Review Article

Gut Microbiota and the Ways to Correct it in Chronic Kidney Disease

Abstract

Approximately 13% of the Russian population suffers from chronic kidney disease (CKD). Such a high prevalence of the disease, as well as the complexity and high cost of renal replacement therapy, explain the need for developing and implementing new approaches to treat patients at the pre-dialysis stages. The data collected in recent decades highlight the importance of gut microbiota in the progression of CKD. This review provides information about the microbiota composition in healthy individuals and patients with CKD and discusses the mechanisms of interaction in the intestine–kidney system. The article also presents the specifics of the violation of gut microbiota (GM) and correction thereof in CKD.

Keywords: *Chronic kidney disease, dysbiosis, enterotype, gut microbiota, intestine–kidney*

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Introduction

Chronic kidney disease (CKD) is an important medical and public health problem. According to several authors, the true epidemiology of this disease in the Russian Federation remains unknown due to the limited amount of data.[1-3] It is known that in the period from 2003 to 2013, the number of patients with CKD increased 2.2 times, and the average annual increase was approximately 9%.[1] Extrapolation of data from other countries suggests that the prevalence of CKD in the Russian Federation corresponds to that in the world (13.4%)[4,5] and is comparable with the figures obtained in many countries [Table 1]. Economic and social features (including the cost of treatment and the level of regional development) make the problem of CKD extremely relevant for domestic medicine.[3] Over the past 15 years, the average increase in the dialysis group among CKD patients was 10%, and 13% in 2018, but despite significant improvements in the availability of renal replacement therapy (RRT) in the Russian Federation, the availability of hemodialysis (HD) for the population is 2.5–7 times lower than that in the European Union.[3,6,7] This situation is aggravated by the fact that more than a quarter of patients seek specialized nephrological care at the stages when the possibility of administering nephroprotective therapy is missed and HD is required.[7] Although the impact of the new coronavirus infection on CKD has not yet been established, experts predict an increase in its incidence as up to 20% of hospitalized patients need RRT.[8,9]

In addition to the social burden associated with the disease, CKD has a significant impact on the healthcare system from an economic point of view. For example, the cost of kidney transplantation and RRT is 2%–3% of the national health expenditure in the Russian Federation. CKD is a comorbid disease in 16% of the working-age population of the country.[6] The data accumulated in recent decades emphasize the relationship of gut microbiota (GM) with the course of CKD. When entering the bloodstream, the toxins synthesized by GM in CKD patients contribute to a decrease in the glomerular filtration rate (GFR) and the progression of renal failure.[10] Moreover, there are no recommendations for the treatment of GM disorders in patients with CKD.

Composition of the Gut Microbiota

According to the Russian Industry Standard for the treatment of intestinal dysbiosis (OST 91500.11.0004-2003), the normal flora means the ratio of diverse populations of microorganisms of individual organs and systems that

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Table 1: The prevalence of CKD in the world according to population studies[5]

Country	Studies, year	CKD prevalence	
		Stages 1-5	Stages 3-5
USA	NHANES, 1999-2006	15%	8%
Netherlands	PREVEND, 2005	18%	No data
Spain	EPIRCE, 2005	13%	No data
China	Beijing study, 2008	14%	7%
Japan	Imai *et al*., 2007	No data	19%
Australia	AusDiab, 2008	13%	8%
Congo	Kinshasa study, 2009	12%	8%

CKD - Chronic kidney disease

maintain the biochemical, metabolic, and immunological balance necessary to preserve human health.[11] GM is a complex community of microorganisms inhabiting the gastrointestinal tract (GIT) of a human: bacteria, viruses, prokaryotes, eukaryotes, and archaea.[12]

During prenatal development, the intestine is sterile, and its primary colonization occurs when passing through the birth canal.[13] It is known that the first colonizers of the GIT are aerophilous representatives of the *Proteobacteria* and *Actinobacteria* phyla, which form a favorable microenvironment for further colonization by representatives of *Firmicutes* and *Bacteroides.*[14] The microbial diversity of the intestine increases during the first 12 months of human life, and at about 2.5 years of age, the GM composition approaches that of adults.[15] In the course of life, the difference in the GM composition of a particular person from the average decreases, and the diversity between people, on the contrary, increases.[14]

In general, the total GM mass amounts to 1.5–2.0 kg, and the taxonomic diversity, once estimated at 500 species, is now more than 1500 species.[16,17] Because the human GIT is an extended structure that differs in morphological and physiological terms in different segments, the composition and functions of the microbiota also differ. For example, the jejunum is dominated by aerobic bacteria: enterobacteria, streptococci and staphylococci, lactobacilli, and yeast, while the anaerobic flora makes up a small part of the local diversity. In total, the jejunum contains up to 10^5 colony-forming units (hereinafter referred to as CFU) per 1 g of contents.

