**Response letter**

Dear editor,

We gratefully thank the editors and all reviewers for their time spend making their constructive remarks and useful suggestions, which has significantly raised the quality of the manuscript and has enabled us to improve the manuscript. Each suggested revision and comment, brought forward by the reviewers was accurately incorporated and considered. Below the comments of the reviewers are response point by point and the revisions are indicated.

Reviewer(s)' Comments to Author:

Reviewer: 1

Comment 1

-As the topic is related to aging it would be nice to add separate paragraph introducing general studies of microbiota in aging which could be right after no. 1 The symbiotic microbiome’s new identity in human diseases

Response：Thanks for the invaluable comments to increase the integrity of the article. We have added a separate paragraph in Part I that discusses microbiome and aging-related studies. (See manuscript, page 3, line 84)

Comment 2

-In second paragraph the authors introduced the analysis of microbiota a presented in figure 2, yet this part lacks introducing the readers to the information regarding the source of data and details of analysis as well as the authors could expand on interpretation of these data.

Response：We gratefully appreciate for your professional advice. We've added an explanation of the figure in the manuscript and a more detailed description in the figure legend. Detailed results regarding the analysis of the literature in the figure are also summarized in the supplementary data to increase the reader's understanding. Thank you again for the invaluable comments. (See manuscript, page 7, line 145)

Comment 3

- Paragraph 2 could be started with general description of Chronic kidney disease, which is now 2.1 and then continue as it is or incorporate the earlier paragraph with data presented in Figure 1 and 2 and continue

Response： We have restructured the manuscript to integrate the first paragraph of the second part as well as the figures into the first part. The second part begins with a description of chronic kidney disease. We appreciate your suggestions to make the manuscript more structured and more readable. (See manuscript, page 4, line 95; page 7, line 160)

Comment 4

- Major comment: The authors went through the studies presenting microbiota changes in different types of kidney diseases, but it would be helpful to include a final paragraph indicating the analysis common microbiota changes in general in kidney disease if such can be detected.

Response：We add in the final section the changing characteristics of the microbiome common in kidney disease. Due to the complexity of disease mechanisms and manifestations, we have also added summaries of characteristic microbial changes to the paragraphs discussing specific diseases. (See manuscript, page 15, line 411)

Reviewer: 2

Comment：

- The authors provide an extensive list of changes in the composition of the microbiome, sometimes intestinal, sometimes oral, sometimes unspecified, in relation to a few notable kidney diseases. Little attention is given to the details of the studies cited, their rigor, soundness of results, and limitations. With a few exceptions, no context is provided on whether studies were conducted on patients or laboratory animals.

Finally, there is no attempt to integrate the scientific literature to provide an overarching theme, a take-home message, a perspective unique to the authors’ work and opinion on the current state of the field, the challenges and the opportunities ahead, or something that would provide value to this manuscript over the superficial overview provided. This is a critical flaw of the manuscript, as reviews are supposed to provide the casual reader with an introductory understanding of the field, and the expert with engagement over how to interpret the state of the art.

Some additional details that require further attention are as follows:

Line 107: It is unclear what figure 1 and its legend are supposed to be

communicating to the reader

Line 113: Neither figure 2 nor its legend provide an explanation of what the acronyms on the left stand for.

Response：Thank you very much for your professional advice about the content and structure of the manuscript.

First, we removed animal-derived experiments and studies of human blood and urine samples. We also reviewed more carefully the studies related to microbiota that may play a key role in kidney disease and removed some redundant and poorly represented studies. We focus on the gut microbiota of patients with kidney disease, which is more structurally stable and informative than the microbiota of other sites. (See manuscript, page 9, line 207; page 10, line 270; page 11)

Second, we summarized the different roles of microbiota in the physiopathological processes of various renal diseases. Microbiota may be involved in different processes of kidney injury and produce different manifestations, such as changes in the structure of the microbiota and an increase in the relative proportion of specific microbiota. We analyzed the highlights of microorganisms in the identification and mechanistic studies of different kidney diseases. We would like to provide some information on the microbial origin in the study of kidney damage and aging. (See manuscript, page 8, line 202; page 10, line 245,263)

Third, we have added the detailed legends of Figures 1 and 2 and the abbreviations. The detailed statistics and analysis section we have also added in the supplementary data. We are sorry for the inconvenience caused by your reading. (See manuscript, page 6, line 135; page 7, line 157)

We sincerely thank all editors and reviewers for their careful and professional comments on this manuscript. Thank you very much for giving us this opportunity to revise the manuscript.

