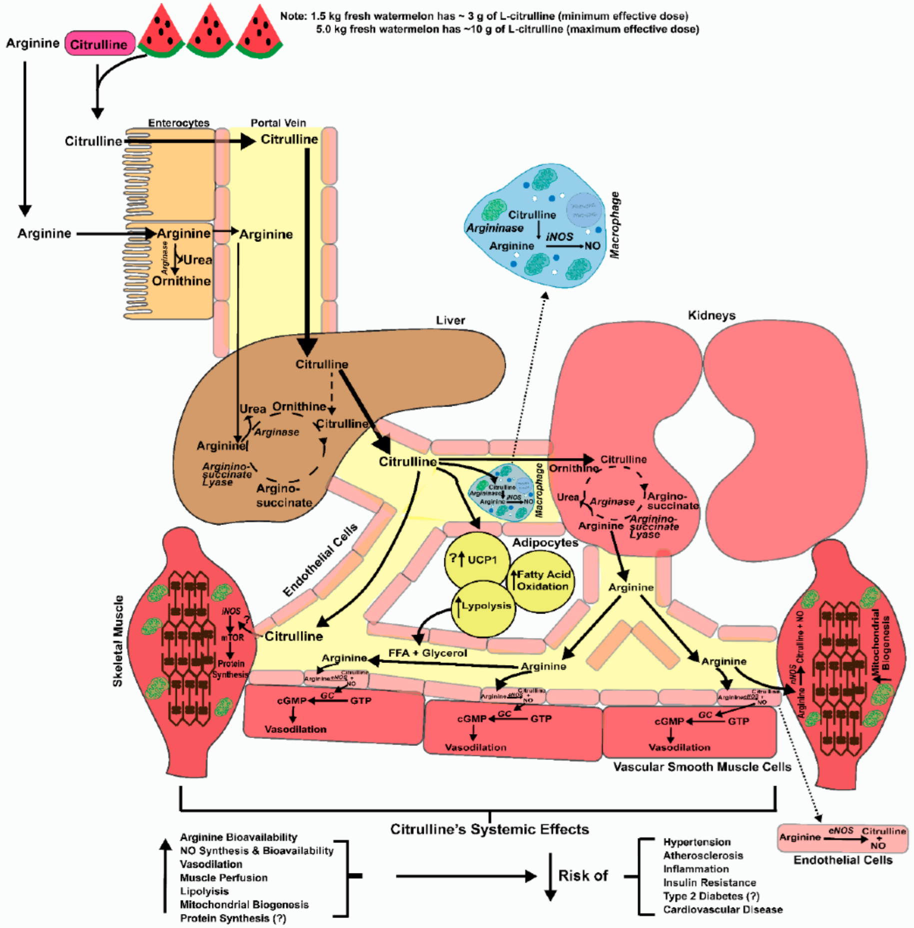
Zobel EH, von Scholten BJ, Reinhard H, et al. *Cardiovasc Diabetol*. 2017;16(1):1-9. doi:10.1186/s12933-017-0569-8
Garibotto Giacomo G, Sofia A, Saffioti S, Bonanni A, Mannucci I, Verzola D. *Clin Nutr*. 2010;29(4):424-433. doi:10.1016/j.clnu.2010.02.005

Citrulline/Arginine: It's Complicated





- Citrulline in early stage or non-CKD patients is better at increasing serum arginine levels and NO levels.
- Supplementation is indicated for diabetic nephropathy and hyperfiltration. Protection against endothelial disfunction.
- Polyphenols, ECCG and anthocyanins increase the surface expression of eNOS and decrease ADMA.

