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Changes of gut microbiota in maintenance hemodialysis patients and their impact on patient's microinflammation status

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ABSTRACT

This study was to investigate the changes in gut microbiota in maintenance hemodialysis patients and analyze their impact on patient's microinflammation status. For this purpose, thirty-nine chronic kidney disease (CKD) maintenance hemodialysis patients admitted to our hospital from March 2019 to March 2022 were selected as the experimental group, and 40 healthy individuals with examination results during the same period were selected as the control group. The levels of gut microbiota (Lactobacillus, Bifidobacterium, Escherichia coli, and Enterococcus faecalis) and microinflammation indicators [interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and high-sensitivity C-reactive protein (hs-CRP)] were measured in both groups. The relationship between changes in gut microbiota and microinflammation in maintenance hemodialysis CKD patients was analyzed. Results showed that the levels of Lactobacillus and Bifidobacterium in the experimental group were significantly lower than those in the control group (all, $P<0.05$), while the levels of Escherichia coli and Enterococcus faecalis in the experimental group were significantly higher than those in the control group (all, $P<0.05$). The IL-6, TNF-α, and hs-CRP levels in the experimental group were significantly higher than those in the control group (all, $P<0.05$). Using microinflammation indicators as dependent variables and microbiota indicators as independent variables for stepwise regression analysis, the results showed that the levels of Lactobacillus were negatively correlated with IL-6 and TNF-α levels in patients ($r=-0.358$, -0.942, $P<0.05$); the levels of Bifidobacterium were negatively correlated with IL-6, TNF-α, and hs-CRP levels in patients ($r=-0.394$, -0.211, -0.547, $P<0.05$); the levels of Escherichia coli were positively correlated with IL-6 and TNF-α levels in patients ($r=0.221$, 0.268, $P<0.05$); the levels of Enterococcus faecalis were positively correlated with IL-6 and hs-CRP levels in patients ($r=0.253$, 0.378, $P<0.05$). In conclusion, patients with maintenance hemodialysis for CKD commonly exhibit gut microbiota dysbiosis and varying degrees of low-grade inflammation. Compared to healthy individuals, maintenance hemodialysis patients with CKD have lower levels of Bifidobacterium and Lactobacillus and higher levels of Escherichia coli and Enterococcus in their gut. Bifidobacterium, Lactobacillus, Escherichia coli, and Enterococcus all have a certain impact on the low-grade inflammation status of patients with maintenance hemodialysis for CKD.

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Introduction

In recent years, the incidence of CKD in China has been increasing year by year (1). Clinical studies (2) have shown that CKD has become one of the important factors threatening human survival. Research (3) has pointed out that CKD patients generally have microinflammation in their bodies, and studies (4) have confirmed that whether CKD patients receive dialysis or not, or the method of dialysis, cannot change the fact that patients have different degrees of microinflammation in their bodies. Research (5) has indicated that there is a close correlation between the microinflammation in the body of CKD patients and the many complications of the disease. A statistical study (6) conducted abroad has shown that the risk of CKD patients developing cardiovascular disease can reach 78%, which is much higher than that of healthy people. Another study (7) has indicated that the formation of microinflammation in CKD patients is closely related to their renal function and that blood dialysis technology and disturbances in the gut microbiota may also be the causes of the formation of microinflammation.

The gastrointestinal mucosal layer is the body's largest repository of bacteria, containing 1,000-1,150 species of bacteria, which play a vital role in the body's immune system (8). Human gut bacteria can be divided into three major categories: the first is probiotics, which can resist the invasion of pathogenic bacteria. The second is conditional pathogenic bacteria, which are harmless when the gut microbiota is in balance but can become invasive under certain conditions, posing a danger to the body. The third is pathogenic bacteria, which are normally present in small quantities in the gut microbiota, but when their numbers exceed normal levels, they pose a serious risk of disease (9). To date, the role of gut microbiota in the occurrence and development of CKD has not been clinically valued. IL-6, TNF-α, and hs-CRP are important sensitivity markers for microinflammation in the body of CKD patients (10). This study aims to analyze the influence of quantitative changes in gut microbiota on the microinflammation

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Table 1. Specific primers.

