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Review Article

Microbiome and urine microbiota: modern concepts and gender features

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The review article provides definitions and presents current data on the biological significance of the microbiome and microbiota of urine. The urinary microbiota is less well understood than the intestinal microbiota, but its biological role is complex and multifaceted. To date, its importance in the formation of colonization resistance, which prevents the invasion of uropathogens, is obvious. An analysis of methods for assessing the microbiome and microbiota of urine was carried out. The shortcomings of widely used standard microbiological research methods are shown. The method of *16S* rRNA gene sequencing is described in detail. Information about the gender characteristics of the urine microbiota and the results of its study in healthy women and men are given. Further progress in the study of the urobiome is associated with the acquisition of new technologies for genomic research and the development of bioinformatics.

Keywords: urine microbiota; microbiome; urobiome; sequencing; *16S* rRNA gene.

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Обзорная статья

Микробиом и микробиота мочи: современные представления и гендерные особенности

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В обзорной статье даны определения и представлены современные данные о биологическом значении микробиома и микробиоты мочи. Микробиота мочевыводящих путей изучена хуже по сравнению с микробиотой кишечника, однако ее биологическая роль сложна и многогранна. К настоящему моменту очевидно ее значение в формировании колонизационной резистентности, предотвращающей инвазию уропатогенов. Проведен анализ методов оценки микробиома и микробиоты мочи. Показаны недостатки широко используемых стандартных микробиологических методов исследования. Подробно описан современный метод секвенирования гена *16S* рРНК. Приведены сведения о гендерных особенностях микробиоты мочи и результаты ее исследования у здоровых женщин и мужчин. Дальнейший прогресс в исследовании уробиома связан с получением новых технологий геномных исследований и развитием биоинформатики.

Ключевые слова: микробиота мочи; микробиом; уробиом; секвенирование; ген *16S* рРНК.

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ЭКО•ВЕКТОР

MICROBIOTA AND MICROBIOME: BASIC CONCEPTS

The human body is inhabited by numerous microorganisms that are in symbiotic relationships with each other and with the host organism. All of them are united in the collective concept of microbiota that characterizes the totality of microbial communities more accurately than the term microflora that refers to plants. Organs and systems, namely, intestines, skin, vagina, and biliary tract, etc., have their microbiota. The human microbiota contains approximately 10^{13}–10^{14} cells, including more than 40,000 bacterial strains that belong to 1800 genera and up to 10 million unique genes [1–3]. Moreover, the human microbiota includes not only bacteria but also archaea, eukaryotes, such as protozoa, fungi, nematodes, and viruses. The human microbiota composition is quite specific and individualized. In addition, some changes in the microbiota may be noted with the aging of the organism and in response to various exogenous and endogenous influences.

The totality of all genomes of the human microbiota is referred to as the microbiome. It was proposed by the American scientist Joshua Lederberg in 2001 [4]. The amount of genetic information in the gut microbiota alone is approximately 100 times greater than that of the human genome [5]. In general, the concept of microbiome refers to the ecosystem inhabited by microorganisms, which interact with it and use its resources. The study of genes responsible for the formation of the microbiota of various localizations is recognized as one of the most promising fields of research in biomedicine.

The microbiota of each person is unique and is important in maintaining macro-organism homeostasis. The biological role of the microbiota cannot be overestimated. This system influences its owner and interacts with him/her, adapting to the signals and information coming from him/her. Through microorganisms, a person performs functions that are not encoded by his/her genome, that is, provides protection against virulent pathogens, receives additional energy from food, promotes the synthesis of biologically active substances, performs immunogenic, mutagenic, or antimutagenic functions, and participates in carcinolytic reactions [6].

