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Link between gut microbiota dysbiosis and chronic kidney disease

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Abstract. **During chronic kidney disease (CKD), typical alterations in the gut microbiota are observed. The kidney no longer plays the role of the main excretory organ as this function is performed by the intestine. In CKD patients, an alteration of intestinal permeability and a degradation of the protective mucous layer are observed. These changes in the intestinal barrier allow the passage of bacterial material from the intestine to the bloodstream through the intestinal wall. This phenomenon contributes to the induction of the chronic inflammatory state, typical of CKD. In nephropathic patients, there is an increase in circulation of p-cresyl sulfate (p-CS), indoxyl sulphate (IS), indole-3 acetic acid (IAA) and trimethylamine-N-oxide (TMAO), all gut-derived uremic toxins. The changes in gut microbiota composition are related to CKD stage and this phenomenon is exacerbated in hemodialysis (HD) adult and pediatric patients. Interestingly, it is observed a positive shift in gut microbiota composition after renal transplantation and at the same time a reduction of circulating gut-derived uremic toxins. Either gut dysbiosis or uremic toxins accumulation contribute to the CKD onset and progression.**

Key Words:
Gut microbiota, Chronic kidney disease, P-cresyl sulfate, Dysbiosis, Mediterranean diet, Low-protein diet.

Abbreviations

Ach: Acetylcholine; AH: Arterial hypertension; CKD: Chronic kidney disease; CRP: C-reactive protein; CV: Cardiovascular; DM: Diabetes mellitus; ESRD: End stage renal disease; GABA: γ-aminobutyric acid; GFR: Glomerular filtration rate; GLP: Glucagon-like peptide; HD: Haemodialysis; HPA: Hypothalamus-pituitary-adrenal; IAA: Indole-3 acetic acid; IgAN: IgA nephropathy; IL: Interleukin; IMN: Idiopathic membranous nephropathy; INS: Idiopathic nephrotic syndrome; IS: Indoxyl sulphate; KA: Ketoanalogues; K/DOQI: Kidney Foundation Kidney Disease Outcome Quality Initiative; LOS: Lipooligosaccharides; LPD: Low-protein diet; LPS: Lipopolysaccharide; MD: Mediterranean diet; MYD: Myeloid differentiation; NF-κB: Nuclear factor kappa B; NOX2: Nicotinamide adenine dinucleotide phosphate oxidase; NRF2: Nuclear factor erythroid-2-related factor 2; OS: Oxidative stress; p-CS: p-cresyl sulfate; PD: Peritoneal dialysis; RAAS: Renin-angiotensin-aldosterone system; ROS: Reactive oxygen species; RPF: renal plasma flow; RRT: Renal replacement therapy; SCFAs: Short chain fatty acids; TLR4: Toll-like-receptor 4; TMAO: Trimethylamine-N-oxide; TNF: Tumour necrosis factor α; VLPD: Very low-protein diet.

Introduction

Chronic kidney disease (CKD) is a global health burden, and its prevalence has remarkably expanded in the last decades because of the increase in old age of the general population and the comorbidity associated with it[1], such as arterial hypertension (AH), diabetes mellitus (DM), obesity[2] and metabolic syndrome[3].

The alteration of the gut microbiota is often found in CKD patients and it is related to the low-grade chronic inflammation, the oxidative stress (OS) and the AH, commonly present in CKD patients[4-6].

The relationship between gut microbiota and CKD has been known for a long time[7]. With the

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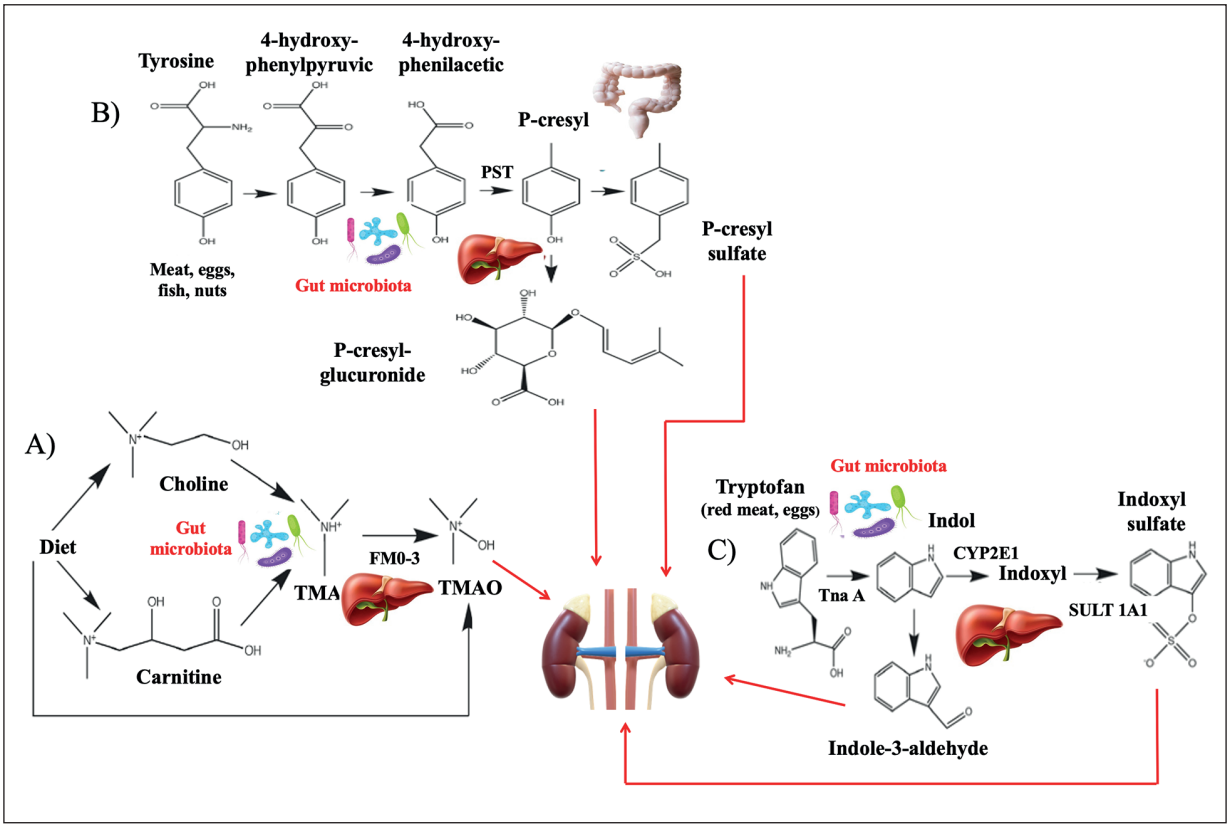

Figure 1. Gut-derived uremic toxins. **A**) Metabolic pathways for TMAO generation from dietary L-carnitine and choline; **B**) Metabolic pathways for p-cresyl-sulfate and p-cresyl-glucuronide generation from dietary tyrosine; **C**) Metabolic pathways for indoxyl sulfate and indole-3-aldehyde generation from dietary tryptophan. Ones generated, these uremic toxins are excreted by the kidneys in healthy subjects while they accumulate in chronic kidney disease.
Abbreviations: CyP, Cytochrome P450; PST, Phenol sulfotransferase; SULT, Sulfotransferase; TMA, Trimethylamine; TMAO, Trimethylamine-N-oxide.

