Cachexia in Chronic Kidney Disease: A role for the Gut Microbiome?

Inès Dufour[1,2], Guillaume Fernandes[2], Björn Meijers[3,4], Laura Labriola[2],

Eric Goffin[2], Laure B. Bindels[1,5 *]*

Affiliations:

1. *Metabolism and Nutrition Research Group, Louvain Drug Research Institute, Université catholique de Louvain, UCLouvain, Brussels, Belgium*
2. *Department of Nephrology, Cliniques universitaires Saint-Luc, Université catholique de Louvain, UCLouvain, Brussels, Belgium*
3. *Laboratory of Nephrology and Renal Transplantation, department of microbiology, immunology, transplantation, KU Leuven, Leuven, Belgium*
4. *Department of Nephrology, University Hospitals Leuven, Leuven, Belgium*
5. *WELBIO Department, WEL Research Institute, Wavre, Belgium*

**Co-senior authors*

Corresponding author:

Prof. Laure B. Bindels, Metabolism and Nutrition Research Group, Louvain Drug Research Institute, Université catholique de Louvain, UCLouvain

Avenue E. Mounier box B1.73.11, B-1200 Brussels, Belgium

E-mail address: laure.bindels@uclouvain.be

Phone: +32 (2) 436 21 85

ORCID: LBB 0000-0003-3747-3234

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Abstract

Chronic kidney disease (CKD) is frequently complicated by wasting syndromes, including malnutrition, protein-energy wasting (PEW), cachexia and sarcopenia, which profoundly impair quality of life and survival. These entities differ in pathophysiology, diagnostic criteria and reversibility. Currently, a consensus CKD-specific definition of cachexia is lacking. Chronic inflammation, metabolic disturbances and accumulation of uremic toxins are recognized contributors to muscle wasting in CKD. Emerging evidence further identifies the gut microbiome as a potential key player in this process. CKD markedly alters gut microbial composition and activity, favoring the generation of gut-derived uremic toxins while reducing the production of beneficial metabolites such as short-chain fatty acids. Among the 130 uremic toxins described to date, more than half originate from the gut microbiota. Protein-bound solutes such as indoxyl sulfate and p-cresyl sulfate, as well as trimethylamine-N-oxide and kynurenine pathway metabolites, accumulate in CKD and are increasingly recognized as mediators of skeletal muscle dysfunction. These compounds promote oxidative stress, mitochondrial dysfunction, insulin resistance and activation of proteolytic pathways. In parallel, alterations in gut barrier integrity may enhance translocation of bacterial products and sustain systemic inflammation, which further amplifies catabolism and anorexia. While these findings add another layer of complexity to CKD-associated cachexia and related wasting syndromes, they also create novel therapeutic opportunities. Microbiome-targeted interventions, including dietary strategies, pre-, pro- and synbiotics, and inhibition of microbial enzymatic pathways involved in uremic toxin generation, may represent promising approaches to mitigate muscle wasting and improve outcomes in CKD patients.

Keywords: Chronic kidney disease - Cachexia – Protein-energy wasting – Gut microbiome – Uremic toxins – Inflammation

Abbreviations:

CKD – chronic kidney disease

DEI – dietary energy intake

DPI – dietary protein intake

ESKD – end-stage kidney disease

EWGSOP2 – European Working Group on Sarcopenia in Older People 2

FMT – fecal microbiota transplantation

GLIM – Global Leadership Initiative on Malnutrition

HD – hemodialysis

IAA – indole-3-acetic acid

IDO – indoleamine 2,3-dioxygenase

IGF-1 – insulin-like growth factor 1

IPA – indole-3-propionic acid

IS – indoxyl sulfate

ISRNM – International Society of Renal Nutrition and Metabolism

LPS – lipopolysaccharide

PCS – p-cresyl sulfate

PBUTs – protein-bound uremic toxins

PEW – protein-energy wasting

PGC-1α – peroxisome proliferator-activated receptor gamma coactivator 1-alpha

PPAR-δ – peroxisome proliferator-activated receptor delta

PPIs – proton pump inhibitors

ROS – reactive oxygen species

SCFAs – short-chain fatty acids

SPPB – Short Physical Performance Battery

TLR4 – Toll-like receptor 4

TMAO – trimethylamine-N-oxide

TNF-α – tumor necrosis factor alpha

Introduction

Chronic kidney disease (CKD) affects approximately 13% of the global population and may progress to end-stage kidney disease (ESKD) requiring dialysis or transplantation. Among its complications, cachexia is particularly severe, being associated with impaired quality of life, increased morbidity and annual mortality rates estimated at 20-40%.[1] However, the mechanisms underlying CKD-associated cachexia remain incompletely understood.

A hallmark of CKD progression is the accumulation of metabolic waste products, known as uremic toxins, due to impaired renal clearance. These toxins exert deleterious systemic effects by promoting chronic inflammation, oxidative stress and mitochondrial dysfunction, contributing to premature aging[2] and complications such as vascular calcification, sarcopenia and frailty.[3] Their accumulation is influenced not only by reduced renal clearance, but also by local inflammation, excessive cytokine production and gut dysbiosis.[4] Uremic toxins are classified into small water-soluble molecules, middle-size molecules and protein-bound uremic toxins (PBUTs), the latter being particularly difficult to remove by dialysis.[3]

Uremic toxins are not the sole contributor to CKD-associated cachexia, whose pathogenesis is complex and multifactorial, involving anorexia, chronic inflammation, dialysate nutrient losses, metabolic acidosis and endocrine disorders such as insulin resistance and hyperparathyroidism.[5] Emerging evidence implicates the gut microbiome as an additional contributor through enhanced production of uremic toxins and exacerbation of systemic inflammation. This review examines current evidence regarding the role of the gut microbiome in CKD-related cachexia, focusing on diagnostic challenges, microbiome alterations and molecular mechanisms linking gut-derived toxins to muscle wasting.

Definition of CKD-associated cachexia and other wasting syndromes, challenges and pitfalls

Several wasting syndromes occur in CKD, including malnutrition, protein-energy wasting (PEW), cachexia and sarcopenia. Although overlapping, they differ in mechanisms, diagnostic criteria and reversibility.

Malnutrition results from insufficient macro- and/or micronutrient intake, leading to weight loss and nutrient deficiencies. It is frequent in advanced CKD and usually reversible with nutritional support. The Global Leadership Initiative on Malnutrition (GLIM) defines malnutrition by combining at least one phenotypic and one etiologic criterion (**Table 1**)[6], although its applicability in CKD remains under evaluation.[7] However, defining all wasting syndromes as malnutrition overlooks important contributors such as inflammation, hypercatabolism and uremic toxicity.

