Asymptomatic and Symptomatic Bacteriuria in Patients with Type 2 Diabetes

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Abstract

Aim: Asymptomatic bacteriuria (ASB) and symptomatic bacteriuria with antibiotic-resistant organisms are common in patients with type 2 diabetes. The aim was to study the prevalence, bacterial profile and antibiotic susceptibility pattern in ASB and symptomatic bacteriuria and the factors associated with *Escherichia coli* bacteriuria in type 2 diabetes. **Materials and Methods:** This was an observational case-control study done on 400 asymptomatic type 2 diabetes patients, 200 symptomatic urinary tract infection (UTI), and 200 nondiabetic controls. Various clinical, biochemical parameters and urine examination and culture were studied. **Results:** The prevalence of ASB and symptomatic bacteriuria in type 2 diabetes was 17.5% and 69%, respectively, and were significantly higher as compared to controls (10%). *E. coli* was present in 52.9% of ASB cases of type 2 diabetes and 70% of nondiabetic control ASB. *E. coli* (55%) was most commonly isolated in symptomatic bacteriuria. Majority of the Gram-negative bacteria isolates in ASB and symptomatic bacteriuria with type 2 diabetes and controls were sensitive to amikacin, imipenem, piperacillin/tazobactam, and nitrofurantoin. *E. coli* were more resistant to quinolones in ASB and symptomatic bacteriuria than controls. Most of the Gram-positive bacteria were sensitive to vancomycin, linezolid, and amoxiclav. The factors associated with *E. coli* bacteriuria in type 2 diabetes were female gender, long duration of diabetes, past history of symptomatic UTI, poor glycemic control, and renal function. **Conclusions:** *E. coli* remains the most common isolated microorganism in asymptomatic and symptomatic bacteriuria. *E. coli* were more resistant to quinolones in patients with type 2 diabetes.

Keywords: Asymptomatic bacteriuria, symptomatic bacteriuria, type 2 diabetes, urinary tract infection, urine culture sensitivity

Introduction

As per the International Diabetes Federation 2019 report, India is harboring 77 million patients with diabetes.[1] Urinary tract infections (UTI) are more common and severe and carry worse outcomes in patients with type 2 diabetes and good diabetic control is recommended to mitigate this risk.[2] UTI is a common cause of morbidity and mortality.[3] The spectrum of UTI ranges from asymptomatic bacteriuria (ASB) to lower UTI (cystitis), and pyelonephritis, emphysematous pyelonephritis (EPN), emphysematous cystitis, and renal abscesses.[4] UTI in diabetes is imposing a significant burden on health care expenditure[5] and the high rates of antibiotic prescription may further induce the development of antibiotic-resistant uropathogens.[6] Uncontrolled diabetes causing glycosuria may promote the growth of pathogenic bacteria.[7] Impairments in the immune system and the multiple effects of diabetes contribute to the pathogenesis of UTI in diabetes.[8]

Escherichia (*Escherichia coli*) is the most common cause of UTI, accounting for 85% of community-acquired and 50% of hospital-acquired infections. Other pathogens isolated include Enterobacteriaceae such as *Klebsiella* spp, *Proteus* spp, *Enterobacter* spp, and Enterococci.[9] Patients with diabetes are more prone to have resistant pathogens as the cause of their UTI.

There is geographical variation in microbiological isolates and also antibiotic susceptibility pattern is changing. In the present study, we looked at the prevalence, bacterial profile, and antibiotic susceptibility pattern in asymptomatic and symptomatic bacteriuria in patients with type 2 diabetes and

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controls and the factors associated with *E. coli* bacteriuria in patients with type 2 diabetes.

Materials and Methods

This was a hospital-based observational case-control study of adult type 2 diabetes patients attending the tertiary care center in North India. The institutional ethical committee approved the study. Informed consent was obtained from all the recruited subjects.

