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Review

Association of Microbiota and Overactive Bladder: A Mini Literature Review

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HIGHLIGHTS

- The urine and urinary tract are not sterile and contain special microbiota.
- Some unique bacterial strains were identified in overactive bladder patients.
- Microbiota is associated with overactive bladder and can be one of the causes of it.

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ABSTRACT

Overactive bladder (OAB) is a common urinary disorder that affects both sexes. This disorder has a very strong and direct effect on the quality of the personal and social life of patients. Some recent studies have shown that urine and urinary tract are not sterile and contain special microbiota (communities of special microorganisms that are found in and on an individual). Thus, the goal of this review was to answer the question of whether microbiota can lead to the overactive bladder.

Keywords: Overactive Bladder; Microbiota; Urinary Tract; 16S rRNA; Metagenomic Sequencing

Introduction

It is well known that microbes and humans have closely related and healthy body have a variety of microorganisms (1, 2). Microbes play a significant role in human health and disease and can cause homeostasis in the body or activities such as metabolism and defense (3). Today, the terms “microbiome” and “microbiota” are widely used in clinical science. Microbiota refers to the collection of microorganisms that reside in the part of the body, while microbiome means that the pool of genomes and genes of the microorganisms that live in the host (4).

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In 2008, the national institutes of health conducted the human microbiome project (HMP) to study the human microbiome in 242 healthy individuals (5). In this interdisciplinary project, the microbiome of different sites of the body (including skin, gastrointestinal (GI) tract, oral cavity, nasal cavity, and vagina) was examined and its relationship with human health and disease was analyzed (5). Initially, urine and urinary track were not included in the HMP studies. One of the reasons for this was that urinary tracts were maintained sterile and it was thought that urinary disorders were caused by the invasion of an external pathogen (6).

For many years, the concept of microbiology was based on the technique of bacterial culture. Accordingly, the presence of bacteria was confirmed if the culture was positive. Currently, with the advent of methods beyond culture, the presence of bacteria in the various parts of the body has been identified even under health conditions. Methods such as metagenomic analysis of bacteria have led to the discovery of the presence of hard or slow-growing bacteria in areas that were considered sterile (7-9).

Microbiota and the Urinary Tract

Advances in quantitative urine culture (EQUC), 16S rRNA and metagenomic sequencing have led to an increase in knowledge of the specific microbiota of urine (9-12). In such studies, urine is taken directly from the bladder (with direct suprapubic aspiration) so that the examined microbiota is exclusively related to the urine and is not contaminated (9). The EQUC technique helps to examine live bacteria, which were not identified by traditional cultures (12). Because this culture technique uses a large amount of urine in specific culture media and temperatures (13). Also, due to the 16S rRNA gene is highly conserved; it is a good target for bacterial sequencing. Because the presence of 9 hypervariable gene regions (V1-V9) in this conserved gene makes it possible to classify the bacteria in the sample by sequencing even one region of these genes (14, 15). The stages of urinary microbiota analysis are shown schematically in Figure 1. Therefore, with the help of these methods, live hard/slow bacteria could be evaluated in the urine and the microbiota pattern of urine and urinary tract were determined (12). This microbiota pattern plays an important role in urinary tract health and disease (8, 16, 17). The association of microbiota with urinary tract health/disease is directly affected by microbiota changes in a variety of conditions, including seasonal, geographical and nutritional conditions (3). Therefore, by targeting specific microorganisms present in the urinary system and their environmental conditions, more efficient diagnosis and treatment can be achieved.

Urinary Microbiota and the Overactive Bladder

Recent studies have shown that alterations in the urinary microbiota can be associated with many urological diseases, such as the overactive bladder, interstitial cystitis, chronic prostatitis, and bladder cancer (14, 16, 18). The international continence society (ICS) defines overactive bladder (OAB) as the sudden urge to urinate, with or without urge incontinence, often accompanied by frequency and nocturia in the absence of identifiable causes such as urinary tract infection (19, 20). OAB has been seen in both sexes and its prevalence increases with aging (21).

In addition to the financial burden, OAB has an adverse effect on people's quality of life, sexual function, sleep, and physical and social activities. Also, it affects people's mental health due to disappointment, anxiety, shame, and stress (22, 23). OAB diagnosis does not have a standard procedure and is performed only by physical examination and voiding diary. However, the possibility of infection and abnormal pathology of the urinary tract should be excluding (14).

