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PII: S1043-6618(17)31031-9
DOI: https://doi.org/10.1016/j.phrs.2018.02.011
Reference: YPHRS 3823

To appear in: *Pharmacological Research*

Received date: 26-8-2017
Revised date: 7-2-2018
Accepted date: 8-2-2018

Please cite this article as: Simõ es-Silva Liliana, Araujo Ricardo, Pestana Manuel, Soares-Silva Isabel, Sampaio-Maia Benedita.The microbiome in chronic kidney disease patients undergoing hemodialysis and peritoneal dialysis.*Pharmacological Research* https://doi.org/10.1016/j.phrs.2018.02.011

Review manuscript

The microbiome in chronic kidney disease patients undergoing hemodialysis and peritoneal dialysis

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Running title: Microbiome in hemodialysis and peritoneal dialysis

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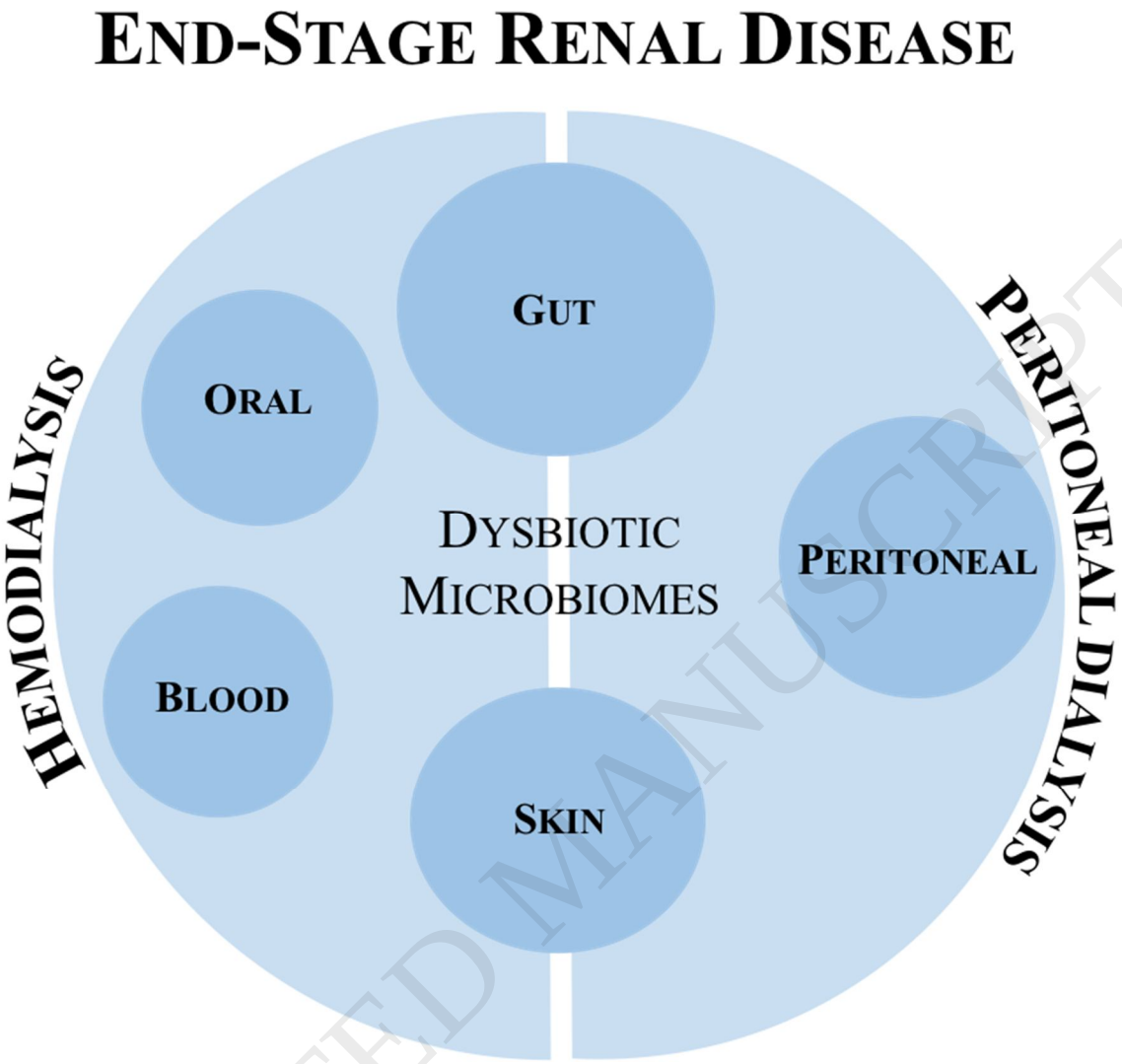
Graphical abstract



