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Alterations of intestinal barrier and microbiota in chronic kidney disease

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FULL REVIEW

ABSTRACT

Recent studies have highlighted the close relationship between the kidney and the gastrointestinal (GI) tract—frequently referred to as the kidney–gut axis—in patients with chronic kidney disease (CKD). In this regard, two important pathophysiological concepts have evolved: (i) production and accumulation of toxic end-products derived from increased bacterial fermentation of protein and other nitrogen-containing substances in the GI tract, (ii) translocation of endotoxins and live bacteria from gut lumen into the bloodstream, due to damage of the intestinal epithelial barrier and quantitative/qualitative alterations of the intestinal microbiota associated with the uraemic milieu. In both cases, these gut-centred alterations may have relevant systemic consequences in CKD patients, since they are able to trigger chronic inflammation, increase cardiovascular risk and worsen uraemic toxicity. The present review is thus focused on the kidney–gut axis in CKD, with special attention to the alterations of the intestinal barrier and the local microbiota (i.e. the collection of microorganisms living in a symbiotic coexistence with their host in the intestinal lumen) and their relationships to inflammation and uraemic toxicity in CKD. Moreover, we will summarize the most important clinical data suggesting the potential for nutritional modulation of gut-related inflammation and intestinal production of noxious by-products contributing to uraemic toxicity in CKD patients.

Keywords: chronic kidney disease, endotoxin, inflammation, intestinal microbiota, uraemic toxicity

INTRODUCTION

Chronic kidney disease (CKD) is a global health issue, since 6–10% of the adult population in different countries can be classified as having CKD in its different stages [1]. In this clinical setting, the most frequent cause of death is cardiovascular disease (CVD), and the increased cardiovascular mortality risk in CKD has been attributed both to traditional risk factors, such as hypertension, diabetes and dyslipidaemia, and to non-conventional risk factors [2]. Among the non-conventional risk factors, chronic inflammation has received increasing attention and has been recently suggested as a major catalyst for CVD in CKD [3].

Many dialysis-related and non-dialysis-related factors are thought to contribute to the chronic inflammatory status in chronic kidney disease/end-stage renal disease (CKD/ESRD): increased production of cytokines along with decreased renal clearance, blood–dialyser interactions, non-sterile dialysis fluids, infection, indiscriminate intravenous iron administration and other chronic comorbidities, such as heart failure [3].

As to inflammation, two important pathophysiological concepts suggesting a close relationship between the gut and the kidney in CKD have been recently highlighted. First of all, even in the absence of clinical infection, the inflammatory status typical of CKD/ESRD could be triggered and/or potentiated by the passage from the gut to the bloodstream (intestinal translocation) of pro-inflammatory molecules and toxins linked to bacterial species in the lumen, the so-called intestinal microbiota [4, 5]. As a matter of fact, the exposure to bacterial structures such as lipopolysaccharides (LPS) from Gram-negative bacterial cell wall yields an inflammatory response mediated by the innate immunity [6].

Second, while it has been shown that the passage of limited amounts of some bacterial-related substances such as endotoxins from the gut to the bloodstream may occur naturally, leading to 'physiological' very low levels of endotoxaemia, yet translocation of other pro-inflammatory molecules or larger amounts of endotoxins—and in some cases live bacteria—is possible only if the intestinal barrier structure/function is damaged. Recent studies have documented the negative effects of uraemia on the gut barrier structure and function, especially on the protein structure/function of the tight junctions [7–10].

Hence, the present review is focused on the complex relationship between the gut and the kidney—the so-called kidney–intestinal axis—in CKD patients, with special regard to the central role played by the derangements of gut microbiota and by intestinal barrier structural/functional alterations.

To this purpose, intestinal bacterial metabolism in healthy subjects and in CKD will be discussed, along with the effects of CKD on the intestinal barrier and the bacterial translocation process.

Finally, we will summarize recent insights on the potential role and efficacy of nutritional modulation of gut-related inflammation and intestinal production of toxins in CKD/ESRD patients by the use of prebiotics and probiotics.