As we move from the ileum to the large intestine, not only does the total number of microorganisms increase (up to 10^9 CFU in the ileum and up to 10^{12} CFU in the large intestine) but the composition of the microbial community also changes, revealing the dominance of anaerobes in the large intestine.[18] In the large intestine, the bacteriodes of the families Prevotellaceae and Rikenellaceae predominate, and among the clostridiae, the family Lachnospiraceae dominates.[15] The composition of the gastrointestinal microbiota by segments is presented in Table 2.

For a long time, the composition of the microbial contents of the intestine was analyzed only with the help of fecal microbiological studies. Currently, metagenomic sequencing of the 16S rRNA gene from amplified bacterial nucleic acid isolated from feces is used.[15] Thanks to the results of the Human Microbiome Project (HMP) and Metagenomics of Human Intestinal Tract (MetaHIT) project aimed at studying the composition of normal GM in American and European populations, current ideas about humans, by analogy with blood groups, were supplemented by the classification of people according to the GM composition [Table 3].

GM growth is limited by the intestinal barrier, which includes physical (epithelial and mucosal layers), biochemical (enzymes and antimicrobial proteins), and immunological (epithelial immune cells and IgA) components.[15]

The variety of GM representatives increases relatively quickly by the age of 25–30 and then gradually reaches a peak at the age of 50, followed by a gradual decline.[16] After age 65, the microbial diversity changes—the number of Bacteroidetes phyla and Clostridium increases.[15] In addition to age, the diversity of the composition is influenced by gender (in women, it is significantly higher than in men of the same age), hematocrit, blood plasma lipid profile, several secreted proteins, and peptides.[16] Among the dietary factors that affect the GM composition, some researchers distinguish the qualitative and quantitative composition of the diet, the content of sugar, polyphenols, fat content of the consumed milk, and other factors.[16,20] Glycosylation of mucus and mucin plays a key role in the formation of the microbiota. In the case of dietary fiber deficiency, mucosal erosion is associated with the switching of GM to the use of secreted mucins as a source of nutrients.[15] The issue of iatrogenic dysbiosis also deserves special attention; for example, changes in GM have been proven with the use of proton pump blockers, metformin, statins, laxatives, neuroleptics, antidepressants, and antibiotics.[16,20]

Researchers pay great attention to studying the relationship of changes in GM and the associated metabolites with the stages of CKD. Thus, in the early stages of CKD, a decrease in the number of *Bacteroides eggerthii* is detected. By reducing the number of *Prevotella sp.* 885, which correlates with the excretion of urea in the daily urine, signs of progression of this disease can be detected. In the late stages of CKD, the increase in serum lipopolysaccharides (LPS) is partly due to an increase in the number of *Escherichia coli* and other representatives of the Enterobacteriaceae family in the large intestine. A significant decrease in the level of propionic acid also indicates a late stage of CKD, and its absence is a reliable sign of a serious condition of a patient.[21]

Enterotypes of the Gut Microbiota

According to the results of 2007–2019 studies, there are three enterotypes of gut microbial

Table 2: Composition of the normal GIT microbiota by segments[11,18] with changes

