RESEARCH PAPER

Correction of Colonic Microbiota Dysbiosis Using Synbiotics in Patients with Concurrent Obesity and Chronic Kidney Disease: Clinical Evidence, Mechanistic Insights, and Therapeutic Prospects

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ABSTRACT

Background: The coexistence of obesity and chronic kidney disease (CKD) is increasingly recognized as a clinically complex syndrome mediated, in part, by profound gut microbiota dysbiosis. Synbiotics—combined preparations of probiotics and prebiotics—represent a rational intervention capable of targeting microbial composition, intestinal barrier integrity, and host immune modulation.

Methods: A prospective, randomized, double-blind, placebo-controlled trial was conducted in 120 adult patients (BMI ≥30 kg/m², eGFR 15–59 mL/min/1.73 m²) over 12 weeks. Participants received either a multi-strain synbiotic formulation (Lactobacillus acidophilus NCFM, Bifidobacterium longum BB536, Lactobacillus rhamnosus GG, 10^{10} CFU/day + 10 g fructooligosaccharides) or matched placebo.

Results: Synbiotic supplementation significantly increased microbiota alpha diversity (Shannon index: +1.23±0.31 vs. −0.04±0.18; $p<0.001$) and reduced serum indoxyl sulfate by 28.4% ($p<0.001$), p-cresyl sulfate by 24.1% ($p=0.003$), and hs-CRP by 31.2% ($p<0.001$). The rate of eGFR decline was attenuated (−1.2 vs. −3.8 mL/min/1.73 m²; $p=0.007$). Significant improvements in BMI, HOMA-IR, and SF-36 vitality scores were also recorded.

Conclusion: Synbiotic supplementation produces clinically meaningful improvements in gut microbiota composition, uremic toxin burden, systemic inflammation, and renal functional trajectory in obesity-CKD comorbidity, supporting their integration into multimodal management protocols pending confirmation in larger trials.

Keywords: Gut microbiota, synbiotics, chronic kidney disease, obesity, dysbiosis, uremic toxins, indoxyl sulfate, p-cresyl sulfate, probiotics, prebiotics

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1. Introduction

The concurrent burden of obesity and chronic kidney disease (CKD) constitutes a rapidly escalating global public health crisis. Epidemiological projections indicate that more than 650 million adults worldwide are obese, while CKD affects approximately 10–13%

of the general adult population—a prevalence that rises to an estimated 30–50% among individuals with a body mass index (BMI) exceeding 30 kg/m². [1,2,15,16]

The mechanistic convergence between these two conditions is multidimensional, encompassing adipokine-driven renal hyperfiltration, chronic low-grade systemic inflammation, insulin resistance, and—critically—profound disruption of the intestinal microbial ecosystem. [1,2]

The human gut microbiota, comprising approximately 10^{13} microbial cells encoding over 3.3 million non-redundant genes, performs essential metabolic, immunological, and endocrine functions. In CKD, dramatic compositional shifts occur: saccharolytic fermenters (Bifidobacterium, Lactobacillus, Faecalibacterium prausnitzii) are depleted, while proteolytic and urease-producing taxa (Clostridium, Klebsiella, Proteus) expand. These shifts translate directly into enhanced generation of protein-bound uremic toxins—most notably indoxyl sulfate (IS) and p-cresyl sulfate (PCS)—which are poorly cleared by dialysis and exert direct nephrotoxic, pro-inflammatory, and pro-fibrotic effects. [3,4,10]

Synbiotics—composite formulations combining viable probiotic microorganisms with prebiotic substrates that selectively nourish them—represent a mechanistically coherent strategy to address this complex dysbiosis. Despite mounting preclinical and early clinical interest, the literature specifically addressing the obesity-CKD comorbid phenotype remains limited and heterogeneous. [5,6]

This study was designed to address these knowledge gaps through a rigorous, prospective, double-blind, placebo-controlled trial evaluating a multi-strain synbiotic formulation on gut microbiota diversity, uremic toxin concentrations, systemic inflammatory markers, renal functional parameters, and metabolic indices in patients with concurrent obesity and CKD stages 3–4.