Sincerely,

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**Human microbiota alterations — emerging predictors of renal diseases and kidney-specific aging**

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**Abstract:**

Rapid advances in sequencing and analytical technologies have increased our understanding of the interactions between the microbiome and the host. The microbiome plays a variety of physiological roles in the health of the host and pathological roles in disease; for example, the microbiome changes significantly when kidney health is compromised and during kidney-specific aging. At present, there is an absence of good diagnostic markers for early renal injury. However, the composition of the microbiome could provide useful indications for disease diagnosis and treatment beyond more conventional diagnostic markers. Such indications are well represented in chronic kidney disease, immunoglobulin A nephropathy, idiopathic nephrotic syndrome, kidney stone disease . With sensitivity, specificity and stability, microbiota can provide more possibilities for the diagnosis of the early recognition of asymptomatic renal injury and aging. Moreover, probiotics and microbial metabolites have shown beneficial effects in the treatment of kidney diseases. Therapeutic measures targeting the microbiota can effectively improve the immune response and inflammatory state of the body. This paper reviews the current evidence on how the microbiome is not only a potentially effective tool for clinical diagnosis, but also an important focus for the study of kidney disease and aging.

**Keywords:** Human microbiota, kidney-specific aging, renal disease, high-throughput sequencing, predictor

The development of sequencing technology has shown that—despite their small size—microbes play a variety of crucial roles in health of the host, as well as the pathogenesis of multiple diseases. In addition to their own cellular functions, microbes are now known to constitute an important part of human organs, tissues and systems[1]. There are at least ten times as many bacteria as human cells in the body[2]. The symbiotic microbiome of the human body is intimately connected to host physiology. Consequently, microbes also play important roles in human health and disease. The symbiotic microbiome can be significantly altered by lifestyle, diet and even exercise[3, 4], and changes in the microbiome have been shown to play a role in the pathophysiological processes of many diseases[5]. Therefore, the interaction between human symbiotic microorganisms and the body may be even far more complex than imagined.

**1. The symbiotic microbiome's new identity in human disease**

The human microbiome has been extensively analyzed in different states in recent years. It is recognized that, when the host is in an abnormal state, it will interact with and induce changes in the symbiotic microbiome. In the healthy state, the human microbiome fluctuates, but is generally quite stable. Organ-specific community structures exist; for example, skin microbes have distinct community characteristics in different parts of the skin[6]. Oral microbes also differ from person to person[7]. The intestinal tract, with the highest microbial load, is also relatively stable[8]. Although the intestinal flora can be temporarily changed by diarrhea, antibiotic consumption, or other influences, the original floral structure reappears after a period of recovery[9]. Thus, even when the organism is in a state of disease, the microbiome also possesses certain stable characteristics. The microbiome and systemic metabolism, endocrine and immune systems have systemic effects at the host level. Microorganisms can often respond to subtle changes in the host under abnormal conditions, thus alterations to the microbiome may potentially have diagnostic or prognostic value.

Evaluation of the microbiota may be useful as a non-invasive method for diagnostic purposes. The sensitivity of the microbial community structure to abnormal states may hold potential as new markers of disease that could complement traditional analysis of body fluid samples, tissue sections and other clinical methods. The diagnostic potential of the microbiota has been identified in many diseases. For example, changes in the characteristics of the intestinal microflora can potentially predict early lung cancer[10]. Moreover, changes in the intestinal microbiome are related to the severity of coronary artery disease[11] and other changes in microbial diversity are directly and indirectly associated with hypertension[12]. In addition, studies have shown that gut microbiome alterations predispose to numerous neurological diseases[13]. Therefore, charting of the microbial map of the microbiome may significantly contribute to the diagnosis and targeted treatment of a wide range of diseases.

