Effects of Menopause on Innate Immune Defense in Urinary Cells

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Introduction

- **Urinary tract infections (UTIs) are the most common bacterial infection worldwide with recurrent infections (rUTI) reported following 20-30% of initial infections within 6 months.**
- **Postmenopausal women have increased susceptibility to rUTI and hypoestrogenism is thought to play a crucial role. To date, the underlying mechanisms influencing this predisposition for rUTI are relatively unknown.**
- **It has been shown that estrogen supplementation enhances the innate immune response of urinary cells via upregulated production of antimicrobial peptides (AMPs), a first-line innate immune response to infection.**
- **We hypothesize that postmenopausal women, at baseline, have downregulated expression of AMPs which contributes to postmenopausal predisposition to developing rUTIs. The AMPs that we assessed were *secretory leukocyte peptidase inhibitor* (encoded by *SLPI*) and *psoriasin* (encoded by *S100A7*), as well as the pro-inflammatory cytokine *interleukin-1 beta (IL-1β)*.**

Methods

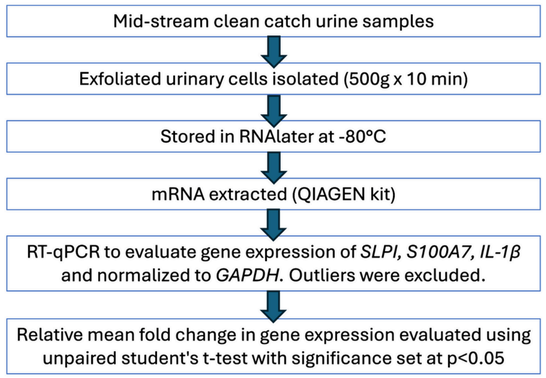
- **Self-identified cisgender women ≥ 18 years old were recruited from the University of Colorado Urogynecology clinics at the Anschutz Medical and Lone Tree campuses. Potential participants were screened based on exclusion criteria (Table 1).**
- **Urine samples from mid-stream clean catch were obtained from all participants and stratified based on menopausal status. Menopause was defined using any of the following 3 criteria: 1) No menses in > 1 year and age >53; 2) history of bilateral salpingo-oophorectomy 3) prior hysterectomy and age > 55.**

Urine processing procedure outlined in Figure 1.

Table 1. Exclusionary Criteria

Active infection
Culture-proven UTI in the last 1 month
Antibiotic therapy in the last 1 month
Use of hormone therapy
Use of estrogen antagonists
Planned surgery in the next 1 year
Supplements known to prevent UTI
Vesicovaginal or urethral-vaginal fistula
Urinary retention requiring indwelling or clean intermittent straight catheterization
Suspected or known genitourinary malignancy

Figure 1. Method for processing urine samples



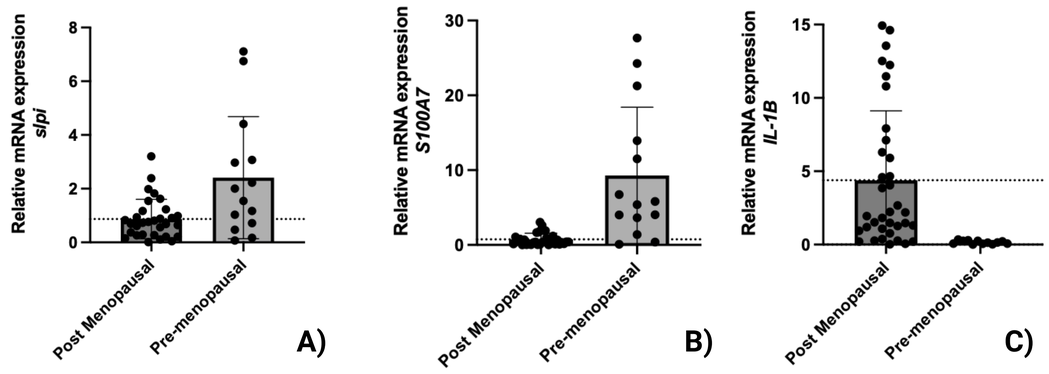


Figure 2: Differences in mRNA expression of AMPs in pre vs postmenopausal urine samples. RT-qPCR expression levels of A) SLPI, B) S100A7, C) IL-1β

Results

- **We enrolled 14 premenopausal and 36 postmenopausal participants. Outliers were removed.**
- **Compared to premenopausal participants, post-menopausal participants had significantly lower expression of *SLPI* (0.8674 vs 2.407, p = 0.0013) and *S100A7* (0.7303 vs 2.913, p=0.0007).**
- **Postmenopausal participants also had significantly higher expression of *IL-1β*, but again did not achieve significance (4.383 vs 0.1558, p=0.0036).**

Demographics	Pre-Menopausal	Post-Menopausal	p-value
Mean Age	41.5	71.2	<0.001
Ethnicity			0.298
Hispanic	3	2	
Non-Hispanic	19	34	
Race			0.953
White	21	34	
Asian	1	2	
Other	0	0	
Prior UTI			0.8
Yes	17	23	
No	5	8	
Prior rUTI			0.55
Yes	3	2	
No	19	24	
Hysterectomy			0.04
Yes	2	14	
No	20	22	

Table 2. Demographics of participants

Discussion

- **Our study showed that postmenopausal participants had significantly lower expression of the gene encoding the AMPs, *S100A7* and *SLPI*. We also showed increased expression of the gene encoding the proinflammatory cytokine, *IL-1β*. S100A7 is known to have patent antibacterial activity against *E. coli (UPEC*), which is reported to cause 65% of rUTI cases.**
- **AMPs serve as an important first response in innate immunity, and a loss of innate immune defense and an upregulation of inflammatory factors may play an important role in increased rUTI incidence in postmenopausal women.**

Acknowledgements