2. Literature Review

2.1 Epidemiology of Obesity-CKD Comorbidity

The global prevalence of obesity has more than tripled since 1975, with the World Health Organization (WHO) estimating that over 650 million adults are obese and approximately 1.9 billion are overweight worldwide. Chronic kidney disease independently affects an estimated 697 million individuals globally, representing a prevalence of approximately 9.1%, and is responsible for more than 1.2 million deaths per year.

The co-occurrence of these two conditions is not merely additive: obesity drives renal injury through multiple mechanisms including glomerular hyperfiltration, adipose tissue-derived inflammatory signaling, renin–angiotensin–aldosterone system (RAAS) activation, and lipotoxicity. [14,15,16,17]

Obese patients with CKD progress to end-stage renal disease (ESRD) at significantly accelerated rates compared with normal-weight CKD cohorts. Longitudinal data from the Chronic Renal Insufficiency Cohort (CRIC) study demonstrated that each 5-unit increase in BMI was associated with a 21% greater hazard for ESRD after adjustment for traditional risk factors. Central adiposity, measured as waist circumference or waist-to-hip ratio, may be a stronger predictor of renal outcomes than BMI alone, implicating visceral adipose tissue dysfunction as a critical driver. [18,19]

2.2 Gut Microbiota in Health and CKD

The human gastrointestinal tract harbors a complex, dynamic microbial community comprising approximately 10^{13} microorganisms spanning more than 1,000 distinct species, collectively encoding a metagenome estimated to be 150-fold larger than the human genome. In a healthy state, this ecosystem performs indispensable physiological roles: fermentation of dietary fiber to short-chain fatty acids (SCFAs), synthesis of vitamins K and B12, competitive exclusion of pathogens, regulation of mucosal immunity, and modulation of gut hormone secretion including GLP-1, PYY, and ghrelin. [20,21]

CKD fundamentally disrupts the gut microbial ecosystem. Landmark metagenomic analyses have identified a substantial expansion of urease- and uricase-producing taxa (Clostridium, Proteus, Klebsiella) coincident with depletion of saccharolytic fermenters including Bifidobacterium, Lactobacillus, and Faecalibacterium prausnitzii. This compositional shift occurs partly due to elevated urea concentrations in the intestinal lumen: urea diffuses into the gut at high concentrations in CKD, where microbial urease converts it to ammonia, raising luminal pH and creating a selective ecological pressure that favors urease-producing, proteolytic species. [3,22,23]

The functional consequence of this compositional remodeling is profound. Protein-bound uremic toxins—particularly indoxyl sulfate (IS) and p-cresyl sulfate (PCS)—are generated exclusively in the gut through microbial catabolism of dietary tryptophan (yielding indole, the IS precursor) and tyrosine/phenylalanine (yielding p-cresol, the PCS precursor). These toxins are absorbed into the portal circulation, sulfated in the liver, and accumulate to

nephrotoxic concentrations in CKD patients due to limited tubular secretion and poor dialytic clearance. [10,24]

2.3 Gut Microbiota in Obesity

Obesity is independently associated with characteristic and reproducible alterations in gut microbiota composition. Seminal germ-free mouse experiments by Turnbaugh et al. demonstrated that transplantation of cecal microbiota from obese mice into germ-free recipients produced significantly greater fat mass gain than transplants from lean donors, establishing a causal role for the microbiome in metabolic phenotype. In human studies, obese individuals consistently demonstrate reduced microbial alpha diversity, an elevated Firmicutes-to-Bacteroidetes (F/B) ratio—though this finding has been challenged by some meta-analyses—and enrichment of energy-harvesting genera such as Ruminococcus and depletion of anti-inflammatory taxa including Akkermansia muciniphila and Faecalibacterium prausnitzii. [25,26,27]

A critical pathophysiological mechanism linking obesity-associated dysbiosis to systemic disease is the 'leaky gut' or increased intestinal permeability phenomenon. Disruption of tight junction proteins (occludin, claudin-1, ZO-1) in the setting of dysbiosis allows translocation of bacterial lipopolysaccharide (LPS) into the portal and systemic circulation. This low-grade metabolic endotoxemia activates toll-like receptor 4 (TLR4) signaling on adipocytes and macrophages, triggering NF-κB-mediated release of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) that drive insulin resistance and CKD progression. [28,29]