The complex role of the microbiome in the aging process of the human body is gradually being elucidated with the advancement of understanding. The composition and structure of human microorganisms are constantly changing with age[14]. This age-related perturbation is accompanied by the occurrence of states such as inflammation, which largely influences the appearance of age-related pathological states[15]. Thus, interactions between the human microbiome and the host largely influence the rate of aging. Microbiome-specific modulation becomes an important part of anti-aging research[16]. The specific gut microbial composition has also been suggested as a predictor of aging[17]. Adequate elaboration of the role of microbiota in the aging process would be very useful in the regulation of the aging process and in the response to diseases of aging.

Kidney aging is one of the important aspects of systemic aging. The physiological structure and function of the kidney become damaged during the aging process, and this damage can result in a series of pathological processes and diseases[18]. Renal disease is an increasingly important global public health problem[19]. Due to the lack of obvious clinical manifestations in the early stages of kidney disease, most patients have developed late-stage disease by the time they are diagnosed and thus have a poor prognosis. Therefore, the discovery of new therapeutic markers and targets for kidney disease is very important[20]. The development of high-throughput sequencing technology and the emergence of databases can help to better understand the relationship between diseases and microorganisms. The strong associations between gut microbiota alterations and kidney disease have also been extensively explored. High abundance of microbiota in patients with kidney disease can distinguish illness (Figure1). High-throughput studies based on renal pathological status and microbiome also confirmed this complex association (Figure 2). As a result of the increasing attention being paid to the complex relationship between microorganisms and diseases in recent years, microorganisms have become a new target in the etiology and clinical diagnosis of renal function injury.



**Figure 1. Receiver operating characteristic (ROC) curves of the top ten genera of gut microbiota associated with kidney disease**

ROC curves of the top ten microbial genera with the highest relative abundance in kidney disease in the gut microbiome database GMrepo(https://gmrepo.humangut. info/phenotypes/);the area under the curve (AUC) is shown for each genus. Gut microbiota show predictive ability in differentiating patients with kidney disease (*P* > 0.05, AUC > 0.5).



**Figure 2. Heatmap of the associations between alterations to specific genera of the gut microbiota and various kidney diseases**

Literature statistics on the relative abundance of specific microbiota in kidney disease and health groups compared. Red indicates a higher proportion of literature with high relative abundance of specific microbiota in the kidney disease; blue indicates a higher proportion of literature with low relative abundance of specific microbiota in the kidney disease. Zero indicates that the genus does not clearly differ between healthy controls and patients with the disease in recent reports. Colorless patches suggest that nostudies found associated microorganisms are detected in the gut microbiome of patients. Detailed data are provided in Supplementary Tables 1 and 2. (CKD: Chronic kidney disease, IgAN: Immunoglobulin A nephropathy, INS: Idiopathic nephrotic syndrome, DN: Diabetic nephropathy)

**2.1 Chronic kidney disease**

Chronic kidney disease (CKD) is defined as a persistent decline in kidney function, with a glomerular filtration rate below 60 mL/min/1.73 m2 and/or markers of kidney damage that persist for at least three months[21]. The clinical diagnosis of CKD is mainly determined based on the glomerular filtration rate and serum creatinine and albumin levels. The interpretation of these markers is complex due to the complex etiology of nephropathy; for example, 30% of patients with diabetic nephropathy do not have abnormal urinary albumin levels, and serum creatinine does not increase until at least 40% of the renal parenchyma is damaged[22, 23]. Early diagnosis of CKD can enable patients to receive treatment to slow down the progression of the disease and improve their prognosis; however, standard laboratory markers of renal deterioration are virtually unaffected in the early stages of kidney disease. Therefore, more useful markers to evaluate the occurrence and development of nephropathy urgently need to be identified.

