The Microbiome: Exploring New Frontiers in Chronic Kidney Disease

NWRD Annual Conference

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Objectives

After this presentation, the participant will be able to:

1. Identify the role of the microbiome in human health and disease.
2. Differentiate between the microbiome and metabolome.
3. Describe three nutrition interventions which may rebalance the microbiome in chronic kidney disease.

Poll Question

How familiar are you with the microbiome and it's connection to CKD?

1. I do not know anything about the microbiome and CKD
2. I know a little about this topic
3. I've done some independent reading and research on the topic
4. I'm very familiar with this topic
5. I've conducted research on the topic (I'm practically an expert!)

Where are we going today?

I. Microbiome: A primer

II. The role of Prebiotics, Probiotics, and Synbiotics

III. Pathophysiology of the Gut in CKD and ESRD

IV. Treatments on the Horizon for Dysbiosis and CKD

I. The Microbiome: A Primer

Definitions:

1. **Microbiome**- the collection of genomes from all the microorganisms found in a particular environment

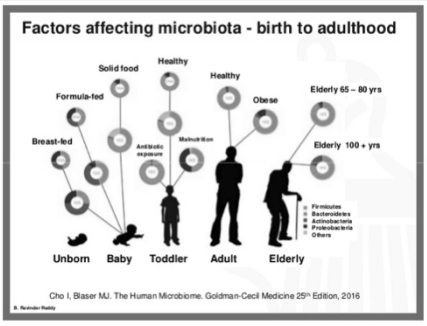
2. **Microbiota**- the specific microorganisms living in the human body, including bacteria, viruses, fungi, and single-celled organisms (archaea)

Microbiome

- Human Microbiome Project completed in 2012
- 100 trillion microbes, outnumbering body cells 10 to 1
- Called “the forgotten organ”, weighs more than the brain
- Fluid during infancy, stabilizes by age 3
- Rainforest ecosystem
- Gut metabolic potential = liver
- Relatively stable, adapts quickly

Biochemical Activities of the Microbiome

- Energy use
- Production of vitamins
- Synthesis of amino acids and short-chain fatty acids (SCFAs)
- Conversion of dietary polyphenolic compounds
- Bile acid transformation
- Hydrolysis and fermentation of non-digestible substrates
- Maintenance of intestinal epithelium integrity and tight junctions
- Repair of intestinal wall after injury



Influences on the Microbiome

- Mother's diet while in utero
- Method of delivery
- Breast vs formula feeding
- Introduction of solids
- Childhood antibiotic exposure
- Early life exposures
- Malnutrition
- Age
- Gender
- Race/Ethnicity
- Geography
- Environmental exposures
- Stress
- Genetics
- Diet

What does a healthy microbiome look like?

- Ideal set of microbes not possible or practical
- Goal is healthy "functional core"
- Resilient
- Abundant microbes in colon (not in small intestine)
- Diverse

Importance of Microbial Diversity

- Firmicutes/Bacteroidetes- account for 99% bacteria in gut
- Ratio important
- Not only "who" is there, but "what" are they doing?

Why the seemingly drastic changes in gut microbiome?

- Hygiene Hypothesis
- Old Friends Hypothesis

Metabolomics

Definition:
The study of the complex metabolic interactions between the host and its symbiotic microbial communities.

Current Research on the Metabolome:
- Identifying biomarkers
- Determining biochemical or environmental stresses
- Characterizing microbial metabolism, human health or disease

Metabolome

Definition:

The metabolome reflects the metabolic interaction between an organism's genome and its environment.

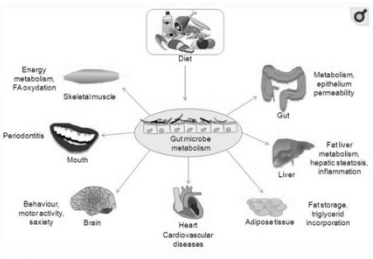


Figure 1
Effect of gut microbiota metabolome on organs and tissues.

Vernocchi, et al. Gut Microbiota Profiling: Metabolomics Based Approach to Unravel Compounds Affecting Human Health. *Front Microbiol.* 2016; 7: 1144.

The Gut-Brain Axis

Definition:

Bidirectional communication between the central and the enteric nervous system, linking emotional and cognitive centers of the brain with peripheral intestinal functions.

Signaling from gut-microbiota to brain and from brain to gut-microbiota by means of neural, endocrine, immune, and humoral links.

