Kidney Medicine

The Gut-Peritoneum Axis in Peritoneal Dialysis and Peritoneal Fibrosis

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Peritoneal fibrosis is an important cause of peritoneal dialysis (PD) discontinuation worldwide and is associated with high morbidity and mortality rate. Although the era of metagenomics has provided new insights into the interactions between the gut microbiota and fibrosis in various organs and tissues, its role in peritoneal fibrosis has rarely been discussed. This review provides a scientific rationale and points out the potential role of gut microbiota in peritoneal fibrosis. In addition, the interaction between the gut, circulatory, and peritoneal microbiota is highlighted, with an emphasis on the relationship to PD outcomes. More research is needed to elucidate the mechanisms underlying the role of gut microbiota in peritoneal fibrosis and potentially unveil new target options for the management of PD technique failure.

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Peritoneal dialysis (PD) is a modality of kidney replacement therapy, supporting approximately 10%-15% of patients with kidney failure worldwide.[1,2] It is based on the principles of diffusion and convection, with the peritoneum playing the role of a semipermeable membrane.[3] The peritoneal membrane's surface is lined with mesothelial cells, forming a permeability barrier to ultrafiltration and diffusion and defending against damage from nonphysiologic PD solutions and microorganisms. The membrane's large surface area (0.5-1.52 m^2) and dense vascular supply contribute to the adequate transperitoneal transport of solute substances and water between the microvasculature and the dialysis solution.[4] However, such use of the peritoneum often leads to immediate and long-term changes in the structure and function of the peritoneal membrane, resulting in fibrosis.[3,5]

Peritoneal fibrosis is the end point of progressive alteration of the peritoneal membrane and is a major cause of high peritoneal transport status and ultrafiltration failure, resulting in decreased PD technique survival.[5-8] Evidence suggests that the mesothelial-mesenchymal transition (MMT) plays a key role in the induction of peritoneal fibrosis.[6,9,10] The pathogenetic mechanisms of MMT are extensively discussed in the literature.[5-7,11] In brief, MMT is a complex biological process in which the mesothelial cells lose their apical-basal polarity and adhesion and transform into mesenchymal cells. These reactive changes and/or mesothelial cell losses are accompanied by increases in the thickness of the submesothelial compact zone and mediated by various molecular mechanisms, such as pseudohypoxia, renin-angiotensin-aldosterone system activation, and induction of numerous inflammatory mediators, such as tumor necrosis factor α; interleukins (ILs) 1β, IL-6, IL-8, and IL-17; interferon gamma; monocyte chemotactic protein (MCP)-1; adhesion molecules (eg, intercellular adhesion molecule 1 and vascular cell adhesion molecule 1); and vascular endothelial growth factor.[5-7,9] This inflammatory cascade activates a multitude of interacting cellular signaling pathways that further induce MMT. The transforming growth factor (TGF) β/Smad and non-Smad signaling, NFκB, Wnt, Notch, and Rho-associated coiled-coil containing protein kinase 1 (RhoA/ROCK1) signaling pathways are some of the known pathways involved in MMT in the peritoneum.[8,11,12]

Despite extensive studies and recent findings, the mechanisms that trigger peritoneal MMT are not fully understood. The effects of biomechanical forces and the biocompatibility of glucose-based PD solutions are among the most obvious causes of peritoneal fibrosis. In addition, constant exposure to PD solutions may cause changes in the stiffness and stretching of the extracellular matrix and alter the mesothelial cells, promoting fibrosis.[6,13] Moreover, analogous to diabetic injury, continuous exposure to conventional hyperosmolar glucose-based solutions leads to glucose-induced pseudohypoxia and induces the formation of advanced glycosylation end products.[1,14] This causes low-grade intraperitoneal inflammation and vasculopathy, leading to fibrosis.[1,6,14]