To address this limitation, the International Society of Renal Nutrition and Metabolism (ISRNM) introduced the concept of **protein-energy wasting (PEW),** a CKD-specific syndrome combining nutritional, metabolic and inflammatory alterations leading to protein and energy depletion.[8] PEW is diagnosed using biochemical, clinical and dietary criteria (**Table 1**), is not fully reversible with nutritional support alone, and becomes more prevalent as CKD progresses, reaching 28-54% in dialysis patients.[5,9]

Cachexia is a severe metabolic syndrome characterized by involuntary weight loss, muscle atrophy, anorexia and systemic inflammation.[10] In CKD, cachexia is often considered the most severe stage of PEW.[8] However, no CKD-specific consensus definition exists. Oncology-based

criteria suggest a prevalence of approximately 16% in dialysis patients,[11] but CKD-specific factors such as fluid retention may mask weight loss and complicate diagnosis.[7]

Sarcopenia, defined by reduced muscle mass, strength and physical performance, is also highly prevalent in CKD and may arise from ageing, chronic disease, inactivity and poor nutrition.[12]

Thus, malnutrition, PEW, cachexia and sarcopenia are related but distinct entities (**Figure 1**). The lack of CKD-specific cachexia criteria hampers prevalence estimates and study comparability. Developing such criteria, as achieved in oncology[10], would improve recognition, research consistency and therapeutic development.

Contribution of uremic toxins to cachexia

Uremic toxins are major contributors to CKD-induced muscle wasting because retained solutes directly alter muscle cell physiology and key molecular pathways.[13] These toxins originate from diverse metabolic pathways, including gut microbial metabolism, endogenous amino acid degradation and inflammatory processes.

Tryptophan-derived metabolites are strongly implicated in muscle dysfunction. **Indoxyl sulfate** (IS), the best-characterized PBUT, is involved in CKD progression, cardiovascular disease, bone disorders and mortality.[14-16] Evidence also supports a role for IS in uremic sarcopenia. In CKD mouse models, IS accumulates in skeletal muscle,[17] and chronic exogenous administration reduces body weight and muscle mass.[18] *In vitro* experiments with C2C12 myotubes revealed that IS impairs cell proliferation and differentiation by downregulating myogenic factors like Myf6/MRF4 and MYH2.[17-20] IS also induces oxidative stress and mitochondrial dysfunction, increasing reactive oxygen species (ROS) production and impairing

ATP synthesis.[21,22] Additionally, IS stimulates the expression of inflammatory cytokines, myostatin and atrogin-1, further promoting catabolism and atrophy.[18] Clinical studies generally report negative associations between IS levels and skeletal muscle index or handgrip strength in CKD patients,[17,23,24] while associations with PEW remain inconsistent.[25]

Other indolic compounds may also be relevant. **Indole-3-acetic acid** (IAA) impairs mitochondrial oxidative phosphorylation and increases oxidative stress in murine skeletal muscle,[19] whereas **indole-3-propionic acid** (IPA) may protect muscle by promoting myocyte proliferation and reducing inflammation, but its levels are reduced in CKD.[26,27] **Kynurenine pathway metabolites**, generated through endogenous tryptophan degradation, have been associated with frailty, slower walking speed and lower handgrip strength in CKD and non-CKD populations.[28-30] These metabolites activate the aryl hydrocarbon receptor, whose activation in muscle appears to promote mitochondrial dysfunction, oxidative stress and reduced protein synthesis.[18,31]

Tyrosine-derived uremic toxins also contribute to metabolic and muscular alterations in CKD. In particular, **p-cresyl sulfate (PCS)**, a gut microbiota-derived metabolite, is implicated in CKD complications.[32] In healthy mice, PCS administration induces insulin resistance, fat mass loss and ectopic lipid accumulation in muscle and liver, mimicking metabolic abnormalities observed in CKD.[33] In skeletal muscle, PCS interferes with insulin and IGF-1 signaling pathways by reducing IRS-AKT activation and enhancing ERK1/2 signaling, impairing protein synthesis and muscle growth.[33] Similar effects were observed in C2C12 myotubes exposed to CKD-relevant PCS concentrations.[33] In dialysis patients, PCS levels were associated with the prevalence of PEW.[25]

Hippuric acid, a uremic toxin derived from gut bacterial metabolism of phenylalanine and polyphenols, remains incompletely understood. Some *in vitro* studies suggest myoprotective effects by enhancing glucose metabolism, preserving mitochondrial function and promoting protein synthesis.[34] Circulating hippuric acid levels are often considered markers of healthier dietary patterns and metabolic health.[35]

Trimethylamine-N-oxide (TMAO), generated from dietary choline and L-carnitine metabolism, is increasingly recognized as a uremic toxin associated with CKD progression and have been associated with the occurrence of PEW in hemodialysis (HD) patients.[36] One study reported that TMAO aggravates sarcopenic obesity in rats via the ROS-AKT/mTOR signaling pathway,[37] while another found that TMAO supplementation decreases lean body mass and increases intramuscular fat content in pigs.[38] In contrast, Zou et al suggested that TMAO may protect C2C12 myoblasts from oxidative stress and enhance exercise endurance in mice.[39]

Inflammatory cytokines are also considered uremic toxins. Although TNF-α and IL-6 participate in muscle repair after injury, their chronic elevation in CKD promotes insulin resistance and atrogenes expression (i.e., the coordinated transcriptional activation of genes that drive protein degradation and loss of muscle mass under catabolic conditions).[40] Elevated TNF-α and IL-6 in CKD muscle biopsies correlate with atrophy,[41] while cytokine blockade or genetic deletion of *Il1β, Il6* or *Tnf*α attenuates cachexia in animal models of CKD.[42] In humans, elevated IL-6 release from muscles during HD has been linked to increased protein catabolism.[43] Together, these findings underscore chronic inflammation as a mediator of CKD-associated cachexia.

The gut microbiota as a new player in CKD

Gut microbiota dysbiosis and CKD, chicken or egg?

Many studies show that the gut microbiota composition of CKD patients differs markedly from healthy individuals.[44-46] In CKD, impaired protein assimilation increases the delivery of undigested proteins to the colon, creating a favorable environment for proteolytic bacterial species.[47,48] Additional factors potentially contributing to this dysbiosis include slow intestinal transit, iron therapy, lower fiber intake and frequent use of proton pump inhibitors and antibiotics.[49]

Importantly, the gut microbiota itself contributes to CKD by generating uremic toxin precursors, thereby reinforcing a deleterious cycle of toxin accumulation and microbiome alteration.[50] The concept of *gut-kidney axis*, first coined in 2011,[51] describes this vicious circle whereby impaired renal clearance leads to the accumulation of uremic toxins that further alter the intestinal microbiota.[44,52,53] Exacerbation of the uremic milieu as CKD progresses causes an influx of urea and uric acid into the intestinal lumen via the enterohepatic cycle, which significantly increases the abundance of bacterial species that express urease, uricase and enzymes that generate indole and p-cresol, while decreasing butyrate-producing species.[45] Elevated plasma levels of uremic toxins also correlate with specific microbial signatures in CKD patients, reinforcing the link between microbiota composition and systemic toxicity.[46,54]