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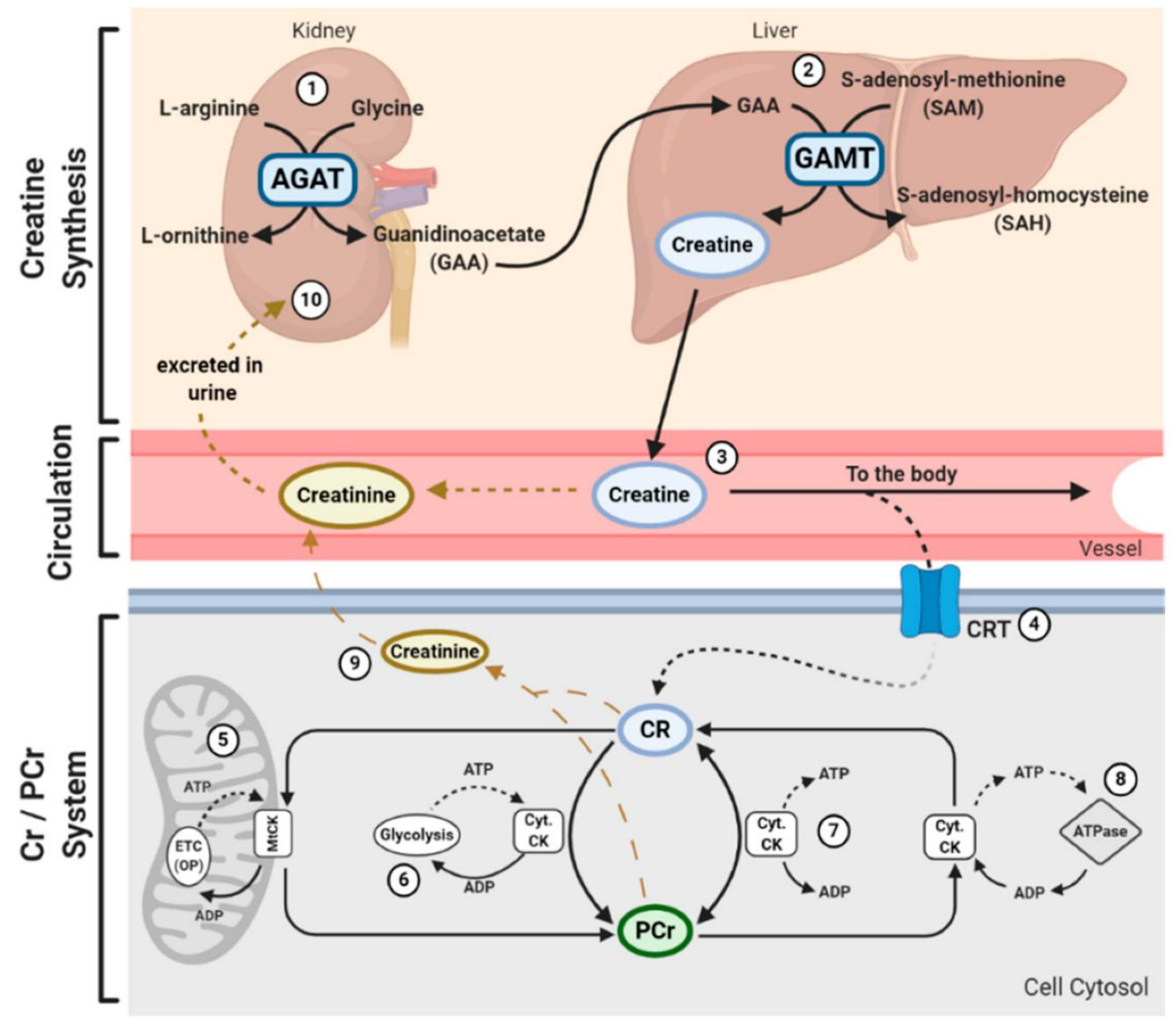
What is the go with Creatine?

- The kidney is a mitochondrial dense organ, it needs energy for maintaining membrane potential and reuptake of key metabolites and nutrients in the urine.
- Creatine phosphate is needed throughout the body cell types as an intermediary to transport ATP from the mitochondria throughout the cytosol.
- The first step in the metabolism of creatine using glycine and arginine occurs in the kidney.
- Creatine deficiency is highly prevalent in renal patients.
- **Neither creatine supplementation nor its metabolite creatinine causes renal damage**. Creatinine is used as a marker. Most studies show creatine supplementation has no significant effect on creatinine levels.
- From 2-5g daily doses, it is recommended to cease supplementation two weeks before diagnostic tests.
- Creatine synthesis can pull 40-70% on the SAMe pool. Supplemental creatine helps the stores of methyl donors therefore methylation as a whole.