Bacteria Primer	Sequence (5`-3`)	Amplification fragment (bp)
Bifidobacterium	F:5`-TCGCGTC(C/T)GGTGTGAAAG-3` R:5`-CCACATCCAGC(A/G)TCCAC-3`	243
Lactobacillus	F:5`-AGCAGTAGGGAATCTTCCA-3` R:5`-CACCGCTACACATGGAG-3`	341
Escherichia coli	F:5`-GTTAATACCTTTGCTCATTGA-3` R:5`-ACCAGGGTATCTTAATCCTGTT-3`	582
Enterococcus	F:5`-CCCTTATTGTTAGTTGCCATCATT-3` R:5`-ACTCGTTGTACTTCCCATTGT-3`	144

in the bodies of CKD maintenance hemodialysis patients by detecting changes in gut microbiota and the above sensitivity markers. The results are reported in their original format.

Materials and Methods

① Preparation of standard samples: Collect patients' feces under sterile conditions, store them at low temperatures, and send them for testing. Use fluorescent quantitative polymerase chain reaction (PCR) for detection. Take freeze-dried powders of Bifidobacterium, Lactobacillus acidophilus, Escherichia coli, and Enterococcus faecalis, dissolve them in PBS, and use the Axygen bacterial genome DNA small amount preparation kit to extract the standard bacterial DNA.

② Design and synthesis of primers: Design specific primers targeting bacterial 16S rDNA. The specific sequence of the upstream and downstream primers is shown in Table 1.

③ Conventional PCR amplification: The specific primers mentioned above were used to amplify the bacterial genomic extraction from standard bacterial strains by conventional PCR amplification. The amplified products were subjected to electrophoresis, and then visualized by UV light and recovered by gel cutting.

④ Standard curve construction: The DNA fragment of the standard bacterial strain was used as the real-time fluorescent quantitative PCR standard, and after dilution, timed quantitative PCR reactions were performed. The logarithm of the copy number of each template was used as the x-axis, and the initial cycle number (Ct) of the fluorescence signal during PCR was used as the y-axis to draw the standard curve. The specific standard curve is shown in Figure 1.

⑤ Quantitative analysis of test samples: The same reaction system and reaction conditions as the standard fluorescent quantitative PCR were used to detect the test samples by PCR, and the copy number of the 16S rDNA gene in the test samples was calculated based on the standard curve of the standard strain.

Statistical methods

The data in this study were analyzed using SPSS 22.0, and measurement data were expressed as ($\bar{x}$±s) and compared by t-test. Counting data were expressed as n (%) and compared by x^2 test. Multiple linear stepwise regression analysis was used for regression analysis. P<0.05 was considered statistically significant. GraphPad Prism 8 was used for graphing. The original format was maintained in the translation.

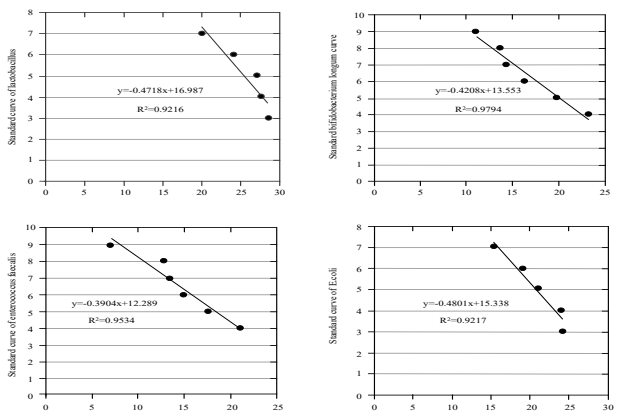

Figure 1. Standard curve.

Results

Basic information

A total of 39 CKD maintenance hemodialysis patients (experimental group) and 40 healthy individuals (control group) were included in this study. Basic information, including gender, age, and laboratory indicators such as total cholesterol, triglycerides, HDL-C, LDL-C, serum iron, hemoglobin, serum albumin, serum cystatin C, blood urea nitrogen, serum creatinine, glomerular filtration rate, blood calcium, blood phosphorus, blood potassium levels, and the cause of renal failure were collected and compared between the two groups. There were no significant differences in gender, age, HDL-C, and blood calcium levels between the two groups (all, P>0.05). However, significant differences were observed in the levels of total cholesterol, triglycerides, LDL-C, serum iron, hemoglobin, serum albumin, serum cystatin C, blood urea nitrogen, serum creatinine, glomerular filtration rate, blood phosphorus, and blood potassium levels between the two groups (all, P<0.05). See Table 2 for details.

