PRE-PRO-BIOTICS IN CKD

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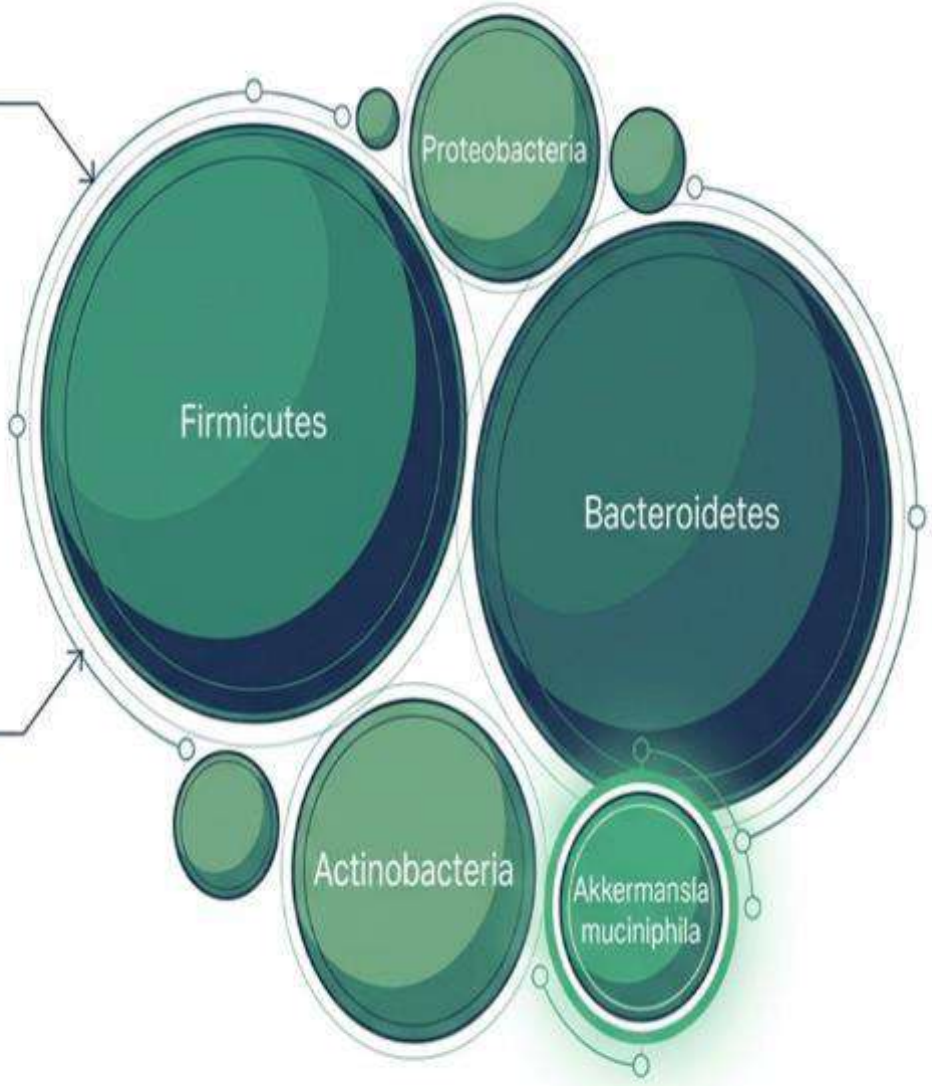
The Commensal Ecosystem: Baseline Homeostasis

Firmicutes & Bacteroidetes: Constitute ~90% of the healthy microbiome.

