

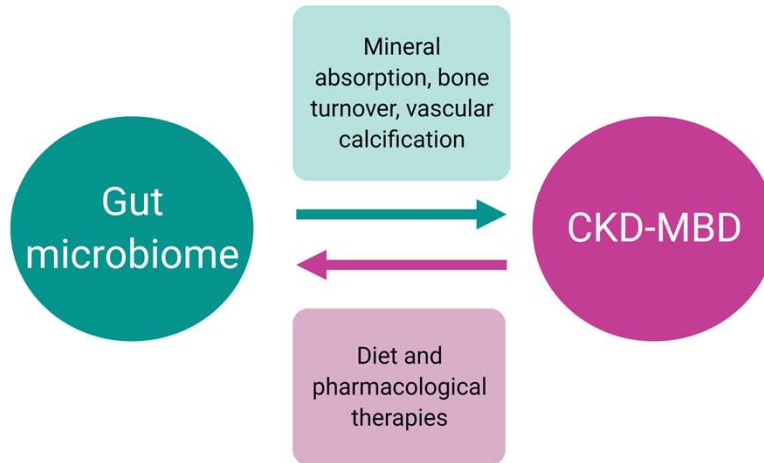
The impact of the gut microbiome in CKD-MBD

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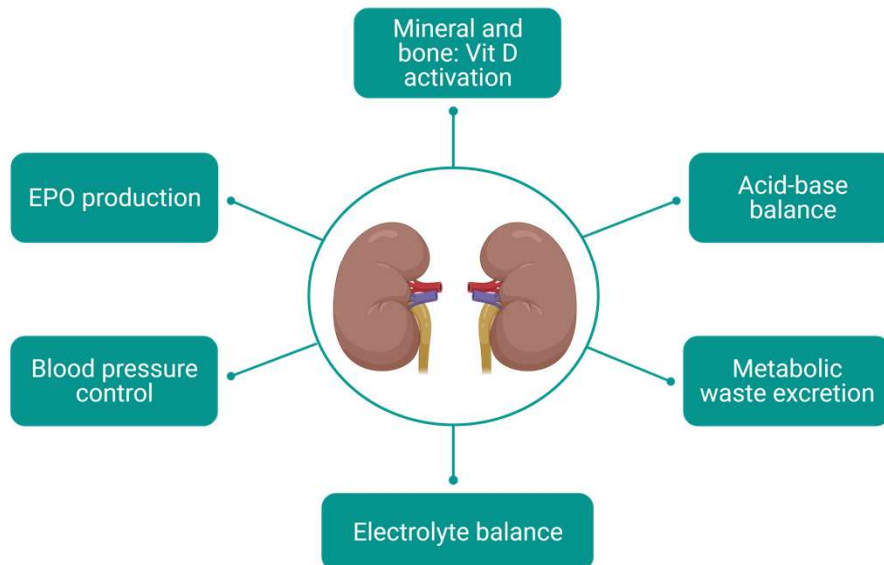
Disclosures

- Employer: Purdue University
- Research Grants: NIH, CTSI, NKF, Showalter Trust, AgSeed
- Honoraria: Amgen, Ardelyx
- Consulting: Academy of Nutrition and Dietetics, Ardelyx, IGH Naturals

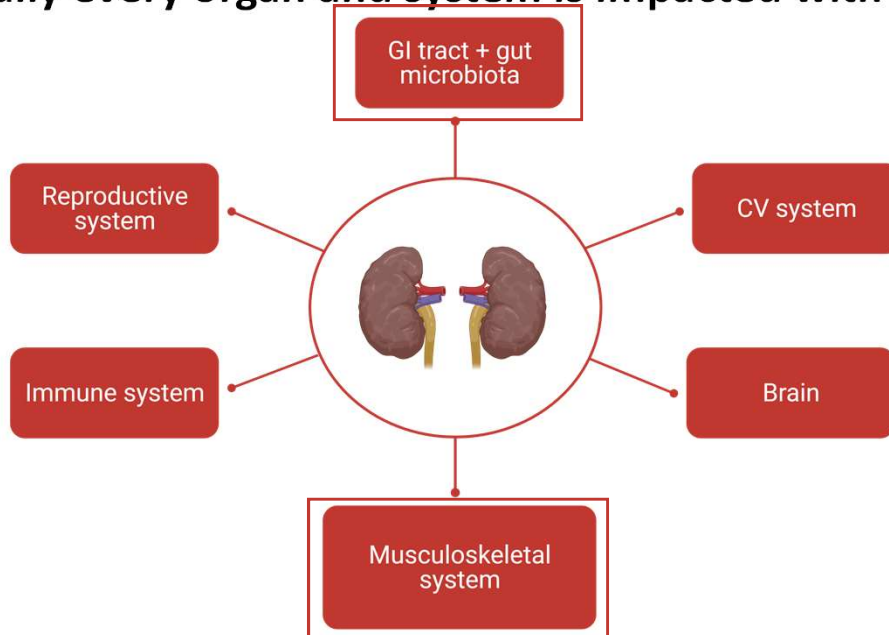
Today's talk...



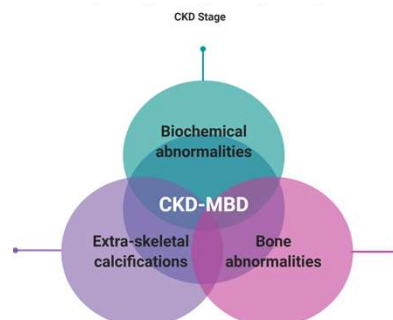
The kidneys are the master regulators of homeostasis



Virtually every organ and system is impacted with CKD

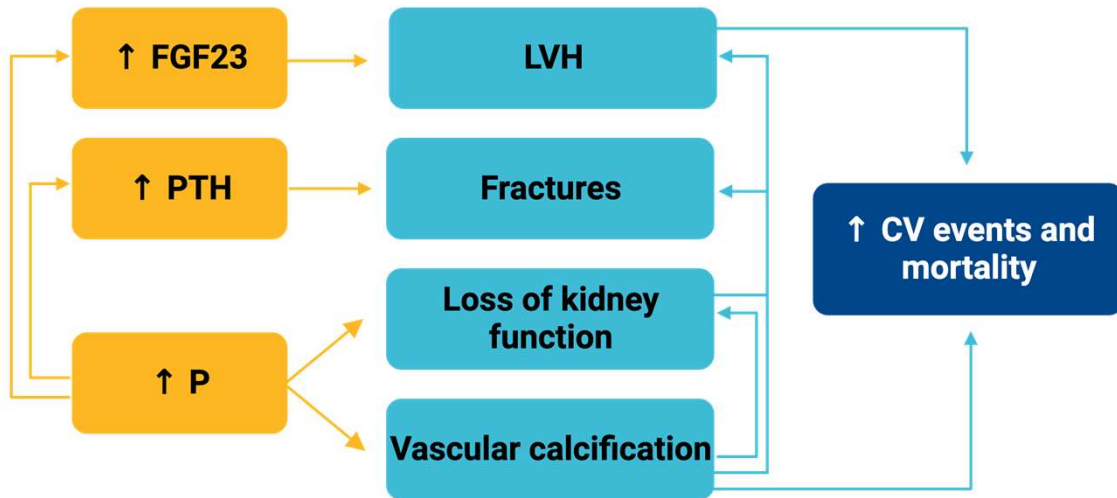


CKD-MBD is highly prevalent in individuals with CKD

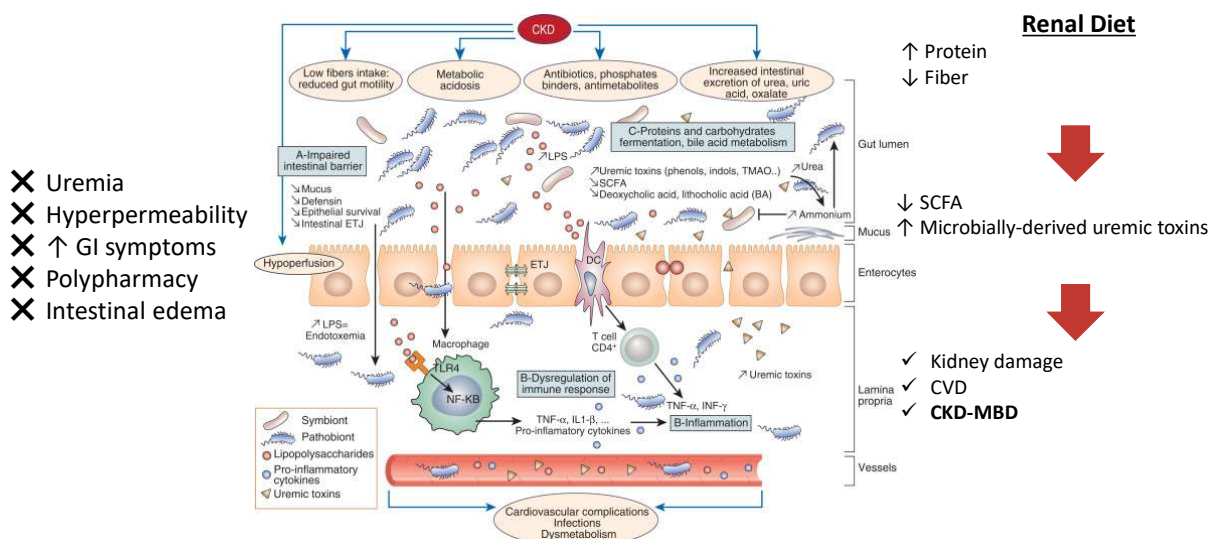


Adapted from Moorthi and Moe. Am J Kidney Dis (2011); Adapted from Wolf. JASN (2010)

