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Review

The Gastrointestinal Microbiota as a Potential Cause and Target in Chronic Kidney Disease Accentuating Treatment and Intervention Strategies

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Abstract: Dysbiosis and impaired gastrointestinal barrier function have emerged as potential chronic kidney disease (CKD) modulators. Accumulation of gut-derived uremic toxins, a subsequent shift in the gut microbiome, and modified expression levels of intestinal tight junction proteins are all contributing factors to hyperpermeability and endotoxemia in CKD. Experimental studies in animals provide evidence that renal decline is linked to gastrointestinal health and that pharmacological or dietary intervention might attenuate this process. In this review, we will highlight the current knowledge on CKD-induced changes in the gut microbiome and the resulting consequences regarding gastrointestinal health with a focus on animal studies. Furthermore, we will explore possible disease management options linking to evidence in humans, if available.

Keywords: chronic kidney disease; dysbiosis; gastrointestinal hyperpermeability; gut microbiome; leaky gut syndrome

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1. Introduction

Chronic kidney disease (CKD) affects approximately 10% of the western population [1]. It is characterized by a continuous failure of nephrons, causing progressive renal function decline that persists for over three months [2]. There are numerous potential causes of CKD, the most common being diabetes mellitus type 2 (30 to 50%) and hypertension (27%) [3]. CKD can also develop after primary kidney damage due to polycystic kidney disease, auto-immune diseases, acute kidney injury, glomerulonephritis, ascending infections, or secondary to nonsteroidal anti-inflammatory drug overuse [3].

CKD is accompanied by multiple comorbidities, such as cardiovascular disease and CKD mineral and bone disease (MBD) [4,5]. However, the gastrointestinal (GI) tract has often been overlooked as a possible contributor to the progression of CKD, and recent studies have highlighted its significance [6–10].

In this review, we will discuss the changes in the gut microbiome that occur during CKD and the concurrent effects on GI barrier function, starting with pathophysiological drivers in CKD and ion homeostasis. In this regard, we will focus on pathomechanisms that have emerged as promising therapeutic targets regarding GI health in CKD. Furthermore, we will address possible disease management options for CKD patients within the context of a disturbed GI barrier.

2. Endocrine Drivers of CKD

Due to CKD's diverse pathophysiology, multiple processes are involved in the disease progression. The critical endocrine signaling mechanism involved in the regulation of CKD progression is the renin–angiotensin–aldosterone system (RAAS), which exerts systemic

and local effects that determine susceptibility to renal damage via different mechanisms. Locally, activation of RAAS instigates glomerular mesangial cells to secrete transforming growth factor-β (TGFβ), a crucial cytokine and driver in renal fibrogenesis [11]. TGFβ is a critical factor for forming extracellular matrix components and is linked to glomerulosclerosis and renal fibrosis [11]. Systemically, RAAS is involved in blood pressure regulation through tubular sodium and water absorption. Furthermore, RAAS and TGFβ are associated with reactive oxygen species (ROS) generation and oxidative damage [12]. This leads to altered expression of transcription factors involved in the inflammatory response in CKD, such as upregulated nuclear factor-kappa B (NF-κB), [13] kelch-like ECH-associated protein 1 (Keap1) [14] and decline in nuclear factor erythroid 2-related factor 2 (Nrf2) [15].

A negative prognostic marker for CKD progression is an elevated plasma level of phosphaturic hormone fibroblast growth factor 23 (FGF23) [16]. FGF23 and its co-receptor α-Klotho bind to fibroblast growth factor receptor-1 in the kidney and downregulate sodium-dependent phosphate transport protein 2a (NaPi-2a), thereby reducing phosphate reabsorption [17]. The underlying molecular mechanism of elevated FGF23 in CKD still needs to be elucidated, but a decrease in phosphate excretion, limited availability of locally produced α-Klotho, and FGF23 accumulation due to decreased glomerular filtration could potentially contribute to the mechanism [5,18]. High serum phosphate levels are an independent predictor of morbidity and mortality among CKD non-dialysis patients [19]. In the kidney, FGF23 also suppresses 1α-hydroxylase, the enzyme responsible for the activation of vitamin D [20]. The primary action of vitamin D is the stimulation of phosphate absorption in the small intestine via the activation of NaPi-2b [21]. Moreover, vitamin D increases GI and renal calcium uptake through the increased luminal abundance of transient receptor potential channel 5 (TRPV5) and 6 (TRPV6) [22]. In CKD, FGF23-induced suppression of vitamin D results in a lack of plasma calcium. This boosts parathyroid hormone (PTH) secretion leading to secondary hyperparathyroidism [18]. The resulting disordered phosphate and calcium homeostasis is the decisive factor in the pathophysiology of CKD MBD [4].

3. The Gastrointestinal Microbiome in CKD

The human microbiome consists of different bacteria, archaea and fungi. Almost all microbiota belong to *Firmicutes*, *Bacteroida*, *Proteobacteria*, and *Actinobacteria* [23]. The microbiome in the small intestine mainly comprises facultative anaerobes, while the large intestine hosts obligatory anaerobes [23]. The microbiome enters a symbiotic and complex relationship with the host providing metabolic, protective and trophic functions [23]. It is involved in immunomodulation, defense mechanisms, synthesizes nutritional factors, such as vitamins and is needed to digest food ingredients not targeted by digestive enzymes [23,24]. In detail, dietary fibers are metabolized to short-chained fatty acids and gases. Short-chained fatty acids are valuable nutritional factors for the intestinal epithelial cell and mediate peristaltic movement [25].