Study subjects

The study recruited alternate (i.e., every 3rd) 400 type 2 diabetes patients with no symptoms of UTI attending the Endocrine clinic and consecutive 200 symptomatic UTI patients. We also recruited 200 randomly selected healthy controls without diabetes standardized for age and gender for the comparison. The study was conducted for 3 years. All patients were interviewed and detailed physical examination was carried out. The eligibility criteria for including subjects in the study were: Both male and female type 2 diabetes patients aged > 30 years. The exclusion criteria were (i) other types of diabetes, (ii) recent hospitalization, (iii) antibiotic use within the previous 2 weeks, (iv) immunocompromised states-patients on steroids, and (v) recent urinary instrumentation.

Clinical parameters including duration of diabetes, complications of diabetes, drug therapy, clinical symptomatology especially urinary complaints and comorbidities were recorded. Fasting blood glucose and 2-h postprandial blood glucose, kidney function test, and glycosylated hemoglobin (HbA1c) were estimated.

Urine examination and culture sensitivity

Voided, clean-catch and midstream urine samples were collected. Urine specimens were inoculated on Hichrome agar media and plates were incubated at 37°C aerobically for 24 h colony-forming unit (CFU) count was determined. The organisms were identified using standard cultural, morphological, and biochemical techniques.[10] The standard strain number for *E. coli* used was ATCC 25922, *Klebsiella pneumoniae* was ATCC 700603, *Pseudomonas aeruginosa* was ATCC 27853, *Enterococcus faecalis* was ATCC 51299, *Staphylococcus aureus* was ATCC 29213 and *Staphylococcus saprophyticus* was ATCC 19701. Antimicrobial sensitivity testing was carried out on Mueller–Hinton agar (plates with commercially available discs by the Kirby-Bauer disc diffusion method and interpreted according to Clinical and Laboratory Standards Institute criteria.[11] Nitrofurantoin (NFT) with disc content (300 mcg), ceftriaxone (30 mcg), levofloxacin (5 mcg), norfloxacin (10 mcg), ciprofloxacin (5 mcg), amikacin (30 mcg), gentamicin (120 mcg), tetracycline (30 mcg), cotrimoxazole (1.25/23.75 mcg), vancomycin (30 mcg), linezolid (30 mcg), amoxiclav (30 mcg), piperacillin/tazobactam (100/10 mcg), imipenem (10 mcg), cefixime (5 mcg), cefpodoxime (10 mcg), and ampicillin/sulbactam (10/10 mcg) were the biograms used, which were manufactured by Microxpress, a division of tulip diagnostics (P) LTD. ASB in females was diagnosed if culture grew the same organism within 2 weeks, but if repeat culture was sterile, then they were taken as non-ASB. Symptomatic UTI patients were divided into lower UTI (cystitis), acute pyelonephritis and EPN based on clinical symptomatology and imaging finding.

Definitions of symptomatic and asymptomatic bacteriuria

ASB is diagnosed in females when two consecutive urine specimens yielding the same bacterial strain in quantitative counts of $\geq 10^5$ CFU/ml in the absence of urinary symptoms, while in males single urine specimen is sufficient for diagnosis.[12] Symptomatic bacteriuria in women was diagnosed when a urine count was $\geq 10^5$ CFU/ml in the presence of urinary symptoms, while in men the urine count $\geq 10^4$ CFU/ml is required.[12]

Statistical analysis

Quantitative variables were expressed as means ± standard deviation, while qualitative variables were expressed in terms of proportion. Categorical variables were compared employing Chi-square test or Fischer's exact tests, whereas continuous variables were compared by using Student's *t*-test for independent observations. Binary logistic regression analysis was carried out to calculate multivariate *P* value. $P < 0.05$ was considered statistically significant. All the analyses were performed by the statistical software SPSS Version 21 (IBM SPSS statistics for windows, version 21 Armonk, NY, USA: IBM Corp).