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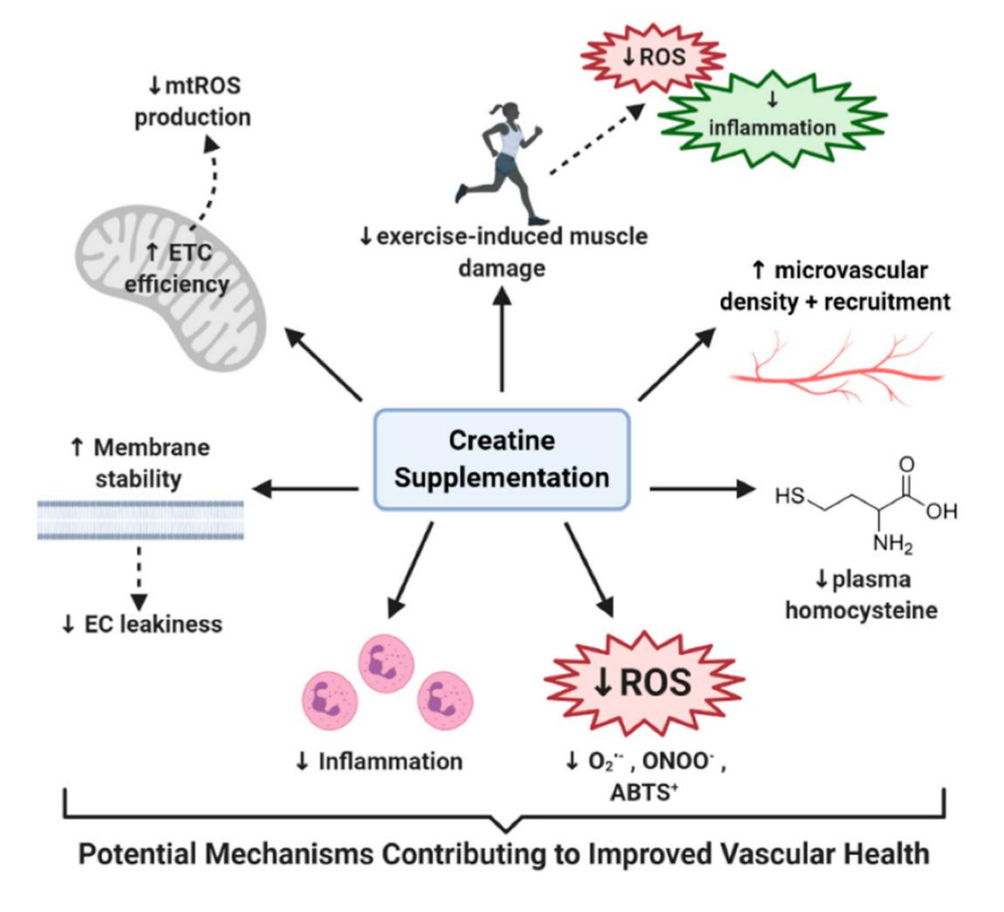
Creatine Essential to Support CKD Patients



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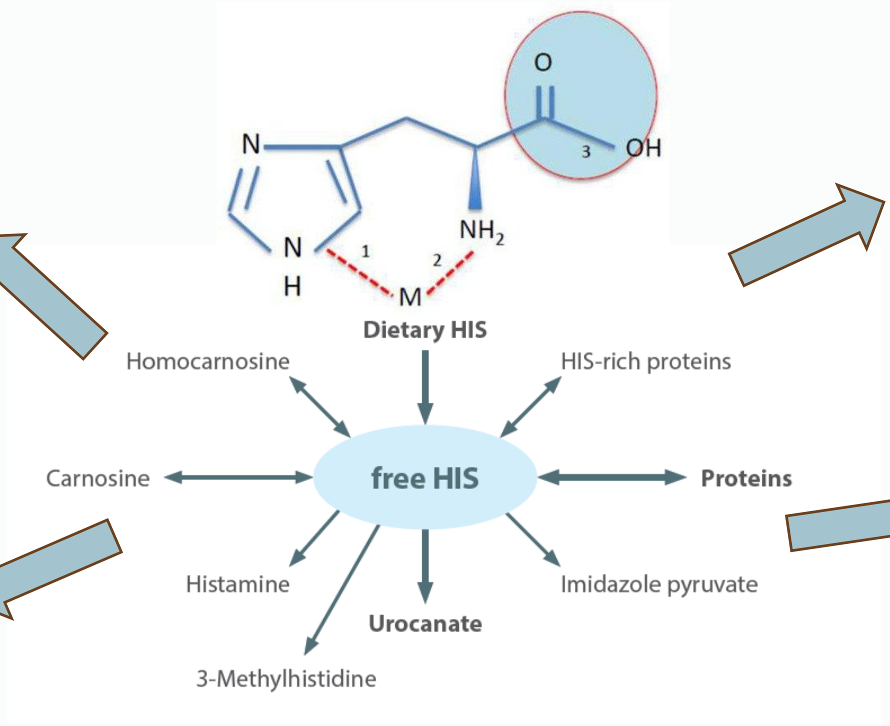
Histidine: The Forgotten Essential Amino Acid

Antioxidant

- Scavenger of reactive oxygen (ROS) and reactive nitrogen (RNS) species & hydroxyl radicals. Mediated by metal ion chelation.
- Sequestering advanced glycation and advanced lipid oxidation end products often related to complications in renal disease, microangiopathy and retinopathy in diabetes

Anti-inflammatory

- The antioxidant effects are associated with the inhibition and regulation of proinflammatory biomarkers IL-6, CRP and TNF-α, particularly in chronic disease states.
- Combines with beta alanine to make carnosine.