The gut ecosystem in healthy subjects

The term microbiota indicates a collection of microorganisms living in a symbiotic coexistence with their host. In humans, up to 100 trillion bacterial cells from ∼500 distinct species are present, with the gastrointestinal (GI) tract being the usual habitat for >70% of those microbes [11, 12]. Five bacterial phyla (*Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia)* and one Archea (*Euryarchaeota*) are the most common species in the human gut, two of which are dominant (90% of all species): *Bacteroidetes* (*Bacteroides*, *Prevotella and Xylanibacter*) and *Firmicutes* (*Ruminococcus*, *Clostridium*, *Lactobacillus*, *Eubacterium*, *Faecalibacterium* and *Roseburia*) [13]. Most of the bacterial species have a strict anaerobic metabolism; thus, as a consequence of the decreasing oxygen tension, bacterial density progressively increases along the intestinal length, reaching its maximum in the colon [5]. The intestinal ecosystem includes both the intestinal microbiota and the gut itself, where bacteria live in a sort of dynamic and mutualistic interaction with the host structures and metabolism, in order to obtain the symbiotic benefits. In fact, the gut microbiota has relevant trophic and protective functions on the GI tract, by providing the host with complementary metabolic pathways for essential compounds (for example, vitamins) and energy substrate production [14], as well as by regulating key aspects of immunity [5] (Table 1). Moreover, gut microbiota participates in the biotransformation of conjugated bile acids, signalling molecules implicated in the modulation of fat/glucose metabolism [15]. On the other hand, the biochemical milieu has a major influence on the composition and function of the gut microbiota. The distal GI tract represents a favourable environment for bacterial growth since it is rich in molecules that can be used as nutrients by microbes [11]. Host diet significantly influences the diversity of microbiota species, since they thrive on both luminal availability of food and host-derived nutrients [16]. The intestinal microbiota is generally stable, despite its high metabolic activity, but is also highly adaptive to modifications in the intestinal environment, through changes in nutrient utilization linked to nutrient availability and composition, induction of enzymes and alterations in the total number/composition of bacteria [11].

The availability of undigested carbohydrates (CHO) and proteins in the gut lumen favours bacterial anaerobic metabolism, i.e. fermentation. Both CHO and proteins are usual substrates of the anaerobic intestinal microbiota metabolism, but the end-products of their fermentation may vary widely, with different effects on the human host. CHO are the most important nutrient used by the colonic microbe metabolism for energy production, with methane, hydrogen and short-chain fatty acids (SCFA) as end-products [17]. The most important SCFA are butyrate, a key energy substrate for the colonic epithelial cells, as well as acetate and propionate, substrates for lipogenesis and gluconeogenesis also involved in positive insulin secretion modulation [14, 17]. In the presence of adequate amounts of undigested CHO (i.e. dietary fibres), proteins are mostly used for bacterial growth, thus favouring saccharolytic bacterial species, i.e. those that predominantly ferment CHO (*Bifidobacterium* and *Lactobacillus* species) [17]. When CHO availability is reduced, proteins are increasingly fermented by proteolytic bacteria—with *Clostridium* and *Bacteroides* as the predominant proteolytic species—to produce energy through deamination. However, protein fermentation pathways also produce potentially toxic metabolites (ammonia, amines, thiols, phenols and indoles) [17], generally excreted in the faeces and by the normal kidney.

A very important regulator of bacterial metabolism is represented by nutrient availability and composition, in particular the ratio between undigested CHO and protein. Because CHO is readily fermented by bacteria, the CHO/protein ratio is reduced along the intestinal length, whereas slowed transit (i.e. constipation) may induce an overgrowth of proteolytic species, thus favouring the production of both toxic metabolites and pro-inflammatory substances [17].

Environmental factors (i.e. intestinal pH, antibiotics, nutrient intake, psychological and physical stress, intestinal wall oedema, iron intake, etc.), host genotype, extra-intestinal non-communicable diseases and inflammatory bowel diseases may lead to a condition of altered intestinal milieu, i.e. intestinal dysbiosis [18], in some cases associated with overgrowth of

Table 1. Physiological effects of gut microbiota

(i)	Integrity and function of GI tract
	- Restoration of tight junction protein structure
	- Induction of epithelial heat-shock proteins
	- Upregulation of mucin genes
	- Competition with pathogenic bacteria for binding to intestinal epithelial cells
	- Secretion of antimicrobial peptides
	- Suppression of intestinal inflammation
(ii)	Immunological effects
	- Maturation of intestinal immune system
	- Reduction of allergic response to food and environmental antigens
	- Promotion of immunomodulation and cell differentiation
(iii)	Metabolic effects
	- Breakdown of indigestible plant polysaccharides and resistant starch
	- Facilitated absorption of complex CHO
	- Synthesis of vitamins (K and B groups)
	- Synthesis of amino acids (threonine and lysine)
	- Biotransformation of conjugated bile acids
	- Degradation of dietary oxalates

pathobionts, i.e. highly pathogenic microbes that may even reach the bloodstream [19].

In healthy subjects, prevention of intestinal translocation (i.e. the passage of substances and microbes from the intestinal lumen to the bloodstream) is usually granted by the intestinal barrier, with its protective structures/systems: tight junctions, enterocyte membranes, mucus secretion and immunological defence mechanisms in the intestinal wall [11, 13]. The epithelial cells are bound together by tight junction complexes that protect against translocation along paracellular pathways. Tight junctions are composed by a cluster of adhesive protein species such as occludins and claudins as major sealing proteins to diffusion of solutes and fluids, the cytosolic proteins called of the zonula occludens (ZO) protein family and the peri-junctional ring of actin and myosin, which regulates paracellular permeability [6]. In addition, tight junctions can adjust their tightness according to physiological needs and represent a very efficient barrier against microbes, LPS, toxic bacterial fermentation end-products, digestive enzymes and other harmful substances at risk of translocation from the GI tract lumen to the internal milieu. The intestinal immune system plays a key role in maintaining the dynamic equilibrium between the symbiotic microbiota and the host. In this regard, a well-balanced interaction between the different components of local adaptive immune responses, combining secretory IgA and different types of regulatory T-cell responses, is required to maintain the intestinal homeostasis by containing microbes and/or microbial products within the gut lumen [20–22].