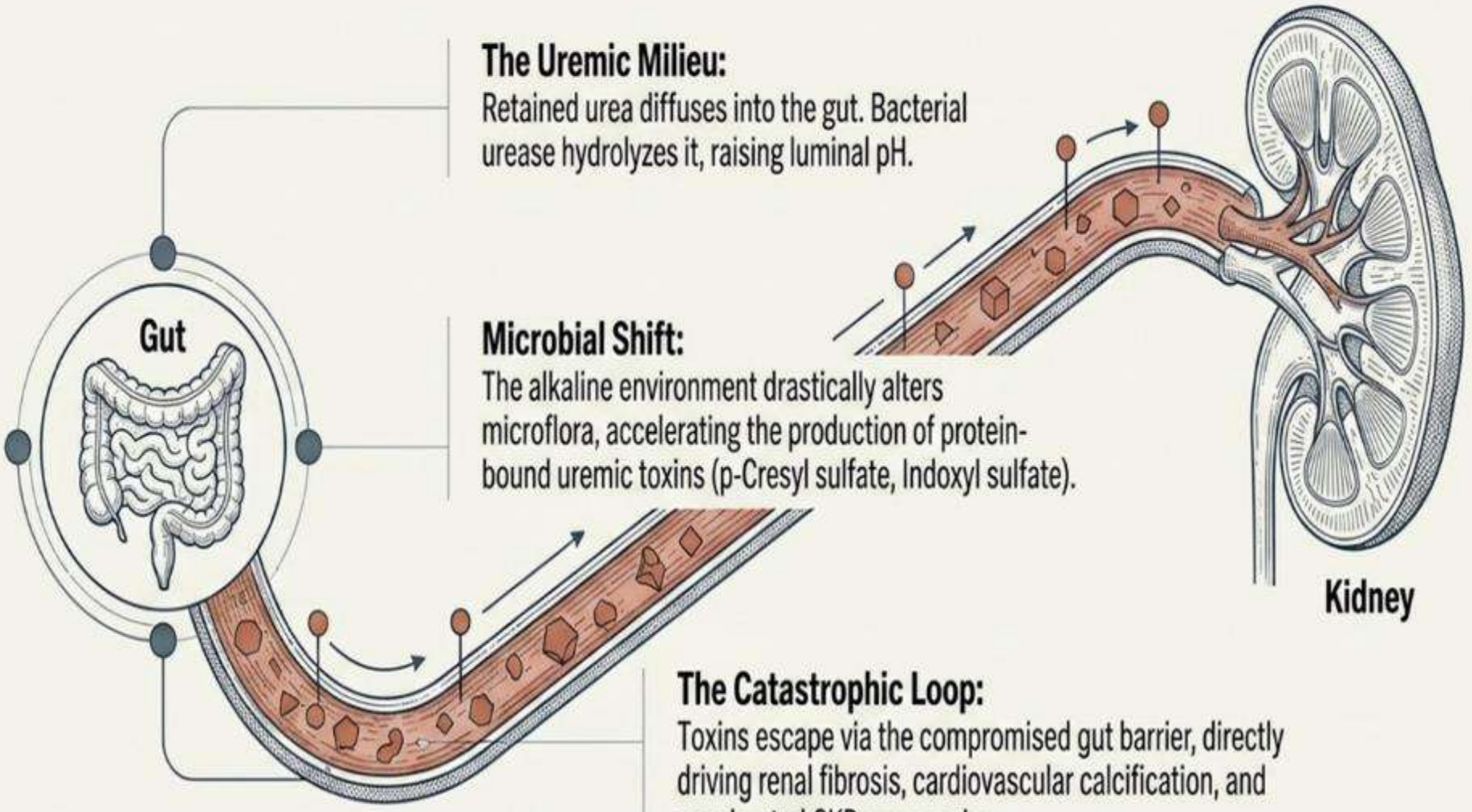
Akkermansia muciniphila: The "Gatekeeper" of the intestinal mucosa.



Core Functions

- Synthesizing B and K vitamins.
- Degrading indigestible plant polysaccharides.
- Maintaining epithelial barrier integrity.
- Inhibiting pathogen colonization.

Axis 1: The Gut-Kidney Connection



The Uremic Milieu:
Retained urea diffuses into the gut. Bacterial urease hydrolyzes it, raising luminal pH.

Microbial Shift:
The alkaline environment drastically alters microflora, accelerating the production of protein-bound uremic toxins (p-Cresyl sulfate, Indoxyl sulfate).

The Catastrophic Loop:
Toxins escape via the compromised gut barrier, directly driving renal fibrosis, cardiovascular calcification, and accelerated CKD progression.

The Pathological Pivot: Dysbiosis and the 'Leaky Gut'