Experimental data from CKD patients and rodent CKD models revealed a shift in the microbiome towards bacterial families that possess proteolytic enzymes [26–28]. They play a vital role in the production of gut-derived uremic toxins such as indoxyl-sulfate (IS), p-cresyl sulfate (PCS) and indole 3-acetic acid (IAA) [29–31]. Physiologically, the kidney excretes these uremic toxins. However, their plasma levels increase during CKD, exerting various adverse effects that contribute to further alterations in the gut–kidney axis. For instance, indole uremic toxins IS and IAA induce ROS production resulting in vascular damage associated with renal anemia, [30] cognitive impairment [32], and potentially eryptosis [33]. Even in patients with mild renal dysfunction, increased production of gut-derived uremic toxins could be observed [31]. In addition, an observational study that recruited pre-dialysis CKD patients found that serum IS and PSC correlate with CKD progression [6]. Experimental studies in rodents also show that adenine-induced CKD goes along with disordered amino acid metabolism that amplifies over time [10]. It has been

proposed that targeting gut microbiota or amino acid metabolism might be a way to manage uremic toxin levels as they provide a substitute energy source for the GI microbiome [10,29].

Nutritional changes associated with dietary intervention, medications, and the secretion of uremic toxins into the gut affect the composition of the microbiome in CKD [27]. In patients with end-stage renal disease (ESRD), analyses of gut microbial DNA revealed an increased abundance of many species, including *Brachybacteria*, *Catenibacteria*, *Enterobacteria*, and *Akkermansia* (Figure 1A) [28,34]. Those were generally accompanied by decreases in *Bifidobacteria* and *Lactobacilla* [28,35]. In a clinical setting, it is challenging to assess if changes in the microbiome observed during CKD are caused by uremia or due to therapeutic interventions. Fortunately, investigative studies in animal models allow us to focus on isolated uremic effects on the gut microbiome. The composition of the gut microbiome after surgical CKD induction (5/6 nephrectomy) in rats mirrored the state in human CKD patients [28]. Furthermore, systemic inflammation and intestinal bacterial translocation accompanied dysbiosis in a murine model of Alport syndrome-induced CKD [9]. Antibiotic treatment ameliorated inflammatory markers and reduced serum levels of endotoxins, which supports the general notion that dysbiosis could be one of the driving factors behind disease progression and systemic inflammation in CKD [9].

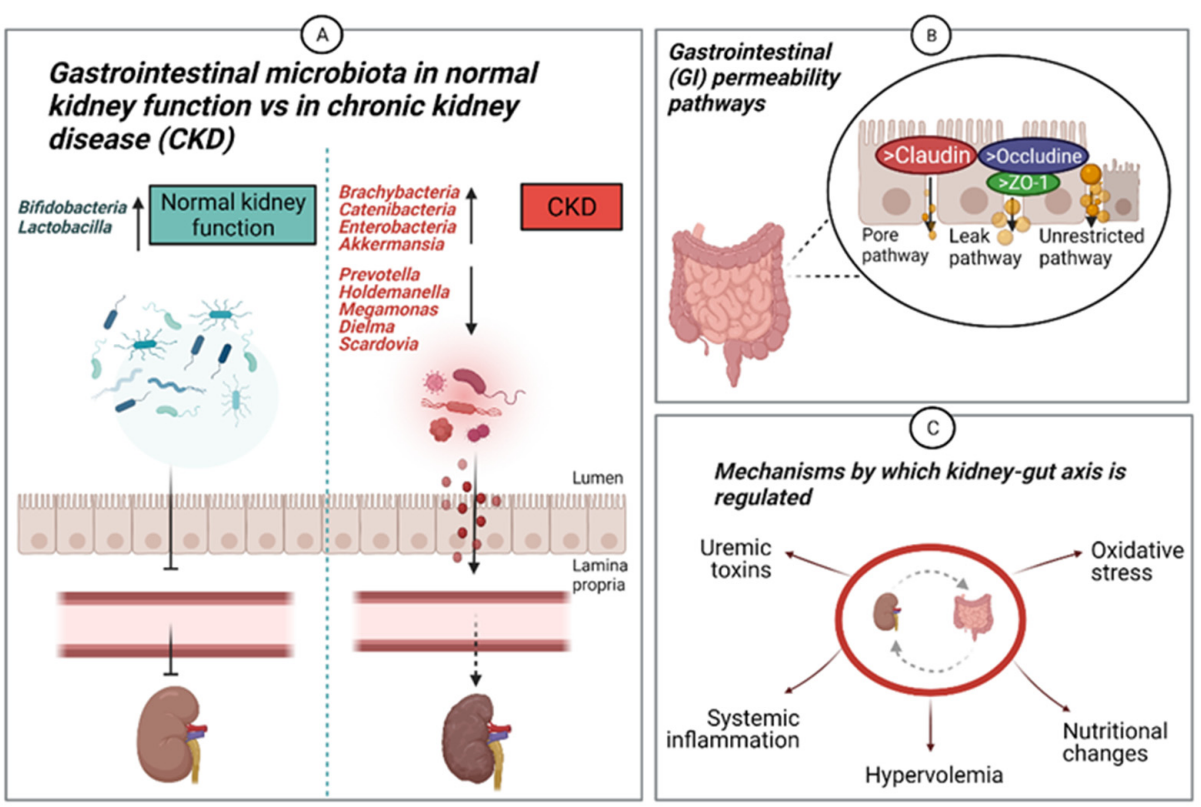

Figure 1. Schematic representation of intestinal microbiota in healthy (**left**) and CKD patients (**right**). (**A**) In physiological conditions, intestinal epithelial cells limit interactions between the gut microbiome in the intestinal lumen and the host. The TJ complex is intact, regulating the transport of selected molecules. (**B**) TJs control the paracellular permeability of ions, water, and macromolecules. Alteration of the TJ proteins involved in ion regulation leads to increased intestinal permeability. The unrestricted pathway is TJ-independent and reflects damage of epithelial cells. (**C**) In CKD, several different mechanisms alter gut microbiota composition leading to disruption of TJ and subsequent bacterial translocation across the gut barrier into the circulatory system, aggravating inflammation.

