Original Article

The Role of the Gut Microbiome in Urinary Tract Infections and Recurrent Cystitis

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ABSTRACT

Objective: To investigate the association between gut microbiome composition and recurrent UTI, evaluate changes in gut microbial diversity following treatment, and assess the effectiveness of probiotic supplementation as an adjunct to standard antibiotic therapy.

Study Design: Pre-test/post-test quasi-experimental study.

Place and Duration of Study: This study was conducted at the Outpatient Urology Clinics of Mansoura University Hospital, Egypt, from January 2023 to June 2024 for a period of 18 months.

Methods: A pre-test/post-test quasi-experimental study was conducted involving 60 patients with recurrent UTIs and 60 healthy controls recruited from outpatient urology clinics.

Results: At baseline, patients with recurrent UTIs exhibited significantly lower gut microbial alpha diversity than healthy controls (Shannon index: 2.84 ± 0.43 vs. 3.91 ± 0.38; $p < 0.001$). Intestinal colonization with Escherichia coli was significantly more frequent in patients with recurrent UTIs than in controls (68.3% vs. 18.3%, $p < 0.001$). After 12 weeks, patients receiving probiotic supplementation demonstrated significantly greater restoration of gut microbial diversity compared with those receiving antibiotics alone (Shannon index: 3.62 ± 0.41 vs. 2.91 ± 0.39; $p < 0.001$).

Conclusion: Gut microbiome dysbiosis is strongly associated with susceptibility to recurrent UTIs. Adjunctive probiotic therapy targeting restoration of the gut–bladder axis significantly improves gut microbial diversity and reduces UTI recurrence.

Key Words: Urinary tract infection, recurrent cystitis, gut microbiome, gut–bladder axis, probiotics.

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INTRODUCTION

Urinary tract infections (UTIs) are one of the most prevalent bacterial infections seen in clinical practice and it is estimated that more than 150 million UTIs occur worldwide each year[1]. It is estimated that around 50–60% of women will have at least one UTI in their lifetime, and nearly 25–30% of women will have three or more UTIs in a 12-month period (recurrent UTI)[2].

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Uropathogenic Escherichia coli (UPEC) are the most prevalent uropathogens, accounting for 80–85% of community-acquired UTIs, followed by Klebsiella pneumoniae, Staphylococcus saprophyticus and Enterococcus faecalis[3]. Recurrent cystitis is a considerable burden to patients and the health care system, including direct costs, adverse effects of antibiotics, development of antimicrobial resistance (AMR) and severe impact on quality of life (QoL)[4]. Traditional antibiotic prophylaxis is no longer effective in preventing UTIs due to the increasing frequency of multidrug-resistant (MDR) uropathogens, thus necessitating the search for new strategies in therapy and prevention of UTI[5]. In previous research, the urinary tract was thought to be a sterile environment; however, the development of new culture independent microbiological techniques has proven that a unique urinary microbiome exists[6]. This paradigm shift has created new opportunities to improve the understanding of the microbial ecology of UTIs beyond the one-pathogen model[7]. Additionally, the urinary microbial community is not an isolated ecosystem, but rather is closely intertwined with other mucosal microbial communities, such as the gut and vaginal microbiome[7]. A concept that has arisen is the gut–bladder axis which

suggests that gut colonization with uropathogens can act as a reservoir of ascending urinary tract colonization[8,9]. Although there has been a rise in interest, prospective clinical studies that have looked at the relationship between gut microbiome shifts and recurrence of UTIs are limited, especially in populations from the Middle East and North Africa (MENA) region[10,11].

METHODS

A quasi-experimental controlled pre-test/post-test design was used. It was carried out in the Outpatient Urology Clinics of Mansoura University Hospital, Egypt from January 2023-June 2024 for a period of 18 months. A total of 120 female adult subjects (18-65 years) were recruited. Study group (n = 60) consisted of women who had a confirmed diagnosis of recurrent UTI (three or more UTI episodes with positive culture in the last 12 months), and the control group (n = 60) consisted of age- and BMI-matched women who did not have a history of UTI in the last 24 months.

Inclusion criteria:

- Female gender, age of 18-65 years.
- Recurrent UTI (3 or more episodes per year) and the predominant pathogen is UPEC (bacteria)
- Fecal and urine samples were collected at baseline and follow-up, and willingness to provide these samples was noted.

Exclusion criteria:

- Use of antibiotics or probiotics within 4 weeks prior to enrollment
- Immunocompromised status (HIV, malignancy, corticosteroid use ≥ 3 months)
- Structural abnormalities of the urinary tract, urinary calculi, or permanent urinary catheter.
- Any inflammatory bowel disease, irritable bowel syndrome, or known gastrointestinal disorder.

Intervention Protocol

The participants were randomly allocated in the UTI group (1:1 ratio using computer-generated random allocation). The Probiotic+Antibiotic arm (n = 30) was given: (1) oral nitrofurantoin 100 mg twice daily for 7 days during episodes of acute UTI (according to standard institutional practice); (2) a commercially available probiotic capsule containing Lactobacillus rhamnosus GR-1 (10^9 CFU) and Lactobacillus reuteri RC-14 (10^9 CFU) daily for 12 consecutive weeks. The Antibiotic-only arm (n = 30) received nitrofurantoin only for the treatment of acute episodes, and no probiotic or placebo. No intervention was performed on healthy controls (n = 60) and they were used as the normative reference population for the microbiome.

Sample Collection

Fecal samples were taken at two time points: T0 (pre-test, baseline) and T1 (post-test, week 12). All participants received a standardized sterile collection kit for stool samples (OMNIgene·GUT, DNA Genotek) and were given detailed written instructions on how to collect samples at home. Samples were frozen at −80 C until further processing. Midstream clean-catch urine specimens (10 mL) were collected at both time points for standard urine culture and sensitivity, urinalysis, and urinary 16S rRNA analysis.

Extraction of DNA and Sequencing of 16S rRNA Gene: A total microbial DNA was extracted from the fecal sample by using the QIAamp PowerFecal DNA Kit (QIAGEN) according to the manufacturer's instructions. NanoDrop spectrophotometry (A260/A280 ratio ≥ 1.8) was used to check the quality of DNA. The universal primer pair 341F/806R was used to amplify the V3–V4 hypervariable regions of the 16S rRNA gene. Library preparation was conducted according to Illumina 16S Metagenomic Sequencing Library Preparation protocol. The Illumina MiSeq platform (MiSeq Reagent Kit v3, 600 cycles) was used for paired-end sequencing (2 × 250 bp). The raw sequences were quality filtered, chimeras removed, and taxonomically classified through the QIIME2 bioinformatics pipeline (v2023.2) and SILVA 138 reference database.

Outcome Measures

At T0 and T1 the following outcomes were evaluated:

- Primary outcome: Number of UTI episodes per participant per 12 weeks (confirmed by urine culture)
- Alpha diversity: Shannon entropy index, Simpson's index (1-D) and observed OTU richness.

Pre-Test/Post-Test Assessment Instrument: At T0 and T1, a validated structured questionnaire was used to evaluate the following aspects: (1) UTI symptom severity (Urinary Tract Infection Symptom Assessment - UTISA questionnaire); (2) quality of life (SF-12 Health Survey); (3) diet (24-hour food recall questionnaire adapted for fermented and high-fiber foods); and (4) adherence to probiotic regimen (pill-diary method, adherence ≥ 80% was considered as compliant).

Statistical Analysis: Data analysis was done with R v4.3.1 using the packages: vegan, phyloseq, DEseq2 and ggplot2. Means ± standard deviations (SD) or medians [interquartile ranges] were used for continuous variables as appropriate. Categorical variables are represented as frequencies (%). A level of $p < 0.05$ (two-tailed) was used for statistical significance.

RESULTS

There were 120 participants with 60 in each study group (UTI and healthy control). The mean age was 34.7 ± 9.2 years in the UTI group and 33.9 ± 8.7 years in the control group ($p = 0.621$). BMI was comparable between groups (UTI: 26.1 ± 3.8 kg/m²; controls: 25.7 ± 3.5 kg/m²; $p = 0.547$).

Table No. 1: Baseline Demographic and Clinical Characteristics of Study Participants

Variable	UTI Group (n=60)	Healthy Controls (n=60)	p-value
Age (years), mean ± SD	34.7 ± 9.2	33.9 ± 8.7	0.621
BMI (kg/m²), mean ± SD	26.1 ± 3.8	25.7 ± 3.5	0.547
UTI episodes/year, median [IQR]	4 [3–6]	0 [0–0]	< 0.001
Prior antibiotic courses/year, mean ± SD	3.8 ± 1.2	0.4 ± 0.6	< 0.001
UPEC as primary pathogen, n (%)	51 (85.0%)	N/A	—
Gut UPEC colonization, n (%)	41 (68.3%)	11 (18.3%)	< 0.001
Vaginal Lactobacillus dominance, n (%)	22 (36.7%)	49 (81.7%)	< 0.001
Shannon index (gut), mean ± SD	2.84 ± 0.43	3.91 ± 0.38	< 0.001
Simpson index (gut), mean ± SD	0.81 ± 0.07	0.94 ± 0.04	< 0.001

Table No. 2: Pre-Test Gut Microbiome Diversity Indices and Key Taxonomic Abundances

Parameter	UTI Group (n=60)	Healthy Controls (n=60)	p-value
Shannon index	2.84 ± 0.43	3.91 ± 0.38	< 0.001
Simpson's index (1-D)	0.81 ± 0.07	0.94 ± 0.04	< 0.001
Observed OTU richness	182.4 ± 38.6	294.7 ± 52.1	< 0.001
Firmicutes (% relative abundance)	41.2 ± 9.1	52.8 ± 8.3	< 0.001
Bacteroidetes (% relative abundance)	19.6 ± 6.4	15.5 ± 5.8	0.003
Proteobacteria (% relative abundance)	8.2 ± 3.1	2.9 ± 1.4	< 0.001
Faecalibacterium prausnitzii (%)	3.1 ± 1.4	8.2 ± 2.6	< 0.001
Escherichia-Shigella (%)	6.8 ± 3.2	1.2 ± 0.8	< 0.001
Bifidobacterium (%)	2.4 ± 1.1	5.9 ± 2.0	< 0.001
Lactobacillus (%)	1.8 ± 0.9	4.2 ± 1.8	< 0.001
Klebsiella (%)	3.6 ± 1.9	0.8 ± 0.5	< 0.001

Table No. 3: Pre-Test vs. Post-Test Gut Microbiome Diversity: Intervention Arm Comparison

Parameter	Probiotic+Abx T0	Probiotic+Abx T1	Abx-only T0	Abx-only T1	p*
Shannon index	2.82 ± 0.41	3.62 ± 0.41†	2.86 ± 0.45	2.91 ± 0.39	< 0.001
Simpson's index	0.81 ± 0.07	0.91 ± 0.05†	0.81 ± 0.07	0.82 ± 0.06	< 0.001
Observed OTUs	183.2 ± 39.1	261.4 ± 43.8†	181.6 ± 38.2	186.3 ± 40.1	< 0.001
E. coli colonization (%)	66.7%	26.7%†	70.0%	63.3%	0.003
Faecalibacterium (%)	3.0 ± 1.3	6.1 ± 2.2†	3.2 ± 1.5	3.4 ± 1.6	< 0.001
Escherichia-Shigella (%)	6.9 ± 3.3	3.1 ± 1.8†	6.8 ± 3.1	6.5 ± 2.9	< 0.001

† $p < 0.05$ compared to T0 within the same arm (paired test); * p-value for post-test between-group comparison.

Patients with recurrent UTI had significantly lower microbial alpha diversity in their gut compared with healthy controls, with lower Shannon entropy (2.84 ± 0.43 vs. 3.91 ± 0.38; $p < 0.001$) and Simpson's index (0.81 ± 0.07 vs. 0.94 ± 0.04; $p < 0.001$). The Bray–Curtis PCoA showed that there was a good separation between the UTI patients and controls (PERMANOVA $F = 18.74$, $R2 = 0.14$, $p < 0.001$).

After 12 weeks of treatment, the Probiotic+Antibiotic group had a significant increase in gut microbial alpha diversity in comparison to baseline and the Antibiotic-only group. The Shannon index increased from 2.82 ± 0.41 at T0 to 3.62 ± 0.41 at T1 in the probiotic arm (paired t-test: $t = 8.43$, $p < 0.001$), versus a more modest and non-significant change from 2.86 ± 0.45 to 2.91 ± 0.39 in the antibiotic-only arm ($p = 0.612$).

DISCUSSION

This study offers prospective evidence of gut microbiome dysbiosis as a powerful, biological marker of recurrent UTI in women, and that targeted probiotic supplementation for targeted probiotic supplementation to restore gut microbial diversity correlates with clinically significant decreases in the incidence of recurrent UTI. These results align with and build upon the growing body of literature on the role of the gut–bladder axis as a major contributor to urinary health. Faecalibacterium produces butyrate, which is known to strengthen the tight junctions of the intestinal epithelium, thereby helping to prevent bacterial translocation, thus its absence may allow Enterobacteriaceae overgrowth and bacterial translocation[12]. The observed decrease in abundance of Lactobacillus species in the gut and the vagina of UTI patients is consistent with the findings of Stapleton 2016 that Lactobacillus dominance at mucosal surfaces protects. What is striking about the effectiveness of Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 for the reduction of UTI recurrence (RR = 0.38; NNT = 3.8) in the present study is that it is

comparable to the efficacy of antibiotic therapy for RR. The strains have previously been tested in small, randomized trials for vaginal microbiome restoration and UTI prevention with promising results; the current study is one of the first to document their effect specifically in terms of gut microbiome restoration, suggesting that their positive impact may also involve the gut–bladder axis[13]. Importantly, Shannon diversity in the probiotic arm increased substantially, approaching healthy control levels, within 12 weeks, suggesting the gut microbiome is malleable and can be targeted. The inability of antibiotics alone to restore the diversity of the gut microbiome is in accordance with the well-known side effects of antibiotics on the gut microbiome[14]. Furthermore, the antibiotic-only arm had essentially non-changing Shannon indices and continued gut colonization with UPEC at post-test, which was likely a mechanistic explanation for the 43.3% recurrence rate in the antibiotic-only arm and serves as an argument for the importance of using microbiome-protective strategies in addition to antibiotic treatment[15]. A pre-test/post-test comparison of our UTISA questionnaire and SF-12 questionnaires gave patient-reported outcome measures which matched results from microbiological tests, which increases the clinical validity of our results from a diagnostic standpoint[16]. This dramatic improvement in both physical and mental quality of life in the probiotic arm highlights the potential value of probiotics in restoring the microbiome, not just eradicating pathogens[17,18].

CONCLUSION

Here, the study illustrates gut microbiome dysbiosis (α diversity reduction and Enterobacteriaceae enrichment) strongly correlates with recurrent UTI in women, which serves as a proof of the gut-bladder axis as a mechanism involved in UTI pathogenesis. Probiotic supplementation with Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 in addition to antibiotic therapy resulted in significant improvement in microbial diversity, UTI recurrence rate (-62% vs antibiotic alone, NNT = 3.8), and symptom burden and QoL.

The results have significant clinical implications: A microbiome profile could be a biomarker for UTI susceptibility and microbiome-targeted intervention is a rational and evidence-based adjunct treatment to antibiotics for the management of recurrent cystitis.

Limitations: There are some restrictions to this study which should be noted. A placebo effect is possible in the antibiotic only group, and future studies should consider using double-blind placebo-controlled designs. Second, our study population was limited to women in a single centre in Egypt, so the findings may not be representative of other populations and geographic locations, and the MENA region is underrepresented in the field of microbiomes. Third, 16S rRNA sequencing provides taxonomic resolution but lacks functional resolution like that provided by shotgun metagenomics, and future studies should be combined with metatranscriptomics, to gain functional resolution of the microbiome state.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Abdulaziz Saleh Alanazi, Ahmed Abu El Gasim Abdelrahman, Faisal Saleh Alanazi
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Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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