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Posted Date: 2 August 2024

doi: 10.20944/preprints202408.0153.v1

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Review

The Role of the Gut Microbiota in Complications among Hemodialysis Patients

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Abstract: The composition of the gut microbiota varies among end-stage renal disease (ESRD) patients on the basis of their mode of renal replacement therapy (RRT), with notably more pronounced dysbiosis in those undergoing hemodialysis (HD). Interventions such as dialysis catheters, unstable hemodynamics, strict dietary restrictions, and pharmacotherapy significantly alter the intestinal microenvironment, thus disrupting the gut microbiota composition in HD patients. The gut microbiota may influence HD-related complications, including cardiovascular disease (CVD), infections, anemia, and malnutrition, through mechanisms such as bacterial translocation, immune regulation, and the production of gut bacterial metabolites, thereby affecting both the quality of life and the prognosis of patients. This review focuses on alterations in the gut microbiota and its metabolites in HD patients. Additionally, understanding the impact of the gut microbiota on the complications of HD could provide insights into the development of novel treatment strategies to prevent or alleviate complications in HD patients.

Keywords: gut microbiota; hemodialysis; complications; uremic toxins

Introduction

The number of patients with chronic kidney disease (CKD) continues to increase, with approximately 10% of the world's adult population suffering from CKD and causing 1.2 million deaths each year [1]. Some CKD patients experience end-stage renal disease (ESRD), and these patients often need renal replacement therapy (RRT) to maintain life. By 2030, the global use of RRT is expected to reach 5.439 billion people [2]. Hemodialysis (HD) remains the most commonly used RRT [3]. HD patients face a series of challenges, such as cardiovascular disease (CVD), infections, anemia, and protein-caloric malnutrition [4]. As these complications are often not effectively solved, the mortality of HD patients remains high [5].

The human microbiome includes bacteria, fungi, and viruses, which form a large and complex ecosystem [6]. The gut microbiota directly or indirectly affects human health, and a complex bidirectional relationship between the gut microbiota and the heart, brain, and kidney has been confirmed [7–9]. The gut microbiota and kidney can interact through metabolic and immune mechanisms to form a bidirectional regulatory axis known as the gut–kidney axis [10]. On the one hand, uremia can change the composition of the gut microbiota and function (known as gut

microbiota dysbiosis) [11]. On the other hand, gut microbiota dysbiosis can disrupt the intestinal barrier, resulting in increased translocation of endotoxins and gut-derived uremic toxins and activation of inflammatory responses, leading to various complications [12,13].

This review discusses the changes in the gut microbiota and its metabolites in HD patients, as well as the effects of the gut microbiota on HD complications, to provide insight into treatment and diagnosis from the perspective of the gut microbiota.

The Gut Microbiota and HD

The gut microbiota plays a crucial role in helping the host resist exogenous bacteria and maintaining the integrity of the intestinal barrier and immune homeostasis [14–16]. In healthy people, *Firmicutes* and *Bacteroidetes* account for approximately 90% of the microbiome, followed by *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, and *Verrucomicrobia* [17].

The gut microbiota of ESRD patients (predialysis and postdialysis) undergoes profound changes [18]. This is related to the rapid decline in renal function in ESRD patients, the accumulation of toxins in the body, the large amount of urea circulating into the gut lumen, and the stimulation of the overproduction of urease-containing bacteria [19,20]. Special dietary restrictions (reduced intake of fruits, vegetables, and dairy products), comorbidities (diabetes, hypertension, etc.), and medications (phosphate binders, iron, and antibiotics) can also lead to gut microbiota dysbiosis [11,21–23]. In HD, some waste products in the blood are removed through the semipermeable membrane, which means that there are vascular access interventions (arteriovenous fistula/graft or venous catheter), inadequate dialysis, and low immunity, which may further aggravate gut microbiota disorders [24,25]. In addition, during the process of dialysis, ultrafiltration or the administration of anticoagulants may induce hemodynamic instability in the gastrointestinal tract, which can cause intestinal barrier disturbances [26,27]. Damage to the intestinal barrier can result in increased translocation of the gut microbiota and toxic metabolites, leading to microinflammation in HD patients [25].