C57Bl/6 mice are generally considered relatively resistant to CKD development after 5/6 nephrectomy, making them a good model for studying microbial changes over time. Luminal urea concentration was significantly increased after 5/6 nephrectomy, but was not

accompanied by upregulation of intestinal urea transporters [36]. Furthermore, the application of urea to healthy mice did not induce dysbiosis comparable to CKD [36]. Therefore, intestinal urea concentration rises independently of its specific transporters and cannot be the only cause of CKD-induced dysbiosis [36]. A recent clinical trial aimed to identify microbiome-derived biomarkers for CKD and further explored the differences within the microbiome between healthy and CKD patients. *Ruminococcus* and *Lachnospira* emerged as potential biomarkers to separate both patient cohorts, but at least for *Lachnospira*, it is well documented that quantity changes with many diseases [37]. Interestingly, five phylotypes were associated with the progression of CKD: *Holdemanella*, *Megamonas*, *Prevotella*, *Dielma*, and *Scardovia* [37]. *Prevotella* is significantly reduced in an adenine-induced murine model of CKD as well [38]. Pharmacological intervention, focusing on the treatment of constipation, a common comorbidity in CKD, restored *Prevotella* prevalence and reduced plasma levels of uremic toxins, directly linking GI health to renal decline [38]. It is conceivable that intestinal microbial changes are different depending on the pathophysiological cause of CKD. Comprehensive studies combining microbiome analysis and causal renal pathology are still lacking.

While the general macroscopic and microscopic anatomy of the GI tract is comparable between rodents and humans, CKD-induced changes in the microbiome might not be directly transferrable, as bacterial fermentation occurs in different regions of the large intestine. Therefore, it is very challenging to analyze isolated effects on the microbiome in an observational setting in humans, which warrants the use of laboratory animals. Porcine intestines might provide a better comparison as they can also be populated with the human microbiome [39].

4. Microbiome-Related Effects on CKD Progression

It is recognized that the gut microbiota can contribute to renal health, as it may affect the underlying molecular pathways involved in the progression of the disease. In the GI system, gut bacteria can modulate local RAAS and, therefore may be involved in various physiological and pathophysiological processes. In uninephrectomized rats, short-chain fatty acids produced by the gut microbiome suppressed the renin receptor and the renal RAAS, resulting in antihypertensive effects, which may indirectly prevent CKD progression [40]. In 5/6 nephrectomized and unilateral ureteral obstruction rat models, alisol B 23-acetate derived from *A. orientale* suppressed RAAS constituents and the TGF-β/Smad3 pathway, which contribute to renal fibrosis and glomerulosclerosis [41]. RAAS can regulate the gut microbiome as well [42]. In the angiotensin II infusion model, significant shifts in metabolites and the microbiome have been observed in C57BL/6 but not in germ-free mice [43]. Alterations of the insulin/PI3K metabolic signaling pathway contribute to the progression of CKD, and gut microbiota is a major player in CKD pathophysiology as it provokes specific NF-kB reduction of the aforementioned pathway and systemic NF-kB-mediated inflammatory response [44]. Moreover, lipopolysaccharide lipid A derived from gut bacteria interacts with the toll-like receptor 4, which activates a pathway for proinflammatory cytokine generation [45]. A further molecular mechanism involved in CKD pathophysiology is Keap1/Nrf2. Oral administration of *B. fragilis* is reported to reduce the upregulated protein expression of Keap1 in unilateral ureteral obstruction mouse model. At the same time, the downregulation of Nrf2 found in this model was significantly increased with the treatment, which indicates the reduction of oxidative stress levels. *B. fragilis* abundance was also associated with an anti-fibrotic effect, as reflected by inhibition of the TGF-β/Smad signaling pathway [46]. These effects indicate how modulation of the gut microbiome is portrayed as a potential therapeutic strategy in a CKD setting.

5. Gastrointestinal Barrier Function in CKD

The surface of the GI tract is lined with epithelial cells connected by tight junction (TJ) proteins. There are two ways of crossing this cellular barrier. The transcellular route is mediated by substrate-specific receptors and involves diffusion through the cell and

basolateral release [47], while the TJ restricts the paracellular route [48,49]. The TJ is a multiprotein complex constituted of structural proteins, such as occludin, tricellulin and zonula occludens-1 (ZO-1), and functional proteins, which belong to the family of claudins [48,49]. The expression and localization of claudin family members vary along the vertical axis of the GI tract [50]. Claudins that mediate ion and small molecule transport (e.g., claudin-2, −12) are predominately present in the small intestine [50]. Claudin-2-mediated pore pathway arbitrates the transition of small uncharged ions up to a radius of 4 Å, [49,51] whereas occludin appears to play a central role in the formation of the leak pathway for larger ion transition across the barrier [52]. Transepithelial leakage and flux of particles of any size through the membrane via the unrestricted permeability pathway is a result of damage to the epithelial cells (Figure 1B) [48]. In contrast, claudins that restrict transport (e.g., claudin-4, −5) are increasingly expressed in the large intestine [50]. Protein production levels are usually stable within singular anatomical segments. An exception is the follicle-associated epithelium (FAE) that covers Peyer's Patches in the distal small intestine. Here, sealing claudins dominate to prevent accidental contact between antigens and the underlying cells of the immune system [53,54].