Microorganisms	Quantity, CFU/g of contents			
	Stomach	Jejunum	Ileum	Large intestine
Total quantity	Up to 10^3	Up to 10^5	Up to 10^9	Up to 10^{12}
Aerobes				
Family Enterobacteriaceae (gram-negative, nonsporeforming), of which (in total):	Up to 10^2	Up to 10^3	102-10^7	10^4-10^{10}
E. coli, typical, lactose-negative, and hemolytic	none	none	none	10^4-10^8
Other potentially pathogenic enterobacteria	none	none	none	Up to 10^4
Streptococci, including lactic acid (gram-positive, nonsporeforming)	Up to 10^3	Up to 10^4	10^2-10^6	10^6-10^{10}
Staphylococci (gram-positive, nonsporeforming)	Up to 10^2	Up to 10^3	10^2-10^6	10^4-10^9
Lactobacilli (gram-positive, nonsporeforming)	Up to 10^3	Up to 10^4	10^2-10^3	10^6-10^{10}
Yeast (gram-positive, sporeforming	Up to 10^3	Up to 10^2	10^2-10^4	10^4-10^6
Anaerobes				
Bacterioids (gram-negative, nonsporeforming)	rarely	0-10^3	10^3-10^7	10^9-10^{12}
Bifidobacteria (gram-positive, nonsporeforming)	rarely	0-10^4	10^3-10^9	10^4-10^{11}
Pepto-streptococci (gram-positive, non-sporeforming)	rarely	0-10^3	10^2-10^6	10^{10}-10^{12}
Clostridia (gram-positive, spore-forming)	rarely	rarely	10^2-10^4	10^6-10^{11} (according to other sources, up to 10^5)
Eubacteria (gram-negative and gram-positive, spore-forming and non-sporeforming)	rarely	rarely	rarely	10^9-10^{12}

Table 3: Comparison of the qualitative composition of the microbiota according to the microbiota research projects of healthy American (HMP) and European (MetaHIT) populations[19]

Nomenclature of bacteria	HPM (American)	MetaHIT (European)
Bacteroidetes phylum:		
Bacteroides spp	51.1%	21.8%
Alisitpes spp	12.3%	8.6%
Prevotella spp	5.7%	11.8%
Other species	6.6%	3.6%
Firmicutes phylum:		
Eubacterium spp	6.9%	14.7%
Ruminococcus spp	3.7%	6.0%
Faecalibacterium spp	3.5%	5.7%
Dialister spp	2.3%	4.0%
Roseburia spp	1.5%	3.9%
Butyrivibrio spp	1.5%	3.0%
Other species	2.6%	6.0%
Protobacteria phylum:		
Sutterella spp	1.1%	0.6%
Escherichia spp	0.8%	1.0%
Other species	0.2%	1.0%
Verrucomicrobia phylum:		
Akkermansia spp	0.9%	2.3%
Actinobacteria phylum:		
Bifidobacterium spp	0.4%	2.1%
Other phyla:		
Other species	0.3%	0.5%

communities.[22] Enterotype 1 is characterized by the predominance of *Bacteroides spp.*, enterotype 2 by *Prevotella spp.*, and enterotype 3 by representatives of the Firmicutes phylum, including species such as Ruminococcus and Faecalibacterium.[19] The researchers found that the enterotypes differ in the ability to process incoming food components, the synthesis of vitamins, etc., It was noted that enterotype 1 is more common in people who prefer to consume a large amount of proteins and fats of animal origin, and enterotype 2 in people whose diet is predominantly plant-based. The formation of enterotype 3 is promoted by a diet rich in carbohydrates.[23-25]

Another aspect that influences the GM composition is the ethnic origin of a person. In 2020, the presence of population and continental specificity of enterotypes was proved due to the fact that the area of residence determines the dietary pattern. It has been established that such differences are caused by the genetic characteristics of certain ethnic groups under conditions of homogeneous environmental factors.[23-25]

Gut Microbiota in CKD

The data accumulated to date on changes in the microbiota in CKD are characterized by high heterogeneity. The predominant number of studies was conducted on patients with stage 5 CKD. The number of studies on pre-dialysis patients is significantly less.

In several studies, the results of quantitative changes coincide. Thus, the authors clearly show a decrease in the number of bacteria from the families Bifidobacteriaceae, Lactobacillaceae, and Prevotellaceae. Members of the families Micrococcaceae, Clostridiaceae, Peptostreptococcaceae, and Pseudomonadaceae are reduced in patients at different stages of CKD in different

countries. Regarding the families Lachnospiraceae and Enterobacteriaceae, the authors demonstrate conflicting results. With regard to representatives of other families, comparison of the results is not possible as the analysis of each of these families of bacteria is presented in only one work. It is important to note that two published studies in patients with pre-dialysis stages of CKD did not reveal quantitative differences in the composition of the intestinal microbiota compared with healthy controls [Table 4].