Proteobacteria and *Firmicutes* were increased in HD patients compared with healthy controls [11]. This observation is consistent with recent findings reported by Wu et al. [28]. However, some investigators have shown that the abundance of *Firmicutes* is significantly reduced in HD patients [25,28]. The abundance of *Bacteroidetes* shows different trends in adult and pediatric HD patients [28,29]. The differences in these research results may be due to variations in the subjects' age, genetic history, diet, lifestyle, and dialysis adequacy. Owing to the lack of comparative studies before and after dialysis in patients with ESRD, we cannot accurately determine the specific causes of the microbiome changes mentioned above. These changes may be caused by dialysis treatment itself, by ESRD itself, or even by the combined effects of both. To gain a deeper understanding of these changes, Lou et al. specifically selected ESRD patients who had not yet started dialysis, peritoneal dialysis (PD) patients, and HD treatment patients for a detailed comparative analysis, and their findings indicated that HD treatment had a more significant effect on the gut microbiota of ESRD patients. Their study revealed that HD significantly increased the proportion of beneficial bacteria in the microbial community but also stimulated the growth and reproduction of certain potentially pathogenic bacteria, which may introduce new risks to the stability of ecosystems [30]. At the phylum level, HD patients presented the lowest levels of *Bacteroidetes* [30]. At the genus level, there was a decrease in the abundance of *Prevotella* and *Paraprevotella* and an increase in the abundance of *Akkermansia*, *Coprococcus*, *Acinetobacter*, *Proteus*, and *Pseudomonas* [30]. *Prevotella* and *Paraprevotella*, two anaerobic gram-negative rods associated with infections of the gastrointestinal, respiratory and urinary tracts, are rich in peptidases [31], which degrade proteins and produce large amounts of ammonia [32]. A high concentration of ammonia destroys intestinal epithelial tight junctions, leading to intestinal mucosal injury [33]. *Akkermansia* and *Coprococcus* are associated with the production of short-chain fatty acids (SCFAs). *Akkermansia* is a promising probiotic resident in the mucus layer that reduces inflammation and improves host metabolism [34]. Studies have shown that increasing the abundance of *Akkermansia* may reduce the chronic inflammatory state of CKD patients [35]. *Acinetobacter* is an important opportunistic pathogen in hospitalized patients [36]. *Proteus*, a family of

Enterobacteriaceae, is a common commensal bacterium in the gastrointestinal tract that secretes virulence factors such as the protease ZapA and is therefore potentially pathogenic [37]. The abundance of *Pseudomonas* was positively correlated with plasma tryptophan levels [38]. *Pseudomonas* is found in the blood of ESRD patients and is associated with increased levels of inflammatory markers (high-sensitivity C-reactive protein (CRP) and IL-6) [39]. He et al. reported that HD increased the abundance of the beneficial bacteria *Bifidobacterium* and *Lactobacillus acidophilus* and reduced the abundance of the pathogenic bacteria *Escherichia coli* and *Enterococcus faecalis* compared with those in ESRD patients who did not undergo dialysis[40].

The immune system, including adaptive and innate immunity, plays a crucial role in the gut-kidney axis. HD can induce T-cell-mediated immunodeficiency, thereby impairing the host immune system [41]. HD-related factors (such as the dialysis process, frequency, ultrafiltration, and intradialytic exercise) and non-HD-related factors (uremia and medication) can both alter the intestinal barrier [42]. Additionally, gut microbiota dysbiosis also plays a role in disrupting the intestinal barrier, further increasing the translocation of bacterial components and toxic metabolites, which may activate the innate immune system and systemic inflammation [43]. After intestinal barrier integrity is compromised, there is a substantial influx of lipopolysaccharide (LPS) from the intestines into the circulatory system through the compromised intestinal wall [44]. LPS is a component of the cell wall of *Escherichia coli* and *Enterococcus faecalis*, which can bind to Toll-like receptors (TLRs), activate the immune system, increase the production of inflammatory cytokines, and thus exacerbate inflammatory responses [45,46].