Dysfunctions in the intestinal epithelium that propagate bacterial, uremic and endotoxin cross-over to the bloodstream are defined as intestinal hyperpermeability or "leaky gut" syndrome (LGS). Hyperpermeability in the intestine subsequently leads to alterations in the GI microbiome, thus promoting inflammation [55]. Precise interplay between persistent systemic inflammatory response observed during intestinal barrier dysfunction and disease progression in CKD remains to be explored.

As CKD progresses, a decline of the glomerular filtration of sodium and activation of the RAAS signaling pathway occurs, causing increased sodium retention. Consequently, osmolarity rises, triggering a negative feedback mechanism that results in fluid retention [56]. Hypervolemia independently correlates with renal and cardiovascular outcomes in patients with stage 3 to 5 CKD [56]. Despite suggested pathophysiological mechanisms of how an edematous bowel wall increases gut permeability in CKD patients leading to sepsis and elevated levels of endotoxins exacerbating the progression, the relative contribution of volume overload to poor outcomes is still unknown.

In 2012, Vaziri et al. highlighted morphological changes in the colonic TJ structure of 5/6 nephrectomized rats. Claudin-1, occludin, and ZO-1 production was markedly reduced [57]. mRNA levels of the above-mentioned proteins remained similar between control and CKD groups, suggesting the changes observed at the protein level were due to post-transcriptional or post-translational modifications [57]. Histological analysis displayed an increase in GI wall thickness and lymphocytic infiltration in rats with CKD [57]. Furthermore, in hemodialysis (HD) patients with ischemic bowel disease, significantly declined expression of claudin-1, occludin, and ZO-1 was marked compared to patients with advanced CKD without ischemic bowel disease [7]. In mice subjected to unilateral ureteral obstruction, depletion of gut microbiota induced by broad-spectrum antibiotics was followed by elevated occludin and ZO-1 gene expression [58]. Therefore, alterations of TJ proteins play a key role in the underlying molecular mechanism of the impaired GI barrier in CKD.

Beneficial gut bacteria *Akkermansia* is a prominent example of direct interaction between the microbiome and the GI TJ. *Akkermansia* is decreased in fecal samples of CKD patients and is negatively correlated with circulating interleukin-10, providing a link between the GI microbiome and inflammation [34]. Furthermore, *Akkermansia muciniphila*-derived extracellular vesicles might be able to directly influence the gut barrier by upregulating occludin, as was recently shown in a mouse model of diabetes type 2 [59]. Additionally, incubation of colonic Caco-2 cells with *Akkermansia*-derived extracellular vesicles stabilized barrier function of the monolayer when challenged by lipopolysaccharides [59]. Human patients suffering from type 2 diabetes mellitus also show decreased fecal excretion of those extracellular vesicles, highlighting *Akkermansia* as a potential candidate to regulate the GI barrier in CKD [59]. Unfortunately, no data in CKD patients is available yet.

6. Systemic Inflammation as a Consequence of Impaired Gastrointestinal Barrier in CKD

Impaired kidney function in CKD is associated with numerous alterations in the bidirectional crosstalk between intestinal hyperpermeability and systemic inflammation. One proposed mechanism to elucidate the aforementioned relationship includes the overproduction and retention of urea and uremic solutes in CKD, shifting to the intestinal tract as the main excretion route [60,61]. Experimental evidence revealed that gut bacteria is an essential mediator of inflammation as it decomposes urea to ammonia (NH_3) and ammonium hydroxide (NH_4OH) [26,60]. Accumulation of NH_3 and NH_4OH causes injury to the protective mucosal barrier due to subsequent elevation of luminal pH and activation of pro-inflammatory cytokines [34,62,63]. This contributes to increased intestinal permeability and consequent bacterial translocation [26,57,62–64]. Endotoxin, the lipopolysaccharide that constitutes the exterior cell wall of most Gram-negative bacteria, is the key initiator for immune system activation [65]. Elevated plasma levels of translocated endotoxin promote the production of ROS following the activation of the inflammatory NF-kB pathway [66] and local RAAS [8].

Experimental evidence from laboratory rodents and humans suggests that systemic inflammation is associated with intestinal dysbiosis and barrier dysfunction [9,55,57,65], so it might be tempting to speculate that hyperpermeability and the microbial shift are the leading causes of systemic inflammation in CKD. In CKD rats, nuclear levels of nuclear factor erythroid 2-related factor 2 (Nrf2—a promising target of antioxidant properties) declined, whereas the nuclear fraction of the pro-inflammatory transcription factor NF-kB increased. Treatment with Nrf2 activator dh404 resulted in a diminished level of pro-inflammatory cytokines. Additionally, untreated CKD rats displayed downregulated protein expression of ZO-1, occludin, and claudin-1. Dh404 treatment restored the protein expression of TJ components [66]. Nevertheless, it should be considered that most studies only focused on a few TJ proteins, and there is no data on TJ protein levels in the FAE covering Peyer's patches yet. The main task of the Peyer's patch is the specific presentation of antigen to the underlying cells of the immune system [67]. Impaired barrier function could trigger an unregulated immune response, subsequently leading to detrimental effects on the patient's health. Thus far, there is a lack of experimental evidence linking the relationship between FAE and CKD. The same can be said for the phosphaturic hormone FGF23. FGF23 is negatively associated with the survival of CKD patients and is currently regarded as an early indicator of disease progression [21]. FGF23 is linked to several inflammatory processes in other organs. It directly induces the production of c-reactive protein and interleukin-6 in murine hepatocytes and tumor necrosis factor-α (TNFα) in macrophages [68,69]. Macrophages also produce FGF23, possibly triggering an autocrine loop of inflammation [69]. Hence, FGF23 can induce inflammatory processes in peripheral organs. It is currently unknown whether FGF23 is only a biomarker for kidney disease progression or actively drives kidney failure, perhaps even through regulation of GI permeability.