Results

The prevalence of ASB in type 2 diabetes was 17.5% as compared to 10% in controls ($P = 0.015$). ASB was significantly higher ($P = 0.049$) in females as compared to males. Table 1 shows the microbiological isolates from asymptomatic and symptomatic bacteriuria in patients with type 2 diabetes and control ASB. *E. coli* was the most common organism isolated from urine culture. *E. coli* was followed by *E. faecalis*. In symptomatic UTI, pyelonephritis was present in 44.5%, cystitis in 55.5% and EPN in 9.5%. Urine culture was positive in 69% of patients. *E. coli* (55%) was most common isolated organism in symptomatic bacteriuria patients followed by *E. faecalis* and others. *E. coli* was again the most common in all types of symptomatic bacteriuria, as shown in Table 2. Most of the Gram-negative bacteria were sensitive to amikacin, imipenem, gentamicin, piperacillin/tazobactam and NFT, as shown in Table 3. *E. coli* in ASB of type 2 diabetes, and controls and symptomatic bacteriuria were sensitive to amikacin > imipenem > gentamicin > piperacillin/tazobactam > NFT. *E. coli* were more resistant to quinolones (levofloxacin and ciprofloxacin) in ASB and symptomatic bacteriuria as compares to control ASB. Table 4 shows the antimicrobial susceptibility pattern of Gram-positive bacteria isolates. Most of the Gram-positive bacteria were sensitive to vancomycin, linezolid, NFT, and amoxiclav.

Table 5 shows the factors associated with *E. coli* bacteriuria in type 2 diabetes patients. There were 208 cases of bacteriuria in

Table 1: Microbiological isolates from asymptomatic and symptomatic bacteriuria in patients with type 2 diabetes in comparison to control asymptomatic bacteriuria

Organism	Asymptomatic bacteriuria (*n*=70), *n* (%)	Symptomatic bacteriuria (*n*=138), *n* (%)	Control ASB (*n*=20), *n* (%)
E. coli	37 (52.9)	110 (55)	14 (70.0)
E. faecalis	21 (30.0)	12 (6.0)	5 (25.0)
Candida spp.	4 (5.7)	6 (3.0)	-
A. baumannii	2 (2.8)	-	1 (5.0)
S. saprophyticus	3 (4.3)	-	-
K. pneumoniae	2 (2.8)	5 (2.5)	-
P. aeruginosa	1 (1.4)	-	-
S. aureus	-	3 (1.5)	-
E. faecalis/E. coli	-	1 (0.5)	-
Yeast	-	1 (0.5)	-

Values represented as, *n* (%). ASB: Asymptomatic bacteriuria, *E. coli: Escherichia coli, E. faecalis: Enterococcus faecalis, A. baumannii: Acinetobacter baumannii, S. saprophyticus: Staphylococcus saprophyticus, K. pneumonia: Klebsiella pneumonia, P. aeruginosa: Pseudomonas aeruginosa, S. aureus: Staphylococcus aureus, E. faecalis: Enterococcus faecalis*

Table 2: Microbiological isolates from symptomatic bacteriuria (pyelonephritis, cystitis and emphysematous pyelonephritis) in patients with type 2 diabetes

Organism	Cystitis (*n*=111), *n* (%)	Pyelonephritis (*n*=89), *n* (%)	EPN (*n*=19), *n* (%)
E. coli	59 (53.1)	51 (57.3)	17 (89.5)
E. faecalis	5 (4.5)	7 (7.8)	1 (5.3)
K. pneumoniae	2 (1.8)	3 (3.4)	1 (5.3)
S. aureus	1 (0.9)	2 (2.2)	-
E. faecalis/E. coli	1 (0.9)	-	-
Candida spp.	4 (3.6)	2 (2.2)	-
Yeast	1 (0.9)	-	-

Values represented as, *n* (%). EPN: Emphysematous pyelonephritis, *E. coli: Escherichia coli, E. faecalis: Enterococcus faecalis, K. pneumonia: Klebsiella pneumonia, S. aureus: Staphylococcus aureus, E. faecalis: Enterococcus faecalis*

Table 3: Antimicrobial susceptibility pattern of gram-negative bacteria isolated from type 2 diabetes patients (asymptomatic bacteriuria and symptomatic bacteriuria) and control asymptomatic bacteriuria