Dosage range
2-6 g/day

Ph buffer

- Of all the amino acid side chains in proteins, only the imidazole ring of HIS functions as a pH buffer – acting as an acid or a base as required.
- It can attenuate changes in intracellular pH in muscles during anaerobic exercise (reducing muscle fatigue) and has even been used in solutions to preserve organs for transplantation

Metal ion chelation & detoxification

- The structure of HIS contains an imidazole ring which allows the efficient chelation with divalent metal ions Fe^{2+}, Cu^{2+}, Co^{2+}, Ni^{2+}, Cd^{2+} and Zn^{2+}, filling the gaps of N-acetylcysteine's thiol group chelation of Fe^{3+}, Pb^{2+} and Hg^{2+}.
- Moderate doses (2-6g daily) of HIS protect against the negative effects of free-floating metal ions and takes them to where they are needed.
- In higher doses (>10g daily) HIS has also been shown to protect against copper-induced neurotoxicity.

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Song, B. C., Joo, N.-S., Aldini, G., & Yeum, K.-J. (2014). Nutrition Research and Practice, 8(1), 3–10. https://doi.org/10.4162/nrp.2014.8.1.3

Histidine: Clinical Effects

- Combines with beta alanine to make carnosine.
- Key for protein function e.g. metalloproteins, albumin and histidine rich glycoproteins.
- Histidine is essential in globin synthesis and erythropoiesis. Histidine deficiency leads to anaemia. Even in chronic uraemic patients. Used with EPO, **~700mg/day** histidine maintained haemoglobin at a higher level after week 12 and week 24.
- Alternate methylation pathway. Through the conversion to N-formimino-L-glutamate and using formimidoyltransferase-cyclodeaminase enzyme acts as a methyl-donor to THF to MTHF.
- Helps iron uptake in the GI and prevents free iron damage in iron infusion in renal patients when co-supplemented.
- Low plasma concentrations are associated with protein-energy wasting, inflammation, oxidative stress, and greater mortality in CKD patients.

Watanabe M, Suliman ME, Qureshi AR, et al. Am J Clin Nutr. 2008;87(6):1860-1866. doi:10.1093/ajcn/87.6.1860

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Histidine: Clinical Effects

- Epidemiological/observational studies and a few small clinical trials show histidine is effective at decreasing BMI, adiposity & metabolic markers (fasting glucose, postprandial blood glucose).
- A clinical trial of **4g/day for 12 weeks** showed increased insulin sensitivity and decreased fasting glucose by reduced gluconeogenesis in the liver via the histamine 1 receptor. Also reduced appetite.
- Another clinical trial of **2g/day for 2 weeks** showed less fatigue, improved sleep, mental focus, peripheral blood flow and anxiety.
- Improves libido, though histaminergic system in the brain to increase arousal of the forebrain and vasodilation and blood flow in peripheral sexual tissue.
- **4g/day for 4 weeks** reduces atopic dermatitis severity by 39%, by increasing filaggrin.