The gut ecosystem in CKD/ESRD patients

The presence of CKD/ESRD contributes significantly to the pathogenesis of intestinal dysbiosis by different mechanisms, linked both to alterations of the intestinal barrier and changes in composition of gut microbiota, and by the effects of dietary restrictions and specific therapies of the syndrome [13, 19] (Table 2).

The relationship between uraemia and the presence of alterations of the intestinal barrier function has been carefully explored in recent experimental and clinical studies [7–10]. The histological examination of tissue specimens from stomach, jejunum, ileum and colon has revealed thickened intestinal wall and increased immune activation in CKD mice compared with healthy animals [7, 10]. A marked depletion of occluding and claudin-1 content in the intestinal wall in uraemic mice has been associated with increased intestinal permeability and leakage of luminal bacterial endotoxins and other harmful products in CKD [7, 10]. In addition, plasma taken from uraemic patients increased intestinal barrier permeability *in vitro*, through a significant reduction of ZO-1 protein, a near complete depletion of claudin-1 and a decrease of occludins [8, 9]. Moreover, the marked decrease of the main proteins forming the epithelial tight junction was accompanied by a reduction in the transepithelial resistance, which denotes increased permeability and epithelial barrier dysfunction [8, 9]. Finally, conditions associated with oedema/hypervolaemia or ischaemia may also increase intestinal wall permeability; in particular, a jeopardized intestinal perfusion, eventually associated with aggressive ultrafiltration volumes and/or intradialytic hypotension, could increase the dysfunction and permeability of the gut barrier in ESRD patients on dialysis [13, 30].

Table 2. Effects of CKD on bacterial metabolism

Effects	Mechanism
1. Reduced intake of dietary fibres [23]	Prescribed potassium restriction leads to reduced intake of fruits and vegetables
2. Prolonged colonic transit time (constipation) [24]	Multifactorial: dialysis modality, lifestyle, inactivity, phosphate binders, dietary restrictions, low fluid intake, primary renal disease and comorbidities (diabetes, heart failure, malnutrition and cerebrovascular disease)
3. Increased amounts of protein available for proteolytic bacterial species [24–27]	Protein assimilation is impaired in uraemia, with increased amounts of intact proteins reaching the colon
4. Changes of the colonic microbiota [13, 28, 29]	Increased blood ammonia concentrations may change intestinal lumen pH; Drug therapies (antibiotics, phosphate binders, antimetabolites, etc.) with local effect in the gut lumen

Relevant quantitative and qualitative alterations of intestinal microbiota have been demonstrated in CKD/ESRD, such as increased counts of both aerobic and anaerobic microorganisms in the proximal portions of the gut (duodenum and jejunum), as well as overgrowth of both the colonic aerobic bacteria species *Proteobacteria* and *Actinobacteria* [28] and the anaerobic species *Firmicutes* [13, 28]. In particular, an expansion of bacterial species possessing urease, uricase, indole- and p-cresol-forming enzymes has been recently demonstrated [29]. Twelve of the 19 microbial families more prevalent in ESRD patients were among those producing urease (e.g. *Alteromonadacea*, *Cellulomonadacea*, *Clostridiacea*, *Dermabacteracea*, *Enterobacteriacea*, *Halomonadacea*, *Methylocaccaceae*, *Micrococcaceae*, *Moraxellaceae*, *Polyangiaceae*, *Pseudomonadaceae* and *Xanthomonadaceae*). Urea is now considered a key factor in the pathogenesis of gut barrier dysfunction. Urea accumulation in CKD increases urea influx into the intestinal lumen, where it is hydrolysed to ammonia by microbial urease; ammonium hydroxide, a by-product of ammonia, increases intestinal pH leading to mucosal irritation and structural damage [31, 32]. Moreover, urea may undergo spontaneous dissociation to cyanate, a reactive species able to increase the blood level of carbamylated proteins, an independent predictor of CVD [33, 34]. In the same way, the intestinal excretion of uric acid and oxalate also increases in CKD [35, 36]. Because of the wide availability of nitrogen waste products in the gut, the overgrowth of microbes capable of utilizing these substrates is thus favoured [29] (Figure 1). Finally, microbes able to produce indole and p-cresol were also included among the above-mentioned 19 most abundant microbial families, such as *Clostridiaceae, Enterobacteriacea* and *Verrucomicrobiacea* [29], whereas microbial families with butyrate-producing enzymes (*Lactobacillaceae* and *Prevotellaceae*) were reduced compared with healthy subjects [29].