Dysbiosis

Definition:

"A state in which intestinal flora have qualitative and quantitative changes in their metabolic activity and local distribution, when compared with a 'normal' functioning gut." (Holzapfel et al, 1998)

Evidence of Dysbiosis in ESRD

- 24 patients with ESRD compared with 12 control subjects
- ESRD patients had different bacterial distribution
- Increased Firmicutes, Actinobacteria, Proteobacteria
- Decreased Bifidobacteria and Lactobacilli

Vaziri ND, Wong J, Pahl M, Piceno YM, Yuan J, DeSantis TZ, Ni Z, Nguyen TH & Andersen GL (2013*a*). Chronic kidney disease alters intestinal microbial flora. *Kidney Int* **83**, 308–315.

Constipation and Dysbiosis

Etiology:
- Slow moving intestinal transit = proliferation of bacteria
- Undigested protein = proteolytic bacteria proliferation

Causes of Constipation in CKD/ESRD/HD

- Low fiber intake
- Decreased fruit and vegetable intake
- Decreased activity
- Use of phosphate binders and iron
- Co-morbidities

II. The role of Prebiotics, Probiotics, & Synbiotics

Prebiotics

Definition:
Nondigestible substances acting as food for the gut microbiota

Examples:
- Green banana
- Jerusalem artichokes
- Chicory root
- Inulin, fructooligosaccharides
- Garlic, onion, leeks
- Asparagus
- Galactooligosaccharides
- Resistant starch

Probiotics

Definition:
Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. World Health Organization, 2001

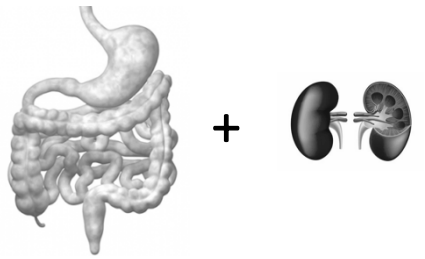
Live microorganisms intended to provide health benefits when consumed, generally by improving or restoring the gut flora.
Wikipedia, 2019

Examples:
- Lactobacillus, bifidobacterium, saccharomyces yeasts
- Found in food: dairy, fermented foods, kombucha, soy products
- Probiotic supplements

Synbiotics

Definition:
Food ingredients or dietary supplements which combine prebiotics and probiotics in a synergistic form

Prebiotic component is chosen to support the activity of the chosen probiotic



III. Pathophysiology of the Gut in CKD and ESRD

Pathophysiology

- Loss of kidney function in CKD ⇨ urea secretion into GI tract
- Hydrolysis of urea ➡ excess ammonia
- Tight junctions loosen ➡ intestinal permeability
- Endotoxins translocate into systemic circulation
- Innate immunity activated
- Causes endotoxemia and systemic inflammation associated with ESRD and CKD ➡ accelerated CVD

Toxins **2018**, *10*, 300

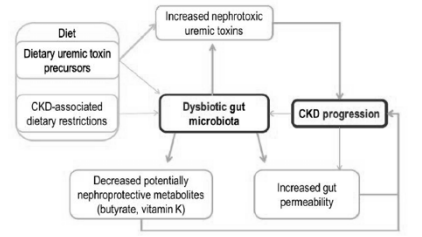


Figure 1. Bidirectional relationship between gut microbiota and chronic kidney disease (CKD) progression that may result in acceleration of CKD progression.

Uremic Endotoxins Generated by Gut Microbiome

They are microbial in nature:

1. Indoxyl Sulfate
2. p-Cresol Sulfate
3. Trimethylamine N-oxide (TMAO)

Endotoxin: Indoxyl Sulfate (IS)

- Produced by bacterial tryptophanase from tryptophan
- Food sources: beef, poultry, pork, fish, milk, yogurt, cheese, eggs, soy products
- Normally cleared by proximal tubules in kidney, impaired in CKD
- Study: Baseline concentration of IS predicted CKD progression
- Study: Elevated IS associated with higher cardiovascular mortality

Endotoxin: p-Cresol Sulfate (pCS)

- Intestinal bacteria ferment tyrosine and phenylalanine to *p*-Cresol. Further metabolized in the liver to become p-Cresol Sulfate
- Food sources: turkey, chicken, beef, fish, brown rice, nuts, milk, cheese, eggs, fruit, vegetables
- Study: PCS levels increase with decreasing GFR
- Study: Elevated baseline levels of p-cresol is independent risk factor for CV events and increased mortality in ESRD

Endotoxin: Trimethylamine N-oxide (TMAO)

- Gut bacteria convert choline and betaine (in seafood) to trimethylamine, oxidized into TMAO
- Efficiently removed by HD
- Study: TMAO elevated in CKD, associated with 70% increased risk of mortality
- Unclear if TMAO is a cause of CKD progression

IV. Treatments on the Horizon for Dysbiosis and CKD

Poll Question

Do you recommend the following microbiota-modulating treatments to your patients?