Proof-of-concept studies establishing the existence of a gut-muscle axis

There is growing evidence of a communication network between the gut microbiota and skeletal muscle, the so-called *gut-muscle axis*. Microbiota depletion through germ-free conditions or antibiotics has been associated with muscle atrophy, altered muscle metabolism and reduced endurance,[55,56] although results vary by mouse strain and antibiotic cocktail.[57] Coherently, several probiotics improved muscle mass, strength and/or endurance in mice.[58,59]

Human studies also support the existence of a gut-muscle axis.[13] Supplementation with prebiotics such as inulin and fructo-oligosaccharides was associated with improved handgrip strength in elderly patients.[60] Some probiotics showed promises,[59,61] although others had no significant impact on muscle parameters.[62,63]

One of the first pathological contexts in which this gut-muscle axis has been investigated is cancer cachexia. Our team identified a reproductible microbial signature in preclinical models, characterized by increased *Enterobacteriaceae*, and associated with cachectic features.[64,65] Other studies confirmed gut microbiota alterations in mouse models of cancer cachexia.[66,67] Enteral administration of lactobacilli in a leukemia mouse model reduced muscle atrophy.[65] Gut microbiota composition has also been associated with cachexia status or parameters in cancer patients.[68,69]

Gut microbiota composition in CKD patients with wasting syndromes

Research investigating the relationship between gut microbiota and wasting syndromes in CKD remains sparse and should be interpreted cautiously given the limited number of studies and absence of longitudinal analyses.

In HD patients, PEW has been associated with reduced bacterial alpha-diversity and altered microbial community structure.[70] Several studies reported decreases in butyrate-producing bacteria, including *Faecalibacterium prausnitzii*, *Roseburia*, and *Phascolarctobacterium*, together with increased inflammatory markers, in patients with PEW.[70,71] A longitudinal study on 115 HD patients suggested *Actinobacteria* and *Bifidobacteriaceae* as potential markers for predicting skeletal muscle mass decrease and PEW development.[72]

Studies focusing on sarcopenia in CKD also reported reduced microbial diversity and compositional shifts, although the specific taxa identified differed substantially between studies.[73,74] These discrepancies may reflect variations in patient characteristics, including age, CKD versus HD status, diabetes prevalence and ethnicity.

Similarly, in peritoneal dialysis patients, malnutrition has been associated with increased abundance of taxa such as *Akkermansia*, *Megasphaera* and members of the *Peptostreptococcaceae* family.[75]

Collectively, these findings suggest that alterations in gut microbiota composition occur during PEW or sarcopenia in CKD patients and raise the hypothesis that such changes may play a role in the progression of wasting syndromes. However, given the limited number of studies and the cross-sectional nature of most studies, further longitudinal investigations are needed to clarify the causal relationships and mechanisms at play.

Mechanisms that may underly a contribution of the gut microbiota to muscle physiology in CKD

Uremic toxins

Many uremic toxins that affect muscle originate from gut bacterial metabolism of dietary components.[48,51,76,77] Among the 130 uremic toxins listed by the EUTox group, 66 (51%) originate from the gut (**Supplementary Figure S1; Supplementary Table S1)**. Supporting evidence includes: (i) markedly lower IS and PCS in ESKD patients after total colectomy[76]; (ii) reduced IS production in germ-free versus conventional rodents[78]; (iii) significant toxin reduction following oral antibiotic treatment in CKD patients.[79]

Most uremic toxins arise from the bacterial metabolism of amino acids. IS is generated from bacterial conversion of tryptophan into indole via a tryptophanase activity, followed by hepatic sulfoconjugation.[77] Around 85 indole-producing bacteria have been identified,[80] including *Escherichia coli*, *Clostridium sporogenes* and *Bacteroides.* PCS derives from bacterial metabolism of tyrosine into p-cresol, notably by *Clostridium*, *Coriobacteriaceae*, *Enterobacteriaceae* and *Fusobacteriaceae.*[77] TMAO originates from microbial metabolism of dietary choline and L-carnitine, while hippuric acid results from microbial conversion of dietary aromatic compounds into benzoate followed by hepatic conjugation with glycine.

A key question is the relative contribution of increased microbial production versus reduced renal clearance to the rise in circulating uremic toxins. Several studies support an increased microbial production in CKD. Wang et al characterized the gut microbiome and serum metabolome of 223 ESKD patients and 69 controls, identifying microbial species enriched in ESKD that correlate with clinical parameters and whose genome encode toxin biosynthesis

genes.[54] Notably, fecal microbiota transplantation (FMT) from CKD patients into kidney-injured germ-free mice increased uremic toxins production.[54] Similarly, Beau et al used an *ex vivo* gut simulator colonized with fecal samples from eight CKD patients and nine healthy volunteers, and observed increased bacterial production of p-cresol and indoles in CKD samples.[81] Recently, Laiola et al profiled the gut microbiome of 240 CKD patients and found enrichment in toxin precursor-producing species.[46]

Intriguingly, Gryp et al observed no differences in microbial PBUT production *ex vivo* across CKD stages and concluded that impaired renal clearance is the main driver of toxin accumulation.[82] These findings may reflect differences between *ex vivo* and *in vivo* conditions. More importantly, they emphasize the need to go beyond genome-encoded functional capacity and focus on *in vivo* microbial activity using functional assays,[83,84] as microbial metabolite production can be influenced by environmental conditions such as media composition and nitrate availability.[85]

Gut barrier and inflammation

Chronic inflammation is central in the development of cachexia in CKD patients,[9] and gut barrier alterations may sustain low-grade systemic inflammation.[86] Vaziri et al showed that incubation of enterocytes with plasma from ESKD patients increased epithelial permeability, with reductions in tight junction proteins (claudin-1, occludin, zonula occludens-1).[87] Similar depletion of tight junction proteins was observed in CKD rats.[88] These findings support the concept that CKD can impair gut barrier integrity, leading to increased translocation of bacterial products such as **lipopolysaccharides (LPS)**, a major component of Gram-negative bacterial cell walls. Consistent with this hypothesis, Szeto et al reported higher circulating LPS levels in ESKD patients compared to controls.[89] LPS binds Toll-like receptor 4 (TLR4), triggering

inflammatory signaling. Doyle et al showed that LPS-TLR4 interaction induces muscle atrophy in C2C12 myotubes and in mice treated with supra-physiological LPS doses (100 ng/mL).[90] Thus, increased gut permeability in CKD may facilitate LPS translocation, which could not only sustain systemic inflammation but also directly contribute to muscle wasting[91] (**Figure 3**). Supporting a possible role of dysbiosis in this process, FMT experiments showed that germ-free mice receiving microbiota from CKD mice developed reduced expression of gut tight junction proteins, further linking microbiota alterations to increased intestinal permeability.[92]

Short-chain fatty acids

An imbalanced gut microbiota in CKD not only produces harmful metabolites and uremic toxins but may also generate fewer beneficial metabolites such as **short-chain fatty acids (SCFAs).** These metabolites derive from bacterial fermentation of dietary fibers. SCFAs exert wide-ranging effects on metabolism and immunity and play key roles in skeletal muscle.[93] Experimental models show they enhance lipid, carbohydrate and protein metabolism, preserve muscle mass and insulin sensitivity, and maintain an oxidative phenotype via AMPK, PPAR-δ and PGC-1α activation.[93] SCFAs also exhibit anti-inflammatory properties by strengthening gut barrier function and suppressing LPS-induced cytokine production.[93] Furthermore, SCFAs may stimulate hunger through ghrelin-related signaling and inhibition of insulin secretion.[94] In CKD, gut dysbiosis seems associated with reduced fecal and systemic levels of some SCFAs.[54,95,96] Such decreases may worsen muscle wasting and metabolic dysfunction.