Organism	Group	Imipenem, *n* (%)	Amikacin, *n* (%)	Gentamicin, *n* (%)	Nitrofurantoin, *n* (%)	Co-trimoxazole, *n* (%)	Piperacillin/ tazobactam, *n* (%)	Ceftriaxone, *n* (%)
E. coli	ASB (*n*=37)	35 (94.6)	37 (100)	31 (83.8)	30 (81.1)	17 (45.9)	32 (86.5)	14 (37.8)
	Symptomatic bacteriuria (*n*=110)	101 (91.8)	105 (95.5)	96 (87.3)	85 (77.3)	52 (47.3)	89 (80.9)	16 (14.5)
	Control (*n*=14)	13 (92.9)	12 (85.7)	11 (78.6)	11 (78.6)	7 (50)	13 (92.9)	5 (35.7)
K. pnemoniae	ASB (*n*=2)	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	1 (50)	2 (100)
	Symptomatic bacteriuria (*n*=5)	5 (100)	5 (100)	5 (100)	0	0	5 (100)	0
A. baumannii	ASB (*n*=2)	2 (100)	2 (100)	-	0	0	1 (50)	0
	Control (*n*=1)	1 (100)	1 (100)	1 (100)	0	0	1 (100)	1 (100)
P. aeruginosa	ASB (*n*=1)	0	1 (100)	-	0	-	1 (100)	-

Organism	Levofloxacin, *n* (%)	Ciprofloxin, *n* (%)	Cefperazone/ sulbactam, *n* (%)	Ampicillin/ sulbactam, *n* (%)	Cefixime, *n* (%)	Amoxiclav, *n* (%)	Cefpodoxime, *n* (%)	Tetracycline, *n* (%)
E. coli	20 (54.1)	9 (24.3)	12 (32.4)	10 (27)	12 (32.4)	9 (24.3)	6 (16.2)	-
	32 (29.1)	14 (12.7)	35 (31.8)	33 (30)	16 (14.5)	42 (38.2)	-	-
	11 (78.6)	5 (35.7)	8 (57.1)	6 (42.9)	1 (7.1)	6 (42.9)	6 (42.9)	-
K. pnemoniae	2 (100)	2 (100)	0	2 (100)	2 (100)	-	-	-
	0	0	0	3 (60)	2 (40)	-	-	3 (60)
A. baumannii	2 (100)	1 (50)	2 (100)	0	0	-	0	1 (50)
	0	0	-	1 (100)	0	-	-	1 (100)
P. aeruginosa	-	-	-	-	0	-	-	-

Values represented as, *n* (%) for sensitivity. *E. coli: Escherichia coli, K. pneumonia: Klebsiella pneumonia, A. baumannii: Acinetobacter baumannii, P. aeruginosa: Pseudomonas aeruginosa*

Table 4: Antimicrobial susceptibility pattern of gram-positive bacteria isolated from type 2 diabetes patients (asymptomatic bacteriuria and symptomatic bacteriuria) and control asymptomatic bacteriuria

Organism	Group	Penicillin, *n* (%)	Ampicillin, *n* (%)	Ampicilli/ sulbactam, *n* (%)	Amoxiclav, *n* (%)	Nitrofurantoin, *n* (%)	Vancomycin, *n* (%)	Linezolid, *n* (%)	Ciprofloxacin, *n* (%)	Levofloxacin, *n* (%)	Tetracycline, *n* (%)	Cotrimoxazole, *n* (%)
E. faecalis	ASB (*n*=21)	8 (38.1)	12 (57.1)	13 (61.9)	13 (61.9)	18 (85.7)	21 (100)	21 (100)	4 (19.1)	3 (14.3)	13 (61.9)	-
	Symptomatic bacteriuria (*n*=12)	5 (41.7)	5 (41.7)	0	8 (66.7)	6 (50)	12 (100)	12 (100)	-	8 (66.7)	5 (41.7)	-
	Control (*n*=5)	3 (60)	4 (80)	3 (60)	4 (80)	4 (80)	5 (100)	5 (100)	0	1 (20)	2 (40)	-
S. saprophyticus	ASB (*n*=3)	0	1 (33.3)	-	2 (66.7)	0	3 (100)	3 (100)	2 (66.7)	3 (100)	1 (33.3)	2 (66.7)
S. aureus	Symptomatic bacteriuria (*n*=3)	0	0	-	0	2 (66.7)	3 (100)	3 (100)	-	1 (33.3)	2 (66.7)	1 (33.3)