CKD progression, the kidney loses the ability to eliminate catabolites produced by human metabolism[8-10] and by its symbiote (gut microbiota)[11]. Some of these substances are included in the "uremic toxins" category. Among those of intestinal derivation, the main and most studied are p-cresyl sulfate (p-CS), indoxyl sulphate (IS), indole 3 acetic acid (IAA) and trimethylamine N-oxide (TMAO)[12] (Figure 1). The latter is a derivative of the catabolism of products of animal origin containing choline, phosphatidylcholine, carnitine, and betaine[13,14].

With the progressive loss of kidney function, toxic compounds accumulate in the bloodstream causing the uremic state. Therefore, it is speculative that CKD not only induces a reduction in the elimination of uremic toxins but it also favors their production[15], involving in this process the gut microbiota.

In fact, an alteration in the gut microbiota composition might be influenced by many factors including smoking, drugs, food patterns and some pathological conditions[16]. Among these, CKD deserves a special mention as several studies have shown that the gut microbiota composition in CKD patients is completely different from those of healthy subjects. This imbalance is called "dysbiosis" (Figure 2).

CKD causes an expansion of the proteolytic bacterial populations (resulting in increased production of ammonia and of other uremic toxins like phenols and indoles) and a reduction of the saccharolytic ones (leading to the decrease of the short chain fatty acids-SCFAs formation)[17]. Depending on the substrate that bacteria use to get energy, the microbiota can follow two main metabolic pathways: saccharolytic or proteolytic. The first one might prevail in a healthy intestine. In the case of food imbalances or pathological conditions, the lack of substrate available for fermentation favors the imbalance towards the second way, in which bacteria use amino acids for energy purposes, rather than for anabolic function, re-

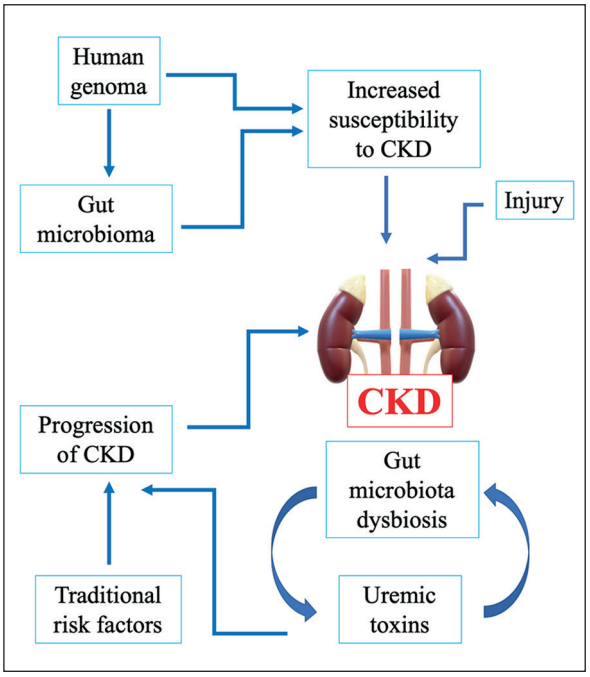

Figure 2. The bidirectional relationship between gut dysbiosis and chronic kidney disease.
Abbreviations: CKD, Chronic kidney disease.

sulting in the toxins production. The balance between saccharolytic fermentation and proteolytic decay might be in favor of the former, due to the different physiological effects of the metabolites downstream of the two pathways. With saccharolytic fermentation, there is the production of SCFAs which, in addition to inhibiting the growth of pathobionts, are endowed with a trophic action for the colon epithelium and with a local and systemic endocrine action (Figure 3). They are also characterized by an anti-inflammatory activity, exercised directly through signalling on some immune cells including neutrophils. This is due to the induction, through epigenetic mechanisms, of the differentiation of Treg lymphocytes, and activation of a tolerogenic phenotype. The anti-inflammatory action is also indirect through the upregulation of tight junctions, a phenomenon that improves the functionality of the intestinal barrier with subsequent systemic anti-inflammatory action. In CKD patients, a vicious circle is established in which proteolytic-derived metabolites (such as p-CS and IS) symbolize the principal circulating uremic toxins. Moreover, their accumulation worsens dysbiosis and it induces CKD progression[18].

Among the possible causes of dysbiosis in CKD patients, there is the long-term and at high dosage assumption of a polypharmacy (like phosphate and potassium-binders, iron-based compounds, etc.)[19]. Phosphorus-binders are taken by CKD patients for the management of hyperphosphatemia and it has been shown that their long-term intake induces an alteration of the intestinal lumen[15].

In a *vitro* model of the human colon it was demonstrated that iron therapy decreases the levels of *Bifidobacteriaceae* and Lactobacillaceae and enhances the concentrations of *Roseburia* and *Prevotella*[20,21]. From the metagenomic analysis of this study, it is clear that the gut metabolism undergoes changes passing from a saccharolytic to a proteolytic profile. The only iron-based compound that would seem to positively modulate the composition of the intestinal microbiota is iron citrate, whose intake, in a rat model, induces the expansion of beneficial species such as *Akkermansia muciniphila*, which plays a key role in maintenance of the intestinal integrity and in the degradation of mucin[22].

The dysbiosis induced by uraemia is attributable also to another series of causes both local (intestinal) and systemic. In fact, with the reduction of renal function, the colon assumes the role of the main excretory organ and the elimination of urea from the intestine impairs the gut chemical microenvironment. The resulting increase in the pH levels in the colon exerts a selective pressure in favor of urease-positive species responsible for the conversion of urea into ammonia. This causes a degradation of the protective mucus layer and an alteration of intestinal permeability due to the destruction of tight junctions[23]. The consequences are the passage of bacterial material through the mucosa in the bloodstream and the activation of a local and systemic inflammatory mechanism.