Abstract

Chronic kidney disease (CKD) is associated with an imbalanced human microbiome due not only to CKD-associated factors such as uremia, increased inflammation and immunosuppression, but also to pharmacological therapies and dietary restrictions. End-stage renal disease patients require renal replacement therapies commonly in the form of hemodialysis (HD) or peritoneal dialysis (PD). HD implies the existence of a vascular access, such as an arteriovenous fistula/graft or a venous catheter, whereas PD implies a long-term peritoneal catheter and the constant inflow of peritoneal dialysate. Also, dietary adaptations are mandatory in both therapies. This revision explores the impact of HD or PD therapies on human microbiome.

HD and PD appear to be associated with different changes in the gut microbiome, for example a decrease in Proteobacteria relative abundance in HD patients and increase in PD patients. Both therapies may also have an impact on the human microbiome beyond the gut, leading to increased relative abundance of specific bacteria in the blood microbiome of HD patients and increased relative abundance of other bacteria in the peritoneal microbiome of PD patients. HD and PD catheter biofilms may also play an important role in the changes observed in these microbiomes.

A more interdisciplinary approach is needed to further clarify the role of microbial groups other than bacteria in all body habitats to allow the complete understanding of the impact of HD or PD on the microbiome of CKD patients. Moreover, strategies that promote a healthy balance of the human microbiome on these patients should be explored.

Keywords (6): chronic kidney disease; end-stage renal disease; gut; human microbiome; microbial diversity; renal replacement therapy.

1. Introduction

The term human microbiome was firstly defined by Lederberg & McCray [1] as the collection of all symbiotic, commensal and pathogenic microorganisms living in association with the human body. It is currently estimated that human microbiome encompasses 10 times more cells and 100 times more genes than the host, and includes a range of organisms, such as bacteria, archaea, fungi, protozoa and viruses [2]. The human microbiome is considered by some authors a metabolically active endogenous "organ" in itself [2-4] that influences the well-being of the host by contributing to its nutrition, metabolism, physiology and immune function [2, 5-7]. The microbiome is now described as a central part of human health. Therefore, it is essential to study its composition and take advantage of the continuous improvement of technology to increase the existing knowledge on microorganisms-host interaction and its role in disease development.

Each individual harbors a unique microbiome with differences in species, abundance and diversity of the microbial communities in various body sites [8]. Much of this diversity found between individuals has been attributed to differences in host genetics, geographical origin, age, lifestyle, dietary habits, and exposure to antibiotics [8, 9]. In healthy individuals, Bacteroidetes and Firmicutes contribute to 49% of all species of the so far characterized human microbiome, being Actinobacteria, Proteobacteria and Verrucomicrobia in a second line of colonization [10].

The homeostasis of the human microbiome is largely dependent on environmental conditions and, therefore, this complex system is greatly influenced by health and disease states and the subsequent therapeutic strategies used. One of the most well studied microbiome is the gut microbiome. Disturbances of the normal gut microbiome, known as gut dysbiosis, are currently recognized in the pathogenesis of diverse chronic diseases, such as obesity [11, 12], insulin resistance and diabetes [13-15], inflammatory bowel disease [16], liver cirrhosis [17], myocardial ischemia [18], cancer [19] and neuronal disorders [20-22]. Gut dysbiosis has also been reported in chronic kidney disease (CKD), in either humans or animal models [23-31].

The effect of some therapeutics on microbial composition has been intensively studied. For instance antibiotics induce long-term decreases in bacterial diversity and their effects may be hard to reverse [10, 32] and corticosteroids and immunosuppressive agents were also shown to disrupt microbial networks in allograft recipients [33, 34]. Moreover, diet strongly influences the composition of human microbiome in a way we are just now starting to understand [18].

End-stage renal disease (ESRD) patients are a complex group of patients with many comorbidities, such as diabetes and hypertension, subjected to life-long medications including

frequently antibiotherapy and appropriate diet recommendations, as the avoidance of sodium and phosphate-rich foods [35]. The most common renal replacement (RRT) therapies, hemodialysis (HD) and peritoneal dialysis (PD), present particularities that may have a further impact on the human microbiome. Hemodialysis implies the existence of a vascular access, in the form of an arteriovenous fistula/graft or a venous catheter, and strict dietary restrictions, as limitation of potassium intake. Peritoneal dialysis implies a long-term peritoneal catheter and the constant inflow of peritoneal dialysate containing a primary microbial nutrient, glucose, as well as sodium, chloride, calcium and lactate (or bicarbonate) [36]. Therefore, in this review, we will explore the influence of the RRTs, HD and PD, on the human microbiome of ESRD patients.