Comparison of fecal microbiota levels

The levels of Bifidobacterium and Lactobacillus in the experimental group were significantly lower than those in the control group (all, P<0.05). Meanwhile, the levels of Escherichia coli and Enterococcus in the experimental group were significantly higher than those in the control group (all, P<0.05). See Table 3 for details.

Comparison of micro-inflammatory index levels

The levels of IL-6, TNF-α, and hs-CRP in the experimental group were significantly higher than those in the control group (all, P<0.05). See Table 4 for details.

Table 2. Comparison of basic information.

	Observation group (n=40)	Experimental group (n=39)	t/x²	P
gender			0.105	0.746
male	twenty-four	twenty-two		
female	16	17		
Average age (years)	54.89±13.19	54.72±13.27	0.057	0.955
cause of kidney failure	-		-	-
chronic glomerulonephritis		14		
diabetic nephropathy		11		
hypertensive nephropathy		7		
drug-induced nephropathy		3		
polycystic kidney disease		2		
other		2		
Total Cholesterol (mmol/L)	4.58±0.47	3.84±0.93	4.48	<0.001
Triacylglycerol (mmol/L)	1.41±0.54	1.19±0.43	2.0	0.049
HDL-C (mmol/L)	1.08±0.16	1.03±0.25	1.062	0.292
LDL-C (mmol/L)	2.93±0.84	2.23±0.76	3.881	<0.001
Serum iron (μmol/L)	12.3±6.9	9.4±2.2	2.503	0.014
Hemoglobin (g/L)	132.86±22.37	106.72±17.63	5.759	<0.001
Serum albumin (g/L)	44.36±4.89	38.68±3.32	6.025	<0.001
Serum cystatin (mg/L)	1.97±0.42	6.41±1.34	-19.977	<0.001
Blood urea nitrogen (mmol/L)	4.53±1.68	24.62±5.92	-20.631	<0.001
Serum creatinine (μmol/L)	69±22	1084±272	-23.526	<0.001
Glomerular filtration rate [ml/(min·1.73 m²)]	102±11	6±2	53.636	<0.001
Serum calcium (mmol/L)	2.32±0.15	2.28±0.26	0.84	0.403
Serum phosphorus (mmol/L)	1.03±0.32	1.87±0.52	-8.671	<0.001
Serum potassium (mmol/L)	4.05±0.38	4.83±0.72	-6.043	<0.001

Table 3. Comparison of fecal microbiota levels [$\bar{x}$±s, Ig (copies/gram feces)].

Test items	Observation group (n=40)	Experimental group (n=39)	t	P
Bifidobacteria	9.27±0.59	8.04±0.77	7.982	<0.001
Lactobacillus acidophilus	8.08±0.65	7.12±0.48	7.452	<0.001
Escherichia coli	9.03±0.48	9.55±0.69	-3.897	<0.001
Enterococcus faecalis	7.61±0.54	8.17±0.45	-5.001	<0.001

Table 4. Comparison of micro-inflammatory index levels [$\bar{x}$±s].

Test items	Observation group (n=40)	Experimental group (n=39)	t	P
IL-6(pg/ml)	28.36±10.95	62.41±18.23	-10.093	<0.001
TNF-α(pg/ml)	51.87±11.74	152.42±33.29	-17.992	<0.001
hs-CRP (mg/L)	1.12±0.34	3.47±0.58	-22.037	<0.001

Regression analysis of fecal microbiota levels and micro-inflammatory status

Stepwise regression analysis was performed with the microbiota index levels as independent variables and the micro-inflammatory index levels as dependent variables. The results showed that the levels of Bifidobacterium were negatively correlated with the levels of IL-6 and TNF-α (r=-0.358, -0.942, P<0.05), while the levels of Lactobacillus were negatively correlated with the levels of IL-6, TNF-α, and hs-CRP (r=-0.394, -0.211, -0.547, P<0.05). The levels of Escherichia coli were positively correlated with the levels of IL-6 and TNF-α (r=0.221, 0.268, P<0.05), while the levels of Enterococcus were positively correlated with the levels of IL-6 and hs-CRP (r=0.253, 0.378, P<0.05). See Table 5 and Figures 2-5 for details.