Several scientific studies[24,25] attributed the inflammatory state to the translocation of intestinal bacterial fragments in the systemic circulation, as demonstrated by the presence of DNA from intestinal bacterial species in the blood. This, in turn, contributes to the onset of endotoxemia and to the systemic inflammation, as proved by Vaziri et al[26]. Therefore, the gut microbiota seems to be a mediator of systemic inflammation in CKD.

In CKD patients, an increase of Bacteroidetes and Proteobacteria and a decrease of *Lactobacillus* have been observed[27,28]. In particular, Proteobacteria are involved in inflammatory response, inducing the impairment of gut mucosal permeability and the enhancement of intestinal T helper 17 cell to T regulatory cell ratio, and promoting the lipopolysaccharide (LPS) translocation[29-31].

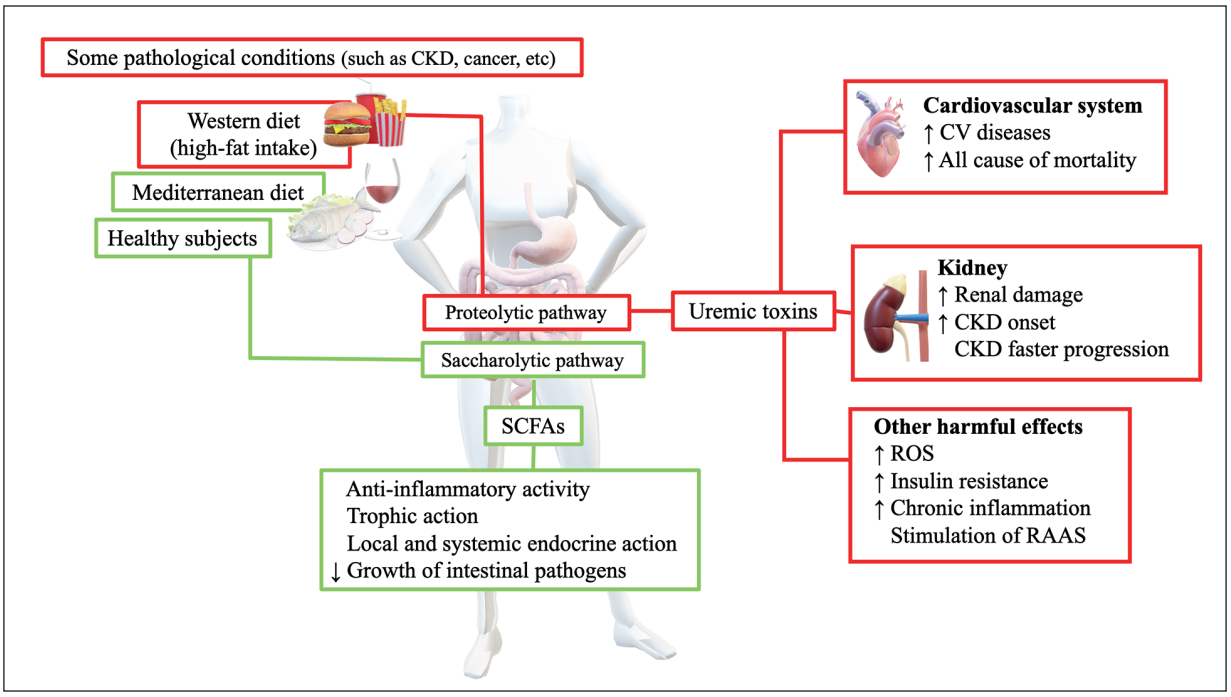

Figure 3. Impact of dietary patterns and pathological conditions on proteolytic and saccharolytic pathways for gut-derived uremic toxins generation.
Abbreviations: CKD, Chronic kidney disease; CV, Cardiovascular; RAAS, Renin-angiotensin-aldosterone system; ROS, Reactive oxygen species; SCFAs, Short-chain fatty acids.

The aims of this literature review are to analyze the impact of CKD on gut microbiota composition both in CKD patients under conservative therapy and in renal replacement therapy (RRT) and to define the possible role of gut dysbiosis on CKD onset and progression.

Materials and Methods

An extensive search of the papers published on the 20th of October 2021 was conducted on PubMed and Scopus online database. Terms included in the search items were: "alteration of gut microbiota" [Title/Abstract] in combination with "chronic kidney disease" [Title/Abstract] and/or "gut microbiota in CKD conservative patients" [Title/Abstract] and/or "gut microbiota in renal replacement therapy" [Title/Abstract].

All the articles were written in English and selected manually by the authors.

Gut Microbiota in CKD Patients Under Conservative Therapy

In CKD patients under conservative therapy, two fundamental factors play a key role in the modulation of the gut microbiota: (1) the accumulation of uremic toxins inversely correlate with the reduction of the glomerular filtration rate (GFR) and (2) the nutritional therapy characterized mainly by a normalized/reduced protein intake[32,33].

Among the uremic toxins deriving from gut metabolism, as above-mentioned, there are IS and p-CS which tend to accumulate progressively with the worsening of renal function, and they are characterized by a high ability to bind albumin. This latter feature makes them difficult to remove also during haemodialysis (HD) session[34]. These compounds are produced in the intestine by proteolytic microbes and they are eliminated through the urine. Their clearance is linked to the excretory capacity of the kidney, so in CKD patients their accumulation is observed[34].

In CKD patients under conservative therapy, the ideal nutritional treatment is represented by the dietetic control of proteins and the reduction of salt intake. The specialist dietician is responsible for customizing this diet according to the clinical and nutritional characteristics of each patient.

In general, this type of dietary-nutritional treatment has several potential benefits confirmed by scientific literature[32,35-38]: it contrasts the intestinal dysbiosis[39], it increases the production of SCFAs

Table I. Changes in gut microbiota observed in CKD patients under conservative therapy.