The proposed mechanisms linking gut microbiota alterations to muscle wasting in CKD are summarized in **Figure 2**.

Considerations regarding the potential for gut microbiome modulation in CKD-associated wasting syndromes

Several approaches have been explored in CKD to modulate the gut microbiome and dampen uremic toxin generation, such as pre-, pro- and synbiotics (**Supplementary Table S2**). However, human evidence remains limited, as most studies lack detailed characterization of microbiome composition and function, longitudinal follow-up and specific assessment of PEW and cachexia outcomes. Heterogeneity of interventions and confounders further complicate interpretation. Krukowski et al recently demonstrated that a large proportion of microbiome variability in CKD patients is explained by host-related covariates such as diet, intestinal transit time, medication use and clinical characteristics.[97]

Another challenge is the identification of the microbiota-derived metabolites that effectively contribute to wasting syndromes. Although IS, PCS and TMAO are among the most studied toxins, their causal role in PEW/cachexia remains unclear, and lowering their circulating levels has not yet been clearly associated with clinical improvement.

Future therapeutic strategies should be mechanistically guided and rationally designed. Selective inhibition of microbial enzymes such as ureases, uricases or tryptophanases could reduce the production of deleterious metabolites like ammonia, uric acid and IS. However, implementation remains challenging, as these enzymes are widely distributed across the bacterial kingdom and exist in multiple isoforms, complicating selective pharmacological inhibition. TMAO represents an exception, as inhibitors of CutC (a key enzyme in trimethylamine synthesis), are in development.[98] Similarly, identifying or engineering bacterial strains capable of degrading toxic compounds such as p-cresol or indole may represent a

promising precision-based approach. Further research is nevertheless required to identify the most relevant microbial pathways and taxa involved in CKD-associated PEW and cachexia.

Conclusion and future perspectives

Cachexia is a severe complication of CKD, impairing physical function and quality of life. Its pathogenesis is multifactorial, involving inflammation, hormonal disturbances, metabolic dysfunction and muscle wasting. Increasing evidence suggests that gut microbial alterations may be a key contributor, promoting uremic toxins production, chronic inflammation and insulin resistance. Because several gut-derived uremic toxins are poorly removed by conventional dialysis, the gut represents a promising therapeutic target in ESKD. Future studies should identify the most relevant microbial pathways and evaluate whether microbiota-directed interventions, including dietary fibers, biotics and microbial enzyme inhibition, can improve muscle function, quality of life and outcomes in CKD patients.

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Table

Table 1 | Criteria for the clinical diagnosis of cachexia and other wasting syndromes in CKD.

Syndrome	Definition	Diagnostic criteria
Malnutrition	GLIM (2025)[6]	**Identify subjects with risks factors for malnutrition** **Assessment criteria** ***→ 1 phenotypic criteria*** - Non-volitional weight loss >5% within past 6 months or > 10% beyond 6 months - BMI < 20 if < 70 years old, < 22 if > 70 years old - Low muscle mass (DXA, BIA, CT or MRI) ***and*** ***→ 1 etiologic criteria*** - Reduced food intake or assimilation - Disease or condition that is typically associated with inflammatory activity
Protein-energy wasting	ISRNM (2008)[8]	**≥ 3 criteria out of the 4 categories :** 1. *Serum chemistry* : Albumin < 38 g/L, prealbumin < 30 mg/dL, total cholesterol < 100 mg/dL 2. *Body mass* : Unintentional weight loss of 5% over 3 months or 10% over 6 months, BMI < 23 kg/m², total body fat percentage < 10% 3. *Muscle mass*: Muscle wasting : reduced muscle mass 5% over 3 months or 10% over 6 months, reduced mid-arm muscle circumference area (reduction > 10% in relation to 50th percentile of reference population), creatinine appearance 4. *Dietary intake* : Unintentional low DPI <0.80 g/kg/day for at least 2 months, unintentional low DEI <25 kcal/kg/day for at least 2 months
Cachexia	Fearon criteria (2011)[10]	**Weight loss > 5 %** over past 6 months (in absence of simple starvation) *or* **BMI < 20 kg/m²** and **any degree of weight loss > 2%** *or* Low **muscle mass** (<5th percentile) and **any degree of weight loss > 2%**
Sarcopenia	EWGSOP2 (2019)[12]	1. **Central criteria :** → *Low muscle strength* (grip strength, chair stand test) 2. **Confirmed if :** → *Low muscle quantity or quality* (DXA, BIA, CT, MRI) 3. **Severe if :** → *Low physical performance* (gait speed, SPPB, timed-up-and-go test)

BIA, Bioelectrical impedance analysis; BMI, Body mass index; CT, Computed tomography; DEI, Dietary energy intake; DPI, Dietary protein intake; DXA, Dual energy X-ray absorptiometry; EWGSOP, European Working

Group on Sarcopenia in Older People; GLIM, Global Leadership Initiative on Malnutrition; ISRNM, International Society of Renal Nutrition and Metabolism; MRI, Magnetic Resonance Imaging; SPPB, Short physical performance battery.

Figures

Figure 1 – Overlap and distinctions between sarcopenia, malnutrition, protein-energy wasting and cachexia.