Gut microbiota dysbiosis can also result in alterations in microbial metabolites. On the one hand, the production of beneficial SCFAs in HD patients is reduced, which may be related to the reduction in SCFA-producing bacteria such as *Lactobacillus*, *Prevotellaceae* and *Ruminococcus* [47,48]. The plasma SCFA levels are linked to the host's energy homeostasis and immune system [49,50]. SCFAs, including acetate, propionate and butyrate, serve as major sources of nutrients for colon cells[49] and can be absorbed into the bloodstream through the intestinal lumen for transport to distant organs, such as the heart, kidney, muscle and adipose tissue, where they provide a source of energy for host metabolism[51–53]. In addition, SCFAs also have anti-inflammatory effects [54,55]. Among them, butyrate has potent anti-inflammatory effects and reduces the levels of the inflammatory factors tumor necrosis factor- α (TNF- α) and IL-6 by inhibiting the activation of the nuclear factor kappa B (NF- κ B) cell signaling pathway[50]. On the other hand, the levels of uremic toxins such as p-cresyl sulfate (pCS) and indoxyl sulfate (IS) in the plasma of HD patients are elevated [56], which is linked to the proliferation of bacteria that produce urease, uricase, p-cresol, and indoles (specifically, *Clostridiaceae* and *Enterobacteriaceae*) [47]. p-Cresol is a byproduct of the putrefactive metabolism of tyrosine. Indole is a compound produced by the fermentation of tryptophan. When p-cresol and indole are absorbed by the body, most of them are further metabolized by the liver. p-Cresol is oxidized into pCS, while indole is oxidized into IS. In normal renal function, these two kinds of metabolites are excreted from the urine [57]. The protein binding rate of pCS and IS is as high as 95%, which leads to limited clearance of HD and is significantly associated with poor prognosis [58]. Furthermore, elevated levels of the gut-derived microbial metabolite trimethylamine N-oxide (TMAO) are closely associated with cardiovascular and all-cause mortality [59,60]. TMAO is a small-molecule, water-soluble poison metabolized by quaternary amines (choline and L-carnitine). Quaternary amine metabolism produces trimethylamine (TMA), which is converted to TMAO by flavin-containing monooxygenase 3 (FMO3) [61]. The plasma TMAO concentration in HD patients is more than 20 times greater than that in patients with normal kidney function [62,63]. In conclusion, higher levels of uremic toxins can have harmful effects on HD patients [64,65].

The Gut Microbiota and CVD

CVD has a high mortality rate among HD patients [66]. Research has revealed that the relative risk of CVD mortality in HD patients is 20 times greater than that in the general population [67]. This is mainly because HD patients are usually accompanied by a series of metabolic disorders, including hypertension, hyperglycemia, and hyperlipidemia. In addition, the chronic inflammatory state,

oxidative stress, and uremic toxins, among other nontraditional risk factors, play key roles in the development of CVD in HD patients [68]. After HD treatment, the increase in intestinal permeability leads to the migration of the gut microbiota and metabolites into the bloodstream, resulting in an increase in inflammatory cytokines. Systemic inflammation can promote the development and progression of CVD [69,70] (**Error! Reference source not found.**).