CKD-MBD leads to poor clinical and patient-centered outcomes

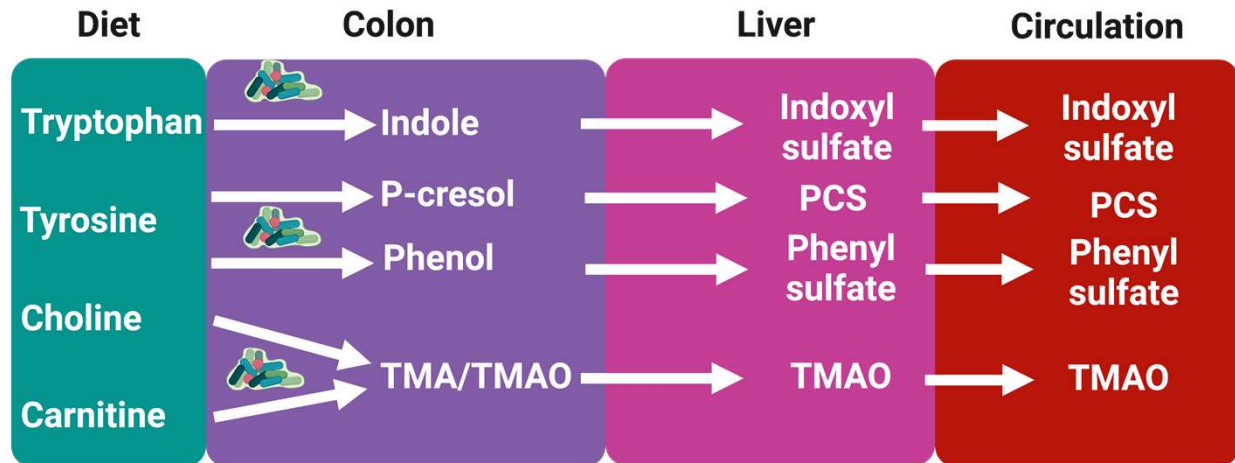


The GI tract and the gut microbiome is affected in CKD



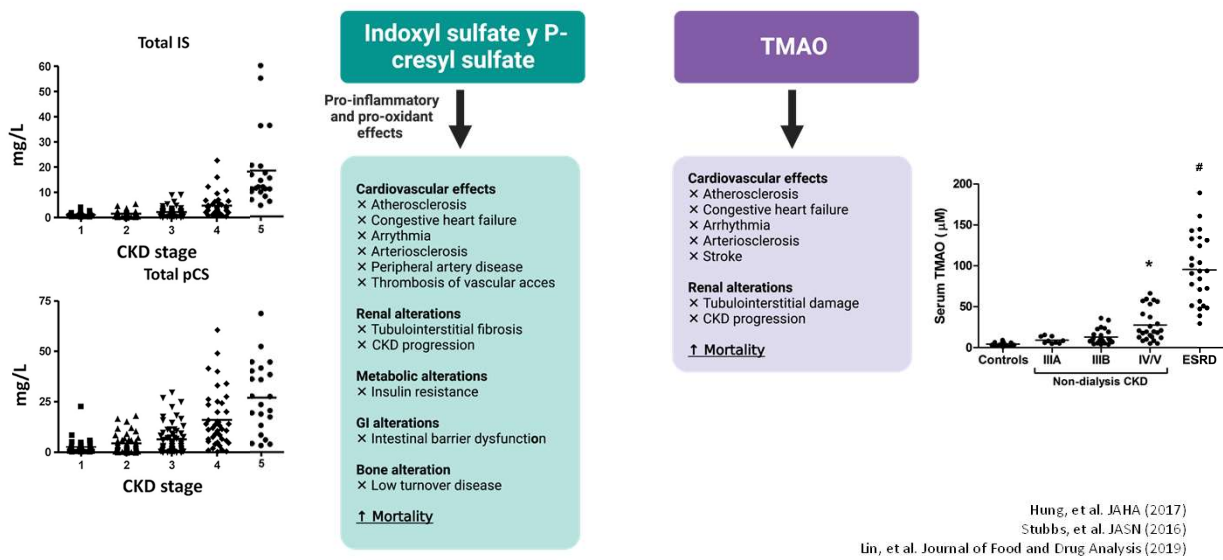
Koppe, et al. KI (2015)

Gut-derived uremic toxins: an area of active research

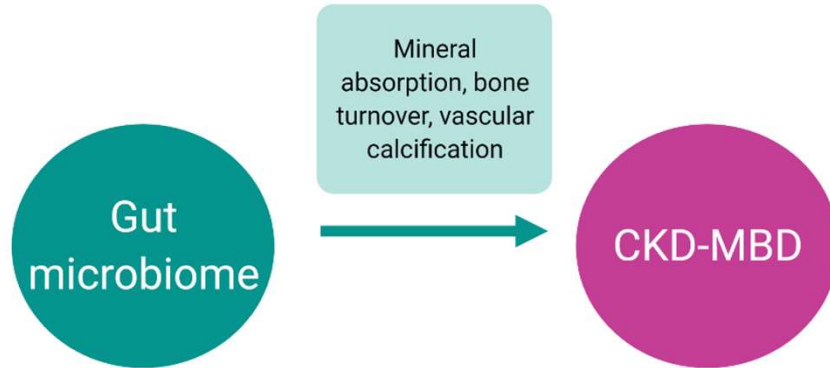


Snelson, et al. JReN (2020)

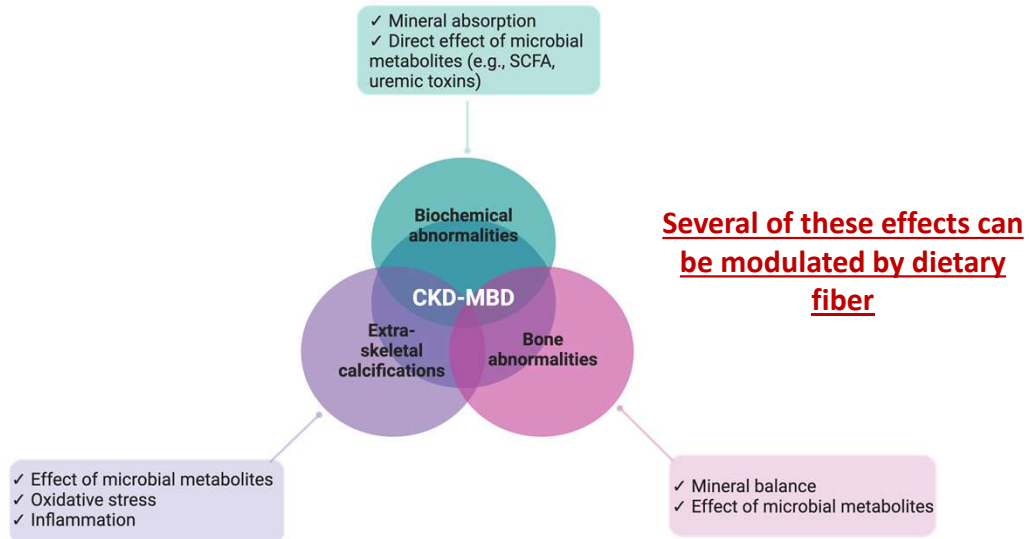
Gut-derived uremic toxins are associated with poor outcomes in CKD