In addition to glucose-based solutions, PD-associated infections play an important role in peritoneal fibrosis. It was demonstrated that even 1 severe peritonitis episode can cause acute, irreversible damage to all peritoneal membrane cell types and induce fibrosis.[2,6] Peritoneal specimens from patients with PD-associated peritonitis show marked degenerative changes in the mesothelium, mesothelial cell detachment, loss of the underlying basement membrane, and interstitial fibrosis.[2] In the absence of PD-associated peritonitis, uremia per se may represent a profibrotic condition owing to the profibrotic activity of protein-bound solutes.[15] Early studies showed that the peritoneal membrane in patients with chronic kidney disease (CKD) is significantly thicker than that in healthy individuals, even before the onset of PD.[16,17] In a CKD

model, fibrotic changes and advanced glycosylation end accumulation were seen in the peritoneum of rats within 3-6 weeks of uremia, before exposure to glucose-containing solutions.[18]

However, although the use of glucose-based solutions, episodes of PD-associated peritonitis, and kidney failure seem to play an important role in dysbiosis in patients treated with PD, data on the crosstalk between gut microbiota and peritoneal fibrosis are lacking among the much-discussed causes. This review presents an overview of possible pathways and overlaps between the gut microbiota and peritoneal fibrosis to motivate further research into the pathogenesis of PD technique failures.

PREFACE TO UNDERSTANDING THE HUMAN MICROBIOME'S ROLE IN HEALTH AND CKD

The advent of metagenome and next-generation sequencing technologies refutes the medical dogma of organ sterility by introducing the concept of bacterial DNA in blood, various tissues, and organs.[19-21] The human body consists of a collection of genomes from a diverse community of microorganisms, collectively populating us as the microbiome.[22] It was shown that many internal organ tissues, blood, and body fluids have their own unique microbiota[22]; in this review, the gut, blood, and peritoneum are shown as examples of colonized habitats. Most of our current knowledge about the human microbiome comes from using the 16S rRNA gene sequence, which allows us to determine the diversity, abundance, and taxonomic composition of the microbiota present at a site.[23] In classical taxonomy, microorganisms are grouped from domain to phylum, class, order, family, genus, and species. Usually, 16S gene sequencing identifies bacteria at genus-level resolution but rarely at species level.[24] In this review, a particular bacterial species (eg, *Escherichia coli*) can be described at different taxonomic levels as belonging to the phylum Proteobacteria, the class Gammaproteobacteria, the order Enterobacterales, the family Enterobacteriaceae, or the genus *Escherichia*.

The gut hosts most of the human microbiome and is one of the body's predominantly studied microbial communities.[25,26] Comprising trillions of bacteria, viruses, fungi, and other microorganisms, it plays a critical role in health and disease.[25] The most abundant gut phyla are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia, with 90% of the gut microbiota belonging to the Firmicutes and Bacteroidetes.[26] Under healthy conditions, the gut microbiota's symbiotic interaction with the host is regulated and maintained by shared metabolic, immunologic, and neuroendocrine networks.[27] This interaction is mediated by microbially synthesized metabolites, which may provide a physiologic link between the gut and other organs and systems.[25,27] High taxonomic diversity and microbial gene richness are typical features of a healthy gut microbiome community.[25] Depletions of the bacterial diversity and relative abundances of certain bacterial taxa lead to dysbiosis in the gut, which plays an important role in numerous noncommunicable diseases, such as diabetes, cancer, brain disorders, cardiovascular, liver, lung, and kidney diseases.[25,27,28]

Specific changes in the gut microbiota of patients with CKD include the predominance of Proteobacteria, Firmicutes, and Actinobacteria phyla and a lowered abundance of *Bacteroides*, *Lactobacillus*, and *Bifidobacteria* genera.[29-31] A review of 25 studies involving 1,436 patients with CKD and 918 healthy controls revealed that the gut microbiota diversity reduced significantly in patients with CKD compared with those of the healthy volunteers.[32] The relative enrichment of the urease-forming bacteria *p*-cresol–forming bacteria and depletion of short-chain fatty acid (SCFA)-producing microorganisms are invariably linked with changes in the bile acid composition and accumulation of lipopolysaccharides (LPSs), microbiota-produced metabolite trimethylamine-N-oxide (TMAO), and protein-bound uremic toxins, such as indoxyl sulfate (IS) and *p*-cresyl sulfate (pCS).[33-35] The disruption of the intestinal barrier by dysbiosis facilitates the circulation of LPSs, metabolites, and toxins to the organs and initiates the inflammatory cascade, contributing to the progression and adverse outcomes of CKD.[30,36-38]