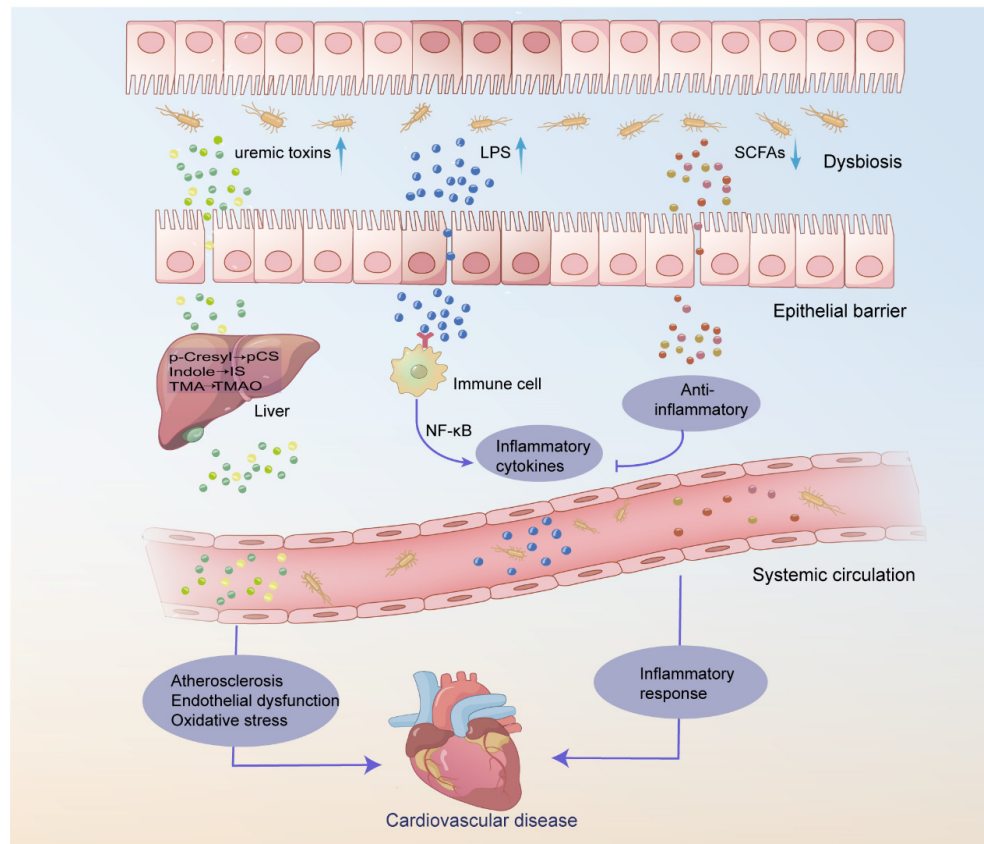


Figure 1. Roles of gut microbiota dysbiosis in the development of cardiovascular disease (CVD) in hemodialysis (HD) patients. Disruption of the gut microbiota in HD patients leads to increased levels of uremic toxins produced in the liver, such as p-cresol sulfate (pCS), indole sulfate (IS), and trimethylamine N-oxide (TMAO), while beneficial SCFA metabolites are reduced. Additionally, gut microbiota dysbiosis causes damage to the integrity of the intestinal barrier, increasing bacterial translocation. This allows lipopolysaccharide (LPS) and uremic toxins to accumulate in the systemic circulation, leading to an increased release of inflammatory factors and triggering a series of pathophysiological changes. These changes include the development of atherosclerosis, endothelial dysfunction, oxidative stress, and chronic inflammation. Ultimately, this increases the risk of CVD.

Several studies have revealed a significant correlation between the gut microbiota composition and CVD incidence. Among them, Sumida et al. studied the composition of circulating microorganisms in HD patients who died from cardiovascular events and reported that the abundance of *Actinobacteria* increased while that of *Proteobacteria* decreased [71]. Similar findings have also been documented in comparative studies involving cohorts of healthy individuals and those diagnosed with CVD [72]. The proportions of the *Actinobacteria* and *Proteobacteria* phyla are significantly correlated with the levels of nuclear factor erythroid 2-related factor 2 (Nrf2) in the blood [71]. Nrf2 is a key regulator of the antioxidant response and plays a crucial role in immune regulation. Dysregulation of Nrf2 activation is associated with the occurrence and progression of CVD [73]. In ESRD patients, analysis of CVD mortality data revealed a decrease in *Bacteroides* and *Phascolarctobacterium*, suggesting that these two bacterial communities may have a protective effect

on CVD [30]. It has been demonstrated that *Bacteroides* can prevent atherosclerosis through a reduction in LPS production [74]. *Phascolarctobacterium*, a genus of SCFA-producing bacteria, inhibits the growth of *Clostridium difficile* and holds promise as a therapeutic option for patients afflicted with this pathogen [75]. However, in psoriatic patients, *Phascolarctobacterium* is considered a risk factor for CVD [76]. Further investigations are warranted to explore the impact of diverse microbial communities on the prognosis of HD patients.