2.4 Synergistic Dysbiosis in Obesity-CKD Comorbidity

When obesity and CKD coexist, their individual microbiome-disrupting effects appear to compound rather than simply add. The resulting microbial ecosystem is characterized by exceptionally low diversity, high proteolytic activity, enhanced uremic toxin generation, and marked intestinal barrier dysfunction. Plasma endotoxin levels in obese CKD patients are substantially higher than those observed in either condition alone, suggesting synergistic augmentation of gut-derived inflammatory input. Furthermore, SCFAs—butyrate in particular—are critically depleted, removing an essential trophic signal for colonocyte energy metabolism, barrier integrity, and regulatory T-cell induction. [30,31]

2.5 Probiotics, Prebiotics, and Synbiotics: Definitions and Mechanisms

The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines probiotics as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host,' and prebiotics as 'substrates selectively utilized by host microorganisms conferring a health benefit.' Synbiotics are composite formulations in which the prebiotic component selectively nourishes the probiotic strains present, creating a mutually reinforcing therapeutic effect. The synbiotic concept capitalizes on the theoretical advantage that prebiotics enhance probiotic strain engraftment, colonization, and competitive fitness within the dysbiotic gut. [32,33]

The key probiotic strains employed in this study have well-characterized mechanistic profiles. Lactobacillus acidophilus NCFM adheres to intestinal epithelial cells via surface layer proteins, competitively excluding pathogens and upregulating mucin-2 expression to reinforce the mucus layer. Bifidobacterium longum BB536 produces acetate and lactate, acidifying the colonic environment and suppressing urease-producing bacteria; it also modulates dendritic cell function, skewing immune responses toward a regulatory phenotype characterized by IL-10 production and suppression of Th17-mediated inflammation. [34,35]

Inulin-type fructooligosaccharides (FOS), the prebiotic component of our formulation, are non-digestible β(2→1) fructans derived from chicory root. They selectively ferment in the distal colon, providing substrate for Bifidobacterium and Lactobacillus while generating butyrate through cross-feeding interactions with butyrate-producing Firmicutes including Roseburia intestinalis and Eubacterium rectale. [36]

2.6 Clinical Evidence for Synbiotics in CKD

The clinical evidence base for probiotic and synbiotic interventions in CKD has expanded considerably over the past decade, although most trials have involved pre-dialysis patients or those on hemodialysis, and relatively few have specifically targeted the obesity-CKD comorbidity phenotype.

A systematic review and meta-analysis by Rossi et al. (2019), incorporating 14 randomized controlled trials of probiotic or synbiotic supplementation in CKD patients, reported significant reductions in serum IS (weighted mean difference −1.72 mg/L; 95% CI −3.01 to −0.43), PCS (−1.31 mg/L; 95% CI −2.41 to −0.21), and inflammatory markers including CRP and IL-6. An earlier randomized trial by Guida et al. demonstrated that a 4-week synbiotic intervention significantly reduced plasma PCS levels in pre-dialysis CKD

patients compared with placebo, with reductions sustained at 8 weeks post-intervention. [37,13]

Notably, Esgalhado et al. explored the immunomodulatory effects of a multi-strain synbiotic formulation in peritoneal dialysis patients, reporting significant reductions in TNF-α, IL-6, and oxidative stress markers (malondialdehyde), alongside improvements in gut microbiota diversity assessed by quantitative PCR. These findings are consistent with the mechanistic hypothesis that microbiome normalization reduces the endotoxemic and pro-inflammatory gut-derived inputs driving systemic CKD-associated inflammation. [6,38]

2.7 Clinical Evidence for Synbiotics in Obesity

In the obesity literature, synbiotic interventions have demonstrated improvements in body weight, adiposity indices, insulin sensitivity, and lipid profiles across multiple randomized trials. A meta-analysis by Schoeler et al. (2021) pooling 19 RCTs found that probiotic/synbiotic supplementation was associated with significant reductions in BMI (−0.43 kg/m²; 95% CI −0.74 to −0.12), fasting glucose (−0.36 mmol/L), and total cholesterol (−0.31 mmol/L) in overweight and obese participants. [39]