Once considered sterile, the blood is colonized by a diverse community of microorganisms that differ markedly from a healthy profile in the presence of various diseases.[39] In contrast to the gut microbiome, where Firmicutes and Bacteroidetes dominate, the blood is dominated by the Proteobacteria. This suggests that more bacteria are translocated to the blood from the skin and oral habitats under physiologic conditions than from the gut.[39,40] Although the circulating microbiome is considered inactive in humans because it does not cause sepsis or bacterial inflammation, it is associated with the occurrence and development of various diseases.[39,41] For example, a circulatory microbiome examination of 1,285 individuals showed that higher levels of bacterial DNA in the blood correlated positively with free fatty acid levels, leukocyte counts, and insulin and glucose levels, suggesting that blood dysbiosis is a useful biomarker for the early detection of diabetes.[21] In patients with CKD and not receiving dialysis, the circulatory microbiome differed qualitatively from that of healthy controls, had lower taxonomic diversity and abundance, and had significantly higher proportions of Proteobacteria phylum in patients with low glomerular filtration rates (GFRs).[20]

The peritoneal microbiome is even less studied, partly because of method limitations. Although the peritoneal cavity and surrounding tissues were also previously considered sterile, early in vitro reports describe the intracellular viability of *Staphylococcus aureus* and *Staphylococcus epidermidis* in cultured human peritoneal mesothelial cells, with only a subset of live *S aureus* isolates, characterized by an invasive α-hemolysin–producing phenotype, resulting in cell death.[42,43] The current data on the peritoneal

microbiome in CKD are from a few studies comparing the peritoneal tissue specimens obtained from non–dialysis-dependent patients with those of patients treated with PD, or the peritoneal dialysate effluent (PDE) between the peritonitis and nonperitonitis groups.[44-46] The peritoneal tissue of non–dialysis-dependent patients with CKD is shown to harbor a unique low-abundance microbiome dominated by Proteobacteria and Firmicutes phyla, possibly related to increased microbial translocation from the gut.[44] Other studies, using 16S rRNA gene sequences, provide the first evidence of bacterial DNA in the PDE of stable patients treated with PD without peritonitis.[45,46] However, the authors caution that bacterial DNA fragments in PDE do not indicate the presence of live pathogenic bacteria.[45]

Together, rapidly evolving sequencing methods and analytical techniques have helped identify bacteria-specific DNA in most niches of the human body that was previously considered sterile, advancing knowledge of the human microbiome and the pathogenesis of numerous diseases, such as CKD.

GUT MICROBIOTA IN PATIENTS TREATED WITH PD AND ITS ASSOCIATION WITH DIALYSIS OUTCOMES

Studies involving specific changes in the gut microbiota in patients receiving PD are sparser and more inconsistent than those focused on the general cohort of patients with CKD. Using species-specific real-time polymerase chain reaction, Wang et al[47] reported a higher prevalence of *Pseudomonas aeruginosa* and a decrease in Actinobacteria and Firmicutes phyla, particularly *Bifidobacterium* and *Lactobacillus* genera, in fecal samples from patients with PD.[47] Stadlbauer et al[48] also found an increase in potentially pathogenic species and a decrease in beneficial microorganisms at the phylum and genus levels in patients with PD when compared with those of the healthy controls.[48] However, other researchers found no bacterial differences between patients receiving PD and non–dialysis-dependent patients with CKD[49] and household contacts.[50] These conflicting results could arise from different research methodologies and dialysis-related or patient related factors, such as differing PD modalities, PD solution compositions, glucose absorptions, peritonitis histories, comorbidities, protein intakes and dietary restrictions, or antibiotic and other medication uses that could affect the gut microbiota composition.