The uremic toxins (TMAO, pCS, and IS) are associated with increased CVD risk. Several studies have demonstrated that elevated TMAO levels represent an independent and significant risk factor for cardiovascular events in HD patients [60,77,78]. TMAO is associated with the progression of atherosclerosis, and its mechanisms include affecting cholesterol metabolism, promoting thrombosis, activating inflammation, and damaging endothelial cells [79,80]. TMAO increases the expression of receptor cluster of differentiation (CD) 36 and scavenger receptor A on macrophages, thereby inhibiting reverse cholesterol transport (RCT) and promoting the formation of foam cells [81]. TMAO induces mitogen-activated protein kinase and NF- κ B signaling, thereby promoting vascular inflammation [82,83]. TMAO induces inflammation and endothelial dysfunction by activating the ROS-TXNIP-NLRP3 inflammasome pathway [84]. Moreover, elevated TMAO levels can upregulate the expression of thrombin, ADP, and collagen and trigger intracellular calcium release and platelet hyperreactivity, thereby contributing to the modulation of platelet function and thrombosis in vivo [85]. Recent studies also suggest that TMAO is closely associated with increased arterial stiffness and vascular calcification in HD patients [86,87]. An increase in arterial stiffness may lead to increased blood pressure and increased heart burden. Vascular calcification may cause the vessel wall to become fragile, increasing the risk of CVD. Cardiovascular calcification (CVC) is a well-known cardiovascular risk factor in HD patients[88].

Unlike TMAO, the protein-bound molecules pCS and IS are challenging to remove through conventional dialysis. The pathophysiological mechanisms associated with cardiovascular injury in pCS and IS include the induction of endothelial dysfunction, inflammatory responses, and oxidative stress[89]. Clinical studies have revealed a close association between these metabolites and the overall mortality and cardiovascular event mortality of HD patients [90–94]. These studies provide strong evidence that abnormal changes in metabolites may have a significant impact on the prognosis of HD patients. However, not all researchers have observed this significant correlation[95–97]. Therefore, further research is needed to determine the relationship between these metabolites and the prognosis of HD patients and whether changes in these metabolites can serve as biomarkers or targets for HD treatment.

The Gut Microbiota and Infection

Infection is the second leading cause of death among ESRD patients, and sepsis accounts for more than 75% of all infection-related deaths, posing a serious threat to their lives and health [98]. Owing to impaired immune system function, these patients are more susceptible to infection by various pathogens, leading to infection and sepsis. In a 7-year follow-up of 4005 HD patients, 11.7% of HD patients had at least one episode of sepsis [99]. The mortality rate for sepsis in HD patients is significantly greater, ranging from 100–300 times greater than that of the general population [4]. The presence of an arteriovenous fistula/graft or a dialysis catheter, older age, malnutrition, diabetes, and the frequency of dialysis are predisposing factors for infections [100–103]. Immune dysfunction and dysbiosis of the gut microbiota also play critical roles in the occurrence and development of infections [104,105]. Elevated concentrations of free pCS in HD patients have been shown to increase the risk of infection-related hospitalizations (IH) [106,107].