Recent advancements in multiple omics techniques have broadened the search for such biomarkers, and the intestinal flora has been identified to play an important role in the pathophysiology of CKD. Evidence is accumulating that changes in the characteristics of the intestinal flora may be clinically useful for the early identification of CKD. Patients with CKD have lower gut microbiota diversity than healthy controls[20] and have a lower total number of bacteria in their feces. Moreover, patients with CKD have a lower abundance of probiotic-producing microbiota, such as *Lactobacillus* and *Prevotella*[24], and significant enrichment of some opportunistic pathogens, such as *Actinomycetes* and *Proteobacteria*[25]. Several microbial markers of diagnostic significance have also been identified. *Ruminococcus* and *Roseburia* can distinguish patients with CKD from healthy controls[26] and patients with CKD were found to have a significantly lower abundance of *Roseburia*, *Faecalibacterium* and *Clostridium* and significantly increased abundance of *Klebsiella* and *Akkermansia*[20, 24]. In addition, *Bacteroides eggerthii, Cetobacterium somerae* and *Candidatus Stoquefichus sp*. KLE1796 can better distinguish early CKD than traditional biochemical markers. *Bacteroides eggerthii*, in particular, showed good diagnostic specificity for CKD, both alone and in conjunction with other alterations to the microbiome[27]. A core microbiome associated with the course of CKD was identified, consisting of nine genera (*Escherichia\_shigella, Dialister, Lachnospiraceae*\_ND3007\_group, *Pseudobutyrivibrio, Roseburia, Paraprevotella, Ruminiclostridium, Collinsella stercoris* and *Bacteroides eggerthii*). In particular, *Paraprevotella*, *Pseudobutyrivibrio* and *Collinsella stercoris* more accurately identified CKD than the classic measure of urinary protein/creatinine. These microbial markers are highly stable, even in the early stages of the disease[28]. Moreover, butyrate production by *Roseburia inulinivorans* and *Ruminococcus* is significantly reduced in the early stages of CKD[29]. These characteristic changes suggest that changes in the microbiome in CKD patients can be an early indicator of an unhealthy state of the organism. CKD is an important component of aging-related diseases. The ability of microbial markers to accurately identify clinical symptoms before they appear will further improve clinical outcomes in aging-related diseases.

**2.2 Immunoglobulin A nephropathy**

Immunoglobulin A nephropathy (IgAN), the most common type of primary glomerular disease worldwide and the leading cause of end-stage renal disease in adults, has become an important global health problem[30, 31]. Diagnosis of this disease requires a renal biopsy to examine the deposition of immune complexes in the mesangium. This invasive procedure can lead to kidney inflammation and failure[32]. Although IgAN has distinct clinical features, some patients do not show significant symptoms due to rapid changes during the disease course[33]. Therefore, less invasive, more accurate markers are urgently needed for the diagnosis of IgAN.

IgA regulates symbiotic bacterial homeostasis in the body and the intestinal flora play an important role in maintaining intestinal immune stability[34]. However, many studies have shown that intestinal mucosal immune responses related to intestinal floral disorder promote the development of IgAN[35, 36]. Therefore, microbial characteristics may be potentially useful for the diagnosis of IgAN. A comparison of patients with advanced and non-advanced IgAN found microbial diversity was reduced in patients with advanced IgAN. Patients with both advanced and non-advanced IgAN had fewer types of *Bifidobacteria* than healthy subjects. Moreover, *Enterococcus* and *Lactobacillus* were reduced in patients with IgAN and *Rumencoccus*, *Eubacter* and *Streptococcus* were most abundant in patients with advanced IgAN[37]. Compared to a healthy control group, the abundance of *Fusobacteria*, *Escherichia-Shigella, Hungatella* and *Eggerthella* wereincreased in patients with IgAN; these bacteria have certain pathogenic potential. Moreover, *Escherichia-Shigella* was negatively correlated with the estimated glomerular filtration rate[38, 39] and *Legionella*, *Escherichia-Shigella* and *Ruminococcus* were also enriched in the blood of patients with IgAN[40]. In addition, a relatively recent study showed that an abnormal mucosal immune response to the anaerobic flora of the tonsils (mainly *Bacteroidetes*) was related to the pathophysiology of IgAN[41]. Thus, the decrease in probiotics and the increase in pathogenic bacteria and the resulting disturbance of the intestinal microbiota may be an important part of the pathological process of IgAN. Microbial disorders and the resulting immune activation can be a breakthrough in disease diagnosis and clinical treatment.