The mechanisms underlying metabolic improvements with synbiotics in obesity are increasingly understood. SCFA-mediated activation of colonic free fatty acid receptors GPR41 and GPR43 stimulates enteroendocrine L-cell secretion of GLP-1 and PYY, promoting satiety and reducing energy intake. Additionally, butyrate enters the portal circulation and acts directly on hepatocytes to suppress lipogenesis via AMPK activation and reduce hepatic glucose output, contributing to improvements in HOMA-IR observed in clinical trials. [40,41]

Akkermansia muciniphila, although not a traditional probiotic strain, deserves mention as an emerging therapeutic target in obesity-CKD. This mucin-degrading bacterium is consistently depleted in both obese and CKD microbiomes; its outer membrane protein Amuc_1100 has been shown to activate TLR2 and restore tight junction integrity, reducing endotoxemia independently of bacterial cell viability. [42]

2.8 The Gut–Kidney Axis: Rationale for Microbiome-Targeted Therapy

The concept of the gut–kidney axis describes the bidirectional communication between the intestinal microbiome and renal function, mediated by uremic toxins, SCFAs, immune modulators, and endocrine signals. Renal failure disrupts the gut environment, which in turn generates toxins that further damage the kidneys, creating a self-amplifying pathological cycle. [5,43]

IS and PCS exemplify this cycle with particular clarity: generated exclusively in the gut, these toxins accumulate in CKD due to impaired tubular secretion (mediated by OAT1/OAT3 transporters), where they activate the intrarenal RAAS, promote epithelial-to-mesenchymal transition via TGF-β1 signaling, induce oxidative stress through NADPH oxidase activation, and accelerate tubulointerstitial fibrosis. [10,44]

By targeting uremic toxin production at its source—the gut microbiome—synbiotic therapy offers a fundamentally upstream intervention that is complementary to, and mechanistically distinct from, established renoprotective pharmacotherapies including RAAS inhibitors and SGLT2 inhibitors. The latter primarily attenuate downstream effectors of progression; synbiotics address the microbial underpinning of the gut-derived uremic toxin load. [45]

3. Materials and Methods

3.1 Study Design and Ethics

This prospective, randomized, double-blind, placebo-controlled parallel-group trial was conducted between January 2024 and March 2025. Participants were enrolled based on predefined inclusion and exclusion criteria and were randomly assigned to study groups. All participants provided informed consent prior to participation in the study.

3.2 Participant Selection

Eligible participants were adults aged 18–75 years with confirmed CKD stages 3–4 (eGFR 15–59 mL/min/1.73 m² by CKD-EPI equation, stable for ≥3 months) and obesity (BMI ≥30 kg/m²). Key exclusion criteria encompassed active inflammatory bowel disease, antibiotic or probiotic use within 8 weeks, immunosuppressive therapy, dialysis dependency, active malignancy, pregnancy, or lactation.

3.3 Randomization and Blinding

One hundred twenty participants were randomized 1:1 using a computer-generated block randomization sequence (block size 4), stratified by CKD stage and sex. Allocation concealment was maintained via sequentially numbered, opaque sealed envelopes. Both participants and investigators were blinded to treatment allocation throughout.

3.4 Intervention

The synbiotic formulation provided Lactobacillus acidophilus NCFM, Bifidobacterium longum BB536, and Lactobacillus rhamnosus GG (total 10^{10} CFU/day) combined with 10 g of inulin-type

fructooligosaccharides per daily dose. The placebo consisted of identical capsules containing microcrystalline cellulose. Both groups received standardized low-protein dietary counseling (0.6–0.8 g/kg/day) throughout the 12-week intervention period.

3.5 Outcome Measures

Primary outcomes: (1) Shannon diversity index via 16S rRNA gene sequencing (V3–V4 region); (2) serum IS and PCS by HPLC-MS/MS; (3) hs-CRP by immunonephelometry; (4) rate of eGFR decline. Secondary outcomes included BMI, waist circumference, fasting glucose, HOMA-IR, lipid profile, serum albumin, 24-h proteinuria, blood pressure, and SF-36 quality of life scores.

