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**ORIGINAL ARTICLE**

# Pathophysiological Role of Hormonal Alterations in Recurrent Urinary Tract Infections among Postmenopausal Women: A Clinical Cross-Sectional Study

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## ABSTRACT

**Background:** In postmenopausal women, recurrent urinary tract infections (rUTIs) are common, occurring in most cases due to hormonal changes following the menopause. Urinary microbiota dysbiosis and compromised urothelial integrity have been implicated for estrogen deficiency.

**Objective:** In this study, the role of hormonal alterations, urinary microbiota, and immune markers in predisposing postmenopausal women to rUTI is investigated.

**Methods:** A cross-sectional study was done in n=150 postmenopausal women, n=75 with rUTIs and n=75 controls. ELISA, 16S rRNA sequencing and multiplex immunoassay were used to assess serum hormone levels, urinary microbiota composition and immune biomarkers. T-tests, chi-square tests and logistic regression were used in statistical analysis.

**Results:** Estradiol levels (10.3 ± 3.7 pg/mL vs. 17.6 ± 5.2 pg/mL; p<0.001), Lactobacillus abundance (22.4% vs. 54.1%; p<0.001) were significantly lower in women with rUTIs compared to women without rUTIs. As well, the rUTI group had elevated IL-6 and TNFα levels (p<0.01) and decreased E-cadherin and cathelicidin (p<0.01).

**Conclusion:** rUTIs in postmenopausal women are caused by the combined effect of hormonal alterations, microbiota dysbiosis, and immune dysregulation. These findings underscore the urgent need for personalized therapeutic strategies aimed at these factors.

**Keywords:** Postmenopause, Recurrent urinary tract infections, Hormonal alterations, Estrogen deficiency, Urinary microbiota, Immune biomarkers, Dysbiosis.

## INTRODUCTION

Urinary tract infections (UTIs) are the most common bacterial infections in the world, found in millions of people every year. There are anatomical and physiological differences that create a disproportionately higher incidence of UTIs for women[1]. Among women, such a population is the postmenopausal population that is particularly vulnerable for recurrent urinary tract infections (rUTIs), meaning three or more episodes in a year or two or more episodes in six months. This heightened susceptibility highlights a critical intersection of hormonal, immunological, and microbial factors that require more in depth investigation[2].

Natural biological transition in the form of cessation of ovarian estrogen production leads to profound systemic changes. The myriad effects of estrogen deficiency have been connected closely to urogenital atrophy and a variety of urinary symptoms including increased sensitivity to infections. The structural and functional integrity of the urogenital tract is maintained by estrogen, in part by promoting epithelial barrier health, modulating immune responses, and sustaining a Lactobacillus dominated microbiota. Postmenopausal women lose estrogen, which results in a dysbiotic shift in their urinary microbiota that shifts from Lactobacillus to uropathogenic organisms, like Escherichia coli[3].

Now we know that the urinary microbiota, previously considered sterile, is a dynamic microbial community that is important for urinary tract health. The microbial ecosystem of diverse bacterial species is in close contact with the host's immune system and epithelial barriers, and cooperates with the host to defeat pathogen invasion. Hormonal changes do this in postmenopausal women, increasing their risk of infection[4]. Loss of tight junction integrity in the urothelium is associated with estrogen deficiency, reduced production of antimicrobial peptides, and a pro-inflammatory state that promotes the urinary tract to infection[5].

In addition, estrogen levels drop and the vaginal and urinary microbiota change, which are tightly coupled. Usually, a healthy urinary microbiota consists of lactobacillus species that produce lactic acid, making an acidic environment unfavourable for pathogenic bacteria. The dramatic impact of hormonal changes on microbial composition is highlighted by reduced Lactobacillus populations and increased prevalence of uropathogenic organisms such as Escherichia coli and Gardnerella in postmenopausal women[6]. It is this shift toward dysbiosis that not only makes individuals more susceptible to infection, but also that makes treatment of the infection itself more difficult, as antibiotic treatments often do not restore the balance of microbes[7].

Beyond physical discomfort, rUTIs affect the quality of life and represent an economic challenge in postmenopausal women. Treatment of rUTIs is complicated by the emergence of uropathogens that are multidrug resistant as a result of the frequent use of antibiotics for rUTIs. This scenario shows that there is an immediate need for alternative therapeutic methods that address the root causes of rUTIs, such as hormonal deficiency and microbiota dysbiosis. Although strategies, including local estrogen therapy, probiotics and microbiota targeted interventions, hold promise to mitigate the burden of rUTIs, we do not have the required data[8, 9].