7. Gastrointestinal Motility in CKD

CKD does not only affect the microbiome but also influences GI transit time. Constipation is a common GI disorder in patients with CKD and has been linked to increased colonic transit time in patients with ESRD [70]. A comparable effect could be detected in different ex vivo and in vivo mouse models [71,72]. In adenine-induced CKD, GI transit time doubled while colonic peristaltic movements were markedly reduced and showed an abnormal contraction pattern [71]. Incubation of healthy colonic tissue with uremic serum decreased maximum contractility. This highlights either IS, PCS or both as potential causative agents, as single incubation with urea did not influence contractility [71]. Ex vivo analysis of large intestines from mice with CKD displayed imbalances in GI motility, which could be linked to dysregulated release of acetylcholine in the plexus myentericus [72]. Incubation with different uremic toxins individually, including IS, failed to alter motility, suggesting a multicausal effect on GI peristalsis during CKD. Antibiotic treatment

was able to reverse constipation and dysregulated motility and decrease inflammatory markers in CKD mice [72]. Lack of gastrointestinal motility might be addressed by dietary supplementation of L-carnitine. Subsequently, the frequency of stool passing increased slightly after three months of continuous intake by 15 HD patients [73]. In addition, a recent meta-analysis has found evidence for significant improvement of various serum parameters, including albumin, low-density lipoprotein and hemoglobin [74]. However, more clinical evidence is needed to focus on long-term endpoints such as mortality or survival time.

8. Disease Management Options within the Context of a Disturbed Gastrointestinal Barrier

8.1. Pharmacological Intervention in CKD

There are many options to treat such a complex disease as CKD. These mainly focus on preventing further renal decline and managing the resulting comorbidities. The application of phosphate binders and a phosphate-reduced diet are used to treat hyperphosphatemia as it correlates with increased mortality [75]. It might also prevent an incline in FGF23 [5,18]. A combination of antihypertensive medication and a salt-reduced diet is often prescribed to combat hypertension [76,77].

While these treatments target CKD-induced comorbidities, they can also influence the GI barrier. Frequent consumption of various medications is proposed as a putative contributor to gut dysbiosis and potential intestinal barrier disruption [78]. Intestinal hyperpermeability of iatrogenic origin in CKD is presumed to compromise the gut microbiome, which may lead to increased gut permeability [79]. Even though phosphate binders are the mainstay of therapy, CKD patients receiving iron salts may be more susceptible to LGS due to potential bacterial proliferation and overgrowth caused by iron stimulation [80]. On the other hand, phosphate binder ferric citrate restored colonic ZO-1 abundance in 5/6 nephrectomized rats [81]. This raised interest regarding the overall effect of phosphate binders on GI health and gut-derived uremic toxins. Therefore, the effect of Sevelamer, a phosphate-binding medication, was investigated in a double-blind, placebo-controlled, randomized clinical trial. However, no significant effect on pCS, IS, and IAA serum concentrations could be detected [82]. Phosphate binders themselves can significantly alter the gastrointestinal microbiome. A direct comparison between the treatment of HD patients with ferric citrate and calcium carbonate revealed reduced microbial diversity and altered stool composition in patients treated with calcium carbonate [83]. Therefore, a specific choice of phosphate binders could be an option to tailor treatment to patients. More information on phosphate metabolism and its effect on the GI microbiome in CKD can be found in a recently published review [84].

Orally applied charcoal adsorbents seemed to be another promising option as they bind intestinal urea and ammonia and, therefore, could prevent epithelial damage [85]. Administration of AST-120 in rats with adenine-induced CKD markedly improved general inflammation and partially restored claudin-1, occludin, and ZO-1 protein levels in the colon [85]. In addition, detected endotoxin levels, interleukin-6 and TNFα were significantly reduced in AST-120-treated rats compared to the control group [85]. However, the EPPIC trial, based on a cohort of 2035 patients, did not reveal any difference between AST-120 and placebo-treated groups regarding the primary endpoints creatinine doubling, dialysis initiation or kidney transplant [86]. Post hoc analysis, on the other hand, suggests a slight delay regarding disease progression [87]. A 2016 study of stage 3 to 4 CKD patients revealed no effect on mortality, unplanned hospitalizations, and health-related quality of life score [88]. A meta-analysis of 15 randomized controlled studies confirmed a lack of effect regarding mortality. However, the incidence of ESRD was significantly lower in the treatment group [89]. To summarize, the effect of AST-120 remains debatable, but there is only a little evidence that the positive effects witnessed in rodents can be transferred to humans.

The current treatment guidelines also propose individualized active vitamin D supplementation in patients with advanced CKD to manage the clinical symptoms of CKD MBD [90]. Even though vitamin D analogues, including 1,25(OH)2D and calcitriol, have been efficacious in the treatment of CKD, [91] they might contribute to an increase in circulating FGF23 levels [19]. Thus, they all have the potential to increase serum phosphorous levels through upregulation of NaPi-2b and consequent intestinal Pi absorption and should be applied after careful consideration [92].