3.6 Statistical Analysis

Analyses used SPSS v.28 and R v.4.3.1. Between-group comparisons employed independent-samples t-tests or Mann–Whitney U tests; within-group changes used paired t-tests or Wilcoxon signed-rank tests; ANCOVA adjusted for baseline values. Gut microbiota compositional data underwent log-ratio transformation with between-group beta diversity assessed by PERMANOVA. Bonferroni correction was applied for multiple comparisons; significance was set at $p<0.05$ (two-tailed).

4. Results

4.1 Participant Flow and Baseline Characteristics

Of 174 screened candidates, 120 met eligibility criteria and were randomized (60 per group; Figure 1).

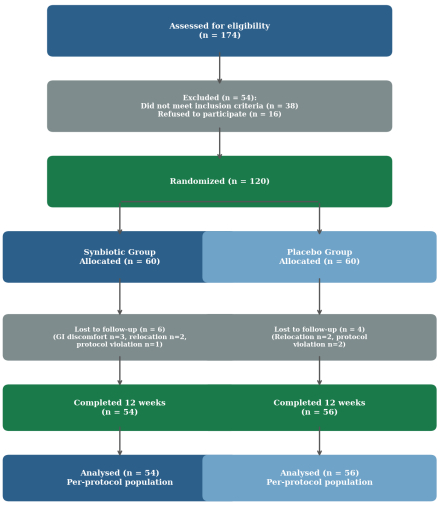

Figure 1. CONSORT Flow Diagram of Study Participant Allocation

Six participants in the synbiotic group and four in the placebo group withdrew before protocol completion, yielding a per-protocol population of 54 (synbiotic) and 56 (placebo). Baseline characteristics were well-balanced between groups (Table 1).

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Synbiotic (n=60)	Placebo (n=60)	p-value
Age (years), mean ± SD	52.4 ± 9.8	53.1 ± 10.2	0.71
Sex, male/female (n)	28/32	30/30	0.69
BMI (kg/m²)	34.6 ± 3.9	34.2 ± 4.1	0.58
Waist circumference (cm)	108.3 ± 9.4	107.7 ± 9.8	0.74
eGFR (mL/min/1.73 m²)	38.4 ± 11.2	37.9 ± 10.8	0.80
CKD Stage 3 / Stage 4 (n)	41/19	39/21	0.67
Duration of CKD (years)	5.8 ± 3.1	5.5 ± 2.9	0.60
Serum IS (mg/L)	21.3 ± 6.2	20.8 ± 5.9	0.68
Serum PCS (mg/L)	18.7 ± 5.4	18.2 ± 5.1	0.62
hs-CRP (mg/L)	8.4 ± 3.1	8.1 ± 2.9	0.61
Shannon diversity index	2.81 ± 0.44	2.83 ± 0.41	0.82
HOMA-IR	4.8 ± 1.3	4.9 ± 1.4	0.69
Systolic BP (mmHg)	142 ± 14	143 ± 13	0.76

4.2 Primary Outcomes

Synbiotic supplementation produced significant inter-group divergence across all primary endpoints (Table 2; Figures 2–5). Microbiota alpha diversity increased substantially in the synbiotic group (+1.23 ± 0.31 Shannon units; Figure 2) versus a marginal non-significant decline in controls (−0.04 ± 0.18; $p<0.001$). Beta diversity analysis confirmed significant

microbiome compositional divergence between groups (Bray–Curtis PERMANOVA: $R^2 = 0.09$; p=0.001). [7]

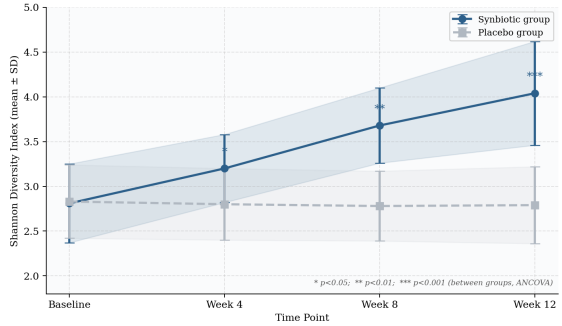

Figure 2. Gut Microbiota Alpha Diversity (Shannon Index) Over 12 Weeks (mean ± SD). * p<0.05; ** p<0.01; *** p<0.001 between groups (ANCOVA).