Although knowledge of UTI pathogenesis has improved, we still lack understanding of the interactions among hormonal changes, immune responses and microbial dynamics in postmenopausal women. How these relationships work needs to be investigated to develop personalized, effective treatment strategies. The aim of this study was to elucidate the pathophysiological mechanisms related to rUTIs in postmenopausal women by analyzing hormonal profiles, urinary microbiota composition and immune markers. In this work we take a cross-sectional approach in order to bridge critical knowledge gaps and inform the development of evidence-based interventions to alleviate the burden of rUTIs in this population[10].

## MATERIALS AND METHODS

A cross-sectional clinical investigation was planned, and undertaken at different tertiary care hospitals of Pakistan from may 2021 till December 2022. All participants provided written informed consent and ethical approval was obtained from Institutional Review Board of hospitals. The relationship between hormonal

alterations and recurrent urinary tract infections (rUTI) in postmenopausal women was studied in this work.

Subjects were postmenopausal women aged 55–80 years recruited from the outpatient urology and gynaecology clinics. They were divided into two groups: one comprising women with a history of rUTIs (n=75) and another of women without such a history (n=75). Participants had to be naturally menopausal for at least 12 months and not have used hormone replacement therapy within six months prior to the study. Excluded were women with active UTIs at recruitment or with a history of pelvic surgery, or urinary tract abnormalities or immune-suppressive disorders. They also excluded those who had previously used probiotics or antibiotics in the three months prior.

All participants provided fasting blood samples to measure serum estradiol, progesterone, and testosterone. Using standardized protocols, levels of hormones were quantified by enzyme-linked immunosorbent assays (ELISA). Samples of urinary microbiota and biomarkers were analyzed from clean catch midstream urine samples. 16S rRNA gene sequencing targeting the V3-V4 hypervariable regions was performed using the Illumina MiSeq platform, and DNA extraction for microbiota analysis was conducted using the QIAamp DNA Mini Kit. Bacterial diversity and relative abundance were assessed using the QIIME2 bioinformatics pipeline.

Biomarkers were quantified in urine samples to evaluate urothelial integrity and immune responses. Enzyme-linked immunosorbent assays (ELISA) were used to measure levels of E-cadherin as markers of epithelial barrier integrity. Multiplex immunoassays were employed to measure proinflammatory cytokines, including IL-6 and TNF-α. Levels of the antimicrobial peptide cathelicidin were assayed using ELISA to assess innate immune defense.

SPSS v 26.0 was used to perform the statistical analysis. Baseline participant characteristics were summarized by descriptive statistics. Independent t tests or Mann Whitney U tests were used to compare continuous variables, according to data normality. Categorical variables were used with chi square tests. Independent predictors of rUTIs were identified using multivariable logistic regression models that included variables including estradiol levels, Lactobacillus abundance, and inflammatory markers. Statistical significance was set at $p<0.05$.

## RESULTS

**Participant Characteristics:** The rUTI group included 75 postmenopausal women and the control group 75. The mean age of participants was 64.3 ± 7.1 years and no differences in BMI or parity between groups. Urinary symptoms, including frequency and urgency, were more prevalent in women in the rUTI group than in controls ($p<0.001$) as shown in table 1.

**Hormonal Profiles:** Women in the rUTI group had significantly lower serum estradiol levels (10.3 ± 3.7 pg/mL) compared to controls (17.6 ± 5.2 pg/mL; $p<0.001$). Progesterone and testosterone levels showed no significant differences between groups as shown in table 2.

Table 1: Baseline Characteristics of Study Participants

| Variable | rUTI Group (n=75) | Control Group (n=75) | p-value |
|---|---|---|---|
| Mean Age (years) | 64.7 ± 7.3 | 63.9 ± 6.8 | 0.524 |
| BMI (kg/m²) | 26.8 ± 5.1 | 26.2 ± 4.7 | 0.421 |
| Parity (mean number of births) | 2.3 ± 1.1 | 2.4 ± 1.0 | 0.632 |
| Urinary Symptoms (%) | 85% | 15% | <0.001 |

Table 2: Hormonal Profiles in Study Groups

| Hormone | rUTI Group (n=75) | Control Group (n=75) | p-value |
|---|---|---|---|
| Estradiol (pg/mL) | 10.3 ± 3.7 | 17.6 ± 5.2 | <0.001 |
| Progesterone (ng/mL) | 0.8 ± 0.3 | 0.9 ± 0.4 | 0.204 |
| Testosterone (ng/mL) | 0.6 ± 0.2 | 0.7 ± 0.3 | 0.108 |

Table 3: Urinary Microbiota Composition in rUTI and Control Groups

| Bacterial Genus | rUTI Group (%) | Control Group (%) | p-value |
|---|---|---|---|
| Lactobacillus | 22.4 | 54.1 | <0.001 |
| Escherichia coli | 38.2 | 14.7 | <0.001 |
| Gardnerella | 19.6 | 8.2 | 0.002 |

Table 4: Immune and Urothelial Biomarker Levels

| Biomarker | rUTI Group | Control Group | p-value |
|---|---|---|---|
| E-cadherin (ng/mL) | 45.3 ± 8.2 | 78.5 ± 10.6 | <0.001 |
| IL-6 (pg/mL) | 12.8 ± 4.1 | 7.2 ± 3.0 | <0.001 |
| TNF-α (pg/mL) | 10.5 ± 3.2 | 6.8 ± 2.1 | <0.001 |
| Cathelicidin (µg/mL) | 3.1 ± 0.9 | 6.5 ± 1.2 | <0.001 |

**Urinary Microbiota Composition:** 16S rRNA sequencing revealed significant dysbiosis in the rUTI group. Lactobacillus abundance was markedly reduced (22.4%) compared to controls (54.1%; $p<0.001$). Conversely, Escherichia coli and Gardnerella were significantly more prevalent in the rUTI group as shown in table 3.

**Immune and Urothelial Biomarkers:** Markers of urothelial integrity and immune response showed significant alterations in the rUTI group. E-cadherin levels were lower (45.3 ± 8.2 ng/mL) compared to controls (78.5 ± 10.6 ng/mL; $p<0.001$). Pro-inflammatory cytokines IL-6 and TNF-α were elevated in the rUTI group ($p<0.01$), while cathelicidin levels were reduced (3.1 ± 0.9 µg/mL vs. 6.5 ± 1.2 µg/mL; $p<0.001$) as shown in table 4.

## DISCUSSION

The results from this study offer important clues into the pathophysiological mechanisms of recurrent urinary tract infections (rUTIs) in postmenopausal women. Our results highlight the contribution of hormonal changes, microbiota composition, and immune dysregulation to the greater susceptibility of this population to rUTIs[11].

The most striking finding is the dramatic reduction in serum Estradiol levels amongst women with rUTIs compared with controls. It is well known that estrogen deficiency causes atrophy and reduced epithelial barrier function of the urogenital tract. Our study corroborated this as the low levels of E-cadherin, a marker of epithelial integrity, present in the rUTI group. Estradiol deficiency is associated with diminished urothelial defence and underscores the importance of hormonal balance in maintaining urinary tract health[5,12].

Urinary microbiota analysis revealed significant dysbiosis in women with rUTIs characterized by reduced Lactobacillus abundance and higher prevalence of Escherichia coli and Gardnerella. It has been shown that Lactobacillus species can protect against uropathogenic colonization by maintaining acidic pH. The likely result of the depletion of these beneficial bacteria and overgrowth of pathogenic species is a microenvironment conducive to recurrent infections. These findings highlight the potential of microbiota targeted therapies, probiotics, as adjunctive treatments of rUTIs[13,14].

Another critical factor identified in this study was immune dysregulation. The rUTI group had higher pro inflammatory cytokines levels (IL-6 and TNF-α) compared to the control group, which indicates that the rUTI group had a higher inflammatory state. Inflammation, on its own, is a natural defence mechanism, but persistent immune activation can break down tissue repair and increase susceptibility to infections[15]. In addition, reduced levels of cathelicidin, an antimicrobial peptide, further suggest an impaired innate immune response in women with rUTIs. These results emphasize the need for interventions to modify the immune response to reestablish homeostasis and prevent recurrent infection[16].

Strengths of this study are due to the comprehensive, integrating hormonal, microbiota and immune analyses to understand the multifactorial etiology of rUTIs in postmenopausal women. But, there are several limitations[17]. The cross-sectional design precludes causal inferences, the study population was

limited and perhaps generalizability of the findings was affected. These factors deserve future longitudinal study to understand their temporal dynamics and the efficacy of targeted interventions.

## CONCLUSION

This study highlights the importance of hormonal alterations, in particular estrogen deficiency, in predisposing postmenopausal women to recurrent urinary tract infections. Reduced Estradiol levels, microbial dysbiosis, and immune dysregulation, an interplay between them, form a permissive environment for recurrent infections. These findings suggest that RUTIs in postmenopausal women are best managed by a multi modal approach including hormonal supplementation, restoration of the microbiome and immune modulation. If we can identify the underlying pathophysiological mechanisms, we can develop personalized therapeutic strategies to enhance outcomes and quality of life of this vulnerable population.

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