Type of the study	Reference	Year	Methods	Main findings	Conclusions
Human study	Black et al[43]	2018	Treatment of CKD patients, for six months, with LPD (0.6 g protein/ kg IBW/ day)	Reduction of p-cresyl sulfate serum and changes in the gut microbiota profile after diet treatment	LPD appears to reduce gut-derived uremic toxins in CKD patients.
Human study	Lai et al[64]	2019	Treatment of CKD patients, for six months, with (i) LPD (0.6 g protein/ kg IBW/ day) and (ii) LPD with inulin (19 g/day) compared to untreated control group.	Significant variation of gut microbiota composition in CKD patients under LPD. Reduction of chronic inflammatory state and oxidative stress of CKD patients in LPD with inulin.	LPD associated with inulin positively changes the gut microbiota and reduces inflammatory and oxidative stress parameters in CKD patients.
Human study	Di Iorio, et al[45]	2019	Gut-microbiota metabolites analysis of CKD patients in free diet, Mediterranean diet and VLPD (0.3 g protein/ kg IBW/ day).	Reduction of inflammatory Proteobacteria and increase of potential anti-inflammatory bacteria in VLPD group.	VLPD presents beneficial effects on gut microbiota modulation in CKD patients.
Animal study	Li et al[39]	2019	Comparison of gut microbiota composition in mice undergoing different dietary and exercise interventions.	Greater abundance of the phylum Bacteroidetes and of the genus Akkermansia after high protein-low carbohydrate diet and greater abundance of Oscillospira and Oscillibacter after obesigenic chronic high-fat diet.	The high protein-low carbohydrate diet improves the gut microbiota and appears to improve the overall health of the mice
Human study	Wu et al[149]	2020	16S rRNA Gene Sequencing of fecal samples from (i) CKD patient in LPD (<0.8 g protein/kg IBW, (ii) CKD patient in ND and (iii) healthy subjects.	LPD induces significant changes in the β-diversity of the gut microbiota respect to ND.	The gut microbiota is profoundly influenced by dietary restrictions.
Human study	Hu et al[81]	2020	Characterization of the gut microbiota by analyzing fecal samples from CKD patients and healthy subjects.	Lower levels of butyrate-producing bacteria and higher levels of potentially pathogenic bacteria in CKD patients.	The alteration of gut microbiota is correlated with CKD severity.
Human study	Rocchetti et al[56]	2021	Treatment of CKD patients, for six months, with MD supplemented with ketoanalogs.	Decrease of *Clostridiaceae, Methanobacteriaceae, Prevotellaceae,* and *Lactobacillaceae*, and increase of *Bacteroidaceae* and *Lachnospiraceae*, after diet treatment.	The MD supplemented with ketoanalogues positively modulates the gut microbiota.

Abbreviations: MD, Mediterranean diet; ND, Normal diet, LPD, Low protein-diet; VD, Vegan diet; VLPD, Very low-protein diet; IBW, Ideal body weight.

in the colon[40], it reduces the intestinal permeability[41], it has greater alkalizing power[42], it decreases the production of uremic toxins[43], it improves the intestinal transit and has also beneficial effects on azotaemia levels[41,44] (Table I).

The important impact on the composition of the gut microbiota, induced by the different dietary-nutritional patterns in CKD patients under conservative therapy, was examined by a study conducted by Di Iorio et al[45], called "Medika Study". This study highlighted that a very low -protein diet (VLPD), after six months, decreases inflammatory Proteobacteria and enhances Actinobacteria phyla[45]. Specifically, the authors carried out a prospective crossover-controlled trial on 60 CKD patients (stages III-IV) in which they investigated the effect of free diet, VLPD and Mediterranean diet (MD) on gut microbiota. According to several studies, the MD is useful in the clinical management of the early stages of CKD[46-48] but with its progression,

it is necessary to reduce the protein intake in order to counteract the CKD signs and symptoms and to delay the RRT beginning, using the vegan diet, the low-protein diet (LPD) and the VLPD supplemented with ketoanalogues (KA)[7,11,38,46,49-53]. The "Medika Study" demonstrated that the MD and, especially, the VLPD increase butyrate-forming species like *Roseburia* spa and *Faecalibacterium prausnitzii*[45]. Among Firmicutes, *Faecalibacterium prausnitzii* plays a pivotal role as it induces an increase in the butyrate production, it deactivates the transcription factor nuclear factor kappa B (NF-κB) and it reduces the production of interleukin (IL)-8 namely macrophage chemotactic factor[54]. Moreover, MD and VLPD, through a controlled protein intake, induce significantly lower urea levels with simultaneous reduction of IS and p-CS promoting intestinal integrity[45].

The reduction of IS induced by a VLPD supplemented with KA had already been demonstrated by a previous study conducted on 32 CKD patients under conservative therapy. In fact, after just one week of this dietary-nutritional treatment, a significant reduction of uremic toxins, produced by gut metabolism, was observed[55].

In "Medika2 Study", the authors evaluated the impact of the MD supplemented with KA on the gut microbiota composition and on the concentration of uremic toxins in CKD patients, showing that six months of a MD supplemented with KA are more effective, compared to MD alone, in reducing *Clostridiaceae, Methanobacteriaceae, Prevotellaceae* and *Lactobacillaceae* and in increasing *Lachnospiraceae* and *Bacteroidaceae.* Moreover, this dietary-nutritional treatment induces a greater decrease of the IS and p-CS levels compared to the free diet and the MD alone, but it is not as effective as the VLPD. This study has highlighted how the reduction in azotemia induced by VLPD supplemented with KA is greater than that obtained by the MD supplemented with KA and consequently the beneficial modifications induced on the gut microbiota by VLPD supplemented with KA are also greater. Therefore, these beneficial effects seem to be caused by the reduced protein intake rather than the KA themselves[56].

Regarding to protein intake, it must be considered that proteins, after digestion and absorption in the small intestine, undergo fermentation process, at the level of the colon, by proteolytic bacteria with the formation of both beneficial (such as SFCAs) and toxic (such as indoles, ammonia, phenols etc.) substances[57-59]. It is very important to evaluate the protein source. In fact, red meats are rich in sulphur-containing amino acids (such as methionine and cysteine) while inorganic sulphur is often used as food additive. The intake of compounds containing sulphur induces an increase in sulphur-reducing bacteria, for example *Escherichia coli* and *Clostridium* spp with increased production of hydrogen sulphide[60,61].

A recent study conducted by Lobel et al[62] on animals showed how dietary modifications can cause post-translational changes in the microbiota proteins. Specifically, the authors observed that a dietary regimen characterized by a high content of sulphur amino acids leads to post-translational reactions of S-sulfhydration of the tryptophanase enzyme.

Therefore, the reduction of protein intake plays a key role in view of the beneficial modulation of gut microbiota in CKD patients, in which the renal pathology induces in itself negative changes, both in the composition of the microbiota and in the intestinal permeability. In fact, the promising data obtained with the VLPD are also confirmed by the studies about the effects of LDP.

A study by Jiang et al[63] examined the possible changes observed in the composition of the gut microbiota in patients with stage V of CKD in LPD, highlighting how this dietary-nutritional treatment induces an increase of rumen bacteria and *faecalis* bacteria which can help the host to digest and to absorb energy so providing an intestinal protection. Moreover, these changes in the gut microbiota composition present in stage V CKD patients in LPD can be transferred from humans to rats by fecal microbiota transplantation.

