

# Microbiome, Prebiotics, Probiotics

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Feb 29, 2020

*Nutritional and Dietary Management of  
Kidney Disease: A Patient Care Approach*



## Disclosures

- Prior or current research funding: NIH, Sanofi, ZS Pharma, American Heart Association, Hub Therapeutics.
- Associate Medical Director for home peritoneal dialysis at FKC University Dialysis Center of Orange.
- Fresenius medical advisory board for Velphoro.
- No conflicts of interest for the current talk.

## Talk Outline

- Altered gut microbiome in CKD
- Role of gut-derived uremic toxins in CKD pathophysiology
- Systemic inflammation linked to cardiovascular morbidity and death
- Findings from microbiome-targeted clinical trials
  - Prebiotics
  - Probiotics
  - Symbiotics

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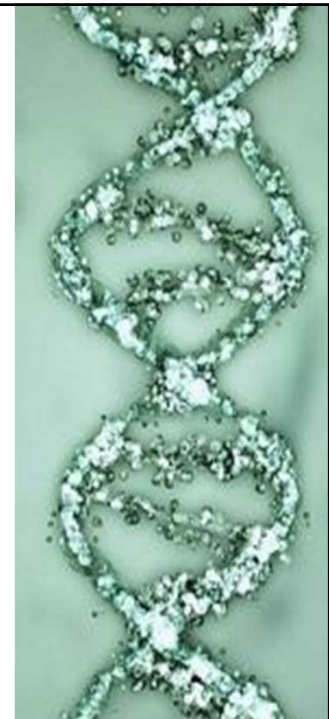



## Gut microbiome

outnumbering the host

- The adult gut harbors 100 trillion bacteria  
*10-fold greater than the number of cells in the human body*
- Gut microbiome encompasses 3.3 million genes  
*150 times larger than the human genome*
- > 50 bacterial phyla colonize the healthy gut  
*Anaerobic Bacteroidetes and Firmicutes make up >90% of species*
- The gut bacteria regulate local and systemic immunity  
*'Outside-in' modifier of T cell and natural killer cells subsets*
- Abundance and diversity of bacteria increases from the stomach ( $10^2$ - $10^4$  cells/ml) to the colon ( $>10^{12}$  cells/ml) as oxygen tension decreases