Watanabe M, Suliman ME, Qureshi AR, et al. Am J Clin Nutr. 2008;87(6):1860-1866. doi:10.1093/ajcn/87.6.1860
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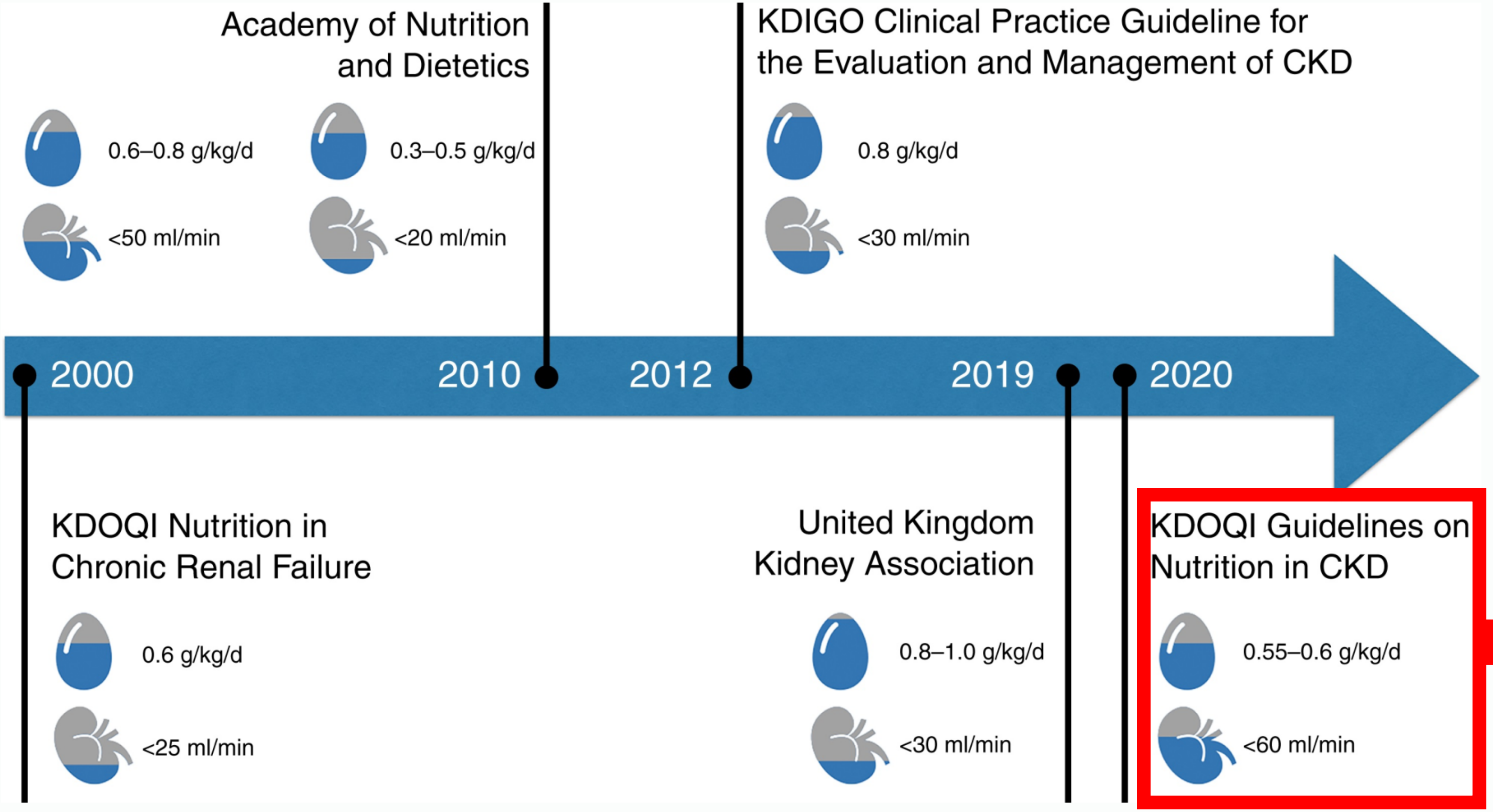
Low Protein Diet - What is the True Evidence?



Able to delay progression to ESRD (dialysis). However, diet was unable to reduce the eGFR decline.

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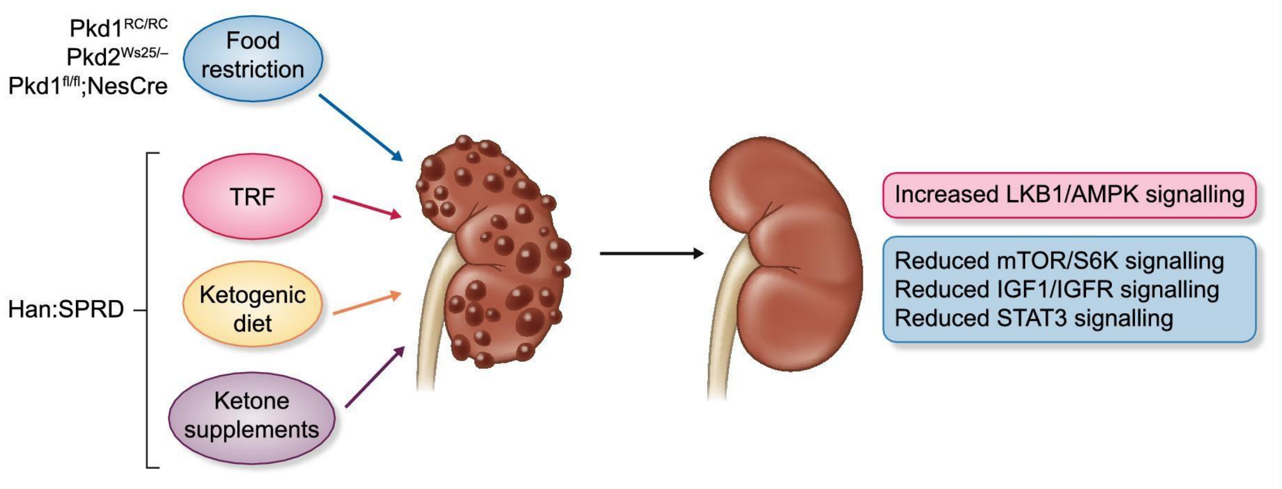
High Protein? Keto? Not all Protein is Equal