2. Chronic kidney disease and renal replacement therapies

Due to the increasing number of patients, CKD is currently considered a public health problem worldwide [37]. CKD has a complex etiology involving both an inherited predisposition and exposure to environmental factors [38, 39]. Within health determinants, the most common causes of CKD worldwide are diabetes and hypertension [37]. Cardiovascular (CV) disease is the major cause of death in CKD patients. Although the life expectancy of patients with ESRD markedly improved since the introduction of RRT in the 1960s, it remains lower than that of the general population [40]. When compared to patients on HD or PD, kidney transplant recipients present reduced CV events and mortality as well as a superior quality of life. However, kidney transplantation as a RRT cannot be performed in all ESRD patients due associated comorbidities and lack of suitable donors. Therefore most patients with ESRD are submitted to dialysis during their lifetime, either HD or PD [41].

Several nutritional guidelines are followed by CKD patients depending on the existence and type of RRT and are mainly focused on protein, energy and ion requirements [42, 43]. The dietary intake recommendations for CKD patients, with and without dialysis therapy are summarized in table 1[42, 44].

In patients undergoing HD, the incidence of vascular access-related infections varies among medical facilities and is closely related to the type of vascular access used, being lowest in HD patients with arteriovenous fistulas or arteriovenous grafts and highest in patients with tunneled and non-tunneled Central Venous Catheters (CVCs) [45, 46]. In HD patients, catheter-related bacteremia can have two sources: 1) migration from the skin to the exterior of the catheter and from there to the bloodstream, and 2) direct inoculation from a biofilm growing on the inner surface of the catheter to the bloodstream [47]. The most common agent responsible for CVC-

related bloodstream infections is *Staphylococcus aureus*, followed by coagulase-negative staphylococci [45, 48]. Together they account for 40-80% of cases in most studies [49]. In addition, *S. aureus* bacteremia is associated with significant morbidity and mortality. Non-staphylococcal dialysis CVC-related bacteremia is due predominantly to enterococci and Gram-negative rods [49]. HIV-positive dialysis patients are more likely to develop polymicrobial infections and infections due to Gram-negative and fungal pathogens [50]. Gram-negative organisms account for 30-40% of all episodes of catheter-related bacteremia and 10-20% of episodes were polymicrobial in several case series [51]. Besides septicemia, other infections also frequently occur in HD patients such as pulmonary, gastrointestinal, genitourinary and soft-tissue infections [52].

Peritonitis and exit-site/tunnel infections are the most relevant PD-related infections and these complications remain the Achilles' heel of the technique, being responsible for catheter loss, transfer to HD, prolonged hospitalization and, in more serious cases, death [53]. Thus, prevention of PD-related infections is critical to the success of the program. Peritonitis in PD patients are frequently caused by single microorganisms, being Gram-positive bacteria responsible for 65% of the cases followed by Gram-negative bacteria (15 to 24%) and fungi (1.5% to 5%) [49, 54-57]. Within Gram-positive bacteria, the most common are coagulase-negative staphylococci, *S. aureus* and *Streptococcus* spp.. Gram-negative organisms are more likely to promote more severe infections with poor outcomes [45]. *Pseudomonas* sp. is probably the most important cause of severe Gram-negative peritonitis in patients undergoing PD [45]. Although fungal peritonitis are less frequent, they represent a clinical challenge due to its difficult resolution. In addition, a fraction of 11 to 21% of PD-related peritonitis may be caused by multiple organisms [49, 54, 56, 57].

Few studies described the microorganisms responsible for exit-site infections. A study by Scalamogna et al. [58] reported the following organisms, in diminishing order of frequency from 102 exit-site infection episodes: *S. aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa, Serratia marcescens* and *Enterobacter cloacae*. A more recent study evaluating 34 exit-site infection episodes reported *P. aeruginosa* as the most common infective organism, responsible for 58.8% of the cases. *S. aureus* was isolated in 29.4% of the cases, and *Klebsiella, E. coli* and *Serratia* species in 12% of the cases [59]. Topical application of antimicrobial agents such as mupirocin, gentamicin and polysporin triple ointment have been successfully used to prevent infections [60, 61].

The complete list of factors responsible for PD-related infections remains not fully understood, nevertheless the most critical factor appears to be the contamination of the peritoneal catheter

with skin-related bacteria [62-64]. Some pathogens may colonize the catheter's exit-site and tunnel during the connection and disconnection procedures of the dialysis transfer-set.

The existence of biofilms on peritoneal catheters was demonstrated long ago from skin-associated bacteria [65, 66]. PD-catheter biofilms are formed by common Gram-positive and Gram-negative bacteria and are frequently associated with clinical peritonitis. Microbial biofilms may persist on the catheter surface, even in the absence of infection, suggesting that it may act as a reservoir of infectious agents; for a review see [67].