Lau et al. Clinical Science 2018: 509–522



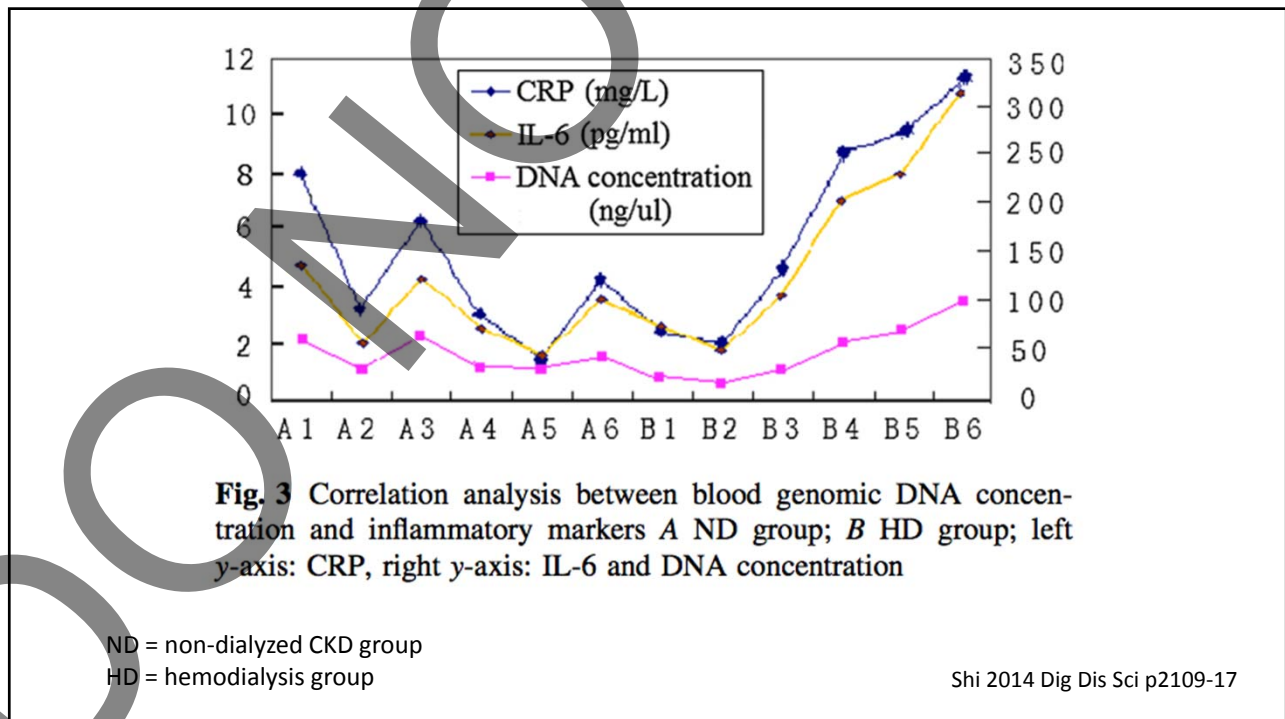


Autopsy studies in the 1980s showed chronic inflammation present throughout the GI tract from esophagus to large bowel.

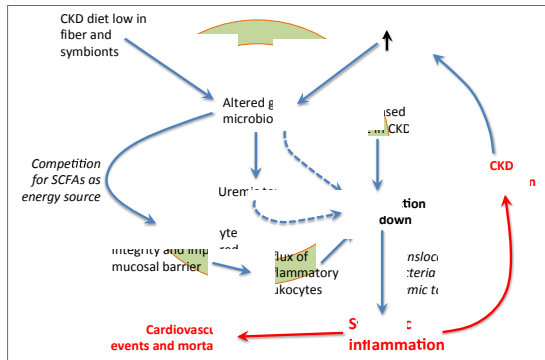
Vaziri 1985 Am J Gastroenterol p608-11

Gut bacterial DNA was detected in blood samples from 20% (6/30) pre-dialysis CKD patients, and correlated with elevated plasma D-lactate and CRP levels.

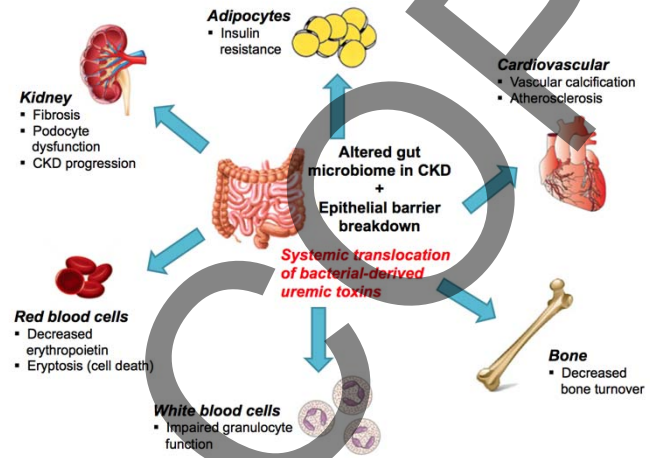
Wang 2012 Nephrology P733-8



# Gut dysbiosis and systemic effects in CKD



Lau et al. Nephron 2015 p92



Lau et al. Clinical Science 2018: 509–522

↑ **Tryptophanase possessing families**  
Clostridiaceae  
Enterobacteriaceae  
Verrucomicrobiaceae