- Keto with a high fat content may be beneficial in CKD.
- Emerging evidence that Keto diet is better suited for polycystic renal disease.
- Patients on Keto diet run the risk of acidosis if not taking a strong plant approach.
- Better on a plant base protein; low carbohydrate (5-45%) and supplementing with mineral citrates.
- Safer in patients in stage 2-3 CKD. Oddly showed no benefit in CKD with T2D.
- Ultimately haven't shown superiority over other diets and have a higher risk factor.



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High Protein? Keto? Not all Protein are Equal

- High protein diets often lead to hyperfiltration. Through neuronal NO synthase β in the macula densa via tubuloglomerular feedback.
- Hyperfiltration is associated with rapid decline of renal function.
- Relative risk of hyperfiltration is 3.48 times higher in the highest protein intake population compared to the lowest in the general population.
- Low carbohydrate and high protein diet in healthy subjects increases acid load, increases the risk of stone formation, decreases estimated calcium balance, and may increase the risk for bone loss.
- Plant based diet that has a low inflammatory index is the most beneficial with normal protein levels. Mushrooms are very useful due to complete amino acid profile, vitamin mix, low acid load, low phosphorous and ergothioneine content.

Banerjee, T., McCulloch, C. E., Crews, D. C., Burrows, N. R., Pavkov, M. E., Saran, R., Morgenstern, H., Bragg-Gresham, J., & Powe, N. R. (2022). Kidney360, 3, 10.34067/KID.0000442022. https://doi.org/10.34067/kid.0000442022
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A Diet is Better Than None at All

- Two-year randomised trial comparing low-carbohydrate (non-restrictive, 22% energy protein) to Mediterranean (calorie restriction, 19% energy protein) and low-fat (calorie restricted, 19% energy protein).
- Improvements in eGFR were achieved in low-carbohydrate (+5.3% [95% CI 2.1–8.5]), Mediterranean (+5.2% [3.0–7.4]), and low-fat diets (+4.0% [0.9–7.1]) with similar magnitude ($P > 0.05$) across diet groups.
- Dietary adherence is key. Adherence American Heart Association (AHA) dietary pattern was significantly associated with the lowest risk of developing CKD (HR=0.63, 95% CI 0.55-0.71, Q5 vs. Q1). In comparison, adherence to other dietary patterns such as the Diabetes Risk Reduction Diet (DRRD) and EAT-Lancet diets conferred weaker protective associations. Conversely, the high adherence to an unhealthful Plant-Based Diet Index (PDI) was linked to an elevated CKD risk (HR = 1.44, 95% CI: 1.26-1.64, Q5 vs. Q1).
- Animal protein higher in sulphuric amino acids (cysteine, methionine) is associated with acidosis and risk of ESRD. Simply changing from red meat to white reduces risk.
- The urea/uric acid from protein metabolism is always going to be an issue. Serum uric acid is associated with renal disease progression.

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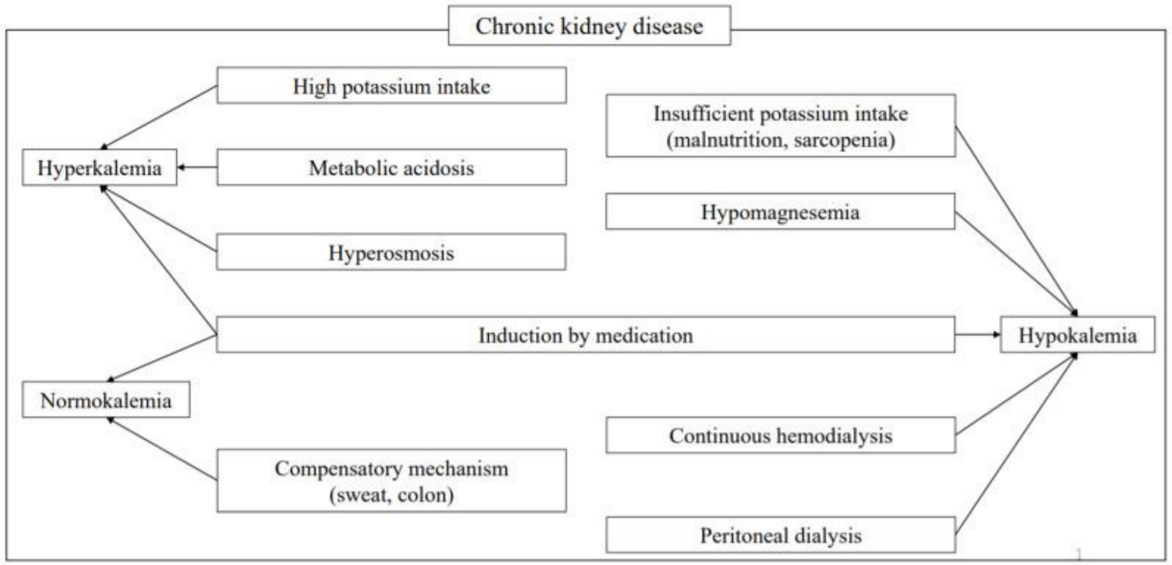
Potassium