Microorganisms colonizing the catheter exit-site can also be associated with peritonitis, but curiously only in a very low percentage of patients [68-70]. Catheter replacement can be sometimes ineffective in preventing subsequent episodes of peritonitis, suggesting other sources of infection [45]. Therefore, alternative routes and factors have been recognized as responsible for peritonitis in PD patients, such as transvisceral microbial migration through the impaired intestinal barrier (e.g., bowel leak), hematogenous and vaginal leak [71]. Previous reports described bacterial DNA in PD effluent or peritoneum cells what supports this hypothesis [72-75]. In addition, the intracellular viability of *S. aureus* after sequestration by mesothelial cells was revealed in different studies, supporting this hypothesis [76, 77]. Lately, the description of the blood microbiome in a non-infectious state added more clues to the limitations affecting PD technique [78-82]. Together these studies reinforce the need to explore the human microbiome in PD patients. This is not only necessary to fully understand the impact of microorganisms in the correct implementation of this RRT technique, but also to identify and limit all routes of infection in these patients.

3. The human microbiome and renal disease

3.1 The microbiome in CKD

As already stated, gut dysbiosis is well described in CKD [23-31]. This intestinal microbial imbalance occurs either quantitative and qualitatively, being frequently associated with the overgrowth of Enterobacteriaceae, Lachnospiraceae and some Ruminococcaceae, and with the reduction of some Bacteroidaceae, Prevotellaceae and particular *Bifidobacterium* and *Lactobacillus* species [31]. CKD associated factors may play a role in the promotion of gut microbiota imbalance, such as increasing the intestinal availability of uremic toxins, metabolic acidosis, intestinal wall edema and reducing the colonic transit and digestive capacity. Pharmacological therapies (e.g., antibiotics and iron deliver) and dietary restrictions (e.g. reduced fiber intake) also alter gut microbiome and may play a significant role on gut dysbiosis

[31]. Within the intestinal epithelia, commensal bacteria compete with pathogens for epithelial adhesion sites and nutrients. In a dysbiotic state this natural defense is reduced, consequently increasing CKD patients' vulnerability to pathogen invasion.

Gut dysbiosis itself plays a role in CKD progression and it is starting to be recognized as a non-traditional factor for CV risk in CKD patients [31]. For example, gut microbiome-produced metabolic compounds, such as indoxyl sulfate, p-cresol sulfate, and trimethylamine N-oxide (TMAO), are associated with the promotion of CV events [3, 18, 83-86]. Uremia is also associated to immune dysfunction characterized by immunodepression in CKD patients, contributing to a high prevalence of infections, increased inflammation and CV risk; for a review see [87]. Moreover, ammonia derived from metabolization of urea by microbial urease, was shown to cause a massive disruption of the intestinal epithelial barrier structure and function [88-92], allowing the translocation of gut derived uremic toxins, endotoxin, antigens and intestinal microorganisms or other microbial products into circulation [3, 88, 90-94]. This 'atopobiosis' (phenomenon describing the microbes that appear in places other than their normal location) is for long recognized as an important route of endogenous infections, but more recently has been associated to the dynamics of a variety of inflammatory diseases [78]. The pathophysiological mechanisms underlying the role of gut dysbiosis in CKD were deeply explored in a previous review [31].

Although several researchers studied the role of the gut microbiome on CKD progression and increased CV risk, a more interdisciplinary approach is still needed in order to clarify the role of each microorganism in the development and progression of kidney diseases. Information regarding other microbial habitats in human body, as well as better characterization of other microbial groups such as archaea, fungi and virus, may also be relevant to understand the complete role of microorganisms in CKD pathophysiology.

3.2 The microbiome in HD

Until now, very few studies compared the gut microbiome in HD and other RRT. However, it can be assumed that the existing specificities of this dialysis type naturally influence the intestinal microbiota of ESRD (Figure 1). Besides the obvious influence of the vascular access, a portal of entrance of microorganisms, HD patients have specific nutritional restrictions as potassium in comparison to PD patients, as previously described. Corroborating this hypothesis is the study conducted recently by Crespo-Salgado et al. [95] that compared the gut microbiome of pediatric patients undergoing PD, HD and post-kidney transplant and healthy controls. According to the authors, the relative abundance of Bacteroidetes was significantly increased

in HD patients compared to healthy controls. In addition, Proteobacteria was significantly decreased in HD patients when compared to PD patients. Regarding the α-diversity levels, the gut microbiome of HD patients was similar to controls, having higher diversity than PD patients. Although HD patients have significantly increased levels of the uremic toxins indoxyl and p-cresyl sulfates, no differences were observed in the taxa usually associated to the production of these toxins, namely Bifidobacteriaceae, Clostridiaceae, Enterobacteriaceae and Lactobacillaceae [95].