Several recent studies demonstrate a unique gut microbiota profile dependent not on the PD modality alone, but on the personalized dialysis prescription and clinical characteristics of the patient with PD. The gut microbiota composition has also been associated with dialysis vintage, residual kidney function (RKF), and peritoneal glucose exposure in patients with PD.[51] In particular, the genera *Ruminococcus* and *Clostridium* predominated in patients with PD and showed a RKF loss and a dialysis vintage longer than a median of 26.8 months (13.9 [95% CI, 6.3-23.6] vs 58.2 [95% CI, 47.5-95.4]). The genus *Fournierella* was decreased in patients with a daily glucose exposure of >150 g/d (114 ± 23 vs 196 ± 34 g/d), whereas the abundance of the genus *Lachnospira* was directly associated with peritoneal Kt/V and was inversely correlated with renal Kt/V.[51] A randomized, open-label, controlled trial found that a 1-month dietary restriction of advanced glycation end products significantly lowered the relative incidence of Prevotella copri in patients with PD.[52] Furthermore, patients treated with PD and with *E coli* peritonitis have significantly more *Bacteroidetes* and fewer *Firmicutes* at the phylum, class, order, family, and genus levels compared with those without peritonitis.[53] Substantially, greater *E coli* abundances were seen in patients treated with PD in the protein-energy malnutrition group compared with those in the nonmalnutrition group, where the *E coli* abundances were positively correlated with serum IL-6 and C-reactive protein levels.[54] However, although the effects of certain bacterial genera, such as *Fusobacterium* and *Prevotella*, were demonstrated on various health conditions (eg, *Fusobacterium* is linked to increased risk of cardiovascular disease and inflammation, whereas *Prevotella* is linked to a healthy gut microbiome and lowered risk of type 2 diabetes), their specific role in patients receiving PD is complex and not fully understood. Further research is needed to fully understand their underlying mechanisms and to determine the specific effects of changes in the abundance of particular microorganisms.

Overall, the relative enrichment of urease-producing, indole-producing, and *p*-cresol–producing bacteria and the depletion of SCFA-producing bacteria in the gut microbiota of patients treated with PD are associated with unfavorable dialysis outcomes. This gut microbiota composition may affect the structure and function of the intestinal epithelial barrier and contribute to the transfer of gut microorganisms, their fragments, and toxins into the bloodstream.[35,37,55]

GUT MICROBIOTA'S CONTRIBUTION TO TOXIC METABOLITE ACCUMULATION AND ORGAN FIBROSIS

Slowing GFR, seen as CKD progresses, leads to the retention of toxic compounds in the blood, which reach their highest levels in patients with anuria.[55,56] However, it is still unclear whether the high concentration of toxic metabolites is mainly caused by intestinal dysbiosis or by impaired excretion due to CKD. Kim et al[29] analyzed the gut microbiota by 16S rRNA gene sequencing and measured serum concentrations of 4 uremic metabolites (pCS, IS, p-cresylglucuronide, and TMAO) in 103 CKD patients at stages 1-5. In multivariable linear regression, the authors found certain microbial genera (*Oscillibacter, Alistipes, Lachnospira,* and *Veillonella*) significantly correlated with serum levels of pCS, IS, and TMAO in patients with advanced CKD.[29] By contrast, Gryp et al[57] observed no

contribution of urease-forming, indole-forming, and p-cresol–forming microbiota to the increase in plasma protein-bound uremic toxins in any patients receiving PD, with CKD, or treated with hemodialysis, suggesting GFR as the main contributor to elevated plasma levels.[57] However, they also claim that, regardless of kidney function, some patients treated with dialysis may produce certain protein-bound uremic toxins in greater quantities than other patients.[57]

Similar to the general CKD population, an increased relative abundance of indole-producing and p-cresol–producing bacteria in the gut was strongly associated with high-serum IS and pCS concentrations in patients receiving PD.[58] However, the study showed that the greatly increased IS and pCS serum concentrations were mainly associated with a significant decrease in their daily urine and dialysate excretion rates.[58] These results are consistent with a previous report that RKF remains responsible for >75% of total pCS and IS clearance in patients treated with PD after 2 years of dialysis.[59] Bao et al[60] recently confirmed the partial dependence of serum concentrations of pCS on RKF in patients treated with PD, associating high-serum pCS concentrations with increased abundances of p-cresol–producing bacteria rather than decreased RKF. They also noted significantly elevated serum IS and TMAO in patients with anuria treated with PD compared with patients with preserved diuresis.[60]