Infections related to vascular access represent a common source of infectious complications [108]. Although only approximately 19% of HD patients utilize central venous catheters (CVCs), catheter-related bloodstream infections (CRBSIs) account for 70% of vascular access infections [109]. *Staphylococcus aureus*, *enterococci* and coagulase-negative *staphylococci* are the most common causative microorganisms implicated in CRBSIs [110]. Moreover, the increasing resistance of HD patients to antibiotics has resulted in a heightened prevalence of infections caused by multidrug-resistant

microorganisms (MDROs) [111]. Vancomycin-resistant *enterococci* (VREs) and methicillin-resistant *Staphylococcus aureus* (MRSA) are common pathogens associated with MDROs [112,113]. An increase in the genes encoding antibiotic resistance in HD patients may result in bacterial insusceptibility to conventional antibiotic therapies, consequently leading to a substantial reduction in the efficacy of antibiotics [114]. Microbial virulence factors are a class of molecules produced by pathogenic microorganisms that have a toxic effect on the host. They play crucial roles in promoting the proliferation, spread, and worsening of infection within the host organism [115]. In HD patients, 12 virulence factors exhibited significant changes. The levels and activities of these factors differ between patients and healthy individuals, which may have a negative impact on the health of patients. Among them, pyridoxamine 5-phosphate oxidase and streptothricin-acetyl-transferase are relatively highly abundant in HD patients and may affect the course of the disease and the treatment effect to some extent [114]. Further research into these two enzymes may provide new ideas and methods for the treatment of HD patients.

The Gut Microbiota and Anemia

Anemia is a common complication in HD patients. According to data from the China Dialysis Outcomes and Practice Patterns Study (DOPPS), 21% of patients receiving HD treatment in China had hemoglobin levels less than 9 g/dl [116]. These data highlight the widespread prevalence of anemia among dialysis patients in China, which significantly impacts their quality of life and prognosis. Notably, the corresponding figures in Japan and North America are 10% and 3%, respectively [116]. This may be related to differences in the level of development of dialysis treatment, medical resource allocation, and patient education in various countries.

There are many causes of anemia in HD patients, including altered iron homeostasis, erythropoietin (EPO) deficiency, hyperparathyroidism, and chronic inflammation [117]. Several in vitro experiments have shown that IS can inhibit the generation of EPO through a hypoxia-inducible factor (HIF)-dependent oxygen-sensing mechanism [118–120]. HIF is a transcription factor that is activated in low-oxygen environments and can bind to the promoter of the EPO gene, thereby regulating EPO generation [121]. Additionally, IS can induce suicidal erythrocyte death or eryptosis, both of which are associated with a shortened lifespan of erythrocytes [122]. However, no significant correlation between IS or pCS and anemia has been reported in clinical studies of HD patients [117,123]. The significant difference between the in vivo and in vitro experiments may be due to the significant differences in the experimental environments. The concentration of uremic toxins in in vitro experiments may be relatively high. Therefore, it is essential to fully consider this possibility when designing experiments to ensure the accuracy and reliability of the experimental results [117].

Iron supplementation and EPO-stimulating agents (ESAs) are commonly used in HD patients. However, EPO hyporesponsiveness (EH) occurs in 10% of patients treated with ESAs [124,125], which may be related to iron metabolism disorders and EPO receptor dysfunction [126]. In a study on the responsiveness to EPO treatment, researchers reported that 9 bacteria in HD patients had predictive value for EH, with *Neisseria* (area under the curve (AUC) = 0.9535 (95% CI, 90.2–100, $P < 0.0001$) showing the highest predictive value [127]. The author also reported that the majority of enzymes related to butyrate synthesis were significantly enriched in HD patients with a good EH response, which may contribute to improving anemia [127]. A recent study has shown that supplementing dietary fiber (DF) can significantly improve anemia in HD patients. There are likely multiple mechanisms by which supplementing DF can improve renal anemia, one of which may be the increased production of butyrate and butyrate-producing bacteria (such as *Bifidobacterium*, *Lactobacillus*, and *Lactobacillaceae*) [126]. However, this discovery provides only a preliminary indication of this possibility. To ensure that this discovery can truly benefit HD patients, it is necessary to conduct multicenter, large-sample, and long-term clinical studies to comprehensively evaluate its clinical value.