Other study analyzed the gut microbiome of ESRD patients during HD therapy and compared it with healthy persons, reporting an increase of Proteobacteria (primarily Gammaproteobacteria), Actinobacteria and Firmicutes (especially subphylum Clostridia) by phylogenetic microarrays [28]. However, because there was no comparison to CKD patients not undergoing HD, the findings can be a consequence of HD or CKD itself (or both).

A recent study carried out on HD patients analyzed the effect of a single dose of oral vancomycin (250mg) in the gut microbiome of these patients, together with the plasma levels of uremic toxins indoxyl and p-cresyl sulfates [96]. As expected, the microbial taxonomic richness of fecal samples decreased after vancomycin administration and the effect persisted for 4 weeks. Enterobacteriaceae, Lachnospiraceae and particularly the genus *Blautia* decreased on 7^{th} day and returned to or above baseline at 28^{th} day after vancomycin administration, coinciding with the decline and subsequent rebound of plasma indoxyl sulfate concentrations. Regarding p-cresyl sulfate levels, vancomycin also induced its decrease in the plasma. This result could be explained by suppression of specific tryptophan or tyrosine degrading microbiota and/or by an increase in competing taxa that bloomed in the vancomycin-perturbed gut [96]. However, the recovery of uremic toxin levels 28 days after vancomycin administration suggests resilience of the taxa responsible for its generation in ESRD patients. Enterococcaceae, Bacteroidales and the genus *Bilophila* also diminished significantly following treatment (7 days after), while Veillonellaceae increased. There was a continued significant decrease in Clostridiales and Lachnospiraceae (*Roseburia* sp.) even 28 days after the vancomycin administration.

Besides the gut, other microbiomes have been characterized in the HD population. Bossola and colleagues [97]analyzed blood DNA by 16S rRNA gene PCR amplification, followed by amplicons purification and sanger sequencing and showed that 20.7% of 58 HD patients presented bacterial DNA in their whole blood samples obtained either from the peripheral vein or from the central venous catheter or the arteriovenous fistula, in contrast to the absence of blood microbiome in healthy controls. The following species were found in HD patient's blood:

E. coli, *S. aureus*, *P. aeruginosa*, *S. epidermidis*, *E. faecalis*, *Proteus mirabilis*, and *Staphylococcus haemolyticus*. Moreover, blood cultures of HD patients and healthy controls were all negative for bacterial growth, suggesting very low levels of microbial load (not detected by this methodology) or lack of microbial viability. In addition, these authors associated the circulating bacterial-derived DNA found in HD patients with higher levels of inflammatory markers such as high-sensitivity C-reactive protein (CRP) and IL-6. More recently, Shi et al. [98] explored the blood microbiome of 22 HD patients and compared to 30 ESRD non-dialysis patients and 10 healthy controls using next-generation sequencing. Blood microbiome was found in 27%, 20% and 0% of HD, ESRD non-dialysis and controls, respectively. The bacterial blood colonization within ESRD patients (HD and non-dialysis patients) was similar, being Firmicutes, Bacteroidetes and Proteobacteria the dominating bacteria phylum. At the genus level, the prevalent bacteria common in both groups were *Escherichia-Shigella*, *Prevotella*, *Faecalibacterium*, *Bacteroides*, and *Ruminococcus*. However, in comparison to ESRD non-dialysis patients, HD patients showed greater complexity at the species level that was correlated with higher levels of CRP and endotoxins, and elevated gut permeability. The authors suggested that the bloodstream bacteria mainly originate from the ESRD dysbiotic gut microbiome and the HD, to some extent, aggravates microinflammation in these patients via promotion of gut microbiota translocation due to the gut barrier impairment. Although with a limited number of patients, other studies showed bacterial DNA in the whole blood of dialysis patients without signs of active infection [99-101].

The periodontal microbiome of HD patients was characterized in a 2015 pilot study focused on the high prevalence of periodontitis in these patients [102]. No major differences were observed in the subgingival microbiome between ESRD and control individuals, but *Prevotella gingivalis* and *Tannerella forsythia* appeared among the most abundant periodontitis-related phylotypes in a subgroup of patients with greater periodontitis extent. The authors highlighted the negative correlation between dialysis vintage and microbial diversity within the ESRD group. In addition, it was suggested that widespread and localized forms of periodontitis could be associated with different microbiomes, particularly if comparing some specific OTUs [102]. Moreover, Kshirsagar et al. [103] described a moderate-to-severe periodontal disease strongly associated with CV mortality in HD patients. Other studies have associated the oral microbiome to the onset of systemic diseases, such as atherosclerosis [104], insulin resistance and CV risk [105, 106].