The gut microbiome changes with CKD progression



The gut microbiome *may* affect CKD-MBD

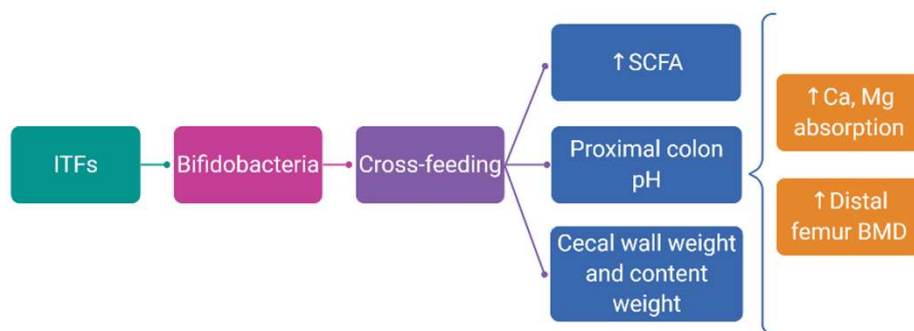


Dietary fiber: a potential key nutrient in CKD-MBD

- Non-digestible CHO polymers + lignin
- Dietary fiber intake in CKD is ~50% of the AI
- Dietary fiber intake is inversely related to CKD incidence and progression
- The properties of dietary fiber may be key for the outcomes of choice
 - ↑ SCFA ↓ GDUT
 - Mineral absorption and homeostasis
 - ↓ Inflammation and oxidative stress

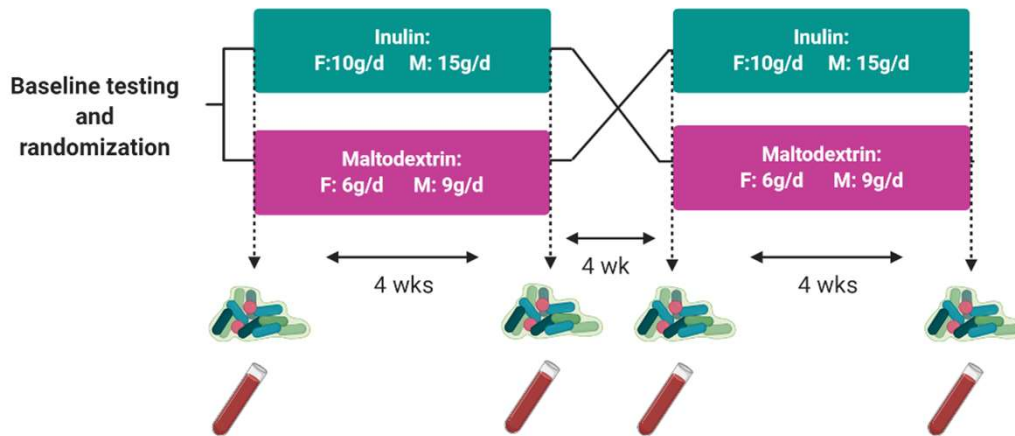
Su, et al. CKJ (2022)

Fermentable dietary fibers can impact mineral and bone-related outcomes



Weaver CM. Curr Osteoporos Rep (2015)
Whisner C, et al. British Journal of Nutrition (2013)

HIT-MBD goal: effects of inulin supplementation on mineral homeostasis and the gut microbiota

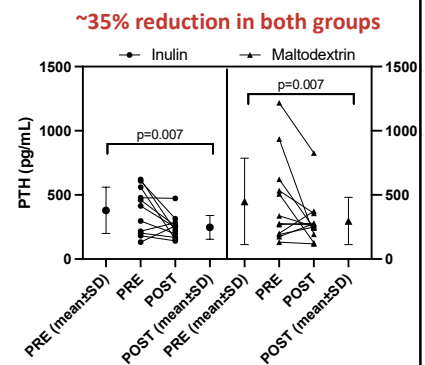
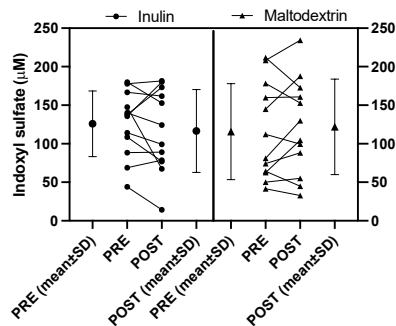
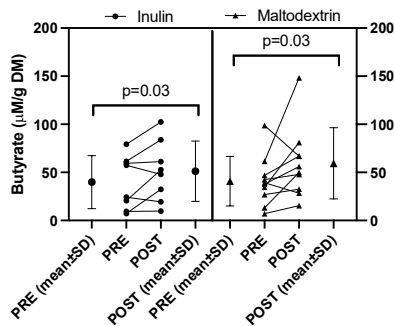


Biruete, et al. JReN (2021)

Inulin (and maltodextrin) ↑ the excretion of SCFA and ↓ PTH



- ↓ *Bacteroides*, ↑ *Akkermansia*, ↑ *Faecalibacterium* (trend)

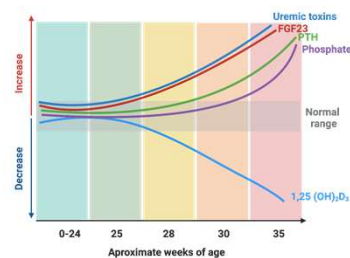
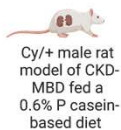


Biruete, et al. JReN (2021)
Biruete, et al. (unpublished)

Working with patients with kidney failure is challenging

- HD becomes a (hard) lifestyle
- Retention of participants is challenging
- Adherence to therapies may be low
- Confounding factors: diet, medications, treatment, cause of CKD

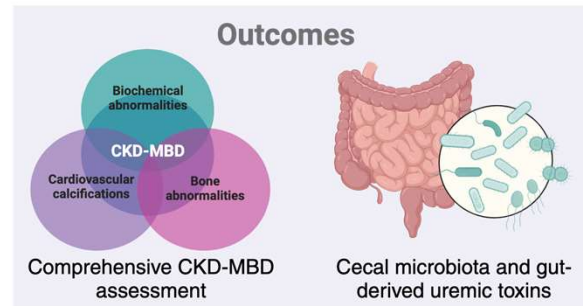
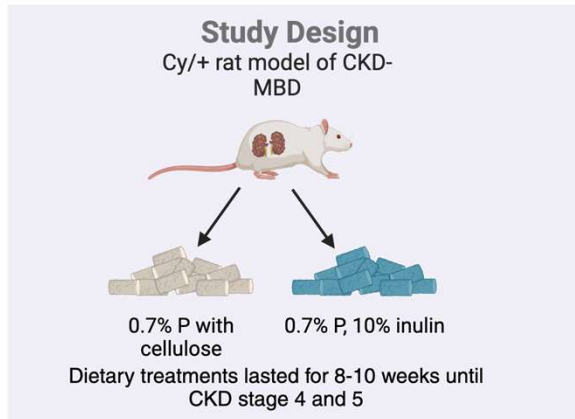
The Cy/+ male rat model is a progressive model of CKD-MBD that responds to diet/medications



- ✓ Slowly, progressive
- ✓ Therapies can be tested at various stages
- ✓ Responds to medications and lifestyle interventions
- ✗ Only males
- ✗ ~33 weeks of age for kidney failure
- ✗ Some may progress fast

Moe, et al. JBMR (2011)

In a controlled environment, what is the effect of inulin supplementation?