1. Prebiotics Only
2. Probiotics Only
3. Synbiotics Only
4. Another treatment not listed
5. I do not recommend any of these treatments to my patients

ORIGINAL RESEARCH

Prebiotic, Probiotic, and Synbiotic Supplementation in Chronic Kidney Disease: A Systematic Review and Meta-analysis

Catherine McFarlane, M NutrDiet,†‡ Christiane I. Ramos, PhD,*§†† David W. Johnson, MBBS, FRACP, DMed(Res), FASN,†¶↔ and Katrina L. Campbell, PhD*††*

Objective: Gut dysbiosis has been implicated in the pathogenesis of chronic kidney disease (CKD). Restoring gut microbiota with prebiotic, probiotic, and synbiotic supplementation has emerged as a potential therapeutic intervention but has not been systematically evaluated in the CKD population.

Design and Methods: This is a systematic review. A structured search of MEDLINE, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials, and the International Clinical Trials Register Search Portal was conducted for articles published since inception until July 2017. Included studies were randomized controlled trials investigating the effects of prebiotic, probiotic, and/or synbiotic supplementation (>1 week) on uremic toxins, microbiota profile, and clinical and patient-centered outcomes in adults and children with CKD.

Results: Sixteen studies investigating 645 adults met the inclusion criteria; 5 investigated prebiotics, 6 probiotics, and 5 synbiotics. The quality of the studies (Grades of Recommendation, Assessment, Development and Evaluation) ranged from moderate to very low. Prebiotic, probiotic, and synbiotic supplementation may have led to little or no difference in serum urea (9 studies, 345 participants: mean difference [MD] −0.30 mmol/L, 95% confidence interval [CI] −2.20 to 1.61, $P = .76$, $I^2 = 53\%$), indoxyl sulfate (4 studies, 144 participants: MD −0.02 mg/dL, 95% CI −0.09 to 0.05, $P = .61$, $I^2 = 0\%$), and p-cresyl sulfate (4 studies, 144 participants: MD −0.13 mg/dL, 95% CI −0.41 to0.15, $P = .35$, $I^2 = 0\%$). Prebiotic supplementation may have slightly reduced serum urea concentration (4 studies, 105 participants: MD −2.23 mmol/L, 95% CI −3.83 to −0.64, $P = .006$, $I^2 = 11$). Of the 2 studies investigating microbiota changes, synbiotic interventions significantly increased *Bifidobacterium*. Supplement effects on clinical outcomes were uncertain.

Conclusions: There is limited evidence to support the use of prebiotics, probiotics, and/or synbiotics in CKD management.

Results from the Meta-analysis

- Primary outcome- change in eGFR and change in kidney damage
- Secondary outcome- decrease in uremic toxins, microbiota composition, change in clinical markers
- 16 studies included, quality ranged from moderate to very low
- Overall adherence was high, and was well-tolerated with few side effects
- Nutritional supplementation made little/no difference in eGFR
- Nutritional supplementation- little/no difference in uremic toxins
  - -Prebiotics- slightly ⇩
  - -Probiotics/Synbiotics- no change
- Small, but statistically significant decrease in serum urea in non-dialysis CKD pts (not in dialysis pts)- with prebiotics, probiotics, and synbiotics

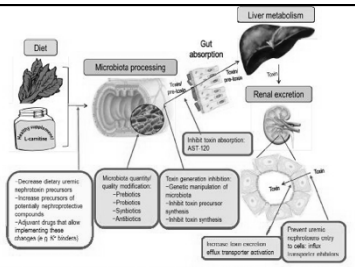


Figure 2. Potential therapeutic approaches on the gut microbiota-CKD progression axis. Only one of these approaches is used routinely in the clinic in some countries (AST-120). The rest are theoretical or have been tested only in preclinical cell culture or animal models.