Lai et al[64] evaluated the effects of LPD and inulin assumption on some clinical parameters and on gut microbiota composition in a group of CKD patients under conservative therapy. LPD seems to significantly increase the presence of species such as *Akkermansiaceae* and *Bacteroidaceae* and reduce the presence of *Christensellenaceae, Clostridiaceae*, *Lactobacillaceae* and *Pasteurellaceae,* while the assumption of inulin in association with LPD seems to enhance *Bifidobacteriaceae*. The inulin treatment seems to reduce the chronic inflammatory state and OS in CKD patients, inducing a decrease of the C-reactive protein (CRP), the tumour necrosis factor α (TNF-α) and the nicotinamide adenine dinucleotide phosphate oxidase-2 (NOX2).

The only study that does not agree with the others previously described was conducted by Wu et al[65]. These authors demonstrated how LPD, in CKD patients, is responsible for a significant change in β-diversity, that represents the intra-individual difference in the bacterial community[66].

In particular, the authors observed a significant reduction in the abundance of bacterial species butyrate-producing (family Lachnospiraceae and Bacteroidaceae) with a consequent reduction of SCFAs serum levels. Moreover, serum concentrations of p-CS and IS were not different between subjects following LPD and normal protein diet. While in LPD patients, it was observed a significant enhancement of glyco λ-muricholic acid (secondary bile acid).

In CKD patients, the reduction of the intake of salt to less than 3 g/day becomes fundamental. Numerous studies have shown that gut dysbiosis represents the link between the high salt intake, typical of the Western diet, and the presence of renal damage or AH. The salt may be able to induce dysbiosis by increasing intestinal osmotic pressure, resulting in the suppression of the growth of *Firmicutes* and the increasing growth of Bacteroidetes[21,35,67].

Gut Microbiota in Renal Replacement Therapy Patients

It has been widely demonstrated that also CKD patients undergoing RRT show chronic low-grade inflammation. The latter can induce bacterial translocation, starting from the gastrointestinal tract, representing an additional risk factor for cardiovascular (CV) mortality and morbidity[68]. In fact, the serum concentration of endotoxins represents a biomarker of bacterial translocation and an independent predictor of mortality in HD patients[69,70]. In particular, a study evaluated the presence of bacterial DNA in the blood of three groups of subjects: HD patients, pre-dialysis CKD patients and healthy subjects. It showed bacterial DNA presence in 27% of HD patients and in 20% of pre-dialysis CKD patients. Most of the bacteria isolated in the blood were also present in the patient's fecal samples, while they were not present in the dialysate[31]. The dialytic treatment itself worsens the gut damage induced by the uremic state. Furthermore, the episodes of intra-dialytic and post-dialytic hypotension can cause ischemic intestinal injury, while intradialytic fluid retention can induce intestinal edema[31,71-73].

Numerous studies have shown that end stage renal disease (ESRD) patients exhibit numerous changes in gut microbiota composition characterized overall by the reduction of the α-diversity, the β-diversity and the richness[19,74] (Table II).

The first systematic study, investigating alterations of the gut microbiota in patients undergoing RRT, was conducted on 24 ESRD patients[15]. The authors highlighted some differences in the composition of the gut microbiota between uremic patients and healthy subjects (control group). In particular, the *Brachybacterium*, *Catenibacterium*, *Enterobacteriaceae*, *Halomonadaceaea*, *Moraxellaceaea*, *Nesterenkonia*, *Polyangiaceae*, *Pseudomonadaceae* and *Thiothrix* families were more abundant in ESRD patients compared to the control group. Subsequently, the same authors studied the composition of the gut microbiota in rats, eight weeks after nephrectomy 5/6, in order to understand how uraemia itself induced changes in the gut microbiota and to limit the possible bias induced by intra-individual variations, eating habits and comorbidities. In uremic rats compared to healthy animals, a reduction of the Lactobacillaceae and Prevollaceae families was observed, allowing speculation that the uremic state is the primary cause of gut dysbiosis in ESRD patients[15].

In support of these data, further investigations confirm that ESRD patients show enhanced urease, uricase, and p-CS-producing bacterial families. On the contrary, the butyrate-producing families are fewer[71].

Therefore, advanced kidney disease induces changes in the gut microbiota due to a series of factors: a) the increased concentration of urea in the intra and extracellular fluids is able to cause a rise in its inflow into the gastro-intestinal tract by passive diffusion. The hydrolysis of urea by the urease enzyme, present in some species of the gut microbiota, leads to the formation of ammonia with consequent pH alteration of the intestinal lumen and development of uremic enterocolitis[75,76]; b) under physiological conditions, uric acid, which is the final product of purine metabolism, is excreted in the urine. In ESRD patients, the colon becomes the primary site of uric acid elimination[77,78]; c) as it is observed for uric acid, also for oxalates, in CKD patients, the colon becomes the main site of their elimination[79]; d) the polypharmacotherapy impacts on dysbiosis, as previously described; e) in the more advanced stages, the dietary-nutritional treatment is characterized by a tight restriction of the fibres and a further imbalance of the microbial metabolism in the proteolytic direction. In fact, to prevent hyperkalemia in RRT patients, the diet is based on a low intake of fruit and vegetables. The reduction of the fibres decreases the substrate for saccharolytic fermentation[15,80].

Table II. Changes in gut microbiota observed in RRT patients.