The Gut Microbiota and Malnutrition

HD patients are at high risk of malnutrition due to impaired kidney function, which makes them prone to sarcopenia and protein-energy wasting (PEW). Under both of these conditions, the loss of muscle mass plays a crucial role in pathogenesis [128]. However, the concept of sarcopenia is no longer limited to a decrease in muscle mass but also includes the loss of muscle strength [129]. Protein loss during dialysis, reduced physical activity, chronic inflammation, etc., can all contribute to the development of sarcopenia [130]. The gut–muscle axis suggests that the gut microbiota plays a crucial role in maintaining skeletal muscle homeostasis [131]. A recent study demonstrated a decrease in gut microbiota diversity and alterations in microbial structure in HD patients with sarcopenia [132]. However, there have been few studies on HD patients, and most of them were observational studies with small sample sizes, which cannot prove a causal relationship between the gut microbiota and sarcopenia. Tang et al. reported significant reductions in muscle function and mass in mice colonized with gut microbiota from HD patients with sarcopenia, accompanied by a decrease in the abundance of *Akkermansia*, a producer of SCFAs [133]. Notably, SCFAs have been proven by multiple studies to have a positive effect on skeletal muscle mass [134,135]. Additionally, a study revealed that IS may cause metabolic disorders, further leading to impaired mitochondrial function [136]. Mitochondria are energy factories in cells and are crucial for the growth and maintenance of muscles. The impairment of mitochondrial function may ultimately result in a reduction in muscle mass [136]. Additionally, IS can induce myotube atrophy by activating the ROS-ERK and JNK-MAFbx signaling pathways, thereby affecting muscle generation and maintenance [137]. However, many aspects of the pathogenesis of sarcopenia remain unknown, and future research will continue to explore these areas to provide more effective treatment options for HD patients.

Similarly, PEW is a disease related to malnutrition that primarily occurs in people who are unable to obtain sufficient food or nutrients, leading to severe deficiencies in body protein and energy [138]. The prevalence of PEW in HD patients is 30% to 75% [139]. Decreased nutrient intake, systemic inflammation, and inadequate dialysis are associated with the development of PEW [140,141]. The abundance of the butyric acid-producing bacteria *Faecalibacterium prausnitzii* and *Roseburia* was reportedly reduced in HD patients with PEW [140,142]. The gut microbiota may also be useful for predicting PEW in HD patients [143]. Another researcher reported a positive correlation between the levels of *Actinobacteria* and *Bifidobacteriaceae* and PEW indicators such as serum albumin levels, lean tissue mass (LTM), and the lean tissue index (LTI) [143]. The level of TMAO was significantly greater in HD patients with PEW [144]. These findings suggest that TMAO may play an important role in this disease process. Further research revealed that circulating TMAO levels are significantly associated with the incidence of PEW in HD patients [144], which means that an increase in TMAO levels may increase the risk of PEW. To better understand this phenomenon, it is necessary to conduct in-depth research on the causal relationship between TMAO and PEW.

Strategies to Attenuate Gut Microbiota Dysbiosis in HD

Research on probiotics, prebiotics, and synbiotics has received widespread attention from scholars at home and abroad in recent years. These three substances are believed to have significant effects on the balance of the gut microbiota and human health. In evaluating the effects of these supplements on diseases, most research currently uses indicators such as endotoxins, uremic toxins, inflammation, and metabolic markers. Probiotics, as active microorganisms, can not only reduce inflammatory responses [145] but also positively impact glucose homeostasis, oxidative stress [146,147], kidney function [147], nutritional status [148], and quality-of-life indicators [149,150]. Moreover, probiotics have been shown to significantly reduce the production of uremic toxin precursors (such as phenol and p-cresol) [151] but have no significant positive effect on IS or pCS in HD patients [152,153].

Prebiotics are nondigestible food ingredients [154]. In fourteen HD patients who were supplemented with curcumin for three months, curcumin significantly lowered plasma pCS levels [155]. Resistant starch (RS) is a prebiotic compound that promotes the proliferation of SCFA-producing groups (such as *Roseburia* and *Ruminococcus gnavus*) [156], increases the production of

SCFAs, reduces the levels of pCS and IS [157], and alleviates inflammation and oxidative stress markers [158,159]. However, the efficacy of RS has been confirmed in many but not all studies. Esgalhado et al. reported that RS only reduced plasma IS levels, with no significant effect on pCS levels [158]. High-amylose resistant starch (HAM-RS2) can reduce serum creatinine and p-cresol levels but has no significant effect on IS levels [160]. Moreover, RS does not seem to play a role in altering plasma TMAO levels, as it does not contribute to any significant changes in the concentration of this metabolite in the bloodstream[161].

Synbiotics are mixtures of prebiotics and probiotics. A trial investigating synbiotic ingestion for four weeks in HD patients revealed that such therapy altered the fecal microbiota (*Bifidobacterium* enrichment) and significantly increased the levels of acetic acid and butyric acid [162]. In 58 HD subjects, a 7-week synbiotic treatment decreased the serum IS, pCS and urea concentrations [163]. Probiotic intervention has demonstrated potential benefits in reducing the levels of serum high-sensitivity C-reactive protein (hs-CRP), IL6, and endotoxins [164]. Furthermore, the combined administration of synbiotics and probiotics for 12 weeks has been shown to ameliorate anemia in HD patients [165].

Conclusions

In general, HD restored the abundance of beneficial microbes but induced some potentially pathogenic bacteria. The gut microbiota can play a crucial role in post-HD complications, such as cardiovascular events, infections, anemia, and nutritional complications, through metabolites and immune regulation. Studies aimed at restoring the appropriate gut microbiota composition and alleviating uremic toxins have been conducted. It seems that dietary interventions consisting of probiotics, prebiotics, and synbiotics are promising strategies. These dietary supplements have been shown to restore the gut microbiota composition, reduce IS and pCS levels, and reduce inflammatory marker levels. However, there is a lack of clear guidelines to inform HD patients when to take these dietary supplements, as well as the types and doses that must be taken, which can confuse clinicians when prescribing them for patients. All of these measures have limited effects. They do not fundamentally solve the problem of gut microbiota imbalance.

In addition, there are many limitations in the study of the gut microbiota and metabolites in HD patients. First, research on the gut microbiota and metabolites in HD patients is mostly based on single-center, small-sample studies at present. These studies largely ignore the influence of diet, dialysis duration, and drug intake on the gut microbiota and metabolites, leading to highly heterogeneous conclusions and difficulty in forming a unified scientific understanding. Second, research on the relationship between the gut microbiota and phenotype in HD patients is relatively limited. Most of the existing studies are observational studies and have not fully demonstrated the causal relationship between the gut microbiota and phenotypes. In addition, the molecular mechanisms by which metabolites regulate HD complications remain unclear, which limits our understanding and means of preventing and treating HD complications. Finally, reliable evidence from the gut microbiota perspective to guide clinical management strategies is challenging to obtain because of the complex relationships between hosts and microorganisms, individual differences, and susceptibility to multiple factors. This requires a deeper understanding of the diversity and dynamics of the gut microbiota, as well as further research on the relationship between the gut microbiota and HD patient phenotypes to reveal the underlying biological mechanisms. In the future, we look forward to gaining a deeper understanding of the gut microbiota and metabolites of HD patients through large-scale clinical trials, considering the effects of diet, dialysis duration, and drug intake, to provide a more comprehensive and scientific basis for clinical management strategies.

Author Contributions: Conceptualization: J.D., X.Z., and H.Z., methodology, validation, and formal analysis: Q.R., H.W., X.W., C.S., and Y.D., writing—original draft preparation: J.D., and X.Z.; writing—review and editing: X.D., Q.H., and D.Z.; supervision: H.Z.; funding acquisition: D.Z., and H.Z. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by The National Natural Science Foundation of China (No. 62271506, No. 61971441), the National Key R&D Program of China (Nos. 2021YFC1005300), sJinzhongzi project of Beijing Chaoyang Hospital (No. CYJZ202203).

Conflicts of Interest: The authors declare no conflicts of interest.

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