The etiology and effective treatment of the OAB is not yet fully clear. Possible causes are neuromuscular and muscarinic receptor dysfunction, but given that in many OAB patients anti-muscarinic receptor, Botox, or other treatments are ineffective. Therefore, OAB can be caused by other reasons or a complex of reasons and microbiota can be one of them (17, 24, 25). The articles related to the relationship between microbiota and active bladder, which are reviewed in this study, are summarized in Table 1.

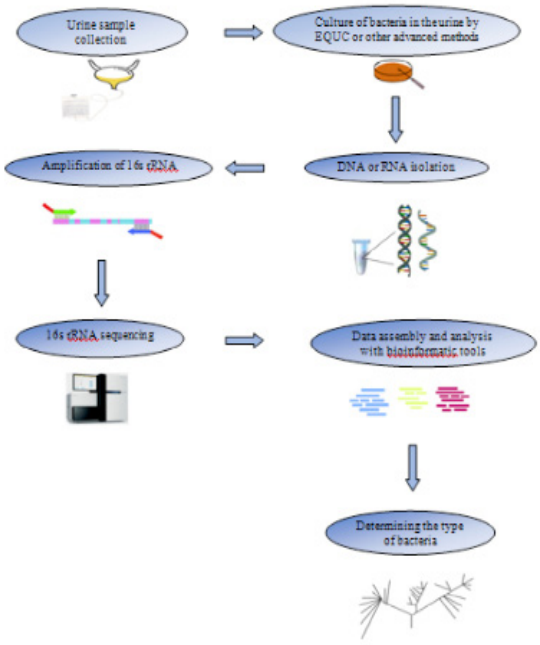

Figure 1: Schematic steps of the urine microbiota examination

Table 1. Summary of publications, addressing the role of urinary microbiota in OAB patients

References	Sample size	Country	Sample collection	Analysis technique	Main finding
Hilt et al., 2014 (24)	41 OAB women and 24 health women	USA	Transurethral catheterization	EQUC1 and 16S rRNA sequencing	Common genera: Lactobacillus, Corynebacterium, Streptococcus, Actinomyces, Staphylococcus, Aerococcus, Gardnerella, Bifidobacterium, Actinobaculum Uniqe genera in OAB group: Aerococcus and Actinobaculum
Siddiqui et al., 2014 (26)	Two samples from one OAB woman	Norway	Not described	16S rDNA sequencing	Streptococcus, Atopobium, Ureaplasma, Prevotella, Bacteroides
Wu et al., 2017 (27)	30 OAB women and 25 health women	China	Transurethral catheterization	16S rRNA sequencing	Decreased genera in the OAB group: Prevotella, Dialister, Fusobacterium, Jonquetella, Campylobacter, Finegoldia, Anaerococcus, Lactobacillu, Pyramidobacter, Ureaplasma, Enterococcus, Novosphingobium, and Lactococcus Increased genera in the OAB group: Sneathia, Staphylococcus, Proteus, Helcococcus, Gemella, Mycoplasma, and Aerococcus
Gill et al., 2018 (28)	24 OAB women and 22 health women	UK	MSU2 collection	Urothelial-cell-sediment culture	Common bacteria in OAB group: E. coli, Enterococcus faecalis, Proteus, Klebsiella, Enterobacter, Serratia and Pseudomonas Common bacteria in health group: Staphylococcus, Streptococcus, Citrobacter and Lactobacillus
Perovic et al., 2019 (29)	6 OAB women	Portugal	MSU2 collection	Optimized CULT and 16s rRNA sequencing	Common bacteria: Bifidobacterium species and Corynebacterium aurimucosum Common bacteria in sever OAB patiants: Gardnerella vaginalis and Ureaplasma urealyticum

EOUC: Enhanced Quantitative Urine Culture; MSU: Midstream Specimen of Urine; OAB: Over Active Bladder

Hilt and colleagues used 16S rRNA gene sequencing and an EQUC protocol to examine live bacteria in the urine of 41 women with OAB and 24 healthy women. According to the EQUC technique, there were 52 positive culture samples (80%), while 92% of them were negatively reported by the standard culture protocol. Among the isolated genera, *Lactobacillus* (15%) was the most prevalent followed by *Corynebacterium* (14.2%), *Streptococcus* (11.9%), *Actinomyces* (6.9%), and *Staphylococcus* (6.9%). In patients with OAB, *Aerococcus* and *Actinobaculum* were unique genera that were not seen in normal samples. The Hilt study showed that urine contains live bacteria that originate from its microbiota and can be unique in OAB (24).

