



Interstitial cystitis/bladder pain syndrome and recurrent urinary tract infection and the potential role of the urinary microbiome

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Abstract

Interstitial cystitis/bladder pain syndrome and recurrent urinary tract infections carry significant burden for those affected. As women enter the menopause, other factors may influence how these conditions manifest. The urinary microbiome has shown that the urine contains extensive numbers of bacteria. There is some evidence to suggest that it is altered depending on the menopausal state of the individual. It is possible that this alteration may go on to influence how the disease course of interstitial cystitis/bladder pain syndrome and recurrent urinary tract infections runs in the post-menopausal group. The review will explore these two conditions and the potential role of the urinary microbiome.

Keywords

Microbiome, urinary microbiome, interstitial cystitis, painful bladder syndrome, overactive bladder, stress urinary incontinence

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) and recurrent urinary tract infections (rUTI) are commonly encountered conditions in urogynaecology. IC/BPS is a condition of unknown aetiology. It presents with persistent pelvic pain perceived to be related to the bladder associated with urinary urgency and/or frequency. Guidelines suggest that history, examination, urine analysis, urine culture and cytology are all important in the assessment of these patients. In addition, where cystoscopy is recommended, the identification of Hunner's lesions (reddish mucosal lesions accompanied by abnormal capillary structures) is specified, as this can influence management plan.¹ A large American study estimated the prevalence to be between 3 and 6% in women over 18.²

rUTIs can be defined as recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs per year or two UTIs in the last six months.³ The prevalence of rUTI shows a higher frequency with very young children which gradually increases with age. Overall, the annual incidence of urinary tract infection is 12.6% in women.⁴ One study showed that 53% of women over the age of 55 reported

UTI recurrence.⁵ Although rUTIs have not been extensively investigated in the postmenopausal population, altered estrogen status has been thought to be a contributing factor to possible mechanisms for rUTIs such as frequent repeat ascending infections and chronic persistent infections in the bladder.⁶ The mechanism for these chronic or recurrent infections could be the IBC-QIR (intracellular bacterial communities (IBCs) and quiescent intracellular reservoirs (QIRs)) model, where uropathogens can persist in the bladder and survive antibiotic treatment and host immune responses.⁷

The term 'microbiome' refers to all microbiota in a defined microbial community.⁸ Molecular tools now allow the assessment of the composition of particular microbiomes and associations between the microbiome in both healthy and disease states can be investigated.

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The bladder was not included in the 'Human Microbiome Project' due to the assumption that urine is sterile until it reaches the urethra in healthy individuals. However, studies using 16S rRNA gene sequencing have identified that urine contains extensive numbers of bacteria. As urine is considered a reflection of what is happening in the bladder, this population of bacteria is referred to as the urinary microbiome.⁹

The aim of this review is to assess how the aging process can affect the urinary microbiome within healthy individuals and explore whether this may have any impact on IC/BPS and rUTIs.

Methods

An extensive search of literature databases was performed (PubMed, EMBASE) for publications (full text and abstracts) written in English. Keywords included recurrent urinary tract infection, postmenopausal women, bladder pain syndrome, interstitial cystitis and urinary microbiome.

Results

Worldwide, most women enter the menopause between the ages of 49 and 52 years. Physiologically, there is an increase in follicular stimulation hormone, widely fluctuating estrogen levels and the loss of the normal reproductive cycles. The postmenopausal period is biochemically characterized by an elevated FSH and lower estradiol levels.¹⁰ Ageing itself is associated with bladder remodelling and a decreased ratio of smooth muscle to collagen in addition to a reduced bladder capacity, detrusor bladder strength, bladder sensation, urethral closure pressure and urinary flow. The effect of menopause has been derived from studies looking at exogenous estrogen treatment in postmenopausal women. Estrogen receptors are found throughout the urinary tract. Observational data on postmenopausal women have shown that exogenous estrogen increases urethral profile pressure and urethral blood flow.¹¹

It is known that the vaginal environment changes during the menopause with the reduction in estrogen, and importantly, studies have shown that one of the effects of exogenous estrogen has been promotion of a *Lactobacillus*-dominant vaginal environment.¹² The nature of the urinary microbiome alters in response to a number of factors including firstly differing in health and disease states, secondly changing after the menopause and the thirdly how this change after the menopause can affect the disease states, for example IC/BPS and rUTI. While we are some way off answering these questions, the evidence base is growing.

The urinary microbiome refers to bacterial DNA and live bacteria that have been detected in the

human urine in the absence of clinical infection. It has been detected using expanded quantitative urine culture and culture independent methods such as high-throughput sequencing of the 16S rRNA gene. It appears to be dominated by *Lactobacillus*, *Gardnerella* and *Streptococcus*.¹³ Lewis et al. studied the urinary microbiome in the voided urine of asymptomatic adults.⁹ They collected samples from six males (age 39–83 years) and 10 females (age 26–90 years). The female samples showed a more heterogeneous mix of bacterial genera. When the female cohort were grouped by age (20–49, 50–69 and 70+ years), there was a core microbiome of 23 genera that was present in all three groups, with each age group having their own distinct subset of genera.