A double-blind, randomized, placebo-controlled study in patients with CKD and type 2 diabetes proposed the effectiveness of bardoxolone methyl regarding increased GFR compared with a placebo. Bardoxolone methyl is considered to have the potential to activate Nrf2 and, thus, modulate antioxidant and anti-inflammatory responses [93]. However, these findings need to be interpreted with caution since the phase 3 trial (BEACON) with the primary efficacy endpoints "ESRD" or "death from heart failure", had to be terminated due to a significant rate of unforeseen adverse cardiovascular events in CKD patients treated with bardoxolone methyl [94]. A series of post hoc analyses were conducted to identify risk factors for heart failure in the BEACON population. Bardoxolone methyl increased cardiovascular events in the proportion of patients with baseline brain natriuretic peptide (BNP) > 200 pg/mL and previous hospitalization for heart failure [95]. However, these clinical trials did not comprise the effects of a disturbed GI barrier on the study outcome. Alternatively, as discussed below, non-pharmaceutical interventions, such as dietary protein restriction, appear to have beneficial effects on Nrf2 activity.

Recent experimental evidence taken from an adenine-induced mouse model of CKD has highlighted SGLT inhibitors as potential modulators of GI health in the context of renal disease. Application of SGL5213, an inhibitor of GI SGLT1, reduced circulating levels of gut-derived uremic toxins, creatinine, and urea [96]. Treatment reduced renal and GI inflammation and restored the *Firmicutes*/*Bacteroidetes* ratio, which is currently discussed as a possible biomarker for gut dysbiosis [96]. This is not limited to CKD but is also associated with other conditions, such as obesity and aging [97,98]. It remains to be seen whether these effects can be transferred to human patients, as no data is available yet. The effect of renal SGLT2 inhibitors was recently meta-analyzed and revealed a lower risk of decreasing kidney function, ESRD or renal death by 30% in patients with GFR < 60 mL/min/1.73 m^2 [99]. However, this effect depended on other comorbidities, as patients with CKD and heart failure did not profit from the medication [99]. GI health was not considered in this analysis.

8.2. The Effects of Dietary Intervention on the Microbiome and GI Barrier

Recently, plant-based diets have emerged as a modifier of the microbiome. Increased dietary fiber promotes carbohydrate fermentation and the growth of *Bifidobacteria* and *Lactobacilla*. This decreases protein fermentation and could improve CKD-induced dysbiosis [100]. Dietary addition of fiber led to a decrease of renal marker creatinine in patients with CKD [101,102]. Association between improved survival and higher dietary fiber intake in CKD patients may be due to lowering inflammatory markers [103]. In HD patients, the dietary addition of high-amylose maize resistant starch type 2 (HAM-RS2) significantly decreased serum urea and creatinine as well as inflammatory markers TNF-α and interleukin-6 [104]. HAM-RS2 altered the composition of the microbiome by increasing *Faecalibacteria* [105]. Further analysis was carried out in adenine-induced CKD in rats, focusing on microbial changes and gut-derived uremic toxins. After three weeks of additional HAM-RS2, decreased serum and urinary IS levels and an increased *Bacteroidetes*/*Firmicutes* ratio were noted [106]. Gum arabica (GA), a tree exudate, has also been named a potential candidate to increase renal function. In an adenine-induced mouse model, GA significantly decreased duodenal TNF-α, Il-6 and TGFβ [107]. Unfortunately, no parameters of renal function were published [107]. Patients with CKD stage 2 or 3 or progressive renal disease benefited from the long-term application of GA [108]. GA generally preserved or even increased estimated GFR [108]. Unfortunately, this study lacked a placebo group as a control. Furthermore, dietary fiber activates peristaltic movements, decreases gut transition

time, and reduces the time for protein fermentation [102,104]. This leads to a decrease in uremic toxin load [102]. A higher intake of fruits and vegetables can also be advantageous as it improves metabolic acidosis, a common symptom of CKD [109].

Phosphate uptake is automatically reduced on a plant-based diet because of low bioavailability [110]. Even short-term dietary modification results in lower serum phosphorus levels and decreased phosphaturic hormone FGF23 [110]. Conversely, evidence in clinical trials suggests that prescribed dietary phosphorus restriction is not associated with survival benefits among HD patients [111] and that the correspondence of phosphate intake with adverse outcomes is speculative [81,82,101]. On the other hand, a low-protein diet, often prescribed in CKD patients to achieve neutral phosphorous balance, has recently emerged as the potential modulator of Nrf2 expression. The longitudinal study that recruited 30 non-dialysis CKD patients investigated the effects of dietary protein restriction for six months. It was demonstrated that a low-protein diet increased Nrf2 mRNA expression and Nrf2/NF-κB ratio in peripheral blood mononuclear cells [112]. However, more clinical evidence is necessary to confirm that a protein-reducing diet is associated with a decline in ROS production and pro-inflammatory cytokines. The high potassium content of plant-based diets seems counterintuitive. However, so far, there is no experimental evidence suggesting that dietary potassium restriction is beneficial for CKD patients [113]. Taken together, a vegetarian diet could likely be beneficial for CKD patients.