Increased indoxyl sulphate and *p*-cresyl sulphate

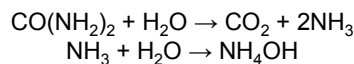
↓ **Fatty acid (butyrate) forming enzymes**  
Lactobacillaceae  
Prevotellaceae

Decreased production of short-chain fatty acids

↑ **Urease possessing families**

Alteromonadaceae  
Cellulomonadaceae  
Clostridiaceae  
Dermabacteraceae  
Enterobacteriaceae  
Halomonadaceae  
Methylococcaceae  
Micrococcaceae  
Moraxellaceae  
Polyangiaceae  
Pseudomonadaceae  
Xanthomonadaceae

Increased metabolism of urea to ammonium hydroxide



**More proteolytic**

Lau et al. Clinical Science 2018: 509–522

## Gut dysbiosis in CKD states

**Table 1** The changes in the gut microbiota in CKD and in various nephropathies

	Increased genera	Decreased genera
CKD	Enterobacteriaceae, Clostridia, Bacteroidia, Pseudomonadaceae	Bifidobacteriaceae, Lactobacillaceae, Prevotellaceae
IgA nephropathy	Enterobacteriaceae, Sutterellaceae, Ruminococcaceae, Streptococcaceae, Lachnospiraceae, Eubacteriaceae	Clostridium, Lactobacillus, Enterococcus, Bifidobacterium
Lupus nephritis		Lactobacillus [29]
Hypertensive nephropathy <sup>a</sup>	Prevotella, Klebsiella, Porphyromonas, Actinomyces, Streptococcus, Turicibacteraceae, Veillonellaceae, Lactococcus, Coprobacterias	Faecalibacterium, Oscillibacter, Roseburia, Bifidobacterium, Coprococcus, Butyrifibrio, Pseudobutyrvibrio, Ruminococcaceae
Diabetic nephropathy <sup>a</sup>	Type 1 DM: Bacteroidia, Blautia, Rikenellaceae, Ruminococcus, Streptococcus, <i>Clostridium perfringens</i> , Veillonella, Faecalibacteria, (Leptotrichia) Type 2 DM: Escherichia, Prevotella, <i>Clostridium bolteae</i> , <i>Clostridium symbiosum</i> , <i>Clostridium ramosum</i> , <i>Clostridium hathewayi</i> , Betaproteobacteria, Desulfovibrio	Type 1 DM: Lactobacillus, Bifidobacterium, Prevotella, Staphylococcus, Lachnospiraceae, Veillonellaceae, <i>Coprococcus euscarius</i> , <i>Dialister inyisus</i> , <i>Roseburia faecis</i> , <i>Faecalibacterium prausnitzii</i> , <i>Clostridium clostridioforme</i> , <i>Blautia coccoides</i> , Pseudobutyrvibrio, Akkermansia muciniphila <sup>b</sup> Type 2 DM: Bifidobacterium, <i>Eubacterium rectale</i> , Faecalibacterium, <i>Roseburia intestinalis</i> , Clostridiales, Lactobacillus, <i>Akkermansia muciniphila</i> <sup>b</sup> (Verrucomicrobiaceae), Streptococcus

Kanbay et al. International Urology and Nephrology 2018; 50: 1453-1466

# JASN

J Am Soc Nephrol. 2011 Sep; 22(9): 1769–1776.  
doi: [10.1681/ASN.2010121220](https://doi.org/10.1681/ASN.2010121220)

PMCID: PMC3171947  
PMID: [21784895](https://pubmed.ncbi.nlm.nih.gov/21784895/)

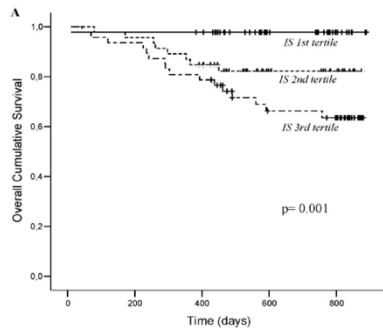
### Colonic Contribution to Uremic Solutes