For a long time, the dogma of sterility of the urine of a healthy person was not questioned in medical science. In such cases, it was assumed that the urine does not contain microorganisms. This concept was supported mainly by the imperfection of laboratory diagnostic methods, although many clinicians noted that in patients with cystitis symptoms and multiple negative results of urine cultures, treatment with antibiotics often leads to the disappearance of symptoms. In 1979, a group of British microbiologists led by Rosalind Maskell, while incubating "sterile" urine under conditions of high carbon dioxide content, isolated slowly growing gram-positive microorganisms, thereby proving the above concept as false [7]. Modern laboratory technologies detect microorganisms of 1210–1420 species in urine, whereas healthy people have no more than 12% of them. Moreover, under various pathological conditions, their number increases significantly, for example, up to 25% of microbial species are detected in patients who underwent kidney transplantation [8]. The microbiome of the urinary tract began to be carefully studied much later than the microbiome of other organs and systems. Thus, in connection with the prevailing concept of urine sterility in a healthy person, its study was included in the Human Microbiome Project of the US National Institutes of Health only in 2012, 5 years after its start. However, the results obtained during this project unequivocally confirmed the fact that the urine of healthy people is nonsterile and contains numerous anaerobic and aerobic microorganisms [9–11]. Therefore, we had to reconsider the existing ideas about the etiology and pathogenesis of many diseases. Nowadays, the imbalance of the urinary microbiota is undoubtedly important in the development of not only urinary infections but also other urological diseases [12–14].

METHODS FOR STUDYING THE MICROBIOTA AND URINE MICROBIOME

Traditionally, the detection of microorganisms in the urine has been based on the results of standard urine cultures. According to the clinical guidelines of the Ministry of Health of the Russian Federation on bacteriological analysis of urine in 2014, for microbiological research, universal, selective, or differential diagnostic media intended for cultivation must be used under a normal atmosphere at 35–37 °C for 18–24 h [15]. International laboratories also used several nutrient media (blood agar and McConkey agar) and aerobic cultivation conditions at 35 °C [16]. These methods have very limited capabilities because they detect a relatively small number of microorganisms, mainly aerobic fast-growing bacteria, such as *Escherichia coli* [17]. In standard cultures, up to 92% of false-negative results were recorded [16].

An expanded quantitative urine culture (EQUC) is much more sensitive and can detect up to 72% of urobiome microorganisms [18]. In EQUC, a 100 μL of urine sample is inoculated on culture media (blood agar, colistin–nalidixic acid agar, and McConkey agar) and incubated in 5% CO_2 for 48 h. In a study by Price et al. [19], only 33% of uropathogens were detected by standard urine culture, whereas the optimized EQUC protocol allowed the identification of 84% of microorganisms. With this method, Hilt et al. [16] identified 35 different genera and 85 bacterial phyla in urine samples of women, and the most common microorganisms were from the genera *Lactobacillus* (15%), *Corynebacterium* (14.2%), *Streptococcus* (11.9%), *Actinomyces* (6.9%), and *Staphylococcus* (6.9%).

The results of both standard and extended urine cultures are influenced by several factors that must be considered in data interpretation. These include the method of urine sampling (suprapubic puncture, bladder catheterization,

and natural urination), uneven spatial distribution of microorganisms in different sections of the urinary tract, sex differences, age-related characteristics, presence of concomitant diseases, intake of antibacterial and other drugs, diet, physical activity, and environmental factors [20].

When studying the urinary tract microbiota, the gold standard is considered the sequencing of the nucleic acids of microorganisms, that is, the determination of their nucleotide sequence. In 2012, Wolfe et al. [21] conducted sequencing of the *16S* ribosomal RNA (rRNA) gene, revealed microflora in the urine of healthy women, and thus put an end to the false myth about urine sterility. Subsequently, sequencing became widespread both in scientific research and clinical practice. However, this technique is not standardized, which limits the possibility of its even wider use. Two types of sequencing are known, namely, whole genome sequencing (WGS) and metagenomic sequencing [22]. WGS is performed to determine the genome of a specific bacterium, whereas metagenomic sequencing is performed on mixed populations of microorganisms. Metagenomic sequencing aimed to identify the microorganisms present in a particular study sample. Most studies of the microbiome, including urine, are based on the sequencing of the *16S* rRNA gene of prokaryotic microorganisms. The *16S* rRNA gene is ubiquitous in all bacteria, whereas it is absent in mammals and contains nine hypervariable regions (V1–V9) [23], which enables identifying various bacteria by taxonomic comparison of the resulting sequences with the reference genomes from international databases. Depending on the sequence and choice of databases, identification can be performed down to the species level; however, usually, it results in a combination of species, genera, and phyla of microorganisms [18]. To describe the results of such identification, the general term "operational taxonomic unit" is often used, which combines decoded *16S* rRNA gene sequences with 97% identity, which is usually sufficient to understand the species of microbes. This process is called metataxonic. Viruses and fungi do not have the *16S* rRNA gene and, therefore, cannot be detected, although they are an integral part of the microbiome.