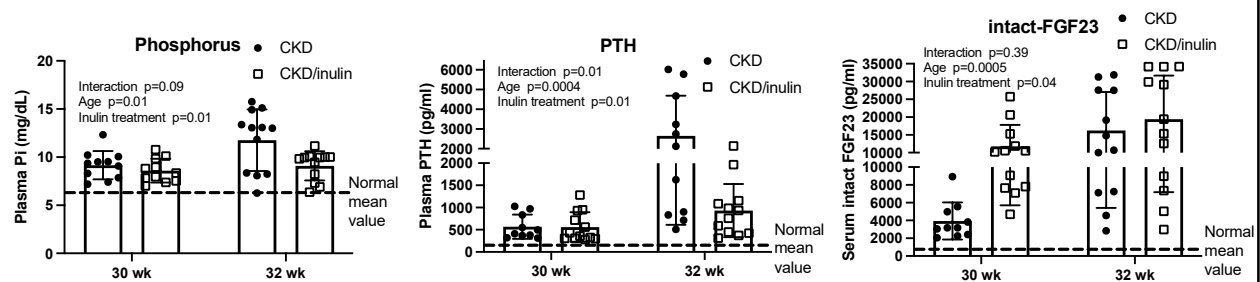


Biruete, et al. JBMR Plus (2023)

Inulin lowered plasma phosphorus and PTH in rats with CKD



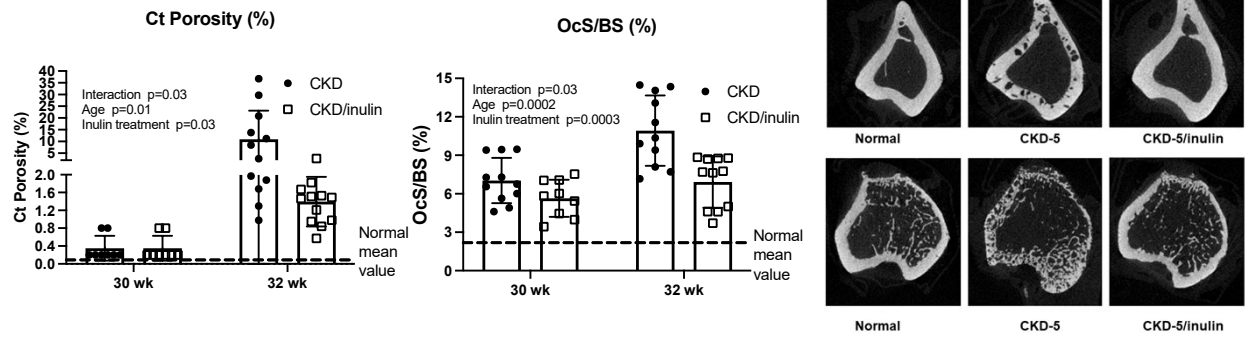
- Kidney function was not different



Biruete, et al. JBMR Plus (2023)



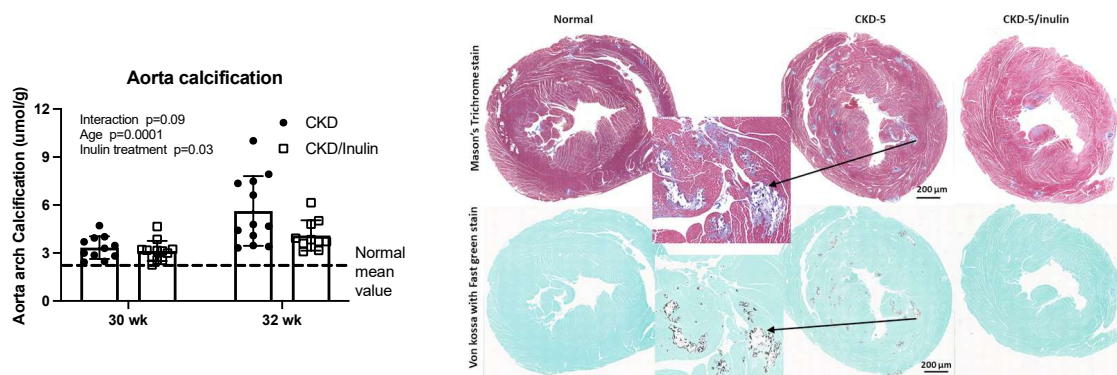
Inulin improved cortical bone but did not improve bone mechanics



Biruete, et al. JBMR Plus (2023)



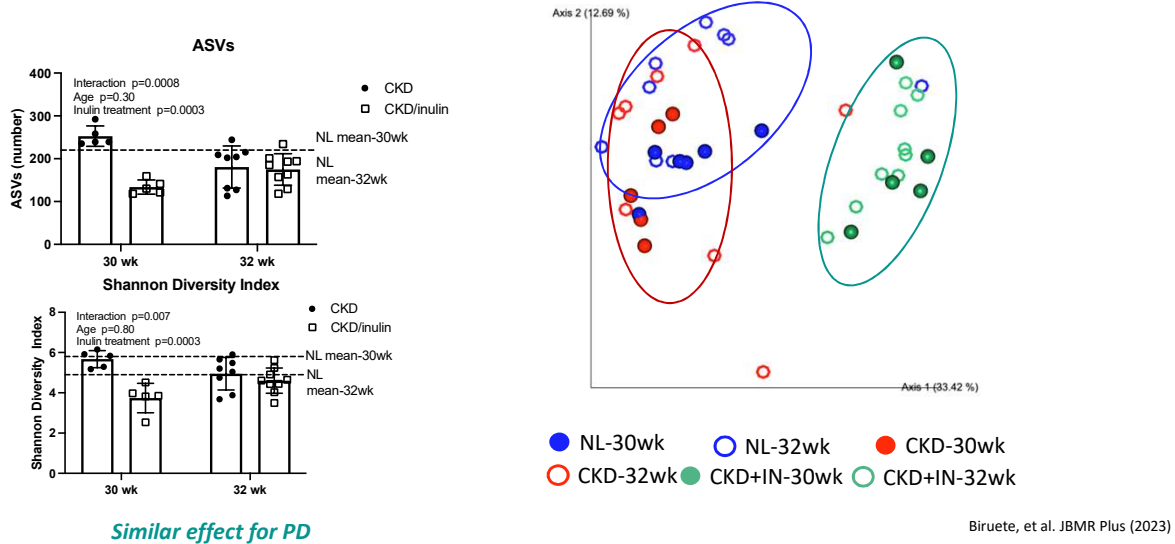
Inulin supplementation lowered aorta and heart calcifications and fibrosis



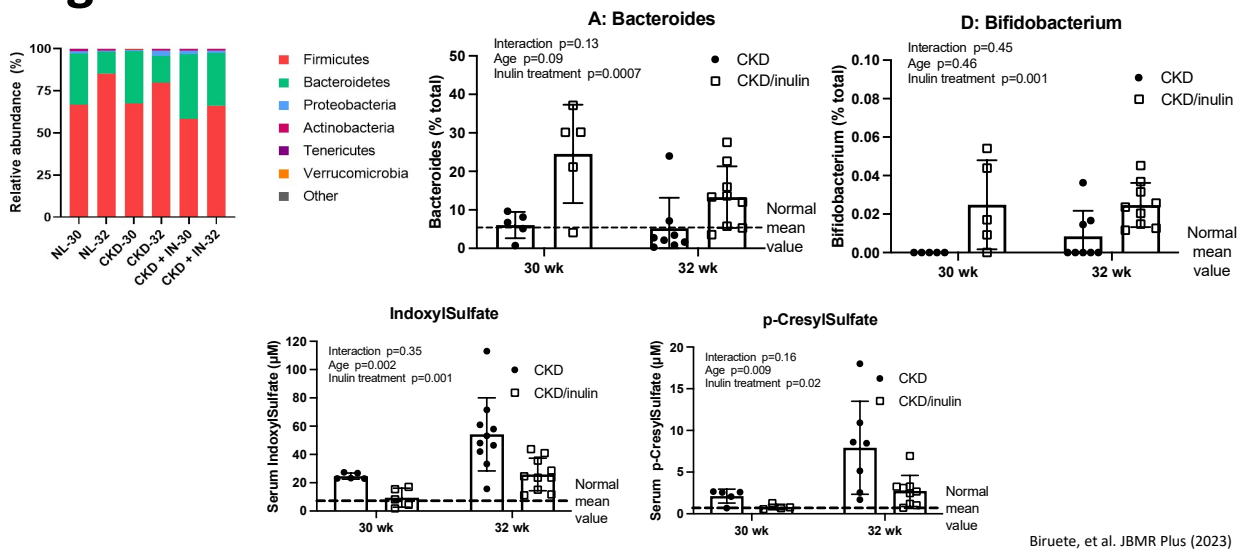
Biruete, et al. JBMR Plus (2023)