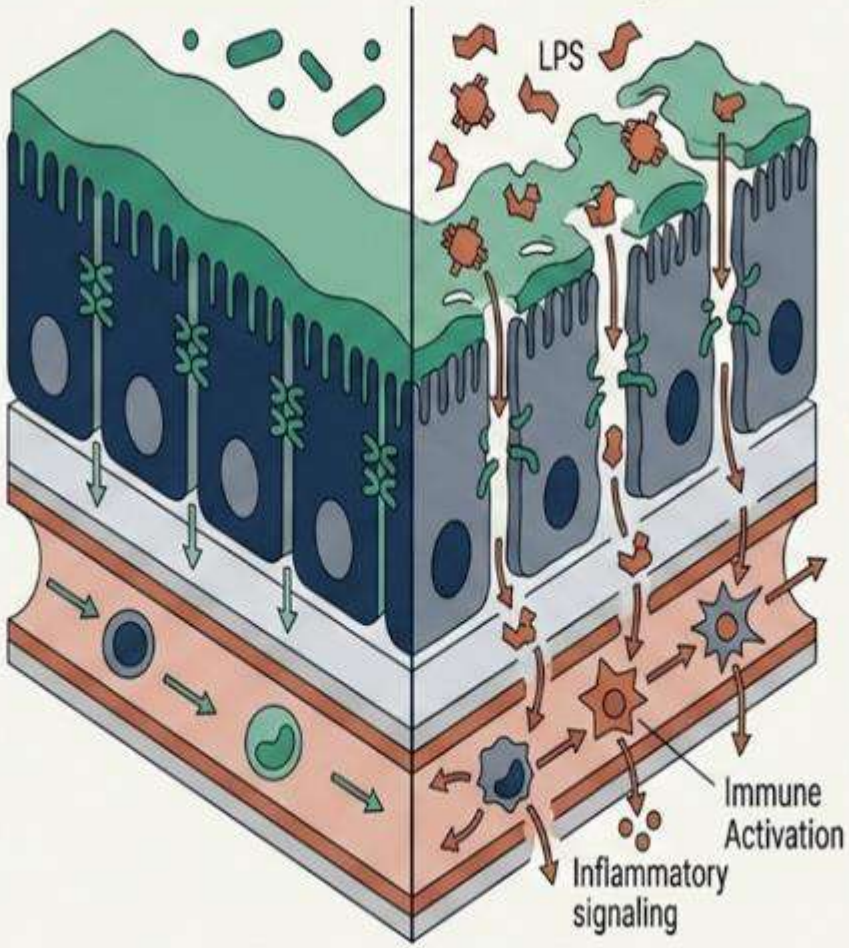
1. Dietary/Environmental Shift:

Loss of saccharolytic (carb-fermenting) bacteria triggers a proteolytic (protein-fermenting) phenotype.

2. Barrier Degradation:

SCFA deficiency weakens tight junction proteins (occludin, claudin-1).

Intestinal Epithelial Barrier (IEB)



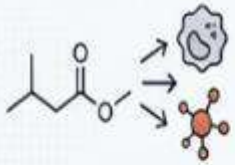
3. Translocation:

Lipopolysaccharides (LPS) infiltrate the systemic circulation.

4. Metabolic Endotoxemia:

LPS activates Toll-like receptor 4 (TLR4), initiating the NF-κB inflammatory cascade.

The Microbial Therapeutics Spectrum

 Fuel/Fiber & Bacteria	**Prebiotics (The Fuel):** Nondigestible ingredients (fructooligosaccharides) that feed native commensals.	Slight but significant reductions in serum urea.
 Pill/Live Bacteria	**Probiotics (The Bugs):** Live strains (Lactobacillus, Bifidobacterium).	Supports barrier integrity, reduces cholesterol, though colonization is often transient.
 Combination/Synergy	**Synbiotics (The Synergy):** Combined pre/probiotics.	Higher abundances of beneficial strains and moderate BMI reduction.
 Isolated Molecule/Metabolite	**Postbiotics (The Output):** Direct delivery of metabolites (e.g., sodium butyrate).	Bypasses fermentation to directly modulate immunity and inflammation.

GUT MICROBIOME -INTERVENTIONS

- **Factors affecting gut microbiome**: Urea in gastric secretions , GI Oxalate secretion , decreased fiber intake , phosphate binder use / PPIs , constipation , GI Uric acid secretion and antibiotic use.
- **Interventions for dysbiosis**: Modulate gut microbiota ,block LPS , attenuate inflammation , adsorption of gut uremic toxin and restricting proteolytic fermentation in colon.
- **Probiotics reduce uremic toxins : Metabolizing toxins in the gut** , c**ompeting with pathogenic bacteria** , **strengthening the intestinal barrier and lowering Intestinal pH.**

Multi species probiotics formulations :

- **Streptococcus thermophilus** acts to reduce blood urea nitrogen (BUN), uric acid, and p-cresol in the blood plasma.
- **Lactobacillus acidophilus** lowers the concentration of uremic toxins in the bloodstream and specifically prevents pathogenic bacteria from growing in the small intestine.
- **Bifidobacterium longum** removes putrefactive bacteria as well as toxic phenolic and indole metabolites, helping to slow the progression of the disease.
- **Bacillus coagulans** → spore-forming nature→ enhanced survivability, stability, and ease of formulation

SYNERGY TRIAL

- Randomized, double-blind, placebo-controlled, cross-over study.
- 37 predialysis adult patients with severe CKD (stages 4 or 5).
- 12 weeks
- Synbiotic therapy combining probiotics (Lactobacillus acidophilus and Bifidobacterium bifidum) with a prebiotic (inulin)

- **Uremic Toxins:** significantly reduced serum levels of *p*-cresyl sulfate

No effect on serum indoxyl sulfate (IS) levels.