Type of the study	Reference	Year	Methods	Main findings	Conclusions
Human study	Bossola et al[72]	2009	Research of bacterial DNA in bloodstream and analysis of CRP and IL-6 level in HD patients and control group.	Presence of bacterial DNA and elevated levels of CRP and IL-6 in the bloodstream of HD patients compared to the control group.	The presence of bacterial DNA in the bloodstream is associated with high levels of inflammatory parameters.
Human study	Vaziri et al[15]	2013	Isolation of microbial DNA from fecal samples of ESRD patients and healthy subjects.	Alterations of gut microbiota mainly increase the Brachybacterium, Catenibacterium, Enterobacteriaceae, Halomonadaceae, Moraxellaceae, Nesterenkonia, Polyangiaceae, Pseudomonadaceae, and Thiothrix families.	The uremic state represents one of the main factors causing intestinal dysbiosis.
Human study	Wong et al[71]	2014	Microbiota composition analysis of ESRD patients and healthy subjects.	Increased presence of microbial families that produce urease, uricase, indole and p-cresyl sulfate and reduced presence of butyrate-producing families in ESRD patients.	The condition of ESRD alters the microbiota composition.
Human study	Fricke et al[83]	2014	Analysis of gut microbiota changes before and after 1 and 6 months of kidney transplantation.	Kidney transplantation and the use of associated drugs bring important changes to the gut-microbiota	The analysis of the gut microbiota of transplanted patients could represent a valid strategy to evaluate the general health status of the patient.
Human study	Shi et al[31]	2014	Analysis of gut microbiota, search for bacteria in the bloodstream and evaluation of inflammatory cytokine levels, in ESRD patients.	Increase of IL-6 and CRP and presence of intestinal bacteria in the bloodstream, in ESRD patients with gut microbiota alteration.	ESRD involves an increase in chronic inflammation, partially due to the alteration of the gut microbiota
Human study	Crespo-Salgado et al[84]	2016	Analysis and comparison of the gut microbiota of patients (i) in PD, (ii) in HD, (iii) after kidney transplantation and (iv) in healthy controls.	Reduction of *Firmicutes* and *Actinobacteria* in PD patients, increase of *Bacteroidetes* in HD patients, reduction of *Bifidobacteria* and α-diversity in PD and transplant patients, compared to controls.	RRT alters the composition of the gut microbiota.
Human study	Stadlbauer et al[82]	2017	Analysis of faecal microbiome composition in HD and PD patients compared to healthy controls.	Increase in potentially pathogenic species and decrease in beneficial species in RRT patients, compared to controls.	The RRT seems to be an important driver of dysbiosis in ESRD.
Human study	Pan et al[86]	2020	Probiotic treatment of CKD patients for two months compared with a control group that did not receive any probiotic treatment.	Decrease of CRP and IL-6 level after two months of probiotic treatment.	Treatment with probiotics improves the inflammatory state, quality of life and malnutrition in CKD patients.

Abbreviations: ESRD, End-stage renal disease; CKD, Chronic kidney disease; CRP, C-reactive protein; HD, Hemodialysis; IL, Interleukin; PD, Peritoneal dialysis; RRT, Renal replacement therapy.

Furthermore, it has been shown that "uremic dysbiosis" varies in relation to the CKD stage[81] and to the type of RRT[82-84].

Hu et al[85] demonstrated the lower levels of butyrate-producing bacteria and higher levels of potentially pathogenic bacteria in CKD patients compared to healthy subjects, it is more evident in stage V of CKD. Therefore, the alterations of composition of the gut microbiota are related also to the severity of the renal dysfunction and they could represent a new valid marker both in CKD early diagnosis and in its monitoring.

A recent study investigated[82] the impact of different dialysis techniques on gut microbiota composition in adult RRT patients, showing that the enhancement in potentially pathogenic microbial species and the reduction in those with beneficial effects is more evident in HD patients compared to those undergoing peritoneal dialysis (PD). The authors explain this data above all with the different state of systemic inflammation detected in the two subgroups of patients rather than with the different dialysis vintage present in the two subgroups of patients examined (HD *vs.* PD).

A longitudinal study examined the possible changes in blood, in urine, in oral and gut microbiota of a group of adult renal transplanted patients before, at one and at six months after transplantation, demonstrating a shift in gut microbiota composition induced by transplantation and immunosuppressive therapy which tends to persist over time[83]. Moreover, in this study some alterations in gut microbiota before transplantation were related to adverse events occurring after transplantation (like rejection and infectious complications). Specifically, a reduction of diversity in gut microbiota seems to be related to a worse outcome, highlighting the possible predictive value of this parameter[83].

The same results were highlighted in RRT pediatric patients[84]. In fact, ESRD children present an altered gut microbiota composition. In particular, it was observed that in PD pediatric patients there was a reduction of Firmicutes and Actinobacteria compared to healthy children, while in HD patients there was a greater presence of Bacteroidetes than in the control group. Therefore, the gut microbiota composition is different according to the dialysis technique. RRT pediatric patients showed enhanced serum concentrations of gut-derived uremic toxins. This phenomenon is evident in both HD and PD patients, but the serum concentration of uremic toxins tends to normalize after renal transplantation[84].

The altered composition of the gut microbiota in RRT patients seems to be related also to chronic inflammation. Therefore, it has been hypothesized that the assumption of probiotics could represent a valid therapeutic tool in the clinical management of RRT patients. This hypothesis was confirmed by Pan et al[86] that evaluated the effect induced by probiotics assumption for two months on the inflammatory state. The study also analyzed the quality of life in a group of patients undergoing PD. The authors demonstrated that probiotics significantly reduce the level of inflammatory biomarkers (such as high sensitivity-CRP and IL-6) and they improve the quality of life and the malnutrition state.

Gut Microbiota Dysbiosis is Caused by CKD or it Represents a Risk Factor for its Onset and Progression and its Related-Complications?

Gut dysbiosis may be associated with onset and progression of CKD and with the comparison of its related-complications[19], especially the CV ones. At the same time, however, as previously described, CKD causes changes in the composition and in the function of gut microbiota. Therefore, there would be a bidirectional link between CKD and the gut microbiota. The mechanisms that are hypothesized to underlie this relationship are mediated by: i) microbiota-derived toxins (like p-CS, IS and TMAO), ii) immune cells, and iii) neurotoxic metabolites[27,87,88].

In CKD patients, p-CS and IS reach levels even a hundred times higher than in healthy subjects and they derive from the degradation of aromatic amino acids, such as tryptophan, phenylalanine, and tyrosine[89].

The microbiota-derived toxins are related to CV morbidity and mortality as well as they are involved in the progression of the CKD[88,90-92]. Some animal studies[12,93] demonstrated that p-CS and IS induced an enhancement production of reactive oxygen species (ROS), a stimulation of intrarenal renin-angiotensin-aldosterone system (RAAS) and tubulointerstitial fibrosis, accelerating and favoring the progression of CKD. In particular, IS seems to be a predictor of the loss of renal function, as an animal study has demonstrated that it influences the renal expression of genes involved in tubulointerstitial fibrosis (like transforming growth factor β 1 and the tissue in-

hibitor of metalloproteases)[94]. Moreover, IS appears to be a new CV risk factor and its concentration is related to developing peripheral vascular disease and thrombosis of the vascular access[95].

Regarding p-CS, a study demonstrated that in a rat model of nephropathy, it was able to rise the ROS production, through the activation of nicotinamide adenine dinucleotide phosphatase oxidase, and to increase of caspase-3 activity with consequent enhancement of cardiomyocytes apoptosis. Therefore, this study demonstrated that p-CS represents a further CV risk factor in CKD, having a cardiotoxic action[90].

As for the other microbiota-derived toxins also for TMAO, scientific studies have highlighted its relevant role in the CKD progression and in the development of CV complications related to CKD[96,97] (Figure 4).