Inulin supplementation impacted α - and β -diversity

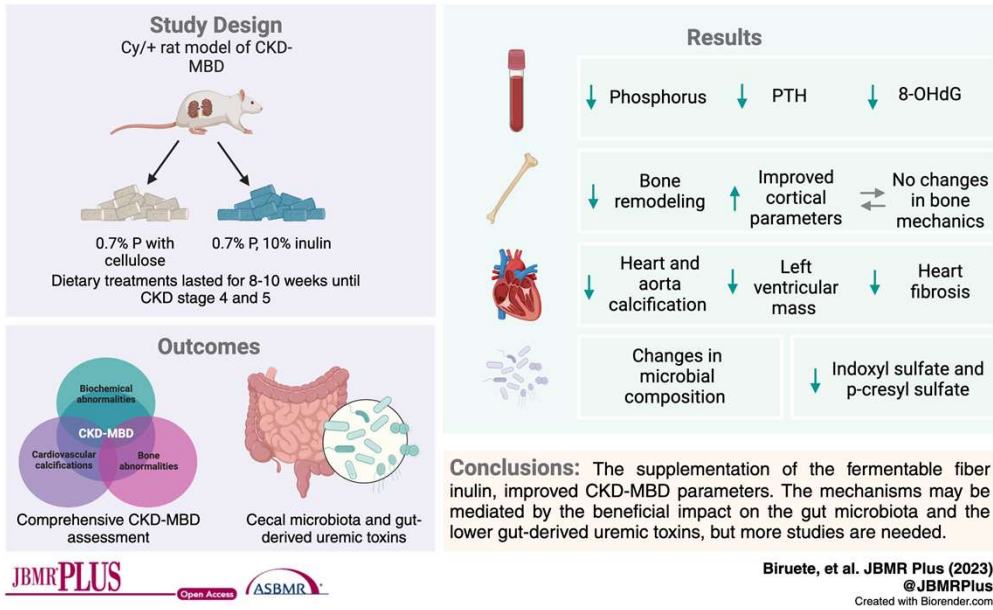


Inulin altered the gut microbiota and lowered gut-derived uremic toxins

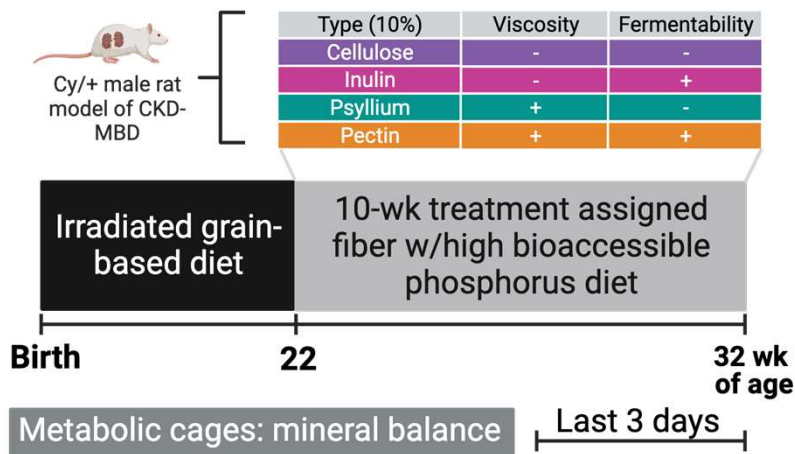


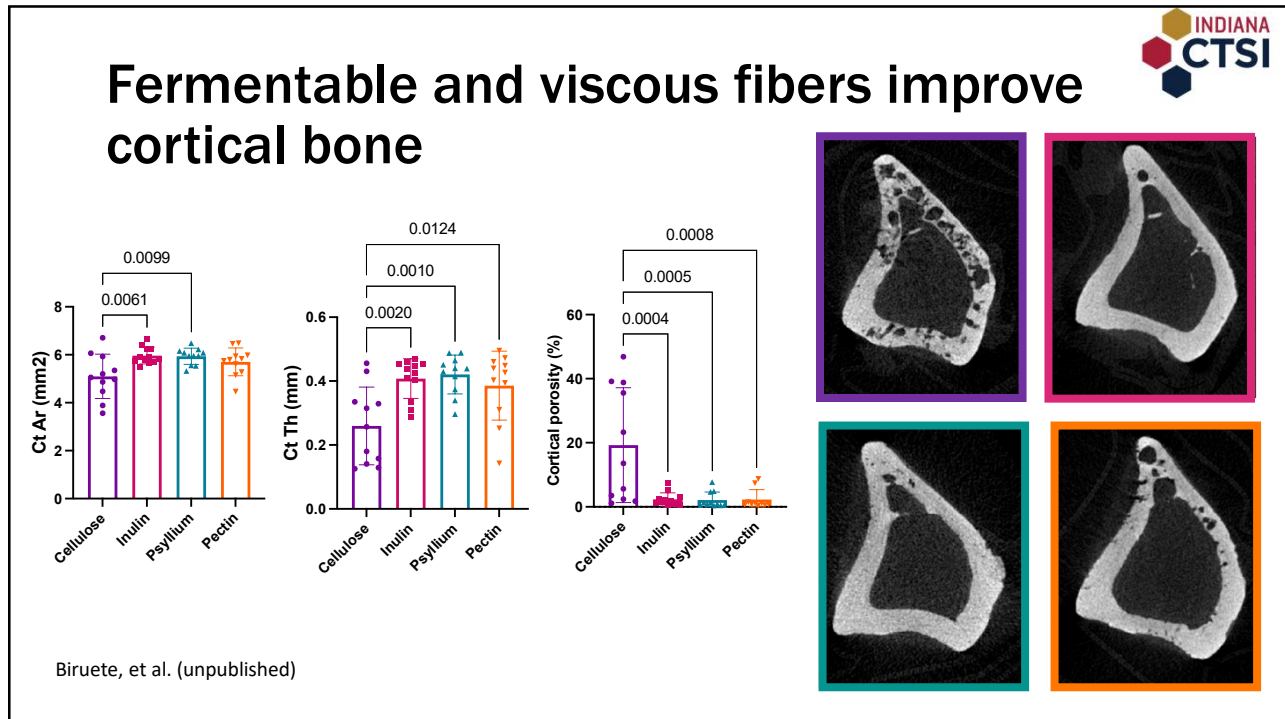
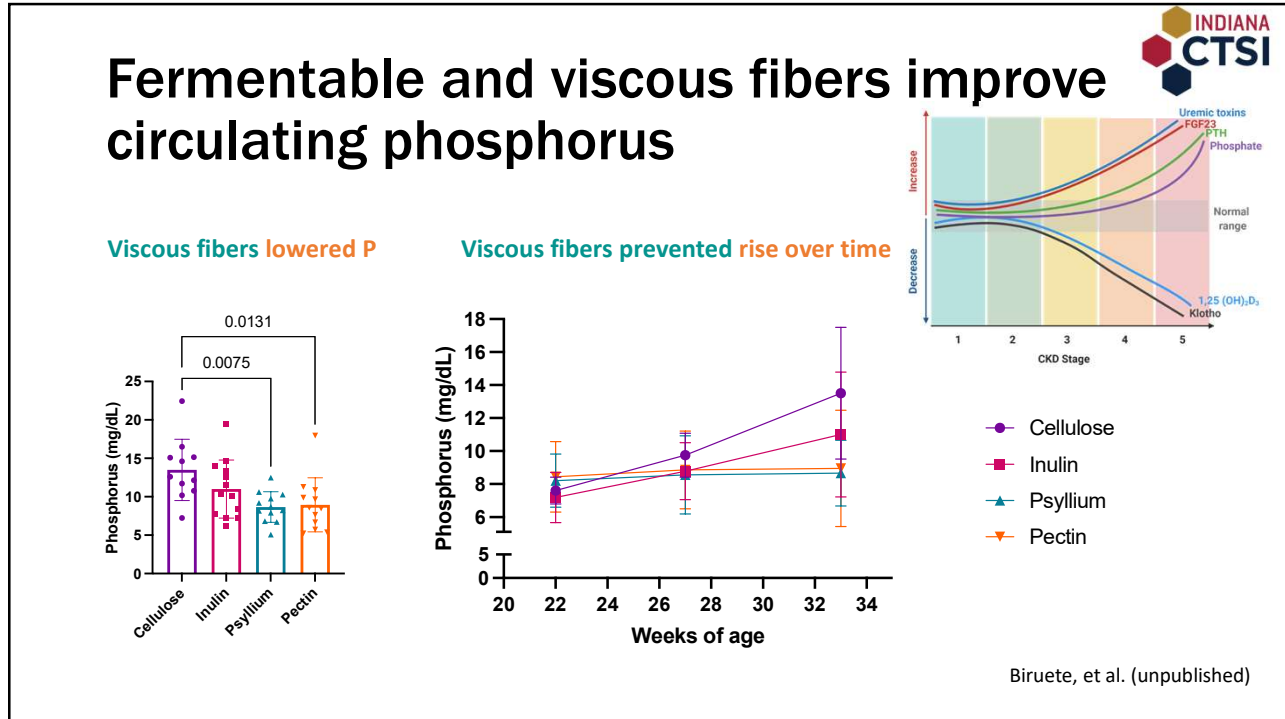