Dietary habit changes associated with dietary restrictions and specific therapies may also contribute to intestinal dysbiosis

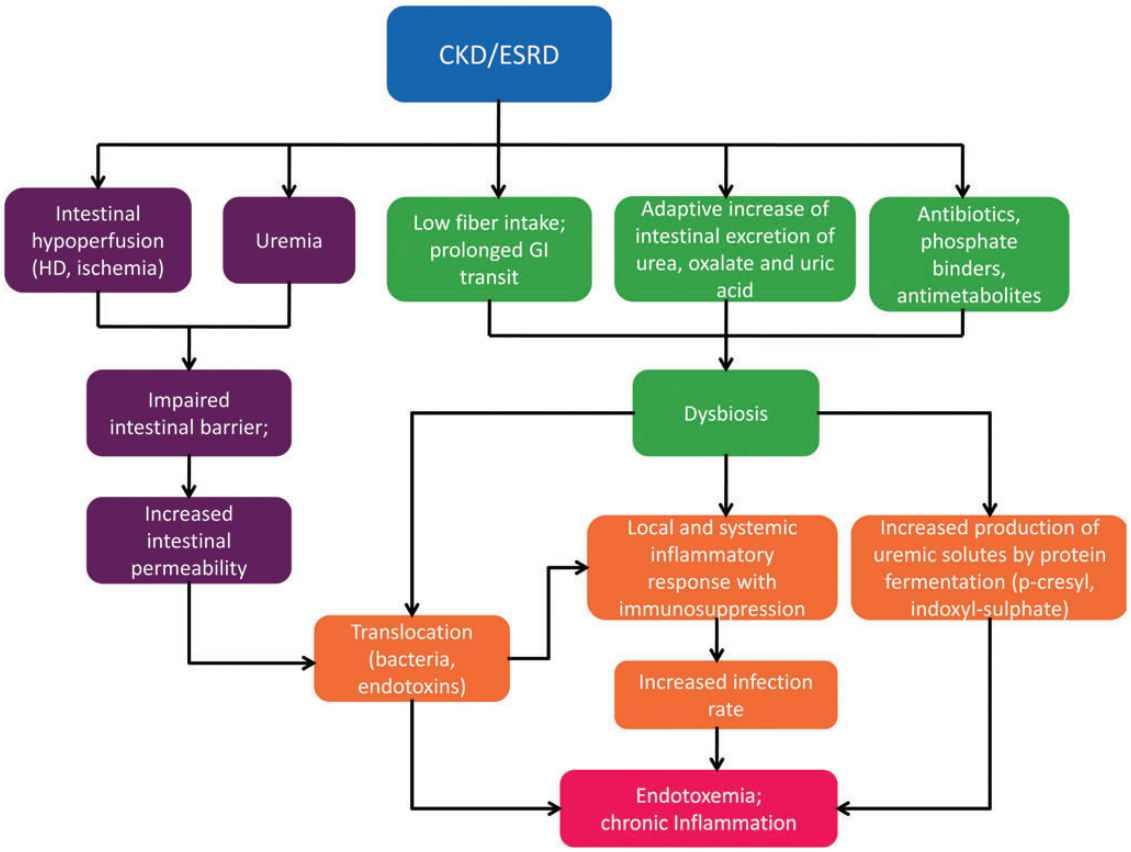

FIGURE 1: Negative effects of CKD/ESRD on intestinal barrier and microbiota. CKD, chronic kidney disease; ESRD, end-stage renal disease; GI, gastrointestinal; HD, haemodialysis.

in CKD. The most represented indigestible CHO in the diet is fibre, known to be the primary source of substrates for bacterial fermentation. However, patients with CKD/ESRD often have a low intake of two major sources of dietary fibre—fruits and vegetables—due to the dietary restrictions of potassium intake. As a matter of fact, a recent study that analysed data from 1105 CKD patients has shown that 56.4% of subjects consumed on average <14.5 g of fibre/day [23], whereas the recommended intake of dietary fibre by the World Health Organization for the average population is at least 25 g/day. The prolonged GI transit may lead to increased CHO fermentation in the proximal segments of the intestine [24]. In addition, CKD patients seem to have impaired protein digestion and absorption, due to disturbances related to protein breakdown, synthesis and oxidation [25]. Alterations in GI tract motility, gastric hypochlorhydria, bacterial overgrowth in the small bowel and pancreatic abnormalities may all concur in impairing protein digestion and absorption in CKD, thus increasing the availability of a larger amount of undigested proteins for proteolytic bacteria in the colon [24, 26, 27]. In addition to the low availability of fibre for saccharolytic bacteria and GI tract slower transit time caused by the reduced bulk of dietary fibre, other factors related to CKD/ESRD therapies itself (e.g. dialysis modality, use of phosphate binders, antibiotics, etc.) are likely to worsen constipation, thus changing the amount and composition of the intestinal microbiota.