Prebiotic supplementation of oligofructose-enriched inulin induced a significant reduction of uremic toxins, urea and PCS in rats with adenine-induced kidney injury [114]. Histological assessment of renal injury revealed less tubular and glomerular damage and interstitial fibrosis than in untreated CKD rats. No effects on the production levels of colonic TJ proteins claudin-1 and occludin could be observed [114]. In a randomized controlled trial, inulin supplementation in HD patients did not change fecal or plasma uremic toxins levels but increased *Akkermansia* in the fecal microbiota [115]. In line with these findings, several clinical trials report a positive association between pre- and probiotic supplementation and CKD progression.

Application of a commercially available synbiotic treatment specifically lowered IS levels in CKD patients stage 3 to 4 and improved GI permeability in the small intestine [116]. However, synbiotic therapy in CKD patients stage 4 to 5 significantly reduced PCS levels, whereas IS levels did not reach statistical significance [117]. Conversely, levels of indole-producing gut bacteria were restored and comparable to healthy controls [118]. Similarly, prebiotic oligofructose-enriched inulin supplementation in HD patients led to a decline in PCS levels by 20% [119]. In CKD patients, lactulose supplementation increased fecal *Bifidobacteria* and *Lactobacillus* counts [120]. Therefore, a combination of pre-and probiotic might be a valid treatment option regarding GI health. Nevertheless, more research is needed to find a combination that addresses more than just one uremic toxin. A recent meta-analysis and a double-blind, placebo-controlled, randomized controlled trial with 68 participants focused on biotic effects in human CKD patients could not detect any positive outcomes regarding GFR, serum creatinine, and serum urea [121,122]. Overall, long-term assessments are needed that focus on complex outcomes such as mortality.

8.3. Colonic Dialysis as Alternative Treatment Option

Another method to attenuate CKD progression could be colonic dialysis [123]. It is an easy and inexpensive method that can be performed at the patient's home. Colonic waste is removed through the rectal instillation of an osmotically balanced solution [124]. A recent study of stage 3 to 5 CKD patients has shown that the intestinal microbiome of patients that underwent colonic dialysis is comparable to that of healthy patients [124]. This could explain why disease progression is slower in patients who regularly undergo colonic dialysis and underlines the importance of gut-derived toxins for disease progression [123].

9. Conclusions

CKD is often insufficiently recognized, but it is the 12th leading cause of death worldwide, with a high impact on mortality and morbidity. Renal and cardiovascular systems were the focus of research to tackle CKD-driven mortality. However, the GI tract and its microbiome have recently emerged as potential targets when addressing CKD-related comorbidities. Human clinical trials and experimental evidence from rodent models provide insight into the role of the GI tract and its microbiome in CKD patients (Table 1). Biotic modulation of the microbiome and dietary addition of fiber is associated with lower values of uremic toxins, less inflammation, and improved renal function. We have highlighted the importance of dealing with uremic-induced shifts in the gut microbiome and summarized interventions with potential clinical applications. Although pharmaceuticals are prominently used to keep health in check, the dietary approach remains an economical and promising avenue to fight against CKD (Figure 2). However, there are insufficient high-quality trials to support one treatment strategy over another. While specific signaling cascades connecting gut health and renal function have not been described, the microbiome is relevant in this context. However, the definite impact still needs to be clarified.