- Na/K ratio needs to be controlled.
- Potassium is important for cardiac function and to counteract the effect of excess sodium. Also helps in buffering.
- CKD results in abnormal potassium metabolism. Excretion drops in chronic renal failure.
- Can lead to hyperkalaemia during acidosis, especially high risk at stage 4/5 and dialysis patients.
- Patient specific sensitivity either retaining or removing potassium during dialysis.
- Target range for CKD patients is 4-5.4 mmol/L. May want to have tighter bounds as renal function declines.
- RDI M: 3400 mg, F: 2600 mg is the safe intake for stages 1 and 2.
- For stage 3 and below best to limit potassium to 2000 mg/day and for stage 4&5 1500 mg/day
- Haemodialysis can go up 2000 mg/day, peritoneal dialysis 2000-2500 mg/day
- Hyperkalaemia risk comes from supplementation, salt substitutes and medication (RAAS inhibitors and MRAs) more than dietary. However, SGTL2 inhibitors and GLP-1 agonists reduce this risk, which now allows more flexibility.



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Nutrients for Mitochondrial Support & Oxidative Stress

- Mitochondria dysfunction is a hallmark in kidney disease; detected by urinary lactate levels.
- CKD associated with deficiency in oxidative defence systems. Vitamins C, D and E are essential along with selenium and B vitamins.
- Mitochondrial support is very important: CoQ10 (any form, 300 mg+), L- & acetyl-L-Carnitine (1 g), lipoic acid (50-300+ mg), B3/NAD producers, creatine (5g).
- Taurine, NAC and histidine can sequester selected non-radical oxidants.
- Taurine is deficient in tissues of CKD patients; low in dialysis patients.
- Taurine can accumulate in tissue quickly at higher dosages, keep below 4g/day. May need to go lower for certain patients.
- Low protein diet with supplemental NAC + taurine or NAC+P5P, both resulted in increase in eGFR, but NAC+P5P strongest with an increase of eGFR ~8.5. Both treatments worked better in patients at stages 3b and above with no signs of acidosis.

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Summary of Integrative Interventions

- DIET
- EXERCISE
- REDUCE STRESS
- IMPROVE SLEEP

- Reduce toxin exposure/load.
- Only small number of trials on the use of pre/probiotics in renal patients.
- Constipation is a major issue for CKD that leads to increased uraemic toxins. Increase waste excretion through other pathways; fibre and polyphenols are vital. Also treats the chronic inflammation and aids gut permeability.
- Curcumin, quercetin, rutin, resveratrol, hibiscus, anthocyanins.
- Bonus effects helpful for hypertension and metabolic syndrome.

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Summary of Integrative Interventions & Considerations

- DIET
- EXERCISE
- REDUCE STRESS
- IMPROVE SLEEP

- Treating malnutrition is key:
  - Minerals: **Zinc** 20mg, Iron**, Magnesium** 300-600 mg (depends on vit D levels >50ng/ml/ 125 nmol/L), **Selenium** and Copper. Citrate form is very useful. Can also look at bicarbonates as well.
  - Detox and methylation: **methyl B12**, **SAMe, folates**, **histidine**, taurine, **NAC**, carnosine, sulforaphane.
  - Fats (brain +CVD): Omega 3 - 4g total (**1.6 g of EPA and 0.8 g of DHA**), phospholipids, choline.
  - Muscle health: **HMB 3g**, **creatine 3-5g**.
  - Mitochondrial metabolic: **CoQ 10** (300-600 mg, any form), **B3/NAD booster**, lipoic acid, acetyl-l-carnitine, resveratrol, inositol
  - Cardiovascular: citrulline, hibiscus anthocyanins, vitamin K2, taurine, P5P, B12 (homocysteine issue)
  - Vitamins: full spectrum (**A,B,C,D,**E,**K**). Although E less important, **Vitamin D is mandatory.**