Castillo-Rodriguez, *et al.* Impact of Altered Intestinal Microbiota on CKD Progression. *Toxins* **2018**, *10*(7), 300. Used with permission

Current Areas of Research

- Modulating gut microbiota
- Absorption of uremic toxins from microbial fermentation
- Creation of genetically-modified bacteria to treat disease

* Patients may be prefer "natural approaches" targeting gut microbiota vs medication treatment

Prebiotics

Those being used in treatment: inulin, fructo-oligosaccharides (FOS), galacto-oligosaccharides, soya-oligosaccharides, xylo-oligosaccharides, pyrodextrins

Proposed mechanisms of action:

- Modulating colonic microbiota
- Delaying gastric emptying and/or altering intestinal transit time
- Increasing SCFA production
- Increasing Bifidobacterium

Resistant Starch

- Fermentable fibers, typically a prebiotic
- Fermented by colonic microbes
- Examples: grains, legumes, seeds, tubers, green bananas
- Animal models- slowed progression of CKD by restoring tight junctions

Probiotics

- Study Conclusion: Probiotic supplementation failed to reduce uremic toxins and inflammatory markers. Therefore, probiotic therapy should be chosen with caution in HD patients.
  Borges *et al.* Probiotic Supplementation in Chronic Kidney Disease: A Double-blind, Randomized, Placebo-controlled Trial. *J Ren Nutr.* 2018 Jan;28(1):28-36.
- Study Conclusion: Treatment of 30 non-HD CKD patients with Lactobacillus casei Shirota resulted in a reduction of urea levels.
  Miranda *et al.* Effect of probiotics on human blood urea levels in patients with chronic renal failure. *Nutr. Hosp.* 29(3), 582–90 (2014).

Synbiotics

- SYNbiotics Easing Renal failure by improving Gut microbiologY (SYNERGY) study
- Reduced pCS, not IS
- Enriched Bifidobacterium and depleted Ruminococcaceae

SCFAs

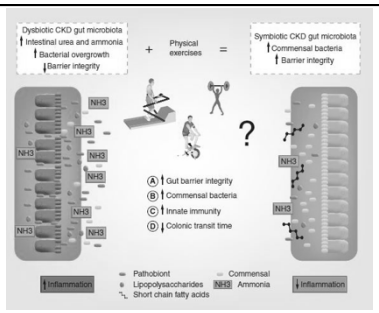
- End products of fermentation of dietary fibers by gut microbiota
- Delivered via fiber intake or probiotic supplements
- Important source of energy
- Modulate immune system, inhibit pathogens, possible tumor suppression
- Examples: Acetate, propionate, and butyrate
- Kidney-protective?

Lubiprostone (Amitiza)

- Synthetic derivative of prostaglandin used to treat constipation
- Animal models- decreased IS and TMAO

Exercise

- Physical inactivity- independent risk factor for progression of CKD
- Decreases transit time
- Goal for exercise in CKD is 30 minutes, five times per week



Esgalhado M, *et al.* Could physical exercise help modulate the gut microbiota in chronic kidney disease? *Future Microbiol.* 2016 May;11:699-707.

Future Studies on Exercise & CKD Needed

"The re-establishment of gut balance by using physical exercise could reduce the effects on oxidative stress and inflammation, and consequently decrease cardiovascular risk in CKD patients."

Esgalhado M, et al. Could physical exercise help modulate the gut microbiota in chronic kidney disease? Future Microbiol. 2016 May;11:699-707.

Oral Activated Charcoal AST-120

- Decreases absorption of uremic toxins
- Large number of pills required
- Animal models- decreased accumulation of IS and pCS
- EPPIC-1 and EPPIC-2 did not show benefit
- Exception: small high risk group may have benefitted from combo tx of AST-120 and renin-angiotensin system blockade

Other Possible Treatments

- Antibiotics, such as rifaximin

What are your patients taking right now?

Kibow Biotech- Renadryl (probiotic) + Kibow Fortis (prebiotic)

Testing for Dysbiosis

american gut

uBiome

thryve

GI-MAP™
DNA Stool Analysis

Diagnos-Techs, Inc.
Clinical and Research Laboratory

As RDNs, what can we do?

- Personalized approach: "N=1"
- Early intervention to take advantage of microbiome's adaptability
- Preserve kidney function
- Discuss use of prebiotics/probiotics/synbiotics with care team
- Look for new evidence-based treatments
- Encourage exercise

Review Objectives

Can you:

1. Identify the role of the microbiome in human health and disease.
2. Differentiate between the microbiome and metabolome.
3. Describe three nutrition interventions which may rebalance the microbiome in chronic kidney disease.

Additional resources

https://www.gutmicrobiotaforhealth.com

GUT MICROBIOTA FOR HEALTH

http://usprobioticguide.com Clinical Guide to Probiotic Products Available in USA Indications, Dosage Forms and Clinical Evidence to Date - 2019 Edition

Questions?

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