Values represented as, *n* (%) for sensitivity. *E. faecalis: Enterococcus faecalis, S. saprophyticus: Staphylococcus saprophyticus, S. aureus: Staphylococcus aureus*

type 2 diabetes, of which 147 (70.7%) were *E. coli* induced and rest 61 (29.3%) were non-*E. coli* induced. The factors which predicted *E. coli* UTI on multivariate analysis were female gender, long duration of diabetes, history of symptomatic UTI in the year before study entry, poor glycemic control, and lower estimated glomerular filtration rate (eGFR).

Discussion

Patients with type 2 diabetes are at increased risk of UTI and its complications. The prevalence of ASB in type 2 diabetes was 17.5% as compared to 10% in the control group ($P = 0.015$). Our results are comparable to previous studies, which showed a prevalence of ASB in people with diabetes as 17%–21%.[13-15] The prevalence of ASB was 19.9% and 10.7% in females and males patients with type 2 diabetes, respectively, in our study. Meiland *et al*.[14] reported the prevalence of ASB in diabetic women as 17% while another study[16] also showed female as a risk factor for ASB. In our study, *E. coli* causing ASB was present in 52.9% of type 2 diabetes and 70% of ASB controls. The results are consistent with the majority of reports where *E. coli* is the major pathogen in ASB.[15,17-19] We noted a lower percentage of *E. coli* in patients with diabetes versus controls, which confirms the results of a study by Geerlings *et al*.[20]

In our study, symptomatic bacteriuria was present in 69% of type 2 diabetes patients. *E. coli* is the commonest organism responsible for UTI in literature, both from western and Indian studies, similar to our study.[17,21-23] The relative higher percentage of *E. faecalis* could be because the patients were hospitalized and higher rates of Enterococcus have been reported in hospitalized patients.[24] In our study, *E. coli* was by far the most common causative organism for EPN, literature reports *E. coli* isolation in 47%–90% followed by Proteus mirabilis, *K. pneumoniae*, Enterococcus species, and *P. aeruginosa*.[21,25]

In our study, most of the *E. coli* in type 2 diabetes ASB were sensitive to Amikacin (100%), Imipenem (94.6%), Piperacillin/tazobactam (86.5%), Gentamicin (83.8%), and NFT (81.1%) which were comparable to control ASB except that *E. coli* in ASB type 2 diabetes patients had higher resistance to quinolones. We observed that the isolated *E. coli* strains were resistant to ciprofloxacin, cephalosporins, cotrimoxazole, and ampicillin/sulbactam in type 2 diabetes patients and controls [Table 3], which are comparable with other studies.[17,19] The high sensitivity of *E. coli* to carbapenems and amikacin in both type 2 diabetes and controls may be due to their broad spectra on bacteria, which is comparable to other studies.[17] The sensitivity of *E. coli* in this study is in agreement with previous reports.[16,18] *Enterococcus fecalis* antibiotic sensitivity was also comparable between type 2 diabetes ASB and control ASB except controls were more susceptible to penicillin, ampicillin and amoxiclav. Study reported that the high prevalence of resistance to some of the commonly used antibiotics such as ampicillin and tetracycline might be due to their abuse and low cost of purchase.[18]

Table 5: Factors associated with: *Escherichia coli* bacteriuria in type 2 diabetes patients