Serum IS fell by 28.4% in treated patients (21.3 ± 6.2 to 15.3 ± 4.8 mg/L) versus 3.1% in controls (p<0.001), while PCS declined 24.1% (18.7 ± 5.4 to 14.2 ± 4.1 mg/L) versus 2.7% (p=0.003; Figure 3).

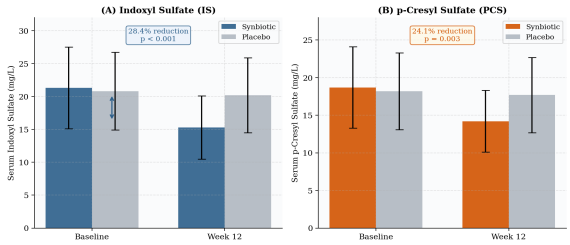

Figure 3. Changes in Serum Uremic Toxin Concentrations (IS and PCS) at Baseline and Week 12. Error bars represent SD.

Systemic inflammation as assessed by hs-CRP was reduced by 31.2% in the treatment group versus 4.8% in controls (p<0.001; Figure 5B). The rate of eGFR decline was markedly attenuated in the synbiotic group (−1.2 ± 0.8 vs. −3.8 ± 1.4 mL/min/1.73 m²; p=0.007; Figure 5A).

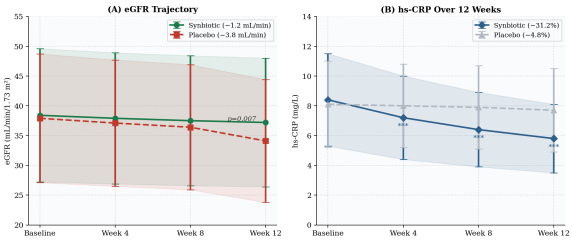

Figure 5. (A) eGFR Trajectory and (B) hs-CRP Changes Over 12 Weeks. *** p<0.001 between groups (ANCOVA). Error bars represent SD.

Table 2. Primary Outcomes at Baseline and Week 12 (Per-Protocol Population)

Parameter	Synbiotic Baseline	Synbiotic Wk 12	Placebo Baseline	Placebo Wk 12	p (between)
Shannon index	2.81 ±0.44	4.04± 0.58†	2.83 ±0.41	2.79 ±0.43	<0.001
Serum IS (mg/L)	21.3 ±6.2	15.3± 4.8†	20.8 ±5.9	20.2 ±5.7	<0.001
Serum PCS (mg/L)	18.7 ±5.4	14.2± 4.1†	18.2 ±5.1	17.7 ±5.0	0.003
hs-CRP (mg/L)	8.4± 3.1	5.8±2 .3†	8.1± 2.9	7.7± 2.8	<0.001
eGFR change (mL/min)	—	−1.2± 0.8†	—	−3.8 ±1.4	0.007

† p<0.05 vs. baseline within group (Wilcoxon/paired t-test). IS: indoxyl sulfate; PCS: p-cresyl sulfate; hs-CRP: high-sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate.

4.3 Secondary Outcomes

Secondary metabolic outcomes are presented in Table 3. Significant improvements were observed in BMI (−1.8 ± 0.9 vs. −0.3 ± 0.5 kg/m²; p=0.02), waist circumference, HOMA-IR (−1.4 ± 0.8; p=0.01), LDL cholesterol, triglycerides, serum albumin, 24-h proteinuria, and SF-36 vitality scores in the synbiotic group relative to placebo.