Presumably, the reason for the high variability of the obtained data is several factors. As shown above, in healthy individuals, the composition of the intestinal microbiota is determined by sex, age, type of diet taken by pharmacotherapy, and biochemical processes in enterocytes. It seems appropriate to conduct a systematic review of the composition of the intestinal microbiota in control groups and evaluate quantitative changes in the light of demographic and environmental data on patients, but such an analysis was not carried out in the reviewed publications. Conducting studies with large numbers of patients, dividing into groups not only by the stage of CKD but also by other factors, will expand the understanding of the mutual influence of external and internal environmental factors, CKD, and the quantitative diversity of the intestinal microbiota in patients. Greater involvement of patients at the pre-dialysis stages and long-term observational studies are also important for understanding the dynamics of GM composition.

The concept of the microbiota as a separate organ, which emerged in the last decade, was naturally advanced to the intestine–kidney system.[35] GM can affect both the function of the intestinal wall and various human organs (kidneys, adipose tissue, hypothalamus–pituitary–kidney system, etc.) through low-molecular-weight mediators and metabolites that enter the blood. In 2016, researchers noted that uremic toxins of intestinal origin play a significant role in the progression of CKD.[10,36,37]

Under the influence of increased concentrations of urea in the microcirculatory bed, the permeability of enterocytes increases due to its direct impact on membrane proteins. As a result, urea enters the lumen of the intestine. In response, intestinal bacteria begin to produce urease, under the influence of which urea breaks down to ammonium hydroxide. Ammonium hydroxide is absorbed through the intestinal wall into the blood along with other toxic waste products of GM, which leads to chronic intoxication and encephalopathy.[38-41]

In the late stages of CKD, a deficiency of *Lactobacillus spp.* and a decrease in the number of *Bifidobacterium spp.* and *E. coli* is observed in the large intestine with a parallel increase in the number of enteropathogenic strains. The number of enterobacteria of *Enterobacter spp.* and *Citrobacter spp.* also increases. The relationship between the level of urea in the blood and the amount of bacteroids in the feces that produce urease has been established. In turn, *E. coli* and *Lactobacillus spp.* are involved in the utilization of ammonia, playing their role in maintaining the integrity of the intestinal barrier. A decrease in *E. coli* and *Lactobacillus spp.* is followed by an increase in the amount of ammonia entering the bloodstream.[42-44]

The relation between intestinal dysbiosis and endotoxemia-mediated inflammation was demonstrated in a pilot study comparing the blood microbiome profile of patients with CKD and a control group with the help of 16S ribosomal RNA sequencing. As a result of metagenomic studies, the possibility of systemic bacteremia was confirmed. According to the results of the conducted studies, it was also confirmed that the GIT in CKD is a source of microorganisms in the bloodstream, leading to systemic inflammation and sepsis in HD patients.[37,45,46]

In the case of azotemia, the function of pancreatic beta cells is compromised and type 2 diabetes mellitus progresses in patients with CKD.[47,48] It is known that in azotemia, the process of protein carbamylation occurring in the patient's body under the influence of excess urea contributes to the development of atherosclerosis and ultimately leads to an increase in the mortality of CKD patients. The authors of the study concluded that the plasma level of protein-bound homocitrulline (PBHCit), which results from carbamylation, is a predictor of increased cardiovascular risk in patients with stage 5 CKD, supporting the relationship between uremia, inflammation, and atherosclerosis.[49]

Uremic toxins include p-cresyl sulfate, indoxyl sulfate, cresol, and trimethylamine-N-oxide (TMAO), the levels of which increase in blood serum as kidney failure progresses. These toxins increase the permeability of the intestinal wall.[50-54] By their nature, these uremic toxins are products of protein metabolism; therefore, a low-protein diet should be considered the most important method of GM correction in CKD.[52,53,55]

In patients with CKD, GM-synthesized toxins when they enter the bloodstream contribute to a decrease in the GFR and the progression of renal failure, which was demonstrated through the example of the tryptophan amino acid.[56] GM-produced toxins that enter the bloodstream also affect the activation of serum protein kinases, increasing the calcification of the arteries mediated by these enzymes.[57-59]