Risk factors	*E. coli* (*n*=147), *n* (%)	*Non-E. coli* (*n*=61), *n* (%)	Univariate *P**	Multivariate *P**
Age (years)	55.04±9.21	52.70±8.37	0.087	
Female gender	121 (82.3)	42 (68.8)	0.032	0.047
Postmenopausal	102 (84.3)	36 (73.5)	0.103	
Diabetes duration (years)	11.58±6.77	9.27±5.76	0.021	0.033
Diabetic complication				
Retinopathy	79 (53.7)	31 (50.8)	0.701	
Nephropathy	87 (59.2)	29 (47.5)	0.125	
Neuropathy	72 (49.0)	23 (37.7)	0.138	
CKD	29 (19.7)	5 (8.2)	0.042	0.132
History of symptomatic UTI in year prior to study entry	51 (34.7)	12 (19.7)	0.032	0.048
Hemoglobin A1c (%)	11.19±2.31	10.35±2.69	0.024	0.042
Creatinine (mg/dl)	1.79±1.46	1.26±0.77	0.007	0.012
eGFR (ml/min/1.73 m^2)	50.66±29.14	67.47±30.92	0.000	0.008
AKI (*n*=47)	38 (34.5)	9 (32.1)	0.811	
Pyuria	110 (74.8)	35 (57.4)	0.013	0.053
Renal cyst	19 (12.9)	6 (9.8)	0.534	
Renal calculi	18 (12.2)	7 (11.5)	0.877	
Cystopathy	21 (14.3)	13 (21.3)	0.215	

Categorical variables, *n* (%) and continuous variables mean±SD, *P<0.05 is considered statistically significant. CKD: Chronic kidney disease, AKI: Acute kidney injury, HbA1c: Glycosylated hemoglobin, eGFR: Estimated glomerular filtration rate, *E. coli: Escherichia coli*, SD: Standard deviation, UTI: Urinary tract infection

In our study, most of the *E. coli* in symptomatic bacteriuria were sensitive to Amikacin (95.5%), Imipenem (91.8%), Gentamicin (87.3%), Piperacillin/tazobactam (80.9%), and NFT (77.3%) as shown in Table 3. Other studies[17,26] showed similar antibiotic susceptibility pattern. Studies have demonstrated that *E. coli* are highly sensitive to carbapenems in symptomatic UTI with diabetes.[17,27] In our study, levofloxacin sensitivity was better than ciprofloxacin, pointing toward escalating ciprofloxacin resistance reported in other studies.[28] Our study reported excellent sensitivity to imipenem among Enterobacteriaceae, which is comparable to study by Banerjee *et al*.[28] but contrast to study by Kumarasamy *et al*.[29]

In our study, the factors associated with *E. coli* bacteriuria were female gender, long duration of diabetes, history of symptomatic UTI in the year before study entry, poor glycemic control, and lower eGFR. The study revealed UTI in the prior year predicted *E. coli* UTI subsequently.[30] The association between clinical characteristics and *E. coli* bacteriuria has not been studied previously. The identification of the clinical characteristics before the culture results are available help in selecting the presumptive antibiotic. A study has shown that *E. coli* correlated with the risk of a decline in renal function and certain virulence factors of *E. coli* might contribute to a decline in renal function.[31] The study has also show that *E. coli* bacteriuria is a risk factor for recurrent UTI.[32] Virulence factors shared by bacterial strains direct them through a particular pathogenesis process. The current understanding of genetic defining the pathotypes is limited. Discovery of additional *E. coli* genes involved in uropathogenesis requires further understanding.[33]

Conclusions

E. coli was the most commonly isolated microorganism in asymptomatic and symptomatic bacteriuria. *E. coli* were more resistant to quinolones in patients with type 2 diabetes. The factors associated with *E. coli* bacteriuria in type 2 diabetes were female gender, long duration of diabetes, history of symptomatic UTI in the year before study entry, poor glycemic control, and renal function. Long-term prospective studies on the effect of bacteriuria in type 2 diabetes patients are required and to identify virulence factors shared by bacterial strains.

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Conflicts of interest

There are no conflicts of interest.

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