The fermentable fiber inulin improves chronic kidney disease-mineral and bone disorder in a rat model of chronic kidney disease

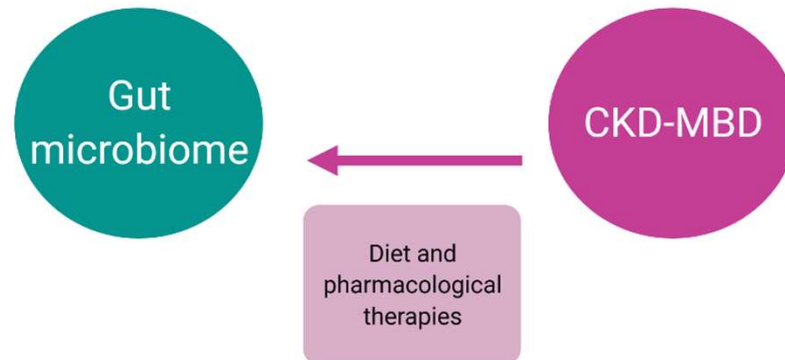


Exploring the effects of dietary fiber based on fermentability and viscosity in CKD-MBD

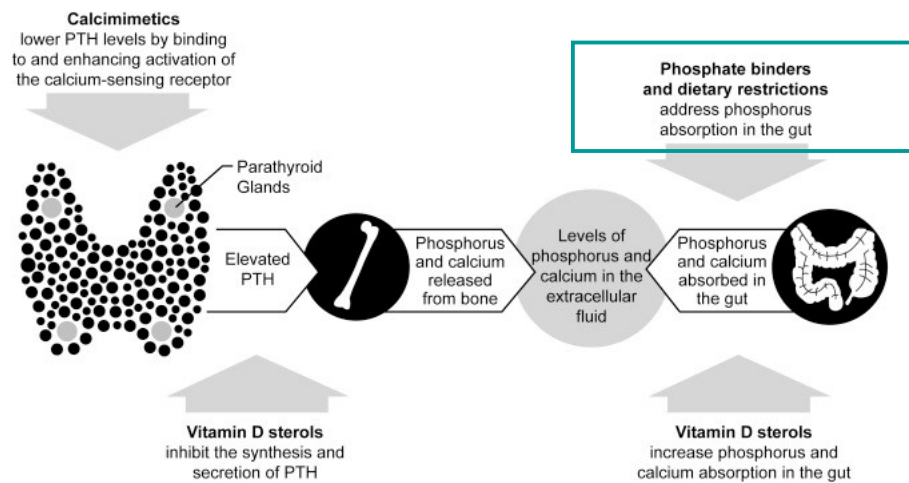




CKD-MBD treatments *may* alter the gut microbiome

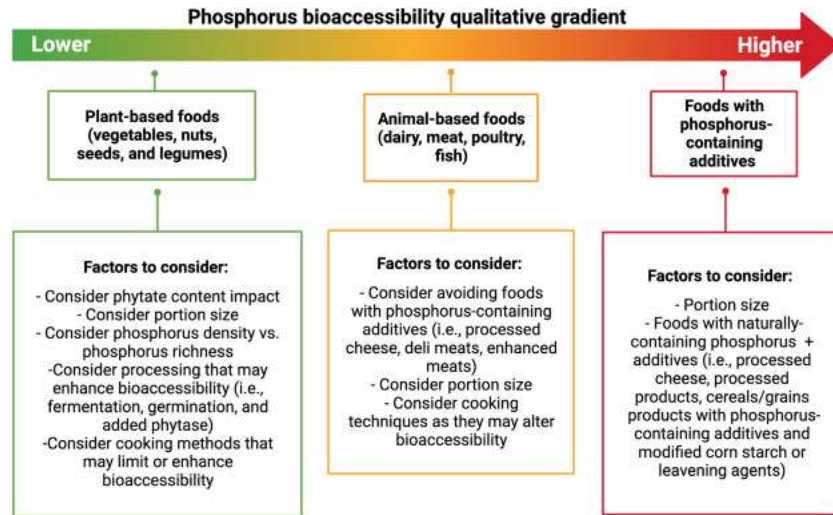


Current treatments for CKD-MBD



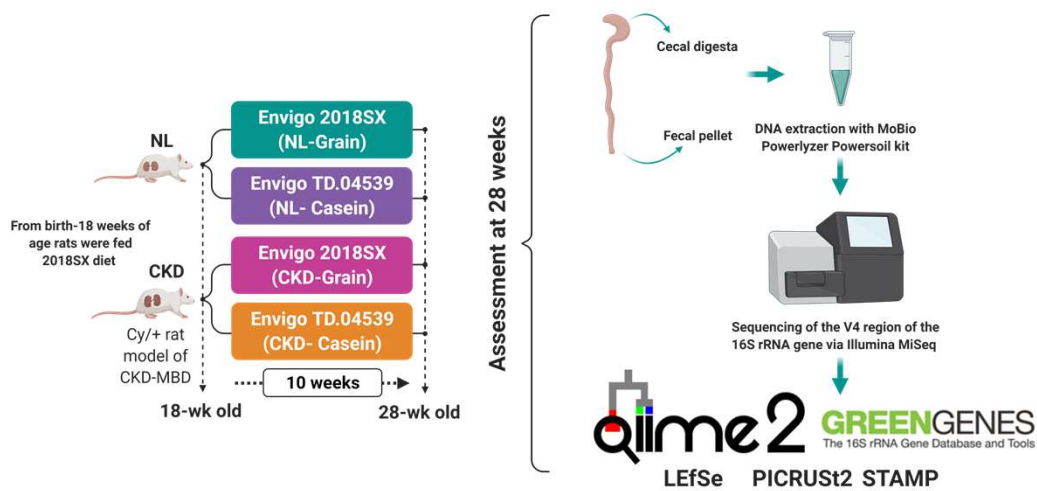
Beto, et al. JReN (2019)

Dietary management of hyperphosphatemia includes education on phosphorus *bioaccessibility*



Biruete, et al. JReN (2023)

A diet with different phosphorus sources may impact the gut microbiota composition

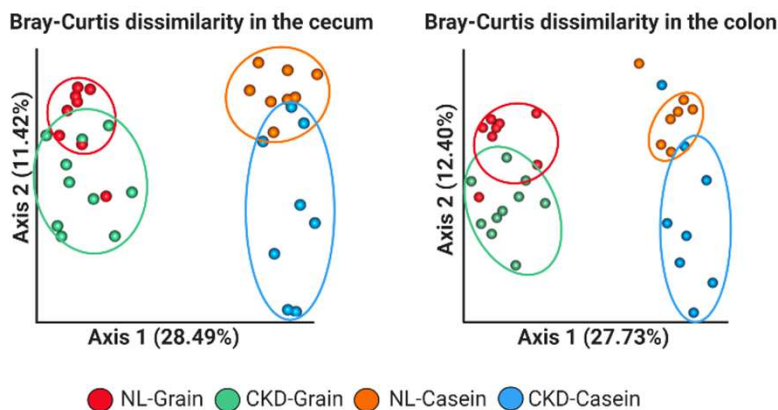


Biruete et al. JASN (Abstract; 2020)

Diet characteristics

	Envigo Autoclaved 2018X (Grain)	Envigo custom diet (Casein)
Protein (% wt)	18.6	15.9
Carbohydrate (% wt)	44.2	62.8
Fat (% wt)	5.2	6.2
Cellulose (%)	N.R.	5
Crude fiber (%)	3.5	N.R.
Calcium (%)	1.0	0.7
Phosphorus (%)	0.7	0.7
Phytate-bound phosphorus	0.3	N.R., but 0% likely
Notes	Macronutrient ingredients: ground wheat, ground corn, wheat middlings, dehulled soybean meal, corn gluten meal, soybean oil, L-lysine, DL-methionine Phosphate additives: dicalcium phosphate	Macronutrient ingredients: casein, sucrose, corn starch, maltodextrin, cellulose, soybean oil, DL-methionine Phosphate additives: dicalcium phosphate

Diet and CKD impact β -diversity, but diet explains a bigger proportion of the observed variability