In accordance with modern concepts, the concept of "sterile" should not be used in relation to the urinary tract [24]. In general, the urine microbiota is less numerous and diverse than that of other localizations. For example, the female urine microbiota averaged 10^4–10^5 colony-forming units (CFU)/mL compared with 10^{12} CFU/g in feces [25].

The data obtained by urinary *16S* rRNA sequencing indicate that the urinary microbiome at the phyla level in men and women is almost the same. In both sexes, the majority of bacteria belong to the *Firmicutes* phylum (men, 65%; women, 73%). The other most common phyla of organisms found in the urine are *Actinobacteria* (men, 15%; women, 19%), *Bacteroidetes* (men, 10%; women, 3%), and *Proteobacteria* (men, 8%; women, 3%) [26]. Representatives of these types of bacteria account for up to 97% of all urine microorganisms. The main sex differences in the urobiome are manifested in the form of the dominance of some genera of microorganisms depending on sex. Thus, bacteria of the *Corynebacterium* and *Streptococcus* are more often found in men, and *Lactobacillus* are more often detected in women [26, 27].

URINE MICROBIOME OF HEALTHY WOMEN

The urine of healthy women of all age groups is nonsterile, which was proven by sequencing in 2012 by Wolfe et al. [21]. The urine contains numerous microorganisms with a predominance of *Lactobacillus spp.*, *Prevotella spp.*, and *Gardnerella spp*. [28].

Representatives of *Lactobacillus* are the most numerous among microorganisms found in the urine microbiome of healthy women [29]. However, not all *Lactobacillus* species are associated with healthy microbiota. Thus, *Lactobacillus crispatus* is characteristic of the urobiome of healthy women, and *Lactobacillus gasseri* is more often isolated from women with urge urinary incontinence [25]. The prevalence of *Lactobacillus spp*. in young women decreased during the postmenopausal period, which contributes to the colonization of the urinary tract by uropathogens and the development of urinary tract infections [29].

Gardnerella is frequently isolated from urine samples of healthy women [30]. However, *G. vaginalis* often causes bacterial vaginosis and contributes to the development of recurrent lower urinary tract infections. The mechanism of the pathological action of *G. vaginalis* was studied by Gilbert et al. [31]. Exposure of the bladder to *G. vaginalis* promotes the release of *E. coli* from intracellular bladder reservoirs and causes cystitis recurrence. The authors revealed that even short-term exposure to *G. vaginalis* causes apoptosis of the bladder epithelium and exfoliation, which persisted even after the disappearance of *G. vaginalis* from the urinary tract [31]. These data indicate that the overgrowth of *G. vaginalis* is a possible trigger for urinary tract infections.

Naboka et al. [32] conducted a consistent series of studies on the structure of microbiota in healthy women by using the polymerase chain reaction (PCR) and microbiological methods, and the test material was inoculated on nutrient media for facultative anaerobic bacteria (FAB) and nonclostridial anaerobic bacteria (NAB). No sterile cultures were found in a bacteriological study of 60 urine samples from healthy sexually active women. In all cases, microorganisms were present in different variants of multicomponent associations of FAB and NAB. In the FAB group, coagulase-negative staphylococci and *Corynebacterium spp*. were detected during the day at >60%. In the NAB group, *Eubacterium spp.*, *Peptococcus spp.*, *Propionibacterium spp.*, and *Lactobacillus spp*. were detected more often. The level of bacteriuria for all microorganisms verified in the urine of healthy women in the vast majority of cases was $<10^3$ CFU/mL. No significant differences were noted in the frequency of detection of various bacterial genera in the urine during the day [32].