Intestinal dysbiosis, uraemic toxin production and cardiovascular risk

CKD, especially in its most advanced stages, is characterized by the progressive accumulation of many substances and solutes, such as electrolytes, hormones and uraemic solutes (small water-soluble molecules, middle molecules and protein-bound uraemic solutes). Uraemic solutes are able to interfere with many biological functions and are indicated as uraemic toxins [37]. Protein-bound uraemic toxins have been receiving much attention in the last decade, especially because of their effects on inflammation and CVD risk, and for their incomplete clearance by conventional renal replacement therapy (RRT) [37, 38]. Their precursors are formed in the GI tract during protein fermentation by the microbiota. The two most widely studied are p-cresol (the precursor of p-cresyl sulphate and of the less studied p-cresyl-glucuronide) and indole (the precursor of indoxyl sulphate), generated, respectively, from tyrosine and tryptophan fermentation. During its transport through the intestinal wall to the bloodstream, p-cresol is converted to p-cresyl sulphate by cytoplasmic sulfotransferase, whereas indole is metabolized in the liver to produce indoxyl sulphate; in healthy subjects, both molecules are excreted by the kidney by active tubular secretion, whereas in CKD, increased blood levels of p-cresyl sulphate and indoxyl sulphate parallel the reduction of renal function [39]. In ESRD patients on dialysis, the clearance of p-cresyl sulphate and indoxyl sulphate is <10% of

that of normal kidneys [40], and their blood levels have been related to poor outcomes [41–47]. These protein-bound uraemic solutes may in fact negatively affect endothelial function and repair by several mechanisms, including inflammation, oxidative stress, impaired nitric oxide production and inhibition of endothelial proliferation and healing [43–48], and they have been associated with increased incidence of CVD and mortality [41, 42, 47].

The immunoregulatory role of intestinal ecosystem in CKD/ESRD

The symbiotic relationship between the gut and its microbiota is actively involved in the regulation of the local and systemic immunity; any derangement of this complex ecosystem, as in the case of CKD-associated dysbiosis, may produce relevant negative effects on patient health status. To maintain the balance between the host and its microbial flora, as well as its own function as a digestive organ, the GI tract requires both the constant induction of different immunoregulatory responses and the continuous modulation of antagonistic signals (i.e. pro- and anti-inflammatory) driven by the host–microbe symbiotic relationship [5, 19]. As a matter of fact, the gut microbiota participates in immune homeostasis and in protection against infections since the postnatal colonization period of the gut, by contributing to the formation and maturation of the immune system, not only at the local level (e.g. for example, the mucosa-associated lymphoid tissue of Peyer's patches of the intestinal wall) but also in the extra-intestinal lymphoid tissues [49]. Many different mechanisms are involved in this 'shaping effect' of the immune system [50] by the gut microbiota: secondary lymphoid structure development, epithelial/vascular structure fostering, stimulation of mucus layer and antimicrobial peptide production [5, 49, 51]. Moreover, the modulation of local immune system in the gut also sets the stage for the symbiotic relationship between the host and its intestinal microbiota. The innate immune response is able to identify microbes by mucosal pattern recognition receptors (PRRs) that recognize molecular products of microorganism, such as microbe-associated molecular patterns, small molecular motifs exclusively present on microbes and LPS [6]. In this regard, toll-like receptors (TLRs) are the key PRR family [6], and their controlled activation is considered a main mechanism of tolerance towards symbiotic commensal microbic species in the gut lumen [5, 19]. The final effector mechanisms originate through the signalling pathways downstream of TLRs, leading to the production of antimicrobial proteins and pro-inflammatory cytokines through the NF-kB pathway activation [5, 19]. In a symbiotic gut, continuous exposure to LPS is associated with desensitization of epithelial cells [52]. In fact, their response is attenuated by different mechanisms, such as LPS-mediated downregulation of the IL-1 receptor-associated kinase 1, the proximal activator of the NF-kB cascade [52], LPS-mediated induction of peroxisome proliferator-activated receptor-g, which can divert NF-kB from the nucleus [53] and commensal bacteria-derived reactive oxygen species-mediated inhibition of polyubiquitination and degradation of the aortic inhibitor of kB [54]. Thus, a dynamic equilibrium is established—and maintained—in the gut between host and microbes, in the sense that persistent, low-grade innate immune activation involves the induction of a coordinated series of immunoregulatory mechanisms partially suppressing the immune response [5]. Moreover, TLR stimulation may contribute to tight junction integrity preservation and repair [55, 56]. However, in the presence of dysbiosis and pathobiont overgrowth, the loss of the gut barrier integrity with the ensuing translocation of bacteria and their components may disrupt tolerance, triggering the intestinal and systemic immune system to an overshooting and potentially harmful pro-inflammatory response, aimed at clearing the invading microbes [5, 19]. This response involves the secretion of IL-1 and -6 from intestinal epithelial cells, the promotion of TH1 and TH17 response by dendritic cells (DCs) and macrophages and the production of higher levels of commensal-specific IgG by B cells [19]. In this context, LPS binding to its receptor complex on macrophages results in highly increased production of inflammatory cytokines such as IFN-β, IFN-γ, IL-1β, IL-6, TNFα and IL-12 [6, 57]. These mechanisms, characterized by persistent inflammation, are considered among the likely missing links between CKD/ESRD and some of the cardiovascular/renal complications typical of the syndrome [3]. In fact, poly(ADP-ribose) polymerase activation by bacterial components and/or translocated microbes is not necessarily a gut-limited phenomenon, but it could spread too many different cell types, including vascular endothelial cells, DCs and macrophages, triggering accelerated atherogenesis [58] and CKD progression [59].