Specifically, in CKD patients, the TMAO higher plasma concentration is related to an increased risk of mortality for all-causes. This data is confirmed also after adjustment for traditional risk factors. Moreover, in CKD animal models increased dietary intake of choline (its precursor) or of TMAO is associated with a greater degree of renal tubulointerstitial fibrosis and renal dysfunction[96]. The TMAO serum concentrations are inversely related to GFR and it was observed a reduction of its levels after kidney transplantation. In CKD patients, enhanced TMAO levels are associated with coronary atherosclerosis and long-term mortality[97,98].

All scientific evidence suggests that microbiota-derived toxins represent a risk factor for the CKD progression and for the development of CV complications related to CKD, therefore therapeutic strategies aimed at reducing the concentration of these toxins could be a valid tool in the clinical management of CKD patients.

The gut dysbiosis that is observed in CKD patients is able to induce immunological effects as the gut microbiota can form bacterial products with immunostimulating action[19,99]. In fact, the alterations of the intestinal wall, present in CKD patients, allow more easily the bacterial translocation, through the intestinal wall, into the bloodstream. Among these, LPS plays a key role in inducing a state of systemic inflammation, which mainly involves one of its components, called lipid A[100-102]. Lipid A represents the glycolipid portion of LPS and it is the endotoxin that carries out the toxic action in the organism[103]. The lipid A interacting with the toll-like-receptor 4 (TLR4) and with myeloid differentiation (MYD) factor 2, leads to the formation of the TLR4-MYD2-LPS complex which is able to activate the pathway responsible for the expression of the genes of inflammation, resulting in an increased production of pro-inflammatory cytokines (like IL-1β, IL- 6, TNF-α)[100-102]. TLR4 is a specific receptor of bacterial endotoxins, and in particular, it recognizes LPS or its fragments, such as lipooligosaccharides (LOS) and lipid A. TLR4 has a protective role for the body, as it triggers immune and inflammatory responses in relation to the presence of pathogens. However, if the TLR4 activation is too powerful or too prolonged, as in the case of the formation of the TLR4-MYD2-LPS complex, it induces an excessive release of pro-inflammatory cytokines[104,105].

A study conducted by McIntyre has shown that the circulating levels of bacterial endotoxins are increased in all CKD stages and in particular in RRT patients, highlighting how the inflammatory state related to gut dysbiosis represents an independent predictor of mortality in renal patients[101].

A further mechanism involved in the CKD progression is the nuclear factor erythroid-2-related factor 2 (NRF2) pathway which its expression appears to be reduced in CKD and inversely related to the inflammation[106]. The chronic inflammatory status and OS, typical of CKD, cause an activation of NF-kβ signalling with a consequent induction of immune response and production of pro-inflammatory cytokines[107]. The inflammation itself could virtually affect all organs through an organ-interaction[108]. Moreover, NRF2 is able to neutralize NF-kβ signalling. In addition to the above-mentioned actions, NRF2 is able to upregulate several antioxidant and anti-inflammatory genes that promote the reduction of OS and inflammatory status[109].

There is a close communication between the intestinal microbiota and the nervous system guaranteed through the production of many hormones and neurotransmitters[110]. Several studies showed that gut microbiota is able to modulate the hypothalamus-pituitary-adrenal (HPA) axis, controlling the secretion of serotonin and other neurotransmitters[111,112]. Therefore, a bidirectional communication between the HPA axis and gut microbiota is observed. In fact, gut dysbiosis is related to an altered activity of the HPA axis and vice versa.

Bifidobacteriaceae, *Lactobacillaceae* and *Prevotellaceae* species secrete some neurotransmitters such as γ-aminobutyric acid (GABA), acetylcholine (ACh) and can produce gut incre-

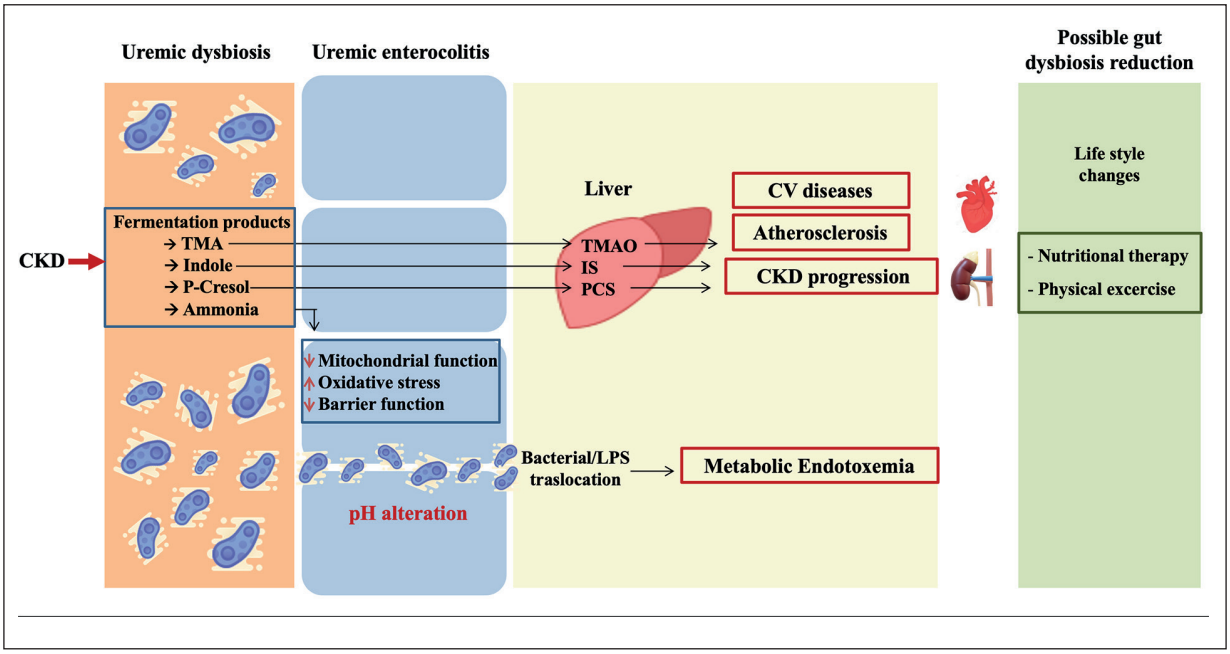

Figure 4. Development mechanisms of uremic enterocolitis and its systemic consequences.
Abbreviations: CKD, Chronic kidney disease; CV, Cardiovascular; IS, Indoxyl sulphate; LPS, Lipopolysaccharide; p-CS, p-cresyl sulfate; TMA, Trimethylamine; TMAO, Trimethylamine-N-oxide.

tins (like glucagon-like peptide-GLP 1 and 2) and intestinal hormone peptide YY[113].