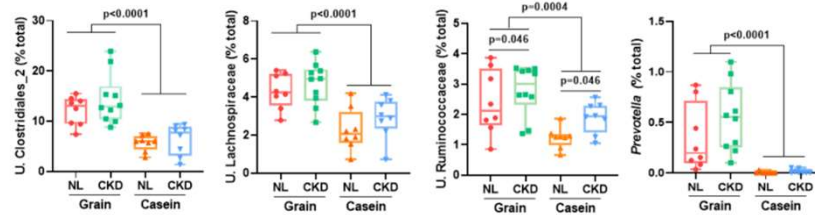


- ✓ Overall PERMANOVA in cecum and colon $p=0.001$; all groups different from each other ($q<0.05$).
- ✓ Other metrics of β -diversity (i.e., unweighted and weighted UniFrac distances) showed similar results in cecum and colon

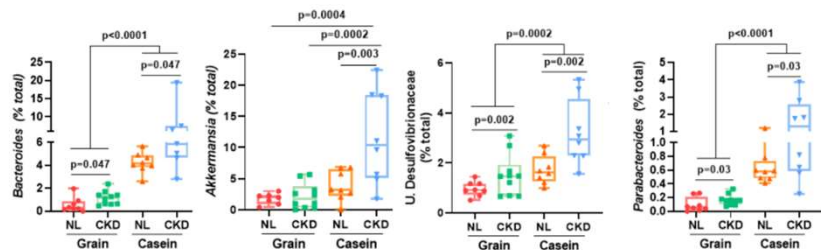
*** β -diversity: between samples**
Birute et al. JASN (Abstract; 2020)

Diet and CKD led to taxonomical changes in the cecum, where most fermentation occurs in rodents

Major effect of diet on SCFA producers



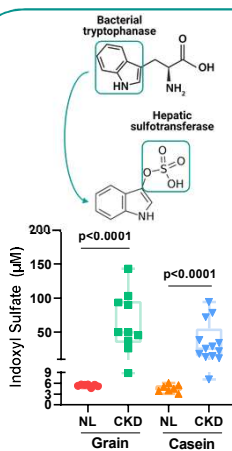
Diet and disease effect on possible uremic toxin producers



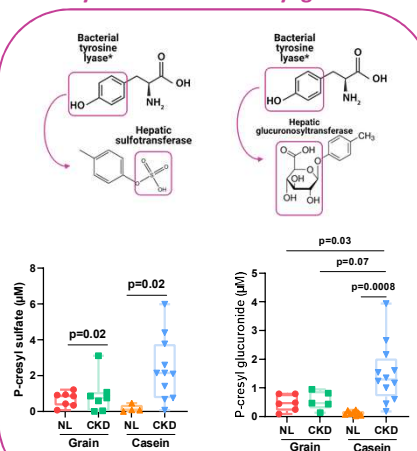
Biruete et al. JASN (Abstract; 2020)

Microbially-derived uremic toxins were not reduced in the grain-based diet in CKD

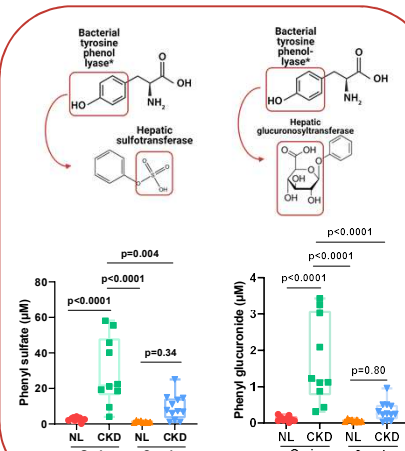
Indoxyl sulfate



P-cresyl sulfate and P-cresyl glucuronide



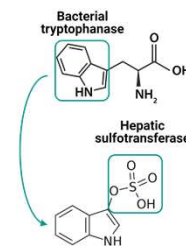
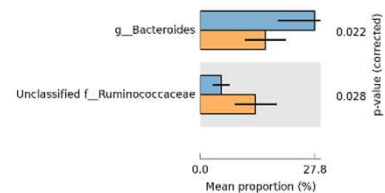
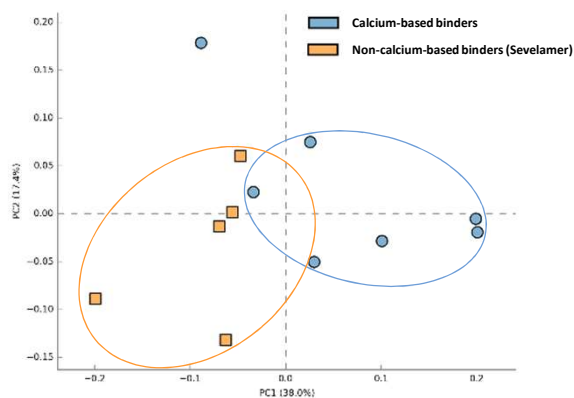
Phenol sulfate and phenol glucuronide



Summary: CKD-MBD treatments and the gut microbiome

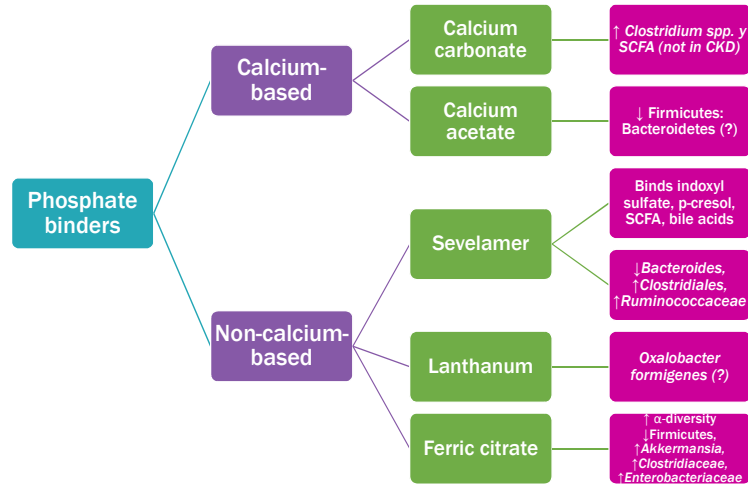
1. Dietary modifications related to phosphorus bioavailability *may* impact the gut microbiota composition, functional capacity, and production of uremic toxins

The fecal microbiota in patients on HD differed depending on type of phosphate binder



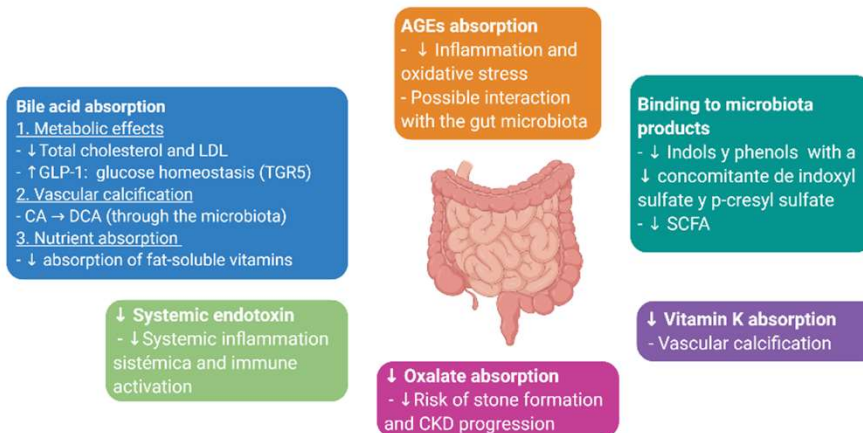
Biruete, et al. JReN (2021)
Devlin, et al. Cell Host & Microbe (2016)

Phosphate binders *may* alter the gut microbiome



Birquete et al. JReN (2020)

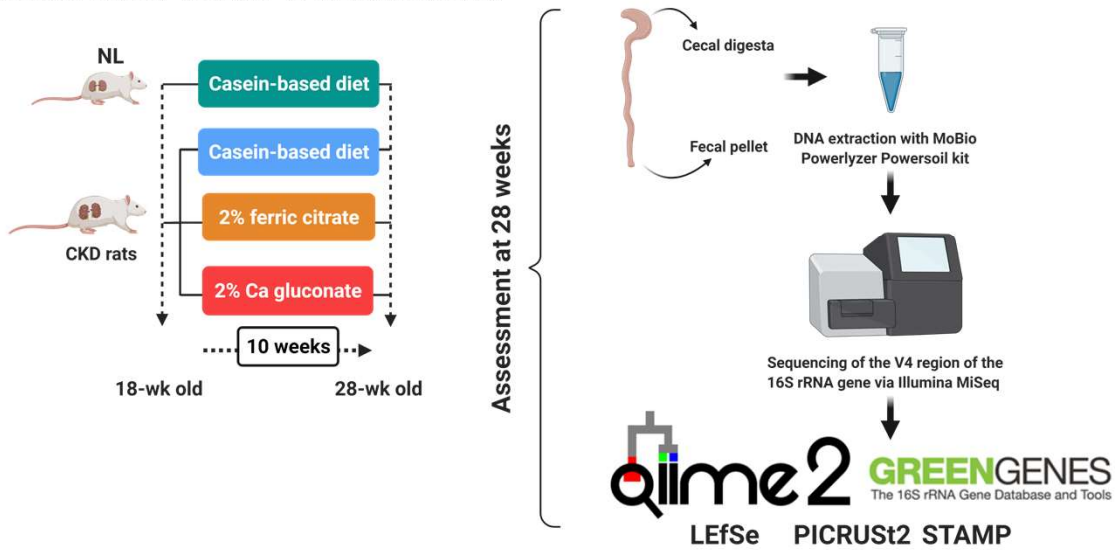
2. Not all phosphate binders have the same effects