Besides being a chronic systemic inflammatory status, CKD/ESRD may also represent a state of acquired immunodeficiency, as testified by the increased incidence of infections in this clinical setting [5]. The chronic inflammatory status of uraemia could be associated with a form of excessive suppression of the adaptive immunity [60], as suggested by the reduced response to viral and mycobacterial infections and by the inadequate priming of antigen-specific T/B cells after vaccination in these patients [61–63]. Within this conceptual framework, it is likely that also in CKD, chronic TLRs stimulation by LPS/bacteria may be followed by a refractory state, a phenomenon well known in the case of sepsis syndrome and referred to as the 'compensatory anti-inflammatory syndrome' or 'immune paralysis' due to endotoxin tolerance [5]. On these theoretical grounds, following an initial and strong inflammatory phase, an ensuing upregulation of anti-inflammatory mediators may lead to suppression of both innate and adaptive immunity, acquired immunodeficiency status, impaired host defence and increased risk of secondary infections [5].

Modulation of intestinal barrier dysfunction and microbiota alterations in CKD/ESRD

Different approaches based on the use of probiotics, prebiotics and synbiotics could allow, at least in theory, the modulation of gut microbiota and intestinal barrier structure/function. Probiotics are 'viable organisms that, when ingested in sufficient amounts, exert positive health effects' [64]. Among the many purported health benefits attributed to probiotic bacteria, the (transient) modulation of the intestinal microbiota and the capability to interact with the immune system—directly or through the autochthonous microbiota—represent basic

mechanisms. The term prebiotic, refers to 'a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microbiota that confer benefits' [65]. Prebiotics promote the growth of bifidobacteria, microbial species that stabilize the mucosal barrier function, and reduce the abundance of pathogenic bacteria by gut lumen acidification, competition for nutrients and production of antimicrobial substances [66]. Although all prebiotics are fibre, not all fibres are prebiotic. In fact, some characteristics must be present in the food ingredient to be classified as a prebiotic, such as resistance to gastric acidity, hydrolysis by mammalian enzymes, absorption in the upper GI tract, fermentation by the intestinal microbiota, selective stimulation of growth and/or activity of intestinal bacteria potentially associated with health and well-being [64, 65]. At present, only bifidogenic non-digestible oligosaccharides [especially inulin, oligofructose and (*trans*) galacto-oligosaccharides] fulfil all of these criteria. Finally, when probiotics are administered in combination with prebiotics, they are referred to as synbiotics. Several studies have approached the issue of intestinal environment modulation to favour the growth of saccharolytic bacteria by using probiotics (i.e. *Lactobacillus*, *Streptococcus* and *Bifidobacteria*) [67–71], prebiotics (i.e. arabic gum and oligofructose) [72–74] or synbiotics (i.e. *Lactobacillus* and *Bifidobacterium* combined to oligosaccharides) [75, 76]. Table 3 summarizes the most recent studies testing the effects of probiotics, prebiotics and synbiotics on concentration of serum uraemic toxins of CKD/ESRD patients. In most of the cases, these potential modulators have been explored in terms of effects on blood accumulation of nitrogen compounds such as blood urea nitrogen (BUN), p-cresyl sulphate and/or indoxyl sulphate (Table 3). Only three randomized controlled trials (RCTs) with probiotics are available [69–71]; in two of them [69, 70], the use of a mix of bacteria (*L. acidophilus KB27*, *B. longum KB31* and *S. thermophilus KB19*) for 6 months reduced BUN and uric acid levels in stage-3 to -4 CKD patients. In the most recent study [71], a 2-month treatment with a dairy product containing 16×10^9 CFU of *Lactobacillus casei Shirota* was able to reduce BUN concentration in CKD patients stages 3 and 4. In non-randomized studies evaluating the effects of probiotics on serum and faecal uraemic solutes in haemodialysis patients [67, 68], reduced excretion of p-cresol and indican (i.e. indoxyl sulphate) and decreased serum levels of indoxyl sulphate [67, 68] were observed, probably owing to lower intestinal production of these toxins. In CKD patients, beneficial effects such as BUN decrease [73], improved estimated glomerular filtration rate [74], higher faecal nitrogen excretion and increased faecal saccharolytic bacterial mass have been demonstrated also with the use of prebiotics [72]. These data suggest that fermentable fibres are able to provide enough energy substrates for the intestinal microbiota, allowing saccharolytic bacteria to incorporate nitrogen for growth, to reduce blood nitrogen compound production and to increase their faecal excretion [72]. Other studies have shown a reduction of serum p-cresyl sulphate and p-cresyl sulphate generation rates in ESRD patients on haemodialysis [73, 74]. The use of synbiotics (i.e. a combination of probiotics and prebiotics) decreased serum p-cresol conjugates levels, normalized the amount and consistency of stools in haemodialysis (HD) patients [75] and increased the counts of *Bifidobacteria* [76].