**2.3 Idiopathic nephrotic syndrome**

Idiopathic nephrotic syndrome (INS) is a common form of podocytosis and the most common glomerular disease in children[42]. The main pathological findings include minimal change disease and focal segmental glomerulosclerosis. The clinical manifestations of INS include glomerular filtration disorder and proteinuria[43]. Compared with healthy children, the proportion of butyric acid-producing bacteria is decreased significantly in the intestines of children with INS[44], and metagenomic analysis confirmed this result[45]. Characteristic changes in the intestinal flora were also observed in adult patients with INS. The bacterial diversity of patients was significantly altered compared to healthy controls; Firmicutes was less abundant and Fusobacteria and Proteobacteria were elevated in patients with INS, whereas butyrate-producing bacteria such as *Lachnospira* and *Roseburia* were more abundant in the healthy control group. In contrast, the bacterial groups *Providencia* and *Myroides* are more common in patients with INS[46]. The apparent difference in the relative abundance of butyric acid-producing bacteria suggests that this variation is not uncommon. Decrease in probiotics and beneficial microbial metabolites can cause a decrease in intestinal homeostasis. A decrease in probiotics and beneficial microbial metabolites can lead to decline in intestinal homeostasis and even directly affect the differentiation and induction of immune cells[44]. Targeting probiotics and their products can provide new thinking for the identification and recurrence of INS.

**2.4 Diabetic nephropathy**

Diabetic nephropathy is one of the most severe and prognostic complications of diabetes mellitus. Disturbances in the gut microbiota have been observed in type 1 and type 2 diabetes, including significant reductions in the abundance of *Lactobacillus* and *Bifidobacteria*,which are involved in maintenance of intestinal epithelial integrity. Other bacteria with high pathogenic potential, such as *Clostridium* and *Bacteroidetes*, were significantly increased in abundance[47]. In addition, intestinal flora that produce short-chain fatty acids (SCFAs) are significantly reduced in patients with diabetic nephropathy[48]. A meta-study suggested that *H. pylori* infection is associated with increased risk of diabetic nephropathy and plays a role in the disease[49]. Moreover, antigens on the surface of *Leptotrichia googfellowii* have been found to stimulate CD8+ T cells to attack islets, which can promote the development of diabetic nephropathy. Short-chain fatty acid metabolites of *Lactobacillus* and *Bifidobacterium* can reduce insulin resistance and delay the progression of kidney disease[47]. Thus, the complex interactions between the intestinal flora, intestinal metabolism and diabetes suggest the microflora play multiple roles in diabetic nephropathy.

**2.5 Renal aging and functional loss**

In fact, aging-related changes in the gut microbiome are mainly caused by systemic inflammation and aging of the immune system[50]. Microbiome alterations have also been demonstrated in aging of the kidney. Gut microbes regulate local and systemic innate and adaptive immunity[51]. When the integrity of the gut barrier is breached, gut bacteria and other toxins can enter into the body's tissues and organs[52]. Immune cells and inflammatory factors produced during immune activation can contribute to the development of kidney disease[53]. Moreover, changes in the composition of the flora and metabolite production by the gut microbiota can promote inflammation, oxidative stress and fibrosis in the kidneys. Dysregulation of the intestinal flora can lead to production of uremic toxins such as indoxyl sulfate, p-cresol sulfate, and trimethylamine-N-oxide (TMAO). The toxin uremia can induce the production of pro-inflammatory factors that trigger inflammation and also promotes cellular aging and kidney fibrosis[54, 55]. TMAO is also considered to be a central link between the gut microbiome and kidney disease[56]. TMAO can promote the development of CKD through inducing inflammation and oxidative stress, upregulating scavenger receptors and inhibiting reverse cholesterol transport[57]. In addition, reductions in intestinal bacteria that produce SCFAs, particularly butyric acid, have been observed in a number of kidney diseases. SCFAs are involved in maintenance of the integrity of the intestinal barrier[58]. SCFAs can also attenuate activation of NF-ĸB, inhibit the production of proinflammatory factors and regulate the activity of Tregs[59, 60]. The SCFA butyrate can also enhance mitochondrial activity, activate intestinal gluconeogenesis, and regulate epigenetic processes by inhibiting histone deacetylases. Thus, butyrate is considered to be a beneficial anti-aging metabolite[61]. A stable intestinal microbial structure is an important component of the gut microbiota. When this homeostasis is disrupted, gut microbiota are responsible for the abnormal immune activation and inflammatory state in the body. The transformed role of gut microbes and their metabolites in these two distinct states also demonstrates the great potential of microbes in anti-aging research.