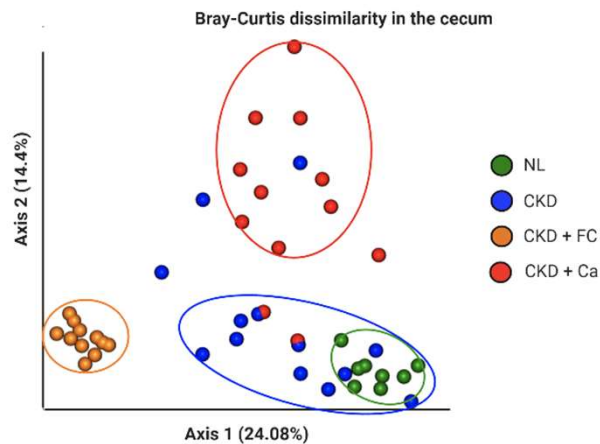
Most studies were observational

Birquete et al. JReN (2020)

Goal: to assess the effects of phosphate binders on the cecal and fecal microbiota



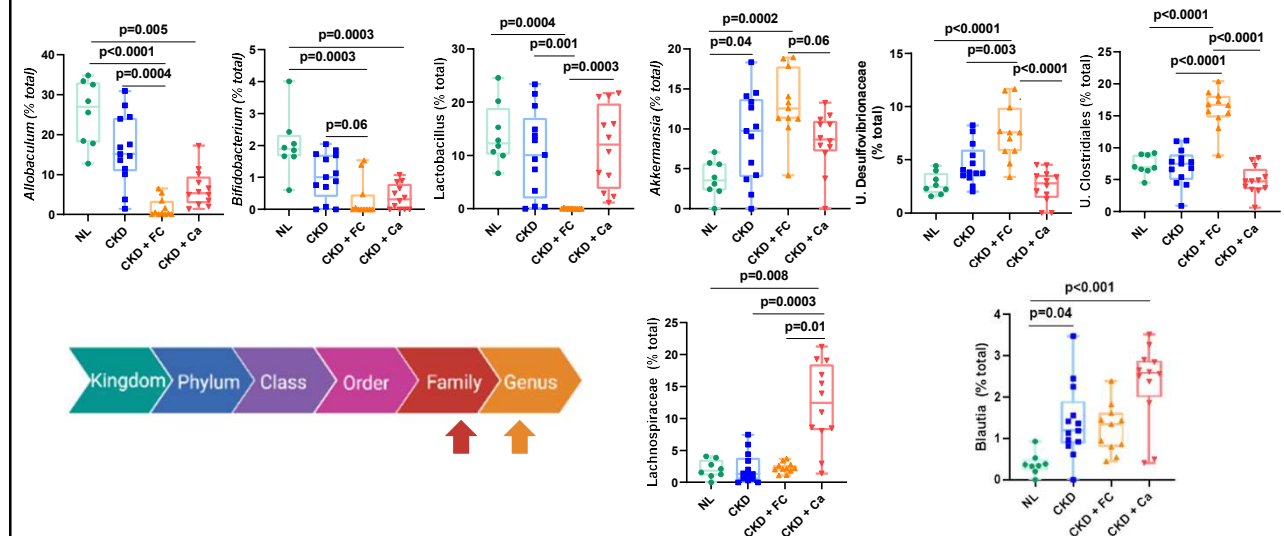
Phosphate binders impacted β -diversity



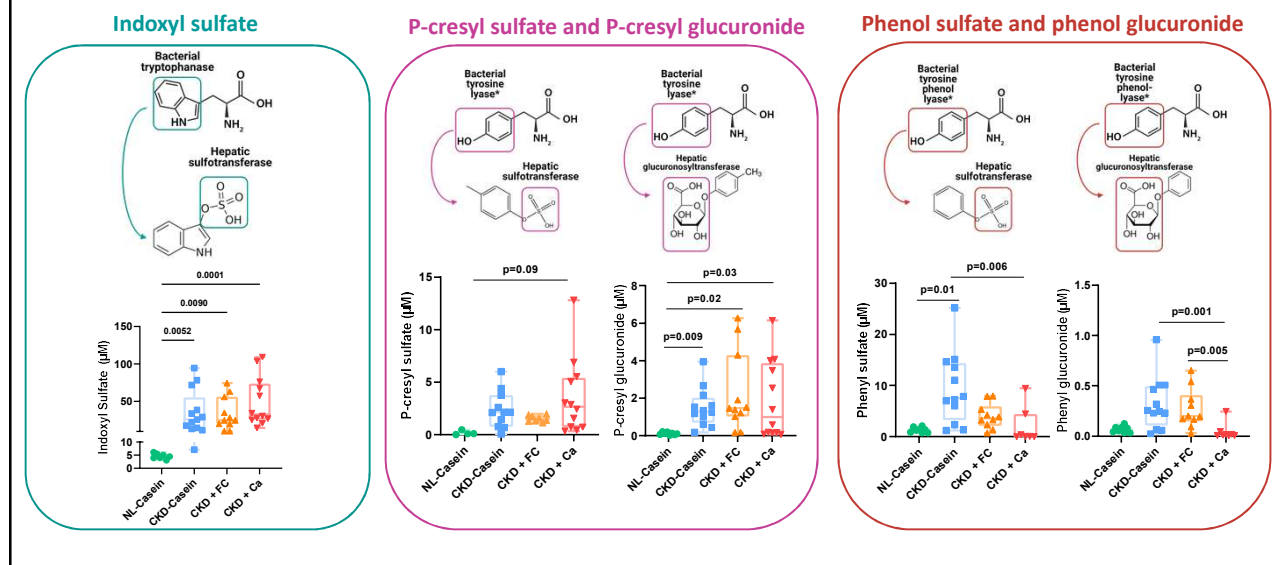
- ✓ Overall PERMANOVA $p=0.001$; all groups different from each other $q \leq 0.003$
- ✓ Other metrics of β -diversity (i.e., unweighted and weighted UniFrac) showed similar results

* β -diversity: between samples

FC and calcium led to unique taxonomical changes at the genera-level



Calcium-based phosphate binder reduced uremic toxins derived from phenyl




Summary: CKD-MBD treatments and the gut microbiome

1. Dietary modifications related to phosphorus bioavailability *may* impact the gut microbiota composition and production of uremic toxins
2. Phosphate binders *may* alter the gut microbiota, but only calcium-based phosphate binder decreased phenyl sulfate and phenyl glucuronide.

Conclusions

- CKD-MBD is a highly prevalent complication in CKD.
- Gut-oriented therapies may be innovative and low-cost interventions to improve CKD-MBD-related outcomes.
- The outcomes may be dependent on the physicochemical properties of dietary fiber.
- Clinical trials are needed
 - We started supplementation in early-to-moderate CKD
 - Is there a benefit for people with kidney failure?
 - What is the therapeutic dose?




VIRTUAL MEETING
GUT MICROBIOTA AND KIDNEY DISEASE
 MAY 28-29, 2024

NIH National Institute of Diabetes and Digestive and Kidney Diseases


Gut Microbiota and Kidney Disease

📅 May 28 - 29, 2024











¡Gracias!

<p>Indiana University Sharon Moe Neal Chen Keith Avin Shruthi Srinivasan Kali O'Neill Matt Allen Corinne Metzger</p>	<p>University of Illinois Ken Wilund Kelly Swanson Jacob Allen</p> <p>University of Minnesota Katie Hill Gallant Kendal Burstad</p>	<p>Purdue University Tzu-Wen L. Cross Brandon Kistler CTNRL</p> <p>KU Leuven Pieter Evenepoel Jetty de Loor</p>
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My support system!

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