Discussion

Research (11) has shown that CKD patients generally have varying degrees of microinflammation in their bodies, and because some patients are in the early stages of microinflammation, there are no obvious clinical symptoms. IL-6, TNF-α, and hs-CRP are all important sensitivity markers of microinflammation in CKD patients. Research (12) has shown that IL-6 and TNF-α are important factors leading to glomerular mesangial cell proliferation, sclerosis, and kidney disease progression. hs-CRP is an acute-phase protein synthesized by liver cells when the body is exposed to inflammatory stimuli such as microbial invasion or tissue damage (13) and has been clinically proven to be an independent risk factor for CKD patients.

Table 5. Regression analysis of fecal microbiota levels and micro-inflammatory status.

Gut flora	IL-6 (pg/ml)		TNF-α (pg/ml)		hs-CRP (mg/L)	
	r	P	r	P	r	P
Bifidobacteria	-0.358	0.026	-0.942	<0.001	-0.112	0.262
Lactobacillus acidophilus	-0.394	0.021	-0.211	0.041	-0.547	<0.001
Escherichia coli	0.221	0.035	0.268	0.009	0.042	0.247
Enterococcus faecalis	0.253	0.012	0.061	0.176	0.378	0.017

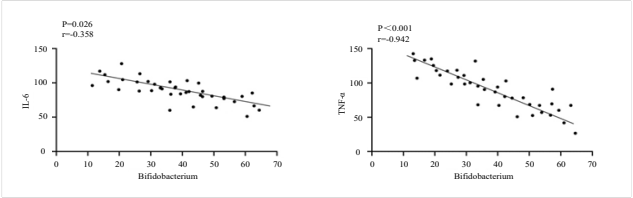

Figure 2. Relationship between Bifidobacterium levels and micro-inflammatory index levels.

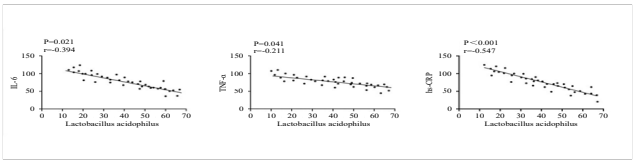

Figure 3. Relationship between Lactobacillus levels and micro-inflammatory index levels.

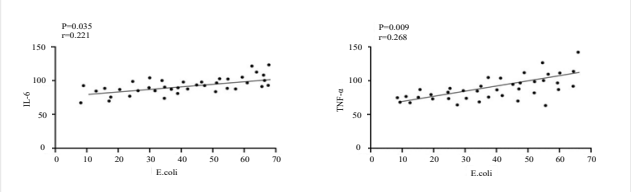

Figure 4. Relationship between Escherichia coli levels and micro-inflammatory index levels.

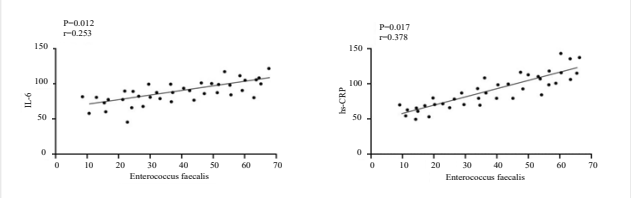

Figure 5. Relationship between Enterococcus levels and micro-inflammatory index levels.

Its concentration plays an important role in the subsequent intervention and prognosis assessment of maintenance hemodialysis patients with CKD (14). Therefore, in this study, IL-6, TNF-α, and hs-CRP levels were used as markers to reflect the microinflammation status of patients. The results of this study showed that the IL-6, TNF-α, and hs-CRP levels in the experimental group were significantly higher than those in the observation group (all, P<0.05), which is consistent with previous research results (15).

A related study (16) has suggested that the microinflammation status in CKD patients may be related to their gut microbiota dysbiosis. The human gut contains a diverse community of bacteria known as the gut microbiota, which forms a natural microbial barrier in the body (17). As an important component of the intestinal mucosal barrier, the structure and composition of the gut microbiota directly or indirectly participate in the development of many diseases in the host (18). The gut microbiota is large in number, complex in structure, and has many bacteria that cannot be cultured or identified. In recent years, with the development of molecular biology techniques, the function of the gut microbiota has gradually been elucidated. However, as the dominant bacterial population in the gut microbiota, probiotics play a crucial role in maintaining gut microbiota balance (19). Lactobacillus and Bifidobacterium are important physiological bacteria in the human body, and they mainly participate in maintaining the integrity of the intestinal mucosal barrier. Currently, most probiotic preparations use these bacterial genera (20).