Pavel A. Aronov,<sup>\*</sup> Frank J.-G. Luo,<sup>†</sup> Natalie S. Plummer,<sup>†</sup> Zhe Quan,<sup>‡</sup> Susan Holmes,<sup>§</sup> Thomas H. Hostetter,<sup>‡</sup> and Timothy W. Meyer<sup>††</sup>

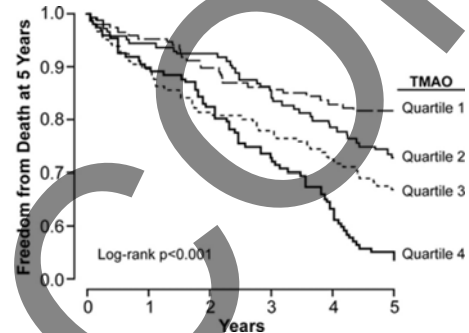
- Compared plasma from hemodialysis patients with and without colons.
- Identified >30 solutes in patients without colons that were either absent or present in lower concentration.
- Five major colon-derived uremic solutes:  $\alpha$ -phenylacetyl-l-glutamine, 5-hydroxyindole, indoxyl glucuronide, p-cresol sulfate, and indoxyl sulfate.

## Gut-derived uremic toxins and mortality risk

Uremic toxin	Source	Class
Indoxyl sulfate	Tryptophan	Protein-bound
Indole-3 acetic acid	Tryptophan	Protein-bound
p-cresyl sulfate	Phenylalanine, tyrosine	Protein-bound
Trimethylamine N-oxide	Choline, L-carnitine, phosphatidylcholine	Water-soluble
Phenylacetylglutamine	Phenylalanine	Water-soluble



Barreto et al. Clin J Am Soc Nephrol 2009;15:151–1558



Tang et al. Circulation Research 2014;448–455

## Gut-derived toxins cause vascular injury

- Exposure of cultured endothelial cells to indoxyl sulfate (IS), p-cresyl sulfate (PCS) or trimethylamine N-oxide (TMAO) induces breaks in monolayer integrity
- IS and PCS inhibit cell proliferation and wound repair
- IS induces reactive oxygen species production in endothelial and smooth muscle cells via activation of NAD(P)H oxidase, reduction of nitric oxide bioavailability and decrease in glutathione
- TMAO triggers inflammasomes and mitochondrial ROS
- Serum levels of these toxins in CKD mice correlate with brain microbleed burden (research focus)

Adelibieke et al. J Ren Nutr 2012;86-89  
Muteliefu et al. J Ren Nutr 2009;19:29-32

Dou et al. J Thromb Haemost 2007;1302-1308  
Chen et al. J Am Heart Assoc 2017



## Prebiotics and Probiotics



- The CKD diet low in potassium and phosphorus goes against the “heart healthy” high vegetables/fruit diet.
- How best to manipulate the natural diet to engender a less pathogenic microbiome is unclear at this time.
- There is interest in the use of refined **prebiotics** (nondigestible food ingredients that can stimulate growth and/or activity of beneficial gut bacteria) and **probiotics** (living organisms ingested via food or supplements that can improve the health of the host). **Symbiotics** combine both prebiotics and probiotics.




## Prebiotics in CKD

Feeding CKD rats the prebiotic amylose maize resistant starch, which reaches the colon undigested and is metabolized by bacteria to short-chain fatty acids, improved creatinine clearance and reduced kidney inflammation and fibrosis<sup>1</sup>

A meta-analysis of controlled feeding trials found that fiber supplementation significantly decreased serum urea levels in a pooled analysis of 143 patients<sup>2</sup>