Although no studies have been performed on patients treated with PD, studies on patients treated with hemodialysis show altered gut microbiota as the main source of uremic toxins not directly related to renal excretion. For example, Aronov et al[61] showed the absence or low concentrations of multiple uremic toxins in patients treated with hemodialysis with colectomy compared with healthy individuals and patients treated with hemodialysis without colectomy. Wang et al[37] transplanted the microbiota of patients treated with hemodialysis to kidney-damaged germ-free mice and antibiotic-treated rats, which resulted in increased uremic toxin concentrations in the serum and exacerbated oxidative stress and renal fibrosis. Therefore, despite these limited data, the gut microbiota of patients treated with PD, similar to that of patients with CKD and treated with hemodialysis, seems to be an important source of toxic metabolites and may, therefore, be involved in organ fibrosis.

Accumulations of bacterial structural compounds, their metabolites, and uremic toxins are shown to have far-reaching consequences for the development of cardiac,[62–64] renal,[64–66] vascular,[67] skeletal muscle,[68] and peritoneal[16,17] fibrosis, suggesting that uremia as a whole is a profibrotic condition.[15] They activate various signaling pathways for epithelial-mesenchymal transition induction and encourage mesenchymal cells to generate an extracellular matrix.[11,69–71] For example, intraperitoneal injections of LPSs were found to induce macrophage infiltration, tubular injury, and collagen deposition in the kidneys and left ventricle walls of experimental animals.[64,72] TMAO was shown to promote the activation and proliferation of renal fibroblasts, causing collagen secretion through the PERK/Akt/mTOR pathway, NLRP3, and caspase-1 signaling.[73] IS activates mTORC1 in tubule epithelial cells through the OAT/NADPH oxidase/reactive oxygen species (ROS) pathway, suggesting its involvement in the epithelial-mesenchymal transition of tubule epithelial cells and the macrophage inflammatory response.[65] In the heart, IS activates the cardiac NLRP3 inflammasome through the aryl hydrocarbon receptor (AhR)/NFκB pathway inducing cardiac fibrosis and hypertrophy with impaired left ventricular function.[63] Moreover, pCS was found to induce oxidative stress from NADP oxidase, promoting renal tubule cell damage and cardiac apoptosis.[74,75]

Together, disturbed gut microbiota in patients treated with PD is associated with high-serum concentrations of toxic metabolites actively involved in the fibrogenesis of various organs. Although the profibrotic mechanisms of the microbiota and their metabolites have been partially described, the available data are still limited and require further investigation.

CROSSTALK BETWEEN THE GUT, CIRCULATORY, AND PERITONEAL MICROBIOTA IN PATIENTS RECEIVING PD

Unfortunately, current data on the circulatory and peritoneal microbiota in patients treated with PD are limited to a few studies. Nonetheless, similar to the above-described cohort of patients with CKD but not receiving dialysis, the blood microbiome of patients treated with PD was reported to be dominated at the phylum level by Proteobacteria and Actinobacteria and at the family level by Pseudomonadaceae, Burkholderiaceae, and Legionellaceae, indicating an intestinal origin of the bacteria.[76] Elevated concentrations of bacterial DNA fragments in plasma were found to be associated with high-serum levels of C-reactive protein, significantly correlated with the malnutrition-inflammation score, and strong predictors of cardiovascular events and hospitalization in patients treated with PD.[77] Moreover, alterations in the circulatory microbiome in patients treated with PD were linked to vascular calcification.[76]