The origin of bacteria from the microbial community of urine remains unclear. The anatomical proximity of the genital and urinary tracts suggests that the vagina may be the main source of the urinary microbial community. In 2016, Naboka et al. [33] studied the microbiota of the urine and vagina of healthy postmenopausal women. For this purpose, 20 conditionally healthy women (mean age 59.0 ± 2.1 years), who were in the climacteric period for >8 years, were examined. A bacteriological examination of urine and vagina was performed on an expanded set of nutrient media for the cultivation of FAB and NAB and PCR of a midstream specimen of morning urine. In both urine and vagina, FAB was detected with a predominance of coagulase-negative staphylococci, and the bacterial patterns of the studied biotopes were comparable. Moreover, NAB *Megasphaera* spp., *Veillonella* spp., *Prevotella* spp., *Mobiluncus* spp., and *Fusobacterium* spp. were detected in the urine, whereas they were absent in the vagina. Cluster analysis did not reveal significant differences in the concentration of the same microorganisms isolated from the urine and vagina. Thomas-White et al. [34] conducted a metagenomic analysis of bacterial strains isolated from the vagina and bladder and revealed a significant similarity between them, for both uropathogens (*E. coli* and *S. anginosus*) and commensal microorganisms (*Lactobacillus iners* and *L. crispatus*). The results of the two aforementioned studies support the need to evaluate the bladder microbiota in women in the context of the vaginal microbiota.

The intestines are a possible source of microorganisms in the urine. Dubourg et al. [35] analyzed 435 urine samples and isolated 450 different types of bacteria; 256 of them had never been found in urine before. Among the identified bacterial species, 161 (35%) were anaerobic microorganisms; 64.1% of all isolated species of bacteria were previously detected in the intestinal microbiota, and only 31.7% were found in the vaginal microbiota. These results suggest that many representatives of the urinary tract microbiota are actually from the gut [35]. The reduction in the recurrence rate of lower urinary tract infections after fecal microbiota transplantation supports the hypothesis of the importance of intestinal microflora in urinary infection development [36].

Curtiss et al. [37] studied the age-related aspects of the urine microbiota in women. Older women have decreased amounts of *Lactobacillus*, and postmenopausal women have increased amounts of *Mobiluncus* representatives in the urine, which are gram-positive rod-shaped anaerobes [37]. A possible reason for such changes is a decrease in estrogen level, which leads both to the elimination of lactobacilli and development of dystrophic and atrophic processes in the mucous membranes of the lower urinary tract.

URINE MICROBIOME OF HEALTHY MEN

Studies that focused on the microbiome of urine in men is much less than that in women. In general, the male urobiome is characterized by lower diversity of microorganisms [30]. Most authors indicate the predominance of *Corynebacterium* spp. and *Streptococcus* spp. in the male microbiota [17, 38, 39]. Nelson et al. [38] identified 72 genera of bacteria in the urine microbiome of healthy men; in addition to the two genera mentioned above, large amounts of *Sneatia* spp. and *Lactobacillus* spp. were noted. The proportion of *Lactobacillus* representatives in men is significantly less than that in women [40]. *Staphylococcus haemolyticus* is also often detected in healthy men [41].

In 2014, authors from the Rostov State Medical University studied the composition of the microbiota of the lower urinary tract and genital organs of healthy men. A bacteriological examination of urine and ejaculate was performed on an expanded set of nutrient media for FAB and NAB. The dominant FAB clusters were *Corynebacterium spp*. and coagulase-negative staphylococci (67.9% each), and *Eubacterium* spp. were dominant among NAB [42].

The urobiome of men aged >70 years is characterized by a high diversity of microorganisms, which potentially correlates with an increased risk of kidney, prostate, and bladder diseases [43].

CONCLUSION

The urinary tract microbiota is less investigated than the intestinal microbiota; however, its biological role is complex and multifaceted. To date, its importance in the formation of colonization resistance, which prevents the invasion of uropathogens, is apparent. The imbalance of microorganisms detected in various urinary system pathologies can be one of the key links in the pathogenesis of their development, the effect on which will help create new treatment and prevention methods in the future. The study of the relationship between the intestinal microbiota and urobiome would radically change the approaches to the treatment of patients with recurrent urinary tract infections.

Further progress in the study of the urobiome is associated with the acquisition of new technologies for genomic research and bioinformatic development. In addition, research on the microbiome is already advancing to a qualitatively new level, from describing its composition and studying the mechanisms of functioning to developing individual therapeutic agents based on the protective properties of the microbiota.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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