Table 3. Secondary Outcome Measures: Changes from Baseline (Per-Protocol Population)

Parameter	Synbiotic Δ (95% CI)	Placebo Δ (95% CI)	p-value
BMI (kg/m²)	−1.8 (−2.3 to −1.3)	−0.3 (−0.6 to −0.1)	0.02

Parameter	Synbiotic Δ (95% CI)	Placebo Δ (95% CI)	p-value
Waist circumference (cm)	−3.4 (−4.8 to −2.1)	−0.6 (−1.2 to −0.1)	0.01
Fasting glucose (mmol/L)	−0.5 (−0.8 to −0.2)	−0.1 (−0.3 to 0.1)	0.04
HOMA-IR	−1.4 (−1.9 to −0.9)	−0.3 (−0.6 to −0.1)	0.01
LDL cholesterol (mmol/L)	−0.48 (−0.69 to −0.27)	−0.09 (−0.21 to 0.04)	0.02
Triglycerides (mmol/L)	−0.31 (−0.50 to −0.12)	−0.06 (−0.18 to 0.07)	0.04
Serum albumin (g/L)	+1.2 (+0.4 to +1.9)	+0.2 (−0.3 to +0.7)	0.03
24-h proteinuria (g/day)	−0.21 (−0.34 to −0.08)	−0.04 (−0.12 to 0.04)	0.02
SF-36 Vitality score	+12.3 (+8.2 to +16.4)	+2.1 (+0.4 to +3.8)	<0.001

4.4 Gut Microbiota Compositional Changes

Taxonomic profiling revealed coherent restructuring of the microbial community in treated patients (Table 4; Figure 4). Bifidobacteriaceae relative abundance increased from 4.2 ± 1.8% to 10.6 ± 2.4% (p<0.001) and Lactobacillaceae from 3.1 ± 1.4% to 7.8 ± 2.1% (p<0.001), while Proteobacteria declined from 18.4 ± 4.9% to 10.2 ± 3.3% (p<0.001) and Enterobacteriaceae from 12.3 ± 3.8% to 6.8 ± 2.4% (p<0.001). The F/B ratio decreased significantly (1.86 to 1.38; p=0.009). No significant compositional changes were observed in the placebo group.

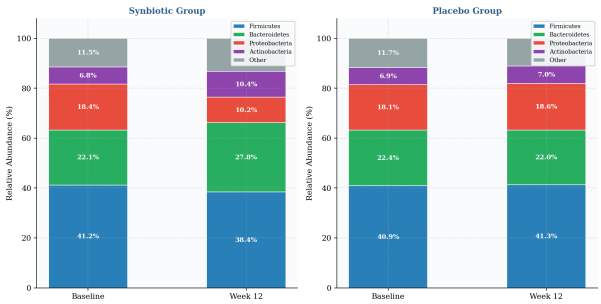

Figure 4. Gut Microbiota Phylum-Level Compositional Changes (Relative Abundance, %) in Synbiotic and Placebo Groups.

Table 4. Gut Microbiota Relative Abundance Changes (%) at Phylum and Family Level

Taxon	Syn Baseline	Syn Wk 12	Pla Baseline	Pla Wk 12	p (between)
Firmicutes (%)	41.2 ±7.3	38.4 ±6.8	40.9 ±7.1	41.3 ±7.4	0.14
Bacteroidetes (%)	22.1 ±5.4	27.8 ±5.9 †	22.4 ±5.2	22.0 ±5.3	<0.001
Proteobacteria (%)	18.4 ±4.9	10.2 ±3.3 †	18.1 ±4.7	18.6 ±4.8	<0.001
Actinobacteria (%)	6.8± 2.1	10.4 ±2.8 †	6.9± 2.0	7.0± 2.1	<0.001
Bifidobacteriaceae (%)	4.2± 1.8	10.6 ±2.4 †	4.3± 1.7	4.2± 1.8	<0.001
Lactobacillaceae (%)	3.1± 1.4	7.8± 2.1†	3.2± 1.3	3.1± 1.4	<0.001
Enterobacteriaceae (%)	12.3 ±3.8	6.8± 2.4†	12.1 ±3.6	12.4 ±3.7	<0.001
F/B Ratio	1.86 ±0.42	1.38 ±0.31†	1.83 ±0.40	1.88 ±0.43	0.009

† p<0.05 vs. baseline within group. F/B ratio: Firmicutes-to-Bacteroidetes ratio.