A further study by Pearce et al.¹⁴ looked at the urinary microbiome in women with urge urinary incontinence and compared it to controls. The UUI cohort was significant older, heavier and less likely to be using estrogen. The urinary microbiome in the UUI cohort was composed of increased *Gardnerella* and decreased *Lactobacillus* compared to the non-UUI microbiome. In addition, nine genera (*Actinobaculum*, *Actinomyces*, *Aerococcus*, *Arthrobacter*, *Corynebacterium*, *Gardnerella*, *Oligella*, *Staphylococcus* and *Streptococcus*) were more frequently cultured from the UUI cohort. *Lactobacillus gasseri* was detected more frequently in the UUI cohort and *Lactobacillus crispatus* most frequently detected in controls.

Curtiss et al.¹⁵ further investigated the effects of age and in particular menopausal status on the urinary microbiome. Clean catch urine from 79 healthy women with no urinary symptoms underwent 16S rRNA gene sequencing. Although there was no significant correlation between the age of a woman and the number of different genera identified, there was a trend towards decreased numbers of different genera from postmenopausal women. *Lactobacillus* was significantly more common in premenopausal women than in postmenopausal women, and *Mobiluncus* was significantly more common in postmenopausal women. The decreased number of genera in the postmenopausal group is similar to the decrease seen with aging in the gut microbiome.¹⁶

Two studies^{17,18} were identified looking at the urinary microbiome in patients with IC/BPS compared to controls. Meriwether et al.¹⁷ analysed vaginal and urinary samples from 23 IC/BPS patients and 18 non-IC/BPS patients. The average age of the entire study group was 33.61 ± 8.97 . This study demonstrated that premenopausal women with IC/BPS were not found to have significantly different urinary microbiomes compared to women without IC/BPS. Bresler et al.¹⁸ carried out a prospective case-controlled study, collecting mid-stream urine from 21 IC/BPS women and 20

asymptomatic female controls. Approximately 50% of each cohort were post-menopausal. Overall, there was no significant difference in the urinary microbiome of women with and without IC/BPS. However, IC/BPS patients with the *Lactobacillus* urotype were more likely to be pre-menopausal than the IC/BPS patients with the non-*Lactobacillus* urotype which were more likely to be post-menopausal. This is in keeping with the study described above.¹⁴ These two studies suggest that microbes may not contribute directly to IC/BPS but menopausal status of the patient might.

The menopause predisposes women to rUTIs. About 8% to 11% of post-menopausal women report rUTIs.¹¹ Animal models have shown that increasing age and multiple previous pregnancies result in an increased susceptibility to chronic uropathogenic *Escherichia coli* (UPEC) infection.¹⁹ Previous pregnancy, post-menopausal reduction in estrogen and aging make the genito-urinary tract distinctly different from the premenopausal state. The decline in estrogen can affect the urogenital epithelium, and we have described above that the urinary microbiome also alters in post-menopausal women with an overall decrease in *Lactobacillus* seen in both the vaginal and urinary microbiome. Vaginal estrogen replacement reduces the risk of UTI,²⁰ and *Lactobacillus* is restored²¹ in the vaginal microbiome but possibly also in the urinary microbiome. A Cochrane database systematic review on the use of estrogens for preventing UTIs in post-menopausal women concluded that when comparing vaginal oestrogens to placebo, vaginal oestrogens reduced the number of UTIs in post-menopausal women with RUTI; however, this varied according to the type of oestrogen used and the treatment duration.²²

Studies carried out in a population of post-menopausal women with antibiotic refractory rUTI looked at urine and bladder biopsy samples.⁷ Diverse bacterial species were cultured from both the urine and bladder tissue in these patients. 16S rRNA fluorescence in situ hybridisation (FISH) showed that bacteria formed communities resembling IBCs and QIRs within the bladder epithelium and within deeper layers. Histology of these specimens showed oedema and alteration of the architecture of the bladder wall. There was also evidence of a local adaptive immune response with the detection of lymphocytes within the mesenchyme and urothelium. In post-menopausal women, bacterial invasion into the human urothelium and the resulting immune response are important in the pathogenesis of rUTIs. Further studies investigating the possible altered urinary microbiome in this diseased state may guide future treatment therapies.

Conclusion

The urinary microbiome alters with age. The change in *Lactobacillus* in the post-menopausal urinary microbiome may be a contributing factor to the increased susceptibility of rUTIs. We have already seen how estrogen replacement can alter the *Lactobacillus* population in the vagina and reduce the risk of UTI. Further elucidation of the postmenopausal microbiome may also influence antibiotic treatment of UTI by offering a more targeted approach for the individual patient.

The urinary microbiome and its role in IC/BPS is less clear. Current evidence suggests that the microbial community within the bladder does not impact on IC/BPS. Studies with larger numbers looking at the urinary microbiome in the various disease states such as overactive bladder and stress incontinence are needed as well as data on how the urinary microbiome can change over time and its response to treatment for urinary disorders.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Guarantor

VK.

Contributorship

VK and AB researched literature and conceived the study. AB wrote the first draft of the article. All authors reviewed and edited the article and approved the final version of the article.

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