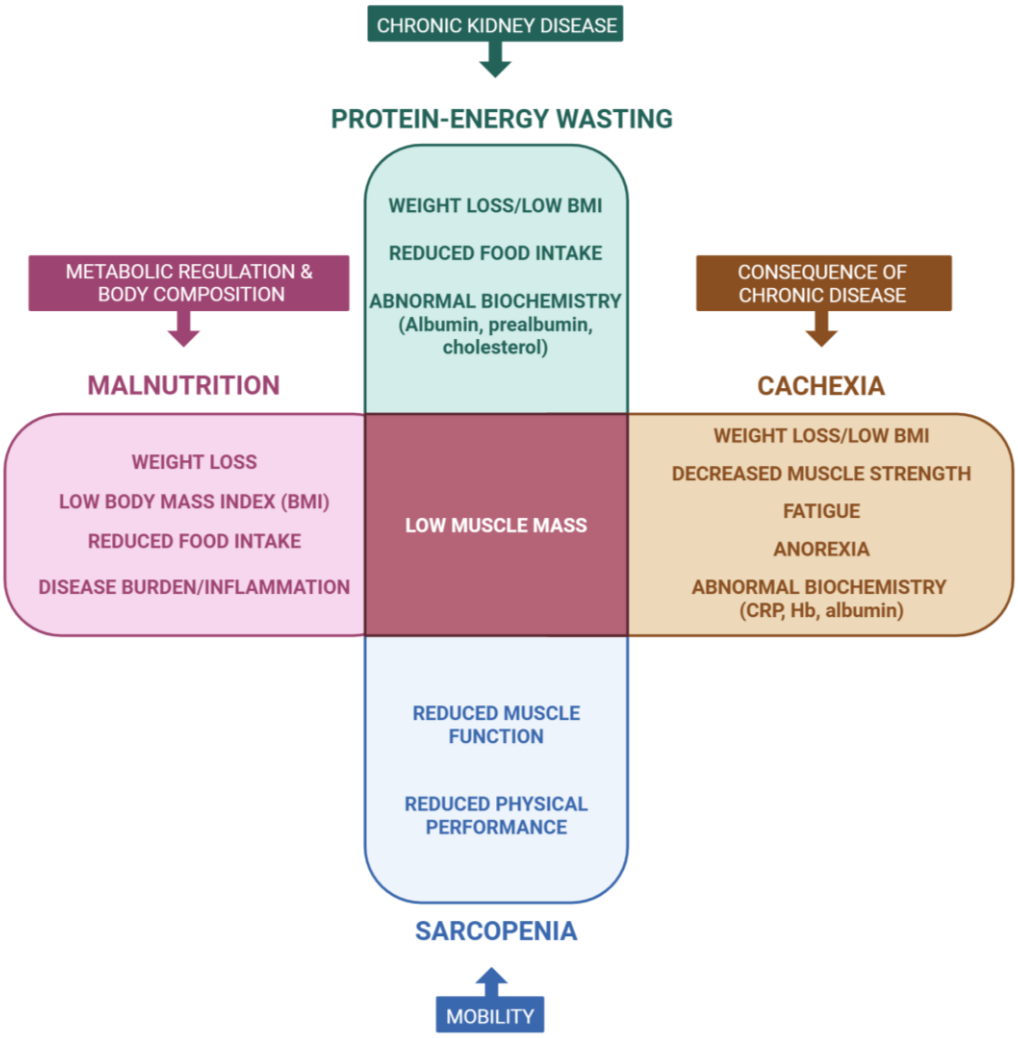


Figure 2 – Proposed mechanisms linking gut microbiota alterations to cachexia and wasting syndromes in chronic kidney disease.

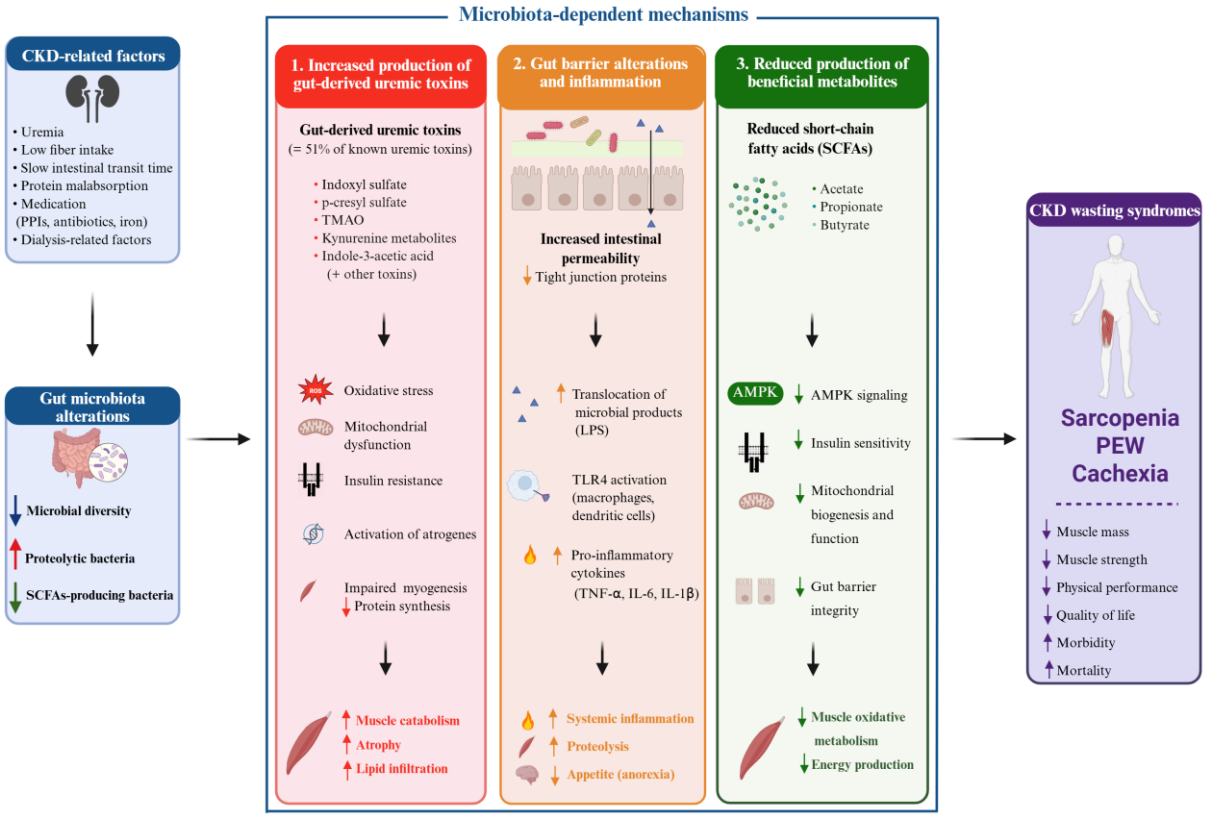
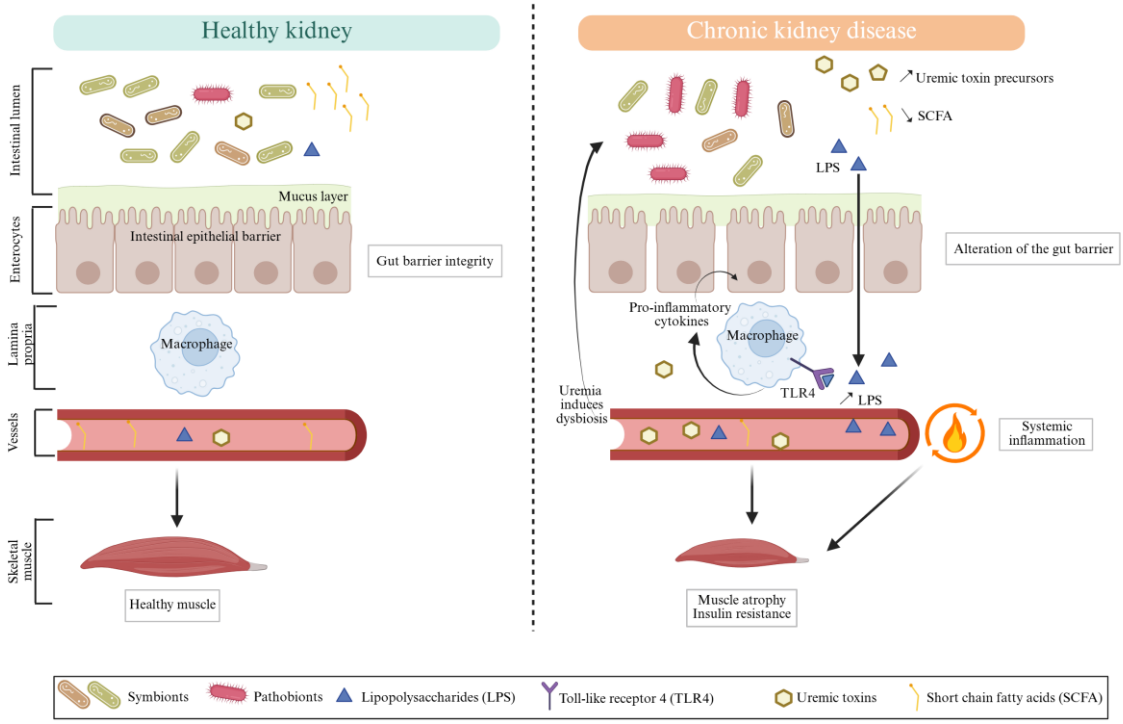