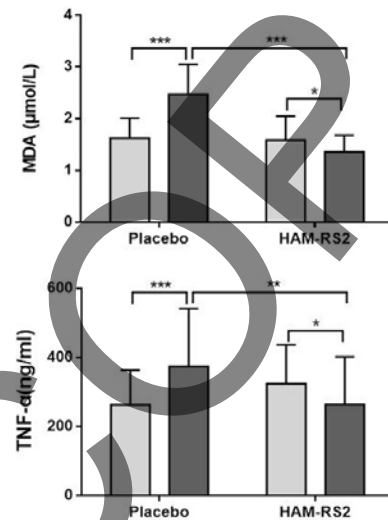
1. Vaziri 2014 PLoS One e114881
2. Chiavaroli 2014 Eur J Clin Nutr

## Hemodialysis International

ORIGINAL ARTICLE |  Full Access

Effect of high amylose resistant starch (HAM-RS2) supplementation on biomarkers of inflammation and oxidative stress in hemodialysis patients: a randomized clinical trial

- 46 chronic hemodialysis patients in Iran randomized to receive amylose (HAM-RS2) or placebo wheat-flour for 8 weeks.
- Serum levels of TNF- $\alpha$ , IL-6, and malondialdehyde declined significantly in the HAM-RS2-treated group
- No significant difference was observed in serum Interleukin-1 $\beta$  (IL-1 $\beta$ ) and hs-CRP concentrations and total antioxidant activity
- Less constipation, no side effects.



Khosroshahi HT, Vaziri ND et al. Hemodial Int. 2018 Oct;22(4):492-500

## Probiotics in CKD: Reducing production of uremic toxins

- In the 1990s, studies in small cohorts of hemodialysis patients showed that Lactobacillus preparations decreased blood levels of uremic toxins such as dimethylamine and indican  
(Simenhoff 1996 Miner Electrolyte Metab p92-6; Hida 1996 Nephron p349-55)
- A multi-national crossover trial in patients with CKD stage 3 and 4 noted significant decrease in BUN and improved quality of life scores after treatment with a proprietary formulation of *S. thermophilus*, *L. acidophilus* and *B. longum* over 6 months
- But a follow up RCT in HD patients showed no benefits  
(Ranganathan 2010 Adv Ther p634-47; Natarajan 2014 Biomed Res Int p568571)



## Synbiotics Easing Renal Failure by Improving Gut Microbiology (SYNERGY): A Randomized Trial

Megan Rossi,<sup>\*†‡</sup> David W. Johnson,<sup>\*†‡</sup> Mark Morrison,<sup>†§</sup> Elaine M. Pascoe,<sup>\*</sup> Jeff S. Coombes,<sup>||</sup> Josephine M. Forbes,<sup>\*†¶</sup> Cheuk-Chun Szeto,<sup>\*\*</sup> Brett C. McWhinney,<sup>††</sup> Jacobus P.J. Ungerer,<sup>††</sup> and Katrina L. Campbell<sup>\*†‡</sup>

CJASN February 2016, 11 (2) 223-231; DOI: <https://doi.org/10.2215/CJN.05240515>

- 37 predialysis CKD participants in Australia and New Zealand (eGFR 10-30)
- Randomized, double-blind, placebo-controlled, crossover trial of synbiotic therapy over 6 weeks (4-week washout)
- Synbiotic therapy altered the stool microbiome and decreased serum p-cresyl sulfate.
- But no differences in: serum indoxyl sulfate, eGFR, urinary kidney injury molecule-1, serum inflammatory biomarkers (IL-1 $\beta$ , IL-6, IL-10, and TNF- $\alpha$ ), serum oxidative stress biomarkers (F2-isoprostanes and glutathione peroxidase), serum LPS, patient-reported health, GI symptoms.
- Synbiotic arm had increase in albuminuria of 38 mg/24 h (P=0.03).

## Summary and Take-Away Points



- CKD results in an altered, proteolytic gut microbiome
- Microbial toxins translocate across the leaky gut and causes systemic vascular injury
- Gut-derived uremic toxins contribute to podocyte injury, CKD fibrosis and cardiovascular events
- More work is needed to clarify the role of prebiotics and probiotics in CKD management