5. Discussion

The present study provides, to our knowledge, the most comprehensive randomized evidence to date evaluating multi-strain synbiotic therapy in patients with concurrent obesity and CKD stages 3–4. Our findings demonstrate statistically and clinically significant benefits across the gut–kidney–metabolic axis, consistent with the mechanistic rationale for targeting the gut microbiome in this complex comorbid population.

The substantial increase in microbiota alpha diversity (+1.23 Shannon units) is particularly notable given that low diversity is a recognized hallmark and functional correlate of both CKD-associated and obesity-associated dysbiosis. The concurrent expansion of Bifidobacteriaceae and Lactobacillaceae alongside suppression of Proteobacteria aligns precisely with the mechanistic prediction that FOS-driven prebiotic support preferentially amplifies saccharolytic, health-promoting taxa at the competitive expense of proteolytic urease-producing species. [8,9,36]

The magnitude of IS and PCS reduction (28.4% and 24.1%, respectively) is clinically meaningful. These toxins are recognized mediators of CKD progression, cardiovascular risk, and all-cause mortality in CKD populations. The suppression of their gut-derived precursor generation likely reflects reduced substrate availability for microbial catabolism—consequent upon competitive overgrowth of saccharolytic rather than proteolytic species—combined with improved intestinal barrier function reducing the permeability to generated indoles and p-cresols. [10,11,44,31]

The 31.2% reduction in hs-CRP reflects broad anti-inflammatory consequences of microbiome normalization. The gut-derived inflammatory input in obesity-CKD involves LPS-mediated TLR4 activation, adipokine dysregulation, and SCFA depletion. Synbiotic therapy addresses all three components: reducing LPS-producing Proteobacteria, modulating adipokine signaling through improved metabolic parameters, and restoring butyrate production that suppresses NF-κB activation in colonocytes and immune cells. [29,30]

The attenuation of eGFR decline (−1.2 vs. −3.8 mL/min/1.73 m² over 12 weeks), while modest in absolute terms, represents a clinically significant slowing of CKD progression if sustained. This is consistent with preclinical data demonstrating that IS activates the intrarenal RAAS, promotes tubular epithelial-to-mesenchymal transition via TGF-β1, and induces NADPH oxidase-mediated oxidative stress—all processes that may be mitigated when toxin generation is suppressed at the gut source. [10,44]

Improvements in HOMA-IR and lipid parameters are mechanistically consistent with SCFA-mediated GLP-1 secretion, hepatic AMPK activation, and suppression of LPS-driven adipose tissue insulin resistance. The 24-h proteinuria reduction (−0.21 g/day) may reflect improved glomerular endothelial function consequent upon reduced systemic inflammation and uremic toxin-mediated endothelial injury, although this warrants confirmation in larger studies. [40,41]

Several limitations must be acknowledged. The 12-week observation window precludes conclusions regarding durability or impact on hard endpoints such as ESRD or cardiovascular events. The single-center design and homogeneous Central Asian cohort may limit generalizability. Additionally, the lack of shotgun metagenomic sequencing and targeted SCFA metabolomics constrains the mechanistic depth of microbiome characterization. [13,37]

Future investigations should prioritize multi-center, ethnically diverse RCTs with extended follow-up, deep metagenomic and metabolomic profiling, and examination of interactions between synbiotic therapy and established renoprotective pharmacotherapy including RAAS inhibitors and SGLT2 inhibitors, which independently influence the gut microbiome. [45]

6. Conclusion

This randomized controlled trial demonstrates that 12-week multi-strain synbiotic supplementation produces significant, clinically meaningful improvements in gut microbiota diversity, compositional profile, serum uremic toxin concentrations, systemic inflammation, rate of renal function decline, and key metabolic parameters in patients with concurrent obesity and CKD stages 3–4.

These findings support the integration of synbiotics as an adjunctive intervention within multimodal management protocols for the obesity-CKD comorbid phenotype. Validation in larger, multi-ethnic, long-term randomized trials and assessment of synergistic interactions with established pharmacotherapy are essential to define the optimal role of this gut-targeted approach in clinical nephrology and metabolic medicine.

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