Figure 3 –Proposed mechanisms linking gut barrier alteration, systemic inflammation and muscle atrophy in chronic kidney disease.



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Figures legend

Figure 1 – Overlap and distinctions between sarcopenia, malnutrition, protein-energy wasting and cachexia.

Schematic representation of the overlap and distinctives features of malnutrition (GLIM criteria), protein-energy wasting (ISRNM), cachexia (ESPEN definition), and sarcopenia (EWGSOP2). Shared core feature is low muscle mass, which each condition defined by additional specific criteria related to body composition, food intake, inflammation, biochemical abnormalities and functional impairment. Adapted from Sayer et al, Age and Ageing, 2022. Created with Biorender.com

Figure 2 – Proposed mechanisms linking gut microbiota alterations to cachexia and wasting syndromes in chronic kidney disease.

Chronic kidney disease (CKD) promotes gut microbiota alterations through several CKD-related factors, including uremia, low dietary fiber intake, slow intestinal transit, protein malabsorption and medication use. These alterations are characterized by reduced microbial diversity, expansion of proteolytic bacteria and depletion of short-chain fatty acids (SCFAs)-producing bacteria.

Three major microbiota-dependent mechanisms may contribute to CKD-associated wasting syndromes. First, dysbiosis increases the production of gut-derived uremic toxins, including indoxyl sulfate (IS), p-cresyl sulfate (PCS), trimethylamine-N-oxide (TMAO), kynurenine

metabolites and indole-3-acetic acid, which promote oxidative stress, mitochondrial dysfunction, insulin resistance and activation of proteolytic pathways in skeletal muscle. Second, CKD-associated disruption of gut barrier integrity increases intestinal permeability and translocation of microbial products such as lipopolysaccharides (LPS), promoting Toll-like receptor 4 (TLR4) activation and systemic inflammation. Third, reduced production of beneficial microbial metabolites, particularly SCFAs, impairs AMPK/PGC-1α signaling, insulin sensitivity, mitochondrial function and gut barrier integrity.

Together, these mechanisms contribute to chronic low-grade inflammation, oxidative stress, metabolic dysregulation and hormonal alterations, ultimately favoring muscle wasting syndromes including sarcopenia, protein-energy wasting (PEW) and cachexia in CKD. Proposed theoretical framework based on the existing literature. Created with BioRender.com. PPIs, proton pump inhibitors.

Figure 3 – Proposed mechanisms linking gut barrier alteration, systemic inflammation and muscle atrophy in chronic kidney disease.

Schematic representation of gut barrier status in healthy individuals versus patients with chronic kidney disease (CKD). In CKD, uremia induces increased intestinal permeability, with depletion of tight junction proteins, facilitating translocation of bacterial products such as lipopolysaccharides (LPS). LPS is known to bind Toll-like receptor 4 (TLR4), triggering pro-inflammatory cytokine production and contributing to systemic inflammation. In CKD, elevated levels of uremic toxins, decrease levels of short chain fatty acids (SCFA) and systemic

inflammation contribute to muscle wasting. Proposed theoretical framework based on the existing literature. Created with Biorender.com.

Supplementary Figure and Tables

Supplementary Table S1 | Overview of uremic toxins: biochemical grouping and gut-derived origin.

Biochemical group	Gut-derived compounds	Non-gut-derived compounds
AGE	Fructoselysine, Glyoxal, Methylglyoxal, N(6)-Carboxymethyllysine	3-Deoxyglucosone, Pentosidine
Aldehyde	2-Heptenal, 2-Hexenal, 2-Nonenal, 2-Octenal, Decanal, Heptanal, Hexanal, Nonanal	4-Decenal, 4-HO-Decenal, 4-HO-Hexenal, 4-HO-Nonenal, 4-HO-Octenal, Malondialdehyde
Amine	Dimethylamine, Ethylamine, Monomethylamine, Trimethylamine, Trimethylamine-N-oxide	-
Amino acid	Dimethylglycine, Homocysteine, Kynurenic Acid, Kynurenine, S-Adenosylhomocysteine	-
Catecholamine	Dihydroxyphenylalanine	-
Cytokine	-	Interleukin-10, Interleukin-18, Tumor Necrosis Factor Alpha
Cytokines	-	Interleukin-1β, Interleukin-6
Guanidine	Asymetric Dimethylarginine, Creatine, Creatinine, Symetric Dimethylarginine, α-N-Acetylarginine, β-Guanidinopropionic Acid	Argininic Acid, Guanidine, Guanidinosuccinic acid, Methylguanidine, α-keto-δ-Guanidinovaleric Acid, α1-Acid glycoprotein, γ-guanidinobutyric Acid
Gunaidine	-	Taurocyamine
Hippurate	Hippuric acid (total)	-
Indole	Indole-3-acetic acid (free), Indole-3-acetic acid (total), Indoxyl sulfate (free), Indoxyl sulfate (total), Indoxyl-β-D-glucoronide, Melatonin, Quinolinic Acid	Indican
Nicotinamide	N-methyl-2-pyridone-5-carboxamide	4-Pyridone-3-carboxamide-1-β-D-ribonucleoside, N-methyl-4-pyridone-3-carboxamide, Nicotinamide