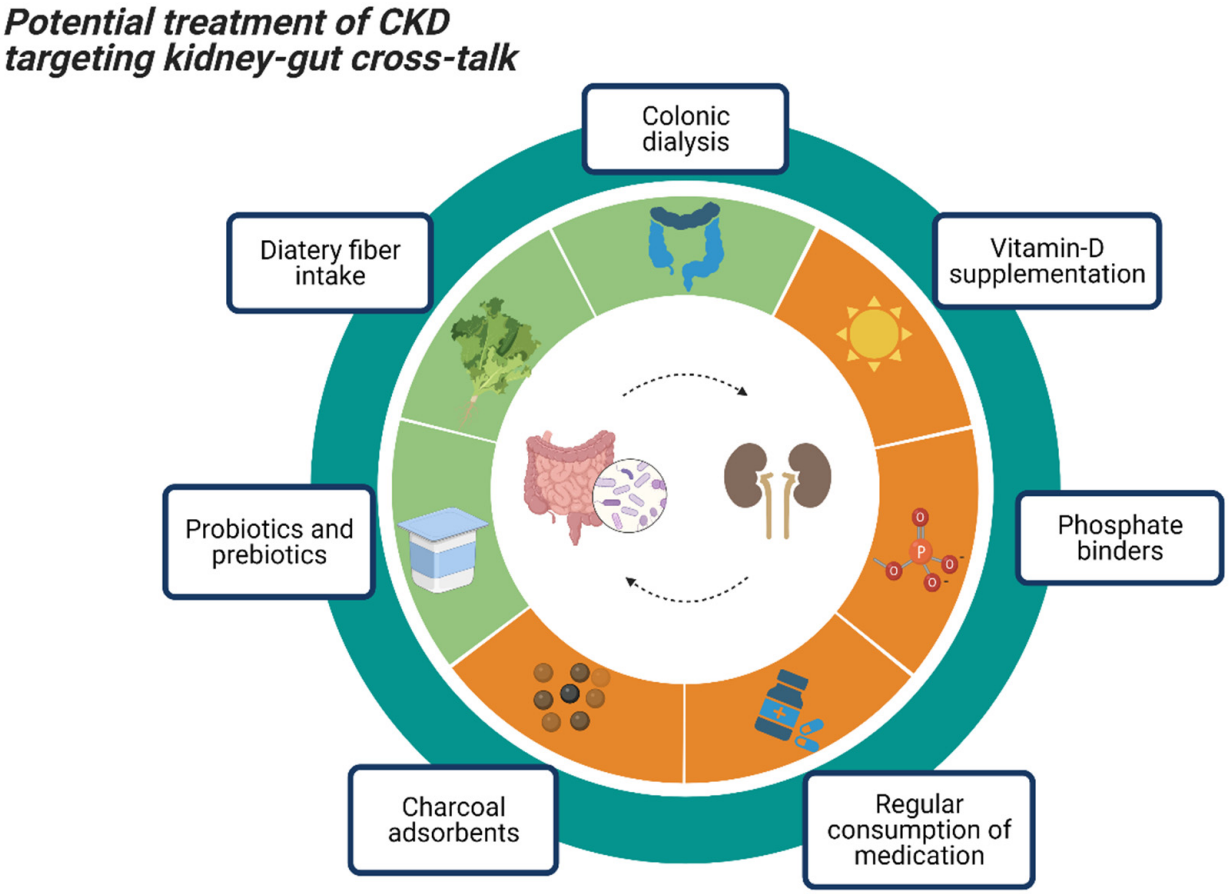

Figure 2. Potential treatment options in CKD patients within the context of a disturbed GI barrier. Treatment considerations are highly dependent on CKD severity. Green indicates promising primary treatment options, whereas orange-marked therapy options require further studies.

Table 1. Summary of gut targeted intervention strategies and outcomes in CKD patients.

	Study Design	Study Population (n)	Intervention	Primary Findings	Reference
Dietary effects	Cross-sectional survey	14, 533 healthy and 1105 CKD patients	High dietary fiber intake (≥l14.6 g/day)	Inflammatory markers ↓ Mortality in CKD ↓	[103]
	Randomized controlled clinical trial	32 CKD stage 3 or 4 patients	Lactulose syrup as a prebiotic (30 mm three times a day for 8 weeks)	*Bifidobacteria* ↑ *Lactobacillus* ↑ Creatinine↓	[120]
	Single-center, double-blind, placebo-controlled, randomized crossover trial	37 CKD patients with moderate to severe CKD	Synbiotics as combination of prebiotic powder (7.5 g) and probiotic capsule (45 billion [1] CFU) for the first 3 weeks with a dose elevation to 15 g of powder and two capsules for the following three weeks	P-cresyl sulfate ↓ Modified stool microbiome	[117]
	Single-blind controlled study	13 CKD patients with an eGFR of ≤50 mL/minute/1.73 m^2	High dietary fiber (1.6 g/day for 2 weeks, followed by 23 g/day fiber for 4 weeks)	[2] BUN ↓ by 10.6% Serum creatinine ↓ eGFR ↑	[101]
	Single-center, non-randomized, open-label phase I/II study	22 maintenance dialysis patients	Oligofructose-enriched inulin (10 g/day for the first week, 20 g/day for the next 3 weeks)	Serum P-cresyl sulfate ↓ 20% p-cresyl sulfate generation rates ↓	[119]
	Pilot-scale, randomized, double-blind, placebo-controlled crossover study	16 CKD stage 3 or 4 patients	Probiotic dietary supplementation (180 billion CFUs/day for 2 months with 2 months washout and crossover period)	BUN ↓ Uric acid ↓	[125]
	Double-blind, randomized, parallel, placebo-controlled trial	46 HD patients	20 g/day for the first 4 weeks and 25 g/day during the second 4 weeks of either HAM-RS2 or wheat-flour biscuits	↓ serum urea ↓ creatinine ↓ TNFα ↓ interleukin-6	[104]
	Randomized, double-blind, placebo-controlled, crossover study	12 HD patients	Inulin (10 g/d for females; 15 g/d for males) or maltodextrin (6 g/d for females; 9 g/d for males) for 4 weeks, with a 4-week washout period	↑ *Akkermansia*	[115]
	Cohort study	70 CKD stage 2 or 3 patients	25 g of *Acacia senegal* var. *senegal* Gum Arabic daily for 12 months	eGFR↑	[108]
Colonic dialysis	Cross-sectional, prospective study	50 CKD stages 3–5 patients 34 healthy subjects	Colonic dialysis (1 h/15–16 L per session)	Greater diversity of microbiota	[124]
	Retrospective study	178 CKD patients stage 3–5	Colonic dialysis (1 h/15–16 L per session three times per week)	Lower risk of CKD progression	[123]

[1] CFU, colony-forming units. [2] BUN, blood urea nitrogen.

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Abbreviations

CKD	chronic kidney disease
MBD	mineral and bone disease
GI	gastrointestinal
RAAS	Renin–angiotensin–aldosterone system
TGFβ	transforming growth factor-β
ROS	reactive oxygen species
NF-κB	nuclear factor-kappa B
Keap1	kelch-like ECH-associated protein 1
Nrf2	nuclear factor erythroid 2-related factor 2
FGF23	fibroblast growth factor-23
NaPi-2a	sodium-dependent phosphate transport protein 2a
TRPV5 and 6	transient receptor potential channel 5 and 6
PTH	parathyroid hormone
IS	indoxyl-sulfate
PCS	p-cresyl sulfate
IAA	indole 3-acetic acid
TJ	tight junction
ZO-1	zonula occludens-1
FAE	follicle-associated epithelium
LGS	"leaky gut" syndrome
HD	hemodialysis
GFR	glomerular filtration rate
NH_3	ammonia
NH_4OH	ammonium hydroxide
ESRD	end-stage renal disease
HAM-RS2	high-amylose maize resistant starch type 2

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