Few data are currently available concerning the effects of dietary fibre, such as prebiotics that occur naturally in whole grain foods, fruits and vegetables—on patient mortality. A recent observational study based on the Third National Health and Nutrition Examination Survey (NHANES III) database has evaluated whether the association between dietary fibre intake, elevated C-reactive protein and all-cause mortality is modified by the presence of CKD [23]. The average intake of fibre (15 g/day) in CKD patients was significantly reduced as compared with the recommended intake. This is not surprising, since the actual dietary recommendations for CKD patients include the restriction of fruits and vegetables to control or prevent hyperkalaemia. In the overall study population (healthy subjects and CKD patients), an increased intake of fibre was associated with a decrease in the inflammatory status; however, only in the CKD subgroup was dietary fibre intake associated with a decrease in all-cause mortality. In particular, each 10 g/day increase in total dietary fibre intake was related to a 17% lower mortality risk, suggesting CKD as a very important modifier of the already known beneficial effects of dietary fibre intake. No clear recommendation is available on the optimal amount of fibre in CKD/ESRD in the currently available guidelines or consensus papers.

Perspectives and future topics for research

At present, in most of the ESRD patients, uraemia can only be treated by RRT, which may fall short of clearing higher-molecular-weight solutes or protein-bound uraemic toxins. Recent observations about the possible role of the gut in the production of some of these toxic substances have led to increased efforts in the development of new therapeutic approaches targeting the intestinal microbiota to improve the uraemic syndrome. Three possible strategies are currently being investigated: (i) modulating bacterial growth by preferential selection of saccharolytic instead of proteolytic species, thus reducing uraemic toxin production, (ii) preventing the absorption of toxic end-products of microbial metabolism, thus reducing their levels in the blood and (iii) improving removal of protein-bound uraemic toxins from the blood by RRT.

The modulation of bacterial growth to reduce the production of uraemic toxins is the most extensively studied GI tract-targeted strategy and involves the use of probiotics and prebiotics. In addition to probiotics and prebiotics, also antibiotics can be used for bacterial selection. At present, there are no published data on CKD patients, but good results with this approach have been obtained in the prevention of hepatic encephalopathy relapses in cirrhotic patients [77]. An alternative method to inhibit early fermentation of indigestible CHO in the small intestine is represented by α-glucosidase inhibitors, such as acarbose [78], which, at least in healthy volunteers, may reduce serum levels and urinary excretion of p-cresol [79].

A second strategy is represented by the inhibition of microbial metabolite absorption by reducing their availability through adsorption onto high-affinity surfaces in the intestinal lumen. Currently, two substances are being studied for this purpose. AST-120 is a spherical adsorbent made of millimetric carbon particles (0.2–0.4 mm diameter) that adsorb various compounds, including indole, p-cresol and other toxins in

Table 3. Current studies testing the effects of probiotics, prebiotics or synbiotics on CKD/ESRD patients