Escherichia coli and Enterococcus faecalis are important opportunistic pathogens in the human body. When there is an imbalance in the intestinal microbiota, they can overgrow, leading to intestinal dysbiosis and the occurrence of infections in patients. Additionally, E. coli and E. faecalis can enter the bloodstream through the gut-liver axis, causing serious adverse reactions such as endotoxemia (21). Therefore, this study used Bifidobacterium, Lactobacillus, E. coli, and E. faecalis as markers to reflect the status of the patient's gut microbiota. Forty healthy individuals were included as a control group. The results showed that the levels of Bifidobacterium and Lactobacillus were significantly lower in the experimental group than in the control group (all, P<0.05), while the levels of E. coli and E. faecalis were significantly higher in the experimental group (all, P<0.05). This confirms that there is a common gut dysbiosis phenomenon in patients undergoing maintenance hemodialysis for chronic kidney disease (CKD), characterized by a decrease in beneficial gut microbiota and an increase in pathogenic microbiota. Based on the results of this study and previous related research (22-24), the possible reasons for gut dysbiosis in CKD patients include: 1) CKD can reduce the adhesion ability of probiotics in the gut, leading to their increased excretion in the feces and a decrease in their numbers; 2) Previous studies have shown that the level of secretory IgA in the gut of CKD patients is significantly lower than that of healthy individuals. As an important indicator of the body's intestinal mucosal immune function, its reduction can significantly weaken the gut microbiota's colonization resistance; 3) CKD can increase the levels of urea nitrogen and amino acids in the gut, which changes the normal pH level and promotes the proliferation of various pathogenic microbiota.

Regarding the impact of gut microbiota levels on microinflammation, this study used the microinflammation indicators in CKD patients' bodies as the dependent variable and conducted stepwise regression analysis on

all included bacterial groups. The results showed that the levels of Bifidobacterium were negatively correlated with the levels of IL-6 and TNF-α in the patients' bodies (r=-0.358, -0.942, P<0.05); the levels of Lactobacillus were negatively correlated with the levels of IL-6, TNF-α, and hs-CRP in the patients' bodies (r=-0.394, -0.211, -0.547, P<0.05); the levels of Escherichia coli were positively correlated with the levels of IL-6 and TNF-α in the patients' bodies (r=0.221, 0.268, P<0.05); and the levels of Enterococcus were positively correlated with the levels of IL-6 and hs-CRP in the patients' bodies (r=0.253, 0.378, P<0.05). These results suggest that dominant bacterial groups in the gut of CKD patients on maintenance hemodialysis are involved in the occurrence and development of microinflammation in the body. Another study (25) pointed out that Enterococcus has extremely strong drug resistance, and CKD patients usually take antibiotics for a longer duration and at a higher dosage than healthy individuals. Long-term and high-dose use of antibiotics can further exacerbate the drug resistance of Enterococcus in the gut, thereby aggravating the microinflammation in the patients' bodies. Based on the results of this study and previous studies (26), we believe that the weakened intestinal barrier function in CKD patients due to their disease can lead to dysbiosis of the gut microbiota, which in turn triggers or exacerbates microinflammation in the body. This is a vicious cycle.

The current study has certain limitations, such as the relatively small sample size, which may result in some bias in the accuracy of the study's conclusions. Additionally, all CKD patients included in this study were receiving maintenance hemodialysis treatment, which prevented exploration of the effects of gut microbiota and microinflammation in CKD patients who did not receive such treatment. Therefore, further clinical research is expected to supplement the analysis with the aforementioned limitations.

Conclusion

CKD patients receiving maintenance hemodialysis generally exhibit gut microbiota dysbiosis and varying degrees of microinflammation. Compared to healthy individuals, CKD patients receiving maintenance hemodialysis have lower levels of bifidobacteria and lactobacilli and higher levels of Escherichia coli and enterococci in their gut. Bifidobacteria, lactobacilli, Escherichia coli, and enterococci all have a certain impact on the microinflammation in the body of CKD patients.

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