An animal study demonstrated that GABA interacts with the cholinergic pathway to regulate urinary excretion of sodium and potassium[114]. In particular, GABA is able to stimulate natriuresis and to inhibit activation of the renal sympathetic nervous system[113]. While ACh and GLP-1 would seem to induce renal vasodilation and reduce the production of angiotensin II, with a consequent increase in renal plasma flow (RPF)[110]. In an animal model, the infusion of ACh in the renal artery at a dose of 40 micrograms/min is able to enhance RPF and natriuresis[115].

Therefore, uremic dysbiosis by reducing the presence of beneficial bacterial species, such as Bifidobacteriaceae and Lactobacillaceae, activates the RAAS, contributing to the development of AH and consequently to the CKD progression.

Finally, an altered production of incretins and peptide YY is capable of impacting on energy expenditure, reducing it, on insulin sensitivity and on the lipolysis process, becoming a risk factor in the development of dyslipidemia and DM and predisposing to obesity. Therefore, indirectly it has an impact on a more sudden progression of CKD, as those previously listed are all CKD risk factors[113,116].

Another mechanism by which intestinal dysbiosis influences and accelerates the CKD progression is proteinuria. In fact, it is well known that proteinuria represents a risk factor for the CKD onset and progression[27,117,118]. There would seem to be a correlation with gut dysbiosis either for IgA nephropathy (IgAN) or for lupus nephritis, glomerulonephritis characterized also by the presence of proteinuria[15,119,120].

Zhang et al[121] examined the impact of nephrotic syndrome on the composition of the gut microbiota. The authors enrolled 158 subjects divided into three subgroups: patients with CKD without the nephrotic syndrome, patients with idiopathic membranous nephropathy (IMN) and healthy subjects (control group), highlighting that subject with IMN had a different α and β-diversity compared to the other groups and a reduction in SCFAs production[121].

The possible correlation between idiopathic nephrotic syndrome (INS) and gut microbiota would seem to occur via control of Treg. A recent study by Tsuji et al[122], conducted in pediatric patients with INS, evaluated if there was a possible association between Treg cells, monitored at the time of the INS diagnosis, and the subsequent and more frequent occurrence of relapses. A lower increment of Tregs, following a steroid treatment,

was related to a higher frequency of relapses and to the presence of gut dysbiosis. Specifically, these patients exhibited a less abundance of butyrate-producing bacterial species.

These promising results were confirmed also in adult patients with INS[123]. In particular, they showed a decrease of α- and β-diversity, characterized by a reduction of *Acidobacteria*, *Negativicutes*, *Selenomonadales*, *Veillonellaceae*, *Clostridiaceae*, *Dialister*, *Rombousia*, *Ruminiclostridium*, *Lachnospira*, *Alloprevotella*, *Clostridium*, *Megamonas*, and *Phascolarctobacterium* compared to healthy subjects.

Therefore, the assumption of prebiotics and/or probiotics could represent a new adjuvant therapy, in association with immunosuppressive drugs, in the treatment of INS patients. Such treatment could amplify the therapeutic effect of immunosuppressive therapy alone. Furthermore, the evaluation of the gut microbiota composition could symbolize a useful parameter for assessing the patient's therapeutic response and the severity of glomerular disease.

IgAN, the most frequent primary glomerulonephritis in the world, is characterized by an impaired production and defective glycosylation of IgA1[124]. In this disease, it is observed a mesangial IgA deposition that causes mesangial proliferation, glomerular fibrosis, and afterwards a progressive reduction of renal function. A recent study demonstrated that IgAN patients present an increased gut bacterial translocation in the blood compared to healthy subjects but at the same time, the authors showed significant taxonomic differences between faecal and blood samples either in IgAN patients or in the control group[125]. It is hypothesized that in the pathogenesis of IgAN, the intestinal bacterial translocation into the blood plays a key role, in particular this link between the IgAN onset and the gut microbiota would seem to be guaranteed by the LPS. In fact, the presence of LPS would appear to be related to the increased production and hypo-galactosylation of IgA1[126].

Finally, a study compared the gut microbiota composition of IgAN and membranous nephropathy patients with that of healthy subjects. It demonstrated that the immune-dysregulation that characterizes the two forms of glomerulonephritis seems to be mediated by gut dysbiosis, confirming how the monitoring of the composition of the gut microbiota is a useful instrument for the diagnosis and staging of glomerular diseases[127].

Lifestyle Changes and Gut Microbiota Composition

Bidirectional communication between gut microbiota and the host can influence several immunological pathways that can promote or affect host health[128]. Lifestyle routine such as diet, pharmaceutical therapy, physical activity, smoke and nicotine-exposure impact on the variable portion of the microbiome composition and on its functions[129]. Among lifestyle modification, nutritional therapy plays a key role in the disease management and could improve gut microbiota balance in CKD patients as it counteracts the uremic toxins formation, reduces high urea levels and favors the SCFAs production. When LDP is necessary, the absorption of dietary fibers could be impaired[130]. For this reason, an expertise team of dietary professionals should prescribe a personalized and balanced nutritional therapy, possibly empowered with pre or probiotics[131].

In addition to renal diet, also physical exercise might positively impact on gut microbiota composition[132]. In fact, as suggested by Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines[133], if compatible with cardiovascular function, physical exercise in CKD patients, should represent an innovative approach to positively modulate gut microbiota composition[134]. The potential effects of physical exercise include the re-establishment of gut barrier integrity, the increase of vagal tone that is able to reduce the inflammatory status in the intestinal-lumen surface, the enhancement of gut commensal bacteria and the decrease of TRLs signalling pathway activation[135] (Figure 4).

Conclusions

Recent studies have highlighted how the progression of CKD can be influenced by dietary patterns and by the impact that they exert on the gut microbiota composition[136].

Some authors underline the importance of personalized nutrition to prevent chronic degenerative non-transmissible diseases[11,137-143], among these CKD. Specifically, some types of dietary-nutritional treatment including MD, the LPD and the VLPD slow down the progression of CKD[38,144]. The reduced production of uremic toxins, induced by nutritional patterns, plays a key role in positive

modulation of gut microbiota and in clinical management of nephropathic patients[8,145].

The hope is that with a proper nutritional treatment, combined, where necessary, with symbiotic integration[146,147], the CKD clinical management can improve with significant beneficial effects on life quality and expectancy. Moreover, nutritional therapy could reduce the health costs related to the treatment of RRT patients and better the signs and symptoms of CKD[148]. The correction of the gut dysbiosis in CKD patients could represent an additional therapeutic goal for clinicians, due to the important implications for the general health status of nephropathic patients.

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Conflict of Interests

The authors declare that they have no conflict of interests.

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