3.3 The microbiome in PD

As PD is not a frequent option of RRT, studies in these patients' population are also scarce. To our knowledge, there are only two studies evaluating the gut microbiome in PD patients. As mentioned above, the gut microbiome of pediatric patients (from 2 to 18 years old) undergoing PD or HD and age-matched healthy controls was compared, showing the α-diversity significantly decreased in PD patients using both phylogenetic and non-phylogenetic diversity measures [95]. The loss of bacterial biodiversity is the most frequent result following intestinal dysbiosis [107] and it has been described for infants with necrotizing enterocolitis [108], inflammatory bowel disease [109], colorectal cancer [110] and CKD [31].

Pediatric PD patients showed relative lower abundance of gut bacteria within the Firmicutes and Actinobacteria, whereas the Proteobacteria were significantly increased [95]. The higher levels of Proteobacteria (iron oxidizing bacteria) could be associated with the oral iron supplementation of PD patients (HD patients receive it directly through the bloodstream). Also, PD patients have increased intestinal absorption of glucose from the PD dialysate that promotes glucose fermentable bacteria, such as the Enterobacteriaceae [95]. Taking into consideration the translocation of gut microbiota to the peritoneal cavity, the increase in intestinal Enterobacteriaceae may be responsible for the development of peritonitis in PD patients. Note that members of the Enterobacteriaceae family account for up to 12 % of all peritonitis episodes in these patients [111].

In another study, Wang et al. [112] compared adult PD patients and control individuals by species-specific real-time PCR. They described a decrease of gut Firmicutes and Actinobacteria, especially *Bifidobacterium catenulatum*, *Bifidobacterium longum*, *Bifidobacterium bifidum*, *Lactobacillus plantarum* and *Lactobacillus paracasei* in adult PD patients [112]. In general, CKD patients showed lower intestinal colonization by *Lactobacillus* and *Bifidobacterium* species [31]. These bacteria are normal colonizers of the human gut and play a critical and beneficial role by inhibiting the growth of pathogens through the production of acetic acid and lactic acid, lowering the pH in the intestinal milieu and competing with pathogens that could colonize the gut mucosa for epithelial adhesion sites and nutrients [113, 114]. Both groups participate actively on the regulation of intestinal microbial homeostasis and may help to reduce the rate of constipation - these bacteria are rarely isolated on adults with chronic constipation [115]. So, reduced populations and diversity of *Lactobacillus* and *Bifidobacterium* in PD patients may be associated to several adverse effects.

Another interesting result from Wang et al. study [112] was the higher prevalence of *P. aeruginosa* in the fecal samples from PD patients. *Pseudomonas* is not a very frequent agent of gram-negative peritonitis, but it is probably one of the most important causes of severe peritonitis in PD patients and is responsible for around 40% of catheter-related infection removals [45, 116-118]. However, due to the lack of CKD controls in the study we cannot clarify if the alterations in microbial species reported by Wang and colleagues [112] are exclusively related to CKD or may be associated to the dialysis therapy.

As described for HD patients, for PD patients the oral cavity may also represent a starting point for dissemination of pathogens through the human body due to the proximity of oral microorganisms to the bloodstream [119]. The oral cavity represents a common but transient source of microorganisms that may be associated to some routine daily activities or invasive dental procedures [119, 120]. Preliminary studies suggest that the oral environment of PD patients in comparison to healthy controls may induce changes in oral microbial colonization [121].

As previously stated, gut dysbiosis may impair the intestinal barrier in PD patients promoting 'atopobiosis', namely the translocation of enteric organisms or bacteria-derived toxins to the peritoneal cavity by migration through epithelial intestinal barrier. This mechanism may represent an important cause of peritonitis in PD patients. The detection of bacterial DNA in PD effluent corroborates the hypothesis of 'apotobiosis' in PD patients [74, 75, 77]. Moreover, our group recently reported the asymptomatic protozoa colonization in peritoneal dialysate of PD patients [122], highlighting the magnitude of intestinal translocations in PD patients. And so, an additional route for PD-related infections that needs further research is the peritoneal microbiome (Figure 1). Recent studies are unravelling microbiome in body sites that were previously considered sterile, as the peritoneum. Other examples are the recently revealed placenta microbiome [7, 123] and breast tissue microbiome [124]. These studies suggest that microorganisms reach these tissues by spreading through hematogenous route. Reinforcing this view are the studies recognizing blood microbiome in a non-infectious state [78-82]. Preliminary results from our group demonstrated that the peritoneum tissue of CKD patients harbours a unique low-abundance microbiome (data not published).