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Nephrotoxic Drugs

- Drugs altering intraglomerular haemodynamic:
  - ACEi, ARBs, NSAIDs, Cyclosporine, Tacrolimus
- Drugs associated with tubular cell toxicity:
  - Aminoglycosides, Amphotericin B, Contrast dye.
- Drugs associated with chronic interstitial nephropathy:
  - Acetaminophen, Aspirin, NSAIDs, Lithium (long term, high dosage)
- Drugs associated with crystal nephropathy:
  - Acyclovir, Methotrexate, Sulfa antibiotics (Sulfonamides) and Triamterene.
- Other drugs:
  - Proton pump inhibitors, Benzodiazepines, Fluoxetine, Statins, Diazepam and other sleeping pills

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Herbal Options

What NOT to take

- x **Toxins & irritants:**
  Aristolochic acid (in many TCM herbs), *Artemisia absinthium*, asparagus root, *autumn crocus*, bucha leaves, cat's claw, ciandanol, Black pearl, horse chestnut, juniper berries, lovage root, parsley, periwinkle, sassafras, Tung shueh, *Vandelia cordifolia*

- x **Use with caution - they may be useful to improve markers but may further damage the kidney or diuretic action that can change mineral balance:**
  Alfalfa, buckthorn (*rhamnus* species), ginger, nettle, vervain, aloe, ginseng, noni juice, bayberry, cascara, horsetail, panax, blue cohosh, coltsfoot, Liquorice, rhubarb, broom, dandelion, mate, senna

What could be useful

- ✓ Astragalus
- ✓ Allicin (garlic)
- ✓ Beetroot (nitrates for NO)
- ✓ Silymarin
- ✓ Herbs that offer anti-inflammatory, anti-oxidative effects and enhance blood flow. Can be a double edged sword.
- ✓ Curcumin, quercetin, rutin, resveratrol, hibiscus anthocyanins.
- ✓ Dark chocolate - AE with the caffeine causing increased heart rate initially with non-regular consumers.

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Ultimate Dietary Recommendations

- Alkaline diet and high in citrates offer protection from unwanted metabolites from protein metabolism.
- Don’t forget gut health!
- Protein content is based on stages of CKD:
  - 0.8–1.0 g/kg ideal body weight (IBW)/day for patients with stage 4–5 CKD not on dialysis
  - 1.1–1.4 g/kg IBW/day for patients treated on maintenance haemodialysis
  - 1.0–1.2 g/kg IBW/day for patients treated with peritoneal dialysis
- Reduce protein to allow for supplemental key and essential amino acids.
  - Improve albumin levels on haemodialysis (not peritoneal) by giving 3.6g essential amino acid supplement. Improvements were also seen in grip strength and SF-12 mental health score.
  - Retrospective cohort study has shown low protein diet + key aminos + keto-analogs vs low protein diet resulted in increased time to renal transplant 345 vs 220 days ($p=0.001$).

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General Treatment Strategy Through Stages of CKD

- **Gut health is a good indicator of renal function. Looking after one of two remaining waste removal pathways is vital. Sweating is another alternate way to remove urea and other toxins.**
- **Mitochondrial nutrients are key focus throughout CKD.**
- **Stage 1-2:**
  - Work out what's driving kidney function loss, treat the co-morbid conditions, explore alternative medications to renal toxic drugs. Mediterranean diet, like anti-inflammatory/alkaline or DASH diet, looking for high intake of plant foods. Look out for rate of decline of eGFR.
- **Stage 3:**
  - More targeted renal protective intervention, must monitor supplementation for side effects; adjust accordingly. Start to implement "lower" protein diet with supplemental amino acids. Start to reduce potassium and phosphates. Digestive enzymes and betaine hydrochloride are important as reduced production is seen in CKD.
- **Stage 4 & 5:**
  - Will require reduction in supplementation as metabolites can be toxic, use low dosages. Moving from gram amino acid supplementation to mg supplementation. Need to rely on other methods of excretion: sweat and making sure gut function is optimal. Detox pathways heavily hit and need more "antioxidant defence". Controlling uraemic toxin production and effects
- **ESKD on dialysis:**
  - Supplement after dialysis sessions, return to higher dosages every 2 to 3 days as nutrients will be stripped.
  - Malnutrition is major issue.
  - Sarcopenia is a big risk, along with immunity.

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Take Home Messages

- It’s a hidden disease
- Watch eGFR rate of decline
- Disease of Malnutrition: Control protein to support supplemental amino acids
- Diet that is anti-inflammatory and low acid load. More plants in the diet; watch for potassium.
- Mitochondrial nutrients to support repair and function.

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