Peptide	Hyaluronic acid (Hyaluronan)	Atrial Natriuretic Peptide, Calcitonin gene-related peptide, Cholecystokinin, Degranulation Inhibiting Protein I, Delta-sleep Inducing Peptide, Endothelin, Guanylin, Methionine-Enkephalin, Neuropeptide Y, Parathyroid hormone, Resistin, Substance P, Uroguanylin, Vasoactive intestinal peptide, Vasopressin, β-2-Microglobulin, β-Endorphin, β-Lipotropin, λ-Ig Light Chain
Peptides	-	Adrenomedullin, Clara cell protein (CC16), Cystatin C, Motiline
Phenol	Phenol, p-Cresylsulfate (free), p-Cresylsulfate (total)	-
Polyamine	Putrescine	-
Polyol	Erythritol, Mannitol, Sorbitol, Threitol	Arab(in)itol, Myoinositol
Protein	-	Adiponectin, Angiogenin, Basic fibroblast growth factor, Complement Factor D, Insulin-like growth factor 1, Leptin, Osteocalcin, Retinol Binding Protein, Vascular endothelial growth factor
Purine	Cytidine, Hypoxanthine, Uric Acid, Xanthine	8-Hydroxy-2'-deoxyguanosine, Neopterin
Pyrimidine	Orotic Acid, Orotidine, Uridine	-
Ribonucleoside	1-Methyladenosine, 1-Methylguanosine, Inosine, N2,N2-Dimethylguanosine, N4-Acetylcytidine, Pseudouridine, Xanthosine	1-Methylinosine, N6-Methyladenosine, N6-Threonylcarbamoyladenosine
Other	3-Carboxy-4-Methyl-5-Propyl-2-Furanpropanoic Acid (CMPF), Oxalate, Phenylacetic acid, Phenylacetylglutamine, Urea	-

Supplementary Table S2 | Oral strategies for reducing the levels of uremic toxins and potential consequences for the nutritional status of CKD patients.

Intervention	Patient type	Impact on uremic toxin levels	Effect on nutritional status	Author/Year
Probiotics				
Bifidobacterium longum	HD patients (n=22)	↓ IS	NA	Takayama et al, 2003 [1]
Bifidobacterium longum	HD patients (n=27)	↓ IS	NA	Taki et al, 2005 [2]
Streptococcus thermophilus, Lactobacillus acidophilus and *Bifidobacterial logum*	HD patients (n=22)	No significant effect on uremic toxins (IS, indoxyl glucuronide, PCS, indole-3-acetic acid, hippuric acid) or inflammatory markers	NA	Natarajan et al, 2014 [3]
Bifidobacterium bifidum, B.catenulatum, B. longum and *Lactobacillus plantarum*	PD patients (n=39)	↓ TNF-α, IL-5, IL-6 and endotoxins; ↑ IL-10; preserve residual kidney function	NA	Wang et al, 2015 [4]
Lactobacillus acidophilus, Lactobacillus casei and *Bifidobacterium bifidum*	Diabetic patients on HD (n=60)	↑ in plasma total antioxydant capacity; ↓ hs-CRP	↓ fasting plasma glucose, serum insulin, HOMA-IR,HOMA-B, HbA1c, SGA scores	Soleimani et al, 2016 [5]
Streptococcus thermophilus, Lactobacillus acidophilus and *Bifidobacterial longum*	HD patients (n=46)	↑ IS and urea; ↓ fecal pH; no change in PCS and indole-3-acetic acid, inflammatory markers (CRP and IL-6) or gut microbial profile	NA	Borges et al, 2017 [6]
Streptococcus thermophilus, Lactobacillus acidophilus and *Bifidobacterial longum*	CKD patients stages 3-5 (n=22)	↑ IL-6; no change in uremic toxins (TMAO, IS, PCS and indole-3-acetic acid), CRP, LPS or calprotectin	NA	Barros et al, 2018 [7]
Lactobacillus rhamnosus	HD patients (n=42)	↓ phenol and p-cresol	NA	Eidi et al, 2018 [8]
Streptococcus thermophilus, Lactobacillus acidophilus and *Bifidobacterial longum*	HD patients (n=21)	No change in TMAO	NA	Borges et al, 2019 [9]
Bifidobacterium longum, Lactobacillus bulgaricus and *Streptococcus thermophilus*	PD patients (n=116)	↓ hs-CRP and IL-6	↑ albuminemia, upper arm circumference, triceps skinfold	Pan et al, 2021 [10]

			thickness, physical and social functioning scores	
Lactococcus lactis, Ligilactobacillus salivarius and *Lactiplantibacillus pentosus*	HD patients (n=56)	↓ IS; no change in hemoglobin, BUN, PCS, inflammatory and microbial translocation markers	No change in body composition, blood glucose and marker of insulin resistance	Lim et al, 2021 [11]
Low-protein diet (0,6g/kg/day) + *Bifidobacterium longum* and *Lactobacillus reuteri*	CKD patients stages 4-5 (n=60)	↑ IS in placebo group; trend in the reduction of uremic toxins in the probiotic group	No change in BMI, fat mass, fat free mass, hand grip or physical functioning	De Mauri et al, 2022 [12]
Prebiotics				
Fermentable carbohydrate mixture (40g of inulin and potato starch)	CKD patients stage 4 (n=9)	↓ plasma urea	↑ body weight; trend ↑ BMI; no change in mid-arm muscle circumference, biceps and triceps skinfold thickness; no change in albumin and prealbumin	Younes et al, 2006 [13]
Oligofructose-enriched inulin	HD patients (n=22)	↓ PCS and generation rate and BUN; no change in IS or generation rates	NA	Meijers et al, 2010 [14]
High-amylose corn starch	HD patients (n=56)	↓ IS and a trend to ↓ PCS; no change in CRP	No change in body weight	Sirich et al, 2014 [15]
Pea hull fiber	CKD patients stages 3-5 (n=13)	↓ PCS; ↑ stool frequency; no change in CRP, cystatin C, BUN, ammonia, eGFR	NA	Salmean et al, 2015 [16]
Arabinoxylan oligosaccharides	CKD patients stages 3b-4 (n=40)	No significant effect on PCS and IS; ↓TMAO	No change in body weight or HOMA-IR	Poesen et al, 2016 [17]
High amylose maize resistant starch	HD patients (n=46)	↓ TNF-α, IL-6, severity constipation, serum urea and creatinine; no change in IL-1b, hs-CRP, total antioxydant activity	NA	Tayebi Khosroshahi et al, 2018 [18]
Resistant starch (Hi-Maize®260)	HP patients (n=31)	↓ IL-6, IS; no change in CRP and PCS	NA	Esgalhado et al, 2018 [19]
Short-chain fructooligosaccharide (NutraFlora®)	CKD patients stages 3b-4 (n=50)	Trend to ↓ PCS; no change in IS, indole-3-acetic acid, serum markers of intestinal permeability; inflammation (hs-CRP and IL-6)	No change in body weight or HOMA-R	Ramos et al, 2019 [20]