- **Impact of Antibiotics:** The reductions in both PCS and IS concentrations were much more pronounced in the subgroup of patients who did not receive antibiotics during the study.
- **Microbiome Modulation:**Successfully and favorably modified the stool microbiome of the patients.

THE TRIAL

- **Strengthened the gut-kidney axis concept.**
- **Opened research into microbiome-targeted therapy in CKD.**
- **Suggested synbiotics may become adjunctive supportive therapy.**
- **But evidence still insufficient.**

EFFICACY OF PROBIOTICS/SYNBIOTICS SUPPLEMENTATION IN PATIENTS WITH CHRONIC KIDNEY DISEASE : CHANG LIU, 06 AUG 2024 - FRONTIERS IN NUTRITION

- A systematic review and meta-analysis of randomized controlled trials.
- The results showed that probiotic/symbiotic supplements significantly reduced blood urea nitrogen (BUN) (standardized mean difference (SMD) -0.23, 95% confidence interval (CI) -0.41, p = 0.02].
- Lowered CRP levels (SMD: -0.34; 95% Cl:-0.62 ; p = 0.01) in CKD patients, compared with the control group.
- **Summary**: probiotic/ synbiotic supplementation seems to be effective in improving renal function indices and inflammation indices in CKD patients.
- **Subgroup analyses :** Suggested that longer-term supplementation is more favorable for CKD patients.

clinical investigation www.kidney-international.org

Association between the gut microbiota and estimated glomerular filtration rate in two Swedish population-based cohorts

see commentary on page 832

OPEN

Yi-Ting Lin[1,2], Tiscar Graells[1], Sergi Sayols-Baixeras[3,4], Koen F. Dekkers[3], Tessa Schillemans[1], Gabriel Baldanzi[3,5], Jonas Wuopio[1,6], Nynne Nielsen[7], Aron C. Eklund[7], Jacob B. Holm[7], H. Bjørn Nielsen[7], Göran Bergström[8,9], J. Gustav Smith[10,11,12,13,14,15], Andrei Malinovschi[16], Gunnar Engström[17], Marju Orho-Melander[17], Tove Fall[3,18] and Johan Ärnlöv[1,6,19]

1. **AIM :** Quantified links between gut microbiota and estimated glomerular filtration rate (eGFR) in two population-based Swedish cohorts.

2. **Study population**: Deep shotgun metagenomics profiled fecal samples from 9788 adults in the Swedish CArdioPulmonary BioImage Study (SCAPIS) discovery cohort (mean age 58 ± 4 years; 52% women) and 2080 adults in the Malmö Offspring Study (MOS) replication cohort (mean age 40 ± 14 years; 52% women).

Take-Home Message: Gut microbiota signatures are closely linked with kidney function, making the microbiome a promising future therapeutic target in CKD.

[ACKNOWLEDGEMENT : SLIDES – DR KISHORE DHARAN]

Use of probiotics in patients with chronic kidney disease on hemodialysis: a randomized clinical trial

BRAZILIAN JOURNAL OF NEPHROLOGY
JORNAL BRASILEIRO DE NEFROLOGIA

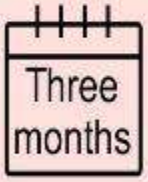
METHODOLOGY

70 patients on hemodialysis

Randomized
Double-blind

Probiotic supplementation (n=32)

Placebo (n=38)



Biochemical data
Inflammatory biomarkers

RESULTS

Before vs after probiotic supplementation

Syndecan-1
Endothelial lesion biomarker
239 ± 113 to 184 ± 106 ng/mL, p = 0.005

Blood glucose
162 ± 112 to 146 ± 74 mg/dL, p = 0.02

Renal parameters (**serum NGAL** and **serum cystatin C**) showed no significant difference

Conclusion: Administration of probiotics to patients with advanced CKD was associated with decreases in syndecan-1 and blood glucose levels, indicating potential improvements in metabolism and decreased systemic inflammation.

Reference

Araújo EMR, et al. *Braz. J. Nephrol.*, 2022. DOI: https://doi.org/10.1590/2175-8239-JBN-2022-0021en.

Visual abstract by Regiane S. da Cunha