**3 The microbiome — a new therapeutic target for renal injury and aging?**

Microbiome research has broadened the diagnostic and treatment options for kidney injury (Figure 3). Evidence indicates the colon-kidney axis plays an important role in renal injury and imbalances in the intestinal flora are implicated in the pathophysiological process of kidney disease, which suggests that the restoration of bacterial homeostasis may be an effective treatment for kidney disease. Probiotics may represent an important potential treatment. Studies have shown that probiotics can effectively reduce the concentration of uremic toxins, especially p-cresol sulphate and p-indoxyl sulphate, in patients with CKD[62]. Moreover, probiotics can reduce the levels of inflammatory markers in the host and affect the immune system[63, 64]. *Lactobacillus salivarius* BP121 and *Lactobacillus* were shown to downregulate renal inflammatory mediators and reduce oxidative stress[65, 66]. Oral probiotics such as *L. plantarum* and *L. brevis* were also found to slow the progression of CKD and KS[67, 68]. Synbiotics are a combination of probiotics and prebiotics. When combined with low protein therapy, synbiotics could reduce the rate of progression of CKD, led to significant enrichment of *Bifidobacterium*, reduced the abundance of *Rumencoccus* and improved the microbial structure of the feces[69, 70]. SCFAs, the final metabolite of the fermentation of complex polysaccharides by the intestinal flora, also play an important role in renal function. SCFAs have strong anti-inflammatory properties and immunomodulatory effects[71, 72]. Supplementation with SCFAs has been shown to prevent the progression of AKI and subsequent CKD[73]. Fecal microbiome transplantation (FMT) is also considered to be an effective therapy to restore homeostasis to a disrupted microbiome. FMT treatment ameliorated intestinal microbiota disorder and limited accumulation of uremic toxins in mouse models of CKD[74]. In the diabetic rat model, FMT also effectively reduced the levels of inflammatory factors and thereby attenuated inflammation and necrosis of the renal tubule interstitium in a model of diabetic nephropathy[75]. In addition, FMT also showed good therapeutic potential in patients with refractory IgA nephropathy[76, 77]. Overall, these microbiome-related therapeutic strategies have high potential to reduce the incidence of kidney disease and improve patient outcomes, and may also represent new strategies to combat the effects of kidney-specific aging.



**Figure 3. Potential therapeutic strategies for renal injury and aging associated with alterations to the microbiome and its metabolites**

**4 Summary and perspectives**

The microbiome is now viewed as a vital “organ” of the body that is closely related to human health and directly or indirectly affects the physiological functions of the body through multiple immune and metabolic pathways. Among the diseases associated with aging, kidney disease is not to be ignored. Decline in microbial diversity, decrease in probiotics and their metabolites, and increase in the relative abundance of disease-specific microorganisms are all signs of kidney aging and disease. The structure of the microbiome is related to health outcomes, and can more accurately describe abnormal states of the host than many traditional clinal markers. Detailed knowledge of microbial alterations may not only help to distinguish between diseased and non-diseased states, but may also help to understand the response of the host to treatments and estimate prognosis. Further development of sequencing analysis technology may enable the disease course of individual patients to be more carefully defined and treatments to be selected more precisely. In addition, the microbiome itself has emerged as an important target of disease. Many treatments targeting the microbiome have shown good efficacy in patients with nephrosis. A few microbial markers of renal dysfunction have been well explored. However, more advanced platforms to collate and analyze such markers and validation of the results in larger clinical cohorts are necessary to identify accurate microbial markers. These efforts may help to uncover the promising potential of microbial research to improve the diagnosis and treatment of kidney diseases and aging.

**Declarations**

**Author contributions**

All authors contributed equally. All authors contributed to the manuscript and agreed to submit manuscript.

**Availability of data and materials**

Not applicable

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**Conflict of interest**

All authors declared that there are no conflicts of interest.

**Ethical approval and consent to participate**

Not applicable

**Consent of publication**

Not applicable

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