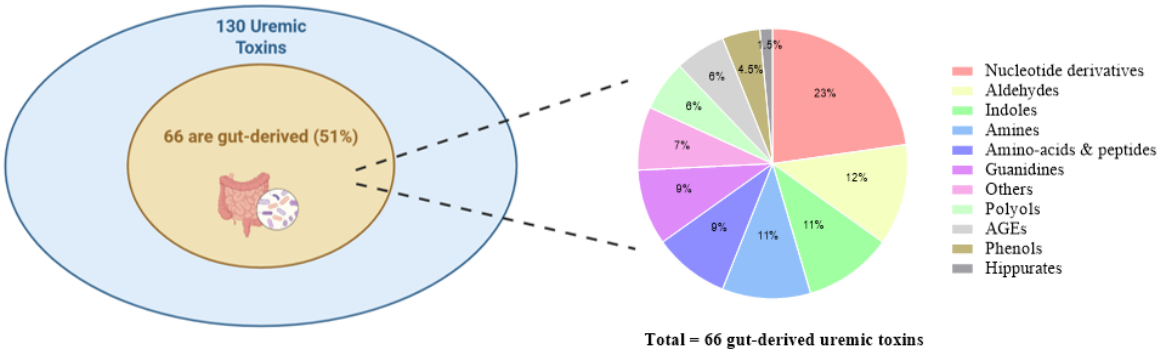
High-amylose maize resistant starch type 2	HD patients (n=20)	↓ serum urea, IL-6, TNF-α, and malondialdehyde	NA	Laffin et al, 2019 [21]
ß-glucan	CKD patients stages 3-5 (n=59)	↓ IS, PCS, p-glucuronide; trend in ↓ indole-3-acetic acid	No change in weight, waist circumference, mid-upper arm circumference	Ebrahim et al, 2022 [22]
Fructooligosaccharides (NutraFlora®)	CKD patients stages 3b-5 (n=46)	↓ IL-6; trend to ↓ PCS	NA	Armani et al, 2022 [23]
Inulin-type fructans	PD patients (n=21)	Trend to ↓ IS	No change in BMI, albumin, prealbumin	Li et al, 2020 [24]
Synbiotics				
Galacto-oligosaccharides, *Lactobacillus casei* strain Shirota and *Bifidobacterium breve* strain Yakult	HD patients (n=9)	↓ serum p-cresol; no change in phenol or IS	NA	Nakabayashiet al, 2011 [25]
Probinul neutro® (inulin, tapioca-resistant starch, *Lactobacillus plantarum, Lactobacillus rhamnosus, Lactobacillus gasseri, Bifidobacterium infantis, Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus salivarius, Lactobacillus sporogenes, Streptococcus thermophilus*)	CKD patients stages 3-4 (n=30)	↓ total plasma p-cresol	No significant difference in BMI, waist circumference, BIA analysis	Guida et al, 2014 [26]
Inulin, *Lactobacillus acidophilus*, *Bifidobacterium lactis*, omega-3 fatty acids, vitamins of complex B, folic acid, ascorbic acid and vitamin E	HD patients (n=42)	No significant difference in CRP, TNF-α and IL-6	Trend to improve nutritional status (SGA); ↓ mid-arm fat area	Viramontes et al, 2015 [27]
Inulin, fructooligosaccharides, galactooligosaccharide, strains from *Lactobacillus*,	CKD patients stages 4-5 (n=37)	↓ PCS; no change in IS, IL-1b, IL-6, IL-10, TNF-α, eGFR, serum oxidative stress biomarkers and LPS	NA	Rossi et al, 2016 [28]

Bifidobacterium and *Streptococcus* genera				
Sorghum breakfast meal + unfermented probiotic dairy beverage with *Bifidobacterial longum*	HD patients (n=58)	↓ PCS, IS, urea	↑ albuminemia	Lopes et al, 2019 [29]
High-resistant starch, strains from *Lactobacillus, Bifidobacterium* and *Streptococcus* genera	CKD patients stages 3-4 (n =68)	No effect on IS and PCS	NA	McFarlane et al, 2021 [30]
Naturen G® (*Lactobacillus casei, Bifidobacterium animalis,* fructoligosaccharides, inulin, and natural antioxidants (quercetin, resveratrol, proanthocyanidins))	CKD patients stages 3b-4 (n=23)	↓ IS; no change in PCS	No change in BMI and albuminemia	Cosola et al, 2021 [31]
Dietary patterns				
Vegetarian diet	15 healthy vegetarian individuals and 11 healthy individuals - normal diet	↓ PCS and IS production rates	NA	Patel et al, 2012 [32]
Very low-protein diet (0.3 g/kg/day) + ketoanalogues	CKD patients stage 3 (n=32)	↓ IS	NA	Marzocco et al, 2013 [33]
Vegetarian diet	HD patients (n=138 with 16 patients strictly vegetarians)	↓ IS and PCS: ↓ urea and phosphate	NA	Kandouz et al, 2016 [34]
Oral adsorbent				
AST-120	CKD patients stages 3-5 (n=132)	↓ IS in a dose-dependent manner	NA	Shulman et al, 2006 [35]

	CKD patients stages 3-4 (n=579)	No change in IS and β2-microglobulin	NA	Cha et al, 2016 [36]

BIA, Bioelectrical impedance analysis; BMI, Body mass index; BUN, Blood urea nitrogen; CKD, Chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HD, Hemodialysis; HOMA-B, Homeostatic model assessment of β-cell function; HOMA-IR, Homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein; IS, Indoxyl sulfate; LPS, lipopolysaccharide; NA, Not assessed; PCS, P-cresyl sulfate; PD, Peritoneal dialysis; SGA, Subjective global assessment; TMAO, Trimethylamine-N-oxid

Supplementary Figure 1 – Overview of uremic toxins: gut-derived origin and biochemical grouping.



Supplementary Figure S1 – Overview of uremic toxins: gut-derived origin and biochemical grouping.

According to the European Uremic Toxins (EUTox) database, 130 compounds are classified as uremic toxins. By cross-referencing with the Microbial Metabolites Database (MiMeDB v1.0), we identified that 66 (51%) of these uremic toxins are derived from gut microbial metabolism. These gut-derived uremic toxins can be further classified into distinct biochemical groups (right panel), including nucleotide derivatives (23%), aldehydes (12%), indoles (11%), amines (11%), amino acids & peptides (9%), guanidines (9%), polyols (6%), advanced glycation end products (AGEs) (6%), phenols (4.5%), hippurates (1.5%) and other compounds (7%).