4. Perspectives on patient nutrition and supplements

The microbiome protection and recovery of HD and PD patients should be an emerging focus on future research. Many different strategies are being implemented with variable outcomes. For example, biotics (pre, pro and/or post) are reemerging as potential modulators of the human

microbiome. Prebiotics refer to non-digestible food components that induce the growth or activity of beneficial microorganisms in the gut (e.g. bacteria and fungi); probiotics refer to the ingestion of living microorganisms and post-biotics refer to the ingestion of the bioactive microbial produced molecules.

The intake of vegetable fibers and some yogurt and cheeses have been described as problematic for ESRD patients. Nevertheless, if these foods are supplemented with potassium binding resins and phosphate binders they may result in a more balanced gut microbiome in ESRD patients [125]. A small trial with HD patients in Belgium evaluated circulating p-cresyl sulfate levels following oligofructose-enriched inulin supplementation [126]. The oligofructose-enriched inulin administration started with 10 g once daily during the first week, at day 8 the dose was escalated to 10 g twice daily, and stopped at day 28 after the midweek dialysis session. These patients were followed for another 4-week run-out period. Interestingly in these HD patients, the oligofructose-enriched inulin supplementation induced a decrease in circulating p-cresyl sulfate levels up to the run-out period. Moreover, prebiotic amylose maize resistant starch can be metabolized by colon bacteria and produce short-chain fatty acids [127]. A study in a CKD rat model showed that a high-fiber diet containing 59% high amylose maize resistant starch for 3 weeks retards CKD progression and attenuates oxidative stress and inflammation [128]. Fiber supplementation and phytochemical-rich foods can modify the composition of gut microbiota, while inulin, fructo-oligosaccharides, galacto-oligosaccharides, soya-oligosaccharides, xylo-oligosaccharides and pyrodextrins are prebiotics that have been tested in CKD patients [125, 126, 129].

Probiotics appear to balance intestinal microbiome following massive changes of the initial biodiversity and reduce the production of uremic toxins. For example, *Lactobacillus acidophilus* (strains NCFM and BG2F04) [26] and Lebenin® (from Wakamoto Pharmaceutical, Tokyo, Japan, includes *Bifidobacterium longum subsp. infantis*, *Enterococcus faecalis* and *L. acidophilus*) showed to improve health in HD patients by reducing the levels of uremic toxins [26, 130]. A formulation of *Streptococcus thermophiles* (KB19), *Lactobacillus acidophilus* (KB27) and *Bifidobacterium longum* (KB31) over 3 months was shown to improve blood urea nitrogen and quality-of-life in patients with CKD stages 3 and 4 [131]. Data is still missing to completely consider the role of synbiotics, a combination of pre and probiotics, in CKD patients but a preliminary study showed a reduction of p-cresyl sulfate blood levels and *Bifidobacterium* enrichment and Ruminococcaceae depletion in stools using a symbiotic constituted by a combination of high–molecular weight inulin, fructo-oligosaccharides, and

galacto-oligosaccharides together with nine different strains from *Lactobacillus*, *Bifidobacteria*, and *Streptococcus* genera [132].

Recently, the first reports on fecal microbiota transplantation were available showing an effective and safe alternative in patients post *Clostridium difficile* infection [133] but its role in the gut of CKD patients still needs to be clarified.

Other strategies are being tested in CKD patients, as the AST-120 therapy, an adsorbent consisting of porous carbon particles capable to adsorb indole in the intestine [134]; sevelamer, a large cationic polymer phosphate binder that also binds endotoxins and reduces endotoxin and CD14 levels in HD patients [135]; acarbose, an inhibitor of α-glucosidase enzymes in the intestinal brush border; among others. However, the particular efficiency of these strategies on HD or PD patients still needs to be explored.

More recently, the microbiome is looked as a therapeutic tool in it-self. "Smart" bacteria [136] may guide our immune system, metabolism, and other commensal microorganisms, envisioning that targeting and modeling specific microbiota will be the design of personal medicine programs in a near future.

With the constant development of new technologies, one day it will be possible to fully understand the function, as well as the existing interactions between microorganisms that compose the human microbiota. It can be envisioned that targeting and modeling specific microbiota will play a central role in the design of more personalized medicine programs in a near future, and vast improvements will be done for disease prevention, diagnosis and therapy.

5. Conclusion

The ultimate goal of any treatment is to improve the patient's well-being while preventing the development of disease. As they interfere with the human microbiome, some frequent therapies may need to be carefully used and/or complemented with additional protective strategies. Manipulations of the microbiota can result on changes of the host's susceptibility to diseases and/or affect its severity.

The specific impact of RRT such as HD or PD on the microbiota imbalance of CKD patients is still underexplored. HD and PD have unique characteristics that may contribute to changes in the human microbiome, not only restricted to the gut, but also affecting the blood microbiome (HD) and the peritoneal microbiome (PD) (Figure 1). Factors promoting these changes may be related to specific dietary restrictions and different types of dialysis access (vascular vs. peritoneal), as well as the continuous inflow of peritoneal dialysate, containing microbial nutrients. Notwithstanding, understanding the impact of HD or PD on the human

microbiome is still in its infancy. A more interdisciplinary approach is still needed in order to better clarify the role of microbial groups other than bacteria and expand the existing research to other human microbial habitats. Moreover, strategies to promote a healthier human microbiome in these patients should be delineated.

Conflict of interest: none (for all the authors).

8. Acknowledgments

This work was financed by FEDER - Fundo Europeu de Desenvolvimento Regional funds through the COMPETE 2020 - Operacional Programme for Competitiveness and Internationalisation (POCI), Portugal 2020, and by Portuguese funds through FCT - Fundação para a Ciência e a Tecnologia/ Ministério da Ciência, Tecnologia e Inovação in the framework of the project "Institute for Research and Innovation in Health Sciences" (POCI-01-0145-FEDER-007274); by the strategic programme UID/BIA/04050/2013 (POCI-01-0145-FEDER-007569) funded by national funds through the FCT I.P. and by the ERDF through the COMPETE2020 - Programa Operacional Competitividade e Internacionalização (POCI). LSS is supported by SFRH/BD/84837/2012 and ISS is supported by SFRH/BPD/101016/2014 from FCT/QREN–POPH/FSE and a Research Grant 2014 financed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). The funding sources had no involvement in study design, analysis and interpretation of data, in the writing of the report and in the decision to submit the article for publication.

Conflict of interest: none for all the authors.

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Table

Table 1: Dietary intake recommendations for CKD patients, with and without dialysis therapy [42, 44].

		Non-dialysis patients[a]	HD	PD
Protein[b]		0.60-0.8 g/kg/d (Low-protein diet)	>1.2 g/kg/d	1.2 – 1.3 g/kg/d
Energy		35 kcal/kg/d (<60 years old)[c] 30 – 35 kcal/kg/d (≥60 years old)[c]		
Mineral	**Sodium**	80-100 mmol/d		
	Phosphorus	800-1000 mg and binders if elevated		
	Potassium	< 1 mmol/kg if elevated		Not usually an issue

[a] GFR <30 ml/min/ 1.73 m,[2b] at least 50% of high biological value; [c] PD - including kcal from dialysate.

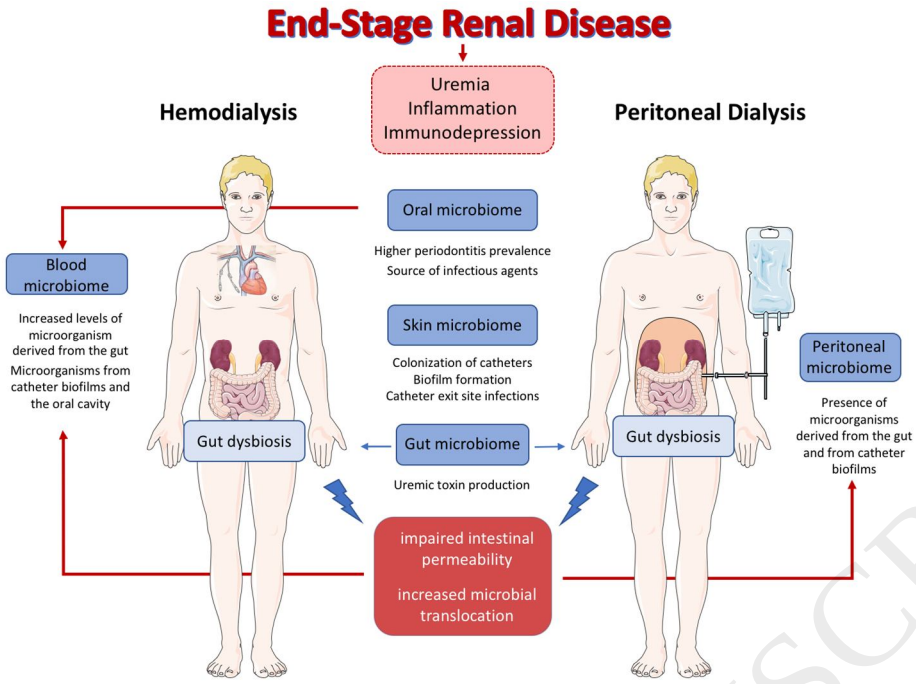

Figure 1