	Study	Primary endpoint	Design	Treatment	Results
Probiotic	Hida *et al.* [67]	Indican, p-cresol	Not an RCT; *n* = 20; HD 1 month	Lebenin (*Bifidobacterium infantis*, *Lactobacillus acidophilus* and *Enterococcus faecalis*); 2 times/day	Reduction of serum p-cresol and indican; reduction of faecal p-cresol and indicant
	Takayama *et al.* [68]	Indoxyl sulphate	Non-randomized CT; *n* = 22; HD 5 weeks	*Bifidobacterialongum:* gastro-resistant seamless capsule (Bifina) versus powder formulation (Lac B)	Decrease of serum indoxyl sulphate in the Bifina group.
	Ranghanathan *et al.* [69]	BUN, creatinine, uric acid	RCT, double-blinded, crossover; CKD stages 3–4; *n* = 13; 6 months	KibowBiotics® (*L. acidophilus* KB27, *B. longum*KB31 and *S. thermophilus* KB19); 90 billion colony-forming units [CFUs]/day	Reduction of BUN and uric acid during treatment period
	Ranghanathan *et al.* [70]	BUN, creatinine, uric acid	RCT, double-blinded, crossover; CKD stages 3–4; *n* = 46; 6 months	Kibow Biotics® (*L. acidophilus* KB27, *B. longum* KB31 and *S. thermophiles* KB19); 90 billion colony-forming units [CFUs]/day	Reduction of BUN
Prebiotic	Bliss *et al.* [72]	BUN, faecal nitrogen excretion and faecal bacterial mass	RCT single-blinded, crossover; *n* = 16; CKD; 8 weeks	Treatment: 25 g arabic gum in 150 mL of juice; Placebo: 0.5 g pectin in 150 mL of juice; 2 times/day	Decrease of BUN, increase of faecal nitrogen excretion and faecal bacterial mass during arabic gum treatment
	Meijers *et al.* [41]	p-Cresyl sulphate	Not an RCT; *n* = 22; HD 1 month	Escalating dose of ORAFITI Synergy 1 (oligofructose + linear fructans); 10 g/day—Week 1, 20 g/day from Week 2	Decrease of serum p-cresyl sulphate; decrease on of p-cresyl sulphate generation rate
	Salmean *et al.* [74]	BUN and creatinine	Not an RCT, single-blinded, crossover; *n* = 13; CKD; 6 weeks	Regular food (cereal, cookies and bars) providing 1.6 g/day of fibre for 2 weeks; enriched food providing 23 g/day of fibre for 4 weeks. Foods were incorporated into patient usual diets.	Decrease of BUN and serum creatinine; improve of eGFR
Symbiotic	Nakabayashi *et al.* [75]	p-Cresol	Not an RCT; *n* = 9; HD; 4 weeks	SYN (*Lactobacillus casei* strain Shirota and *Bifidobacterium breve* and galacto-oligosaccharides); 2 times/day/2 weeks	Decrease of p-cresol levels; normalization of quantity and consistency of stools
	Cruz-Mora *et al.* [76]	Faecal bacterial mass	RCT; *n* = 18; HD; 2 months	Treatment: probiotics (*Lactobacillus acidophilus* and *Bifidobacterium bifidum*), 2.0×10^{12} colony-forming units; 2.31 g of inulin; 1.5 g of omega-3 fatty acids and vitamins (complex B, folic acid, ascorbic acid and vitamin E); Placebo: a gel without prebiotic fibre, probiotics, omega-3 fatty acids and vitamins	Increase of *Bifidobacterium* counts

BUN, blood urea nitrogen; CKD, chronic kidney disease; CT, controlled trial; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, haemodialysis; RCT, randomized controlled trial.

the GI tract [80]. Recently, in an animal model of CKD, AST-120 was able to attenuate uraemia-induced disruption of colonic epithelial tight junction, endotoxaemia, oxidative stress and inflammation [81]. An RCT has demonstrated that AST-120 was associated with a decrease in the rate of loss of kidney function in patients with mild-to-moderate CKD [82, 83]. In addition, in a phase II study, AST-120 decreased serum indoxyl sulphate levels in a dose-dependent fashion, with an improvement of the uraemic syndrome [84]. In a retrospective study of 192 ESRD patients, the initiation of AST-120 before the first dialysis was associated with reduced risk of all-cause mortality compared with controls [85]. Sevelamer hydrochloride, a well-known phosphate binder, has been studied due to its adsorbent effects. An observational study in 20 patients receiving sevelamer hydrochloride has demonstrated a reduction of serum ultra-high-sensitive C-reactive protein and endotoxin levels after 6 months of treatment [86]. However, in animal models [87] and in dialysis patients [88], sevelamer failed to decrease serum concentrations of indoxyl sulphate and p-cresyl.

Finally, a third strategy is aimed at improving the efficiency of removal of protein-bound compounds from plasma by RRT, by either adsorption of these compounds on resin cartridges [89, 90], or by lowering their binding to plasma proteins [91]. A recent study used Hemo-Filtrate-Reinfusion (HFR), an RRT modality that combines diffusion, convection and adsorption through a resin cartridge with binding properties towards many medium- to high-molecular-weight solutes and pro-inflammatory cytokines [92]. In this study, total plasma p-cresol level was significantly reduced by HFR, a technique more effective than conventional HD in clearing p-cresol from plasma (reduction ratio of 56.6 ± 12.5% versus 37.1 ± 20.2%, $P < 0.05$) [92].

CONCLUSION

Cardiovascular disease is the leading cause of death among CKD/ESRD patients and is closely associated with an inflammatory status typical of this clinical setting. Chronic inflammation in CKD/ESRD patients, even in the absence of active infection, has been related at least in part to the passage of bacterial components and live bacteria into the bloodstream (translocation) through a

damaged intestinal barrier and to the accumulation of uraemic solutes generated as end-products of deranged microbiota selection/metabolism in the gut. In fact, CKD/ESRD is associated with a prevalence of protein-fermenting microbial flora and increased production of protein-bound uraemic toxins. The coexistence of impaired kidney function leads to the accumulation of these toxins, worsening the uraemic state and maintaining the inflammation. Modulating the gut microbiota by probiotics or prebiotics could positively modify the gut bacterial composition and metabolism, likely decreasing the production of uraemic solutes and reducing chronic inflammation. However, more RCTs are needed to assess a putative causal relationship between probiotics/prebiotics use and uraemic/inflammatory/CVD risk status in CKD/ESRD patients, as well as to better define the optimal intake of fibre in this clinical setting, and to increase dietary fibre intake despite the well-known restrictions on fruits and vegetables of the renal diets.

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CONFLICT OF INTEREST

None declared.

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