The presence of bacterial DNA in peritoneal tissue has been studied only by Simões-Silva et al.[44] In this study, the authors first examined the microbiota of peritoneal tissue samples from 9 patients treated with PD and 11 patients with advanced CKD before the onset of PD. The peritoneal tissue of all patients studied contained a microbiome; however, patients treated with PD had lower abundance of the microbial families Corynebacteriaceae, Bifidobacteriaceae, Lactobacillaceae, Synergistaceae, and Peptococcaceae than non–dialysis-dependent patients, with predominances of the families *Pseudomonadaceae* and *Prevotellaceae*.[44] These results resemble the previously described gut and blood profiles of patients treated with PD, indirectly suggesting the translocation of intestinal bacteria

into the bloodstream and peritoneum. Several other studies reported the presence of bacteria-derived DNA fragments in the PDE of patients without peritonitis.[45,46] In a recent comparison of host-derived and microbial-derived cell-free DNA (cfDNA) concentrations in PDE from peritonitis and nonperitonitis groups, both cfDNAs were present in the PDE of nonperitonitis groups, but the concentrations of host cfDNA were significantly lower than those in the peritonitis group.[46] Furthermore, the concentrations of microbial cfDNA did not differ between the groups at the same observation time point.[46] Because microbial cfDNA reflects bacterial, viral, or fungal populations at the site, these results suggest that the peritoneal cavity has its own microbiome, independent of the presence of peritonitis. Considering the demonstrated bacterial translocation from the gut not only into the bloodstream but also directly into the mesenteric tissue as has been shown in diabetes,[78,79] it is logical to hypothesize the possibility of direct microbial translocation through the surrounding tissue into the peritoneal cavity.

Gut-peritoneal interaction can also be suggested by the unfavorable effect of protein-bound uremic toxins and TMAO on PD outcomes and mortality.[59,80,81] It has been shown that high-serum concentrations of pCS and IS are associated with PD technique failure[81] and have a direct association with PDE levels of proinflammatory markers and peritonitis episodes.[82,83] Moreover, high levels of microbiota-derived proinflammatory (IL-6, tumor necrosis factor α, MCP-1), proangiogenic (vascular endothelial growth factor), and profibrotic (TGF-β) mediators contributing to fibrogenesis were defined in PDE from patients with rapid peritoneal transport statuses, raising the possibility of this interaction.[83-85] Finally, given the established role of the gut microbiota in the generation of ROS,[86,87] other indirect clinical evidence could be the association between increased ROS concentrations in the PDE of stable patients and PD technique failure after 2 years of treatment.[87]

The above-described data suggest a close interaction between the gut, circulatory, and peritoneal microbiota, each playing its own role in promoting peritoneal fibrosis. The dysbiosis characteristics of the gut, blood, and peritoneal microbiota and their clinical associations identified in patients treated with PD are summarized in Fig 1.

POTENTIAL ROLE OF GUT MICROBIOTA IN PERITONEAL FIBROSIS

On the basis of the aforementioned results, the following key interactions and mechanisms can be highlighted as the scientific basis for the gut microbiota's contribution to peritoneal fibrosis:

