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Urinary tract infection in diabetes: Susceptible organisms and antibiogram patterns in an outpatient clinic of a tertiary health care center

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Abstract
We aimed to determine the influence of diabetes mellitus (DM) on uropathogens and antibiotic resistance pattern in urinary tract infection (UTI) in our center. Three hundred fifty-five DM patients and 165 non-DM patients with UTI were included in this retrospective study. Urine samples were processed in the laboratory following standard protocol. Mean age was higher in DM group (63.9 ± 12.4 vs 59.6 ± 17.3 years, respectively, P = 0.001). Females showed much higher UTI prevalence in both groups (85.6% in DM vs 70.3% in non-DM group, P = 0.000). Mean HbA1c level on