In 2014, another study was performed on a 61-year-old woman who had urinary symptoms and OAB for many years. In the first stage, bacteriuria (*Streptococcus*) was diagnosed with standard bacterial cultures and treated with antibiotics. By performing culture-independent 16S rDNA sequencing on the woman's urine, a set of different bacteria, including fastidious bacteria, were identified. A year later, the patient was re-examined for severe urinary symptoms and no infection was reported by standard culture methods. But, the 16S rDNA results showed the same pattern as last year. Due to negative urine culture, the persistence of urinary symptoms, and the similarity of 16S rDNA results with the previous year, the association between microbiota and OAB becomes stronger (26).

In 2017, Wu and colleagues studied urinary microbiota in people with OAB. In this study, the urine of 30 patients with OAB and 25 healthy individuals (none of them had a urinary tract infection) were analyzed. 16S rRNA Sequencing results showed that 13 genera, including *Prevotella*, *Dialister*, *Fusobacterium*, *Jonquetella*, *Campylobacter*, *Finegoldia*, *Anaerococcus*, *Lactobacillus*, *Pyramidobacter*, *Ureaplasma*, *Enterococcus*, *Novosphingobium*, and *Lactococcus* were decreased in the OAB patients compared to the control group. In contrast, seven genera including *Sneathia*, *Staphylococcus*, *Proteus*, *Helcococcus*, *Gemella*, *Mycoplasma*, and *Aerococcus* in the OAB group were increased compared to the control group. Hence, there was a significant difference between the microbiota of the OAB group and the control. The results of this study showed that certain species, such as *Aerococcus*, were associated with some specific urinary symptoms. Also, urinary microbiota in OAB people is less diverse and is poorer in *lactobacilli* than in normal people. Finally, Wu et al., concluded that the high diversity and dominance of *Lactobacillus* in microbiota were two protective factors against OAB (27).

In another study, urinary tract microbiology activity was evaluated for 12 months in OAB patients and the control group. Microbial evaluation in this study was performed using the culture of urothelial cells from the urine sediment and its results were compared with the standard culture method. Among patients with OAB, *E. coli* was the most common species, followed by *Enterococcus faecalis*, *Proteus*, *Klebsiella*, *Enterobacter*, *Serratia*, and *Pseudomonas*. On the other hand, the most common species in the control group were *Staphylococcus*, *Streptococcus*, *Citrobacter*, and *Lactobacillus*. In this study, there are recurring and consistent differences in microbial load and dispersion of isolated species in the OAB and control group. The difference in the amount and type of bacterial colonization in the patients and healthy individuals indicates the effect of urinary tract microbiota on the incidence and severity of the disease (28).

In 2019, urinary microbiota in six OAB patients without urinary tract infection was examined using optimized CULT and 16S rRNA sequencing by Gill et al., These methods detected a very large number of bacteria in all patients with no criteria for urinary tract infection, which was related to 36 bacterial genera. Most of these bacteria are related to urinary tract infections, while standard culture methods have not been able to detect them. The most common bacteria in this study were *Bifidobacterium species* (28%) and *Corynebacterium aurimucosum* (22%). In patients with severe symptoms of OAB, *Gardnerella vaginalis* (46%) and *Ureaplasma urealyticum* (44%) were more common. Finally, Gill et al., conclude that urinary microbiota analysis is required to diagnosis and treatment of OAB using new culture and sequencing methods (29).

Conclusions

Today, it has been proven that urine and urinary tract are not sterile and have unique microbiota. These studies provide strong evidence that urinary microbiota changes in OAB patients. Therefore, the urinary microbiota was associated with OAB and may be used as a diagnostic and therapeutic marker. Studies with a large sample size can lead to a microbiota signature in OAB disease that can even distinguish between the disease and other urinary tract diseases with overlapping symptoms.

Authors' contributions

All authors contributed equally.

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Conflict of interest

All authors claim that there is no competing interest in this case report of surgery.

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Ethics statement
Not applicable.

Data availability
Not applicable.

Abbreviations
EQUC Quantitative urine culture

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