GM Correction in CKD

In connection with the described role of GM in the pathogenesis of CKD, the need to study the ways to correct is obvious. GM correction in CKD should be carried out to reduce the production of uremic and intestinal toxins and prevent metabolic (insulin resistance, vascular calcification) and other disorders.[60] A low-protein diet, adsorbents, prebiotics, and probiotics can be used to

Table 4: Quantitative changes in the gut microbiota in patients at different stages of CKD[21,26-34]

Nomenclature of bacteria	Stages of CKD	Increase	Decrease	Country	References
Actinobacteria					
Atopobiaceae	4-5		Yes	China	[26]
Beutenbergiaceae	5	Yes		USA	[27]
Bifidobacteriaceae	5		Yes	Taiwan	[28]
	1-5		Yes	Taiwan	[21]
Brachybacterium	5	Yes		USA	[29]
Cellulomonadaceae	5	Yes		USA	[27]
Coriobacteriaceae	4-5	Yes		China	[30]
Corynebacteriaceae	4-5	Yes		China	[26]
Dermabacteraceae	5	Yes		USA	[27]
Micrococcaceae	5	Yes		USA	[27]
	4-5	Yes		China	[26]
Nesterenkonia	5	Yes		USA	[29]
Bacteroidetes					
Prevotellaceae	5		Yes	USA	[27]
	5		Yes	Taiwan	[21]
	5		Yes	China	[31]
Tannerellaceae	5	Yes		China	[30]
Firmicutes					
Acidaminococcaceae	5		Yes	China	[26]
Catabacter	5	Yes		USA	[27,29]
Catenibacterium	5	Yes		USA	[29]
Clostridiaceae	5	Yes		USA	[27]
	5	Yes		China	[26]
		Yes		Austria	[32]
Coprobacillaceae	5	Yes		USA	[27]
Enterococcaceae	5		Yes	Taiwan	[28]
Erysipelotrichaceae	5		Yes	Taiwan	[21]
Lachnospiraceae	5		Yes	China	[26]
	5	Yes		Austria	[32]
	5		Yes	China	[31]
Lactobacillaceae	5		Yes	USA	[27]
	5		Yes	Taiwan	[28]
	1-5		Yes	Taiwan	[21]
Peptococcaceae	4-5	Yes		China	[26]
Peptostreptococcaceae	5	Yes		USA	[29]
	5	Yes		China	[30]
Proteobacteria					
Alcaligenaceae	5		Yes	USA	[27]
Alteromonas	5	Yes		USA	[27,29]
Enterobacteriaceae	5	Yes		USA	[29]
	5		Yes	Taiwan	[28]
Halomonadaceae	5	Yes		USA	[27,29]
Methylococcaceae	5	Yes		USA	[27,29]
Moraxellaceae	5	Yes		USA	[27,29]
Polyangiaceae	5	Yes		USA	[27,29]
Pseudomonadaceae	5	Yes		USA	[27,29]
	5	Yes		Taiwan	[28]
Thiothrix	5	Yes		USA	[27,29]
Xanthomonadaceae	5	Yes		USA	[27]
Verrucomicrobia					
Verrucomicrobiaceae	5		Yes	USA	[27]
All families	3-4	No difference		Brazil	[33]
	1--5			Belgium	[34]

correct GM. In case of successful correction, the intestinal wall permeability improves, the synthesis of intestinal toxins reduces, and the microflora in the large intestine normalizes.[61-63] Probiotics (bifidobacteria, lactobacteria) reduce the concentration of nephrotoxic products in the intestine, improve the intestinal epithelium, inhibit apoptosis of enterocytes, and normalize the barrier function of the intestinal wall.[64-66] Prebiotics, which are non-digestible components of food, also reduce the concentration of toxic products in the intestine and the severity of local inflammation caused by the toxic effect of urea on the intestinal wall, have a positive effect on human health, creating a microenvironment that stimulates the growth of useful components of the microbiota. Fructooligosaccharides, galactooligosaccharides, xylooligosaccharides, inulin, and pyrodextrins are widely used as such additives.[67-70]

Conclusive Statement

Thus, the study of the GM specifics and the nature of changes in its composition depending on the severity of CKD support the development of new approaches to the treatment of this category of patients. The correction of GM in CKD patients can be carried out to improve kidney function, the quality of life, and reduce the mortality rate.

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Visual Abstract