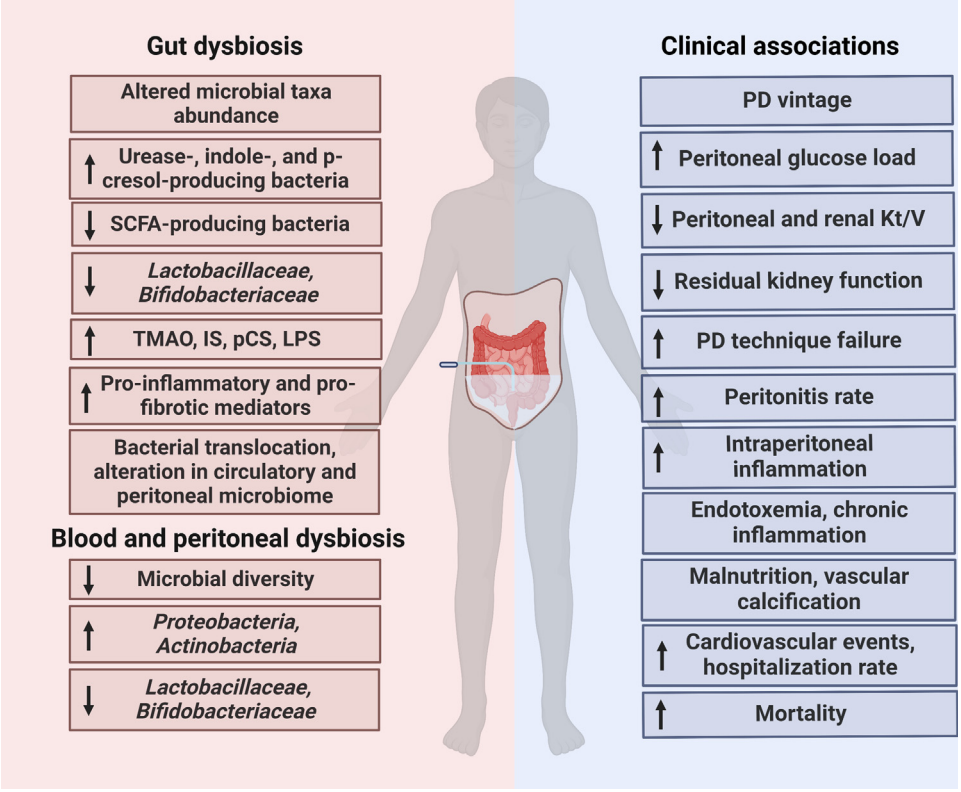

Figure 1. Dysbiosis characteristics of the gut, blood, and peritoneal microbiota and their clinical associations in patients receiving PD (created with BioRender.com). Abbreviations: IS, indoxyl sulfate; LPS, lipopolysaccharide; pCS, *p*-cresyl sulfate; PD, peritoneal dialysis; SCFA, short-chain fatty acid; TMAO, trimethylamine-N-oxide.

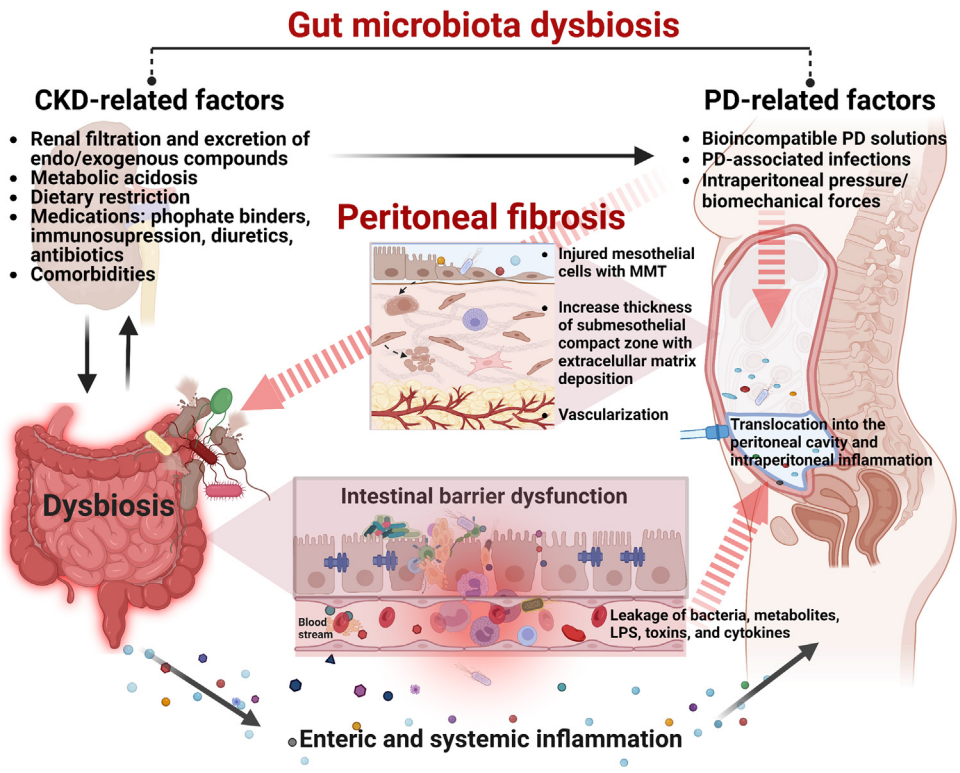

Figure 2. A proposed mechanism of interaction between the gut and peritoneum in the development of peritoneal fibrosis (created with BioRender.com). Gut dysbiosis may play a critical role in peritoneal fibrosis in patients receiving PD. CKD-related alterations in the gut microbiota leads to intestinal barrier dysfunction and translocation of microorganisms, their fragments, and toxins into the bloodstream and peritoneal cavity, resulting in intraperitoneal and systemic chronic low-grade inflammation and promoting peritoneal fibrosis. PD, in turn, per se alters the gut microbiota and peritoneal mesothelial cells and encourages MMT progression and fibrosis. Abbreviations: CKD, chronic kidney disease; LPS, lipopolysaccharides; MMT, mesothelial to mesenchymal transition; PD, peritoneal dialysis.

Gut-Derived Metabolites

Imbalance or excessive growth of certain intestinal bacteria may affect serum concentrations of toxic metabolites and influence the production of SCFA and various molecules, such as proinflammatory cytokines and LPS, leading to fibrosis inside and outside the intestine. Thus, peritoneal fibrosis caused by gut microbiota is also possible. Direct translocations of bacterial structural compounds, their metabolites, and uremic toxins from the gut and surrounding tissues into the peritoneal cavity are also not excluded.

Inflammation and Oxidative Stress

Proinflammatory cytokines and ROS, produced by the gut microbiota, can activate peritoneal fibroblasts and promote collagen production, inducing MMT and leading to fibrosis. ROS and other oxidants cause oxidative damage to peritoneal mesothelial cells, activate fibroblasts, and alter the balance of growth factors and signaling molecules involved in peritoneal membrane repair and regeneration.

Host Immune Response

The gut microbiota may affect the peritoneal membrane by modulating the host immune response, which may interact with and contribute to the development of peritoneal fibrosis through the activation of inflammatory cells (macrophages and T cells), TLRs-dependent, and/or TGF-β signaling pathways.

Identity of the Microbiome

The identities of the circulating and peritoneal microbiota may be the result of gut bacteria translocation, as reflected in various clinical outcomes, ultimately leading to PD technique failure and cardiovascular-related mortality.

Transferring this scientific hypothesis from theory to practice, the gut-peritoneum axis in PD and peritoneal fibrosis can be characterized as follows: CKD-associated gut dysbiosis results in the intestinal barrier dysfunction, accumulation of gut-derived uremic metabolites in the blood, and alteration of the blood and peritoneal tissue microbiota, promoting fibrosis of the peritoneum, even before the onset of PD. Furthermore, profound disruptions of the gut microbiota alter host inflammatory responses, peritoneal mesothelial cells, and multiple intercellular and intracellular signaling pathways that encourage MMT and play a critical role in fibrogenesis. In turn, PD initiation exacerbates intestinal dysbiosis and, therefore, accelerates peritoneal fibrosis through the adverse effects of glucose-based solutions, episodes of PD-associated peritonitis,

and constant changes in peritoneal membrane stiffness. Both CKD-related and PD-related dysbiosis of the gut microbiota form a cycle of molecular mechanisms that are simultaneously involved in intraperitoneal and systemic chronic inflammation, leading to peritoneal fibrosis (Fig 2).

CONCLUSIONS AND FUTURE DIRECTIONS

Gut microbiota dysbiosis is linked to various organ fibroses. In this study, a scientific rationale for the direct and indirect effect of gut microbiota on the development and progression of peritoneal fibrosis is presented.

Notably, no study has investigated the relationship between gut microbiota and peritoneal fibrosis in patients treated with PD, and there are few experimental and clinical data indirectly supporting this scientific hypothesis. Therefore, much work remains to fully understand the role of gut microbiota in peritoneal fibrosis and membrane survival. Moreover, the reported detection of microbial DNA in the bloodstream and peritoneum cannot be directly related to the presence of live bacteria at the site of interest. Studies of the molecular mechanisms of bacterial translocation and the developmental pathways of peritoneal fibrosis are needed to establish the blood and peritoneal microbiota as players in fibrogenesis. Finally, the present data suggest that gut bacterial communities and their clinical associations may exhibit high degrees of individual variability among patients treated with PD; thus, careful selection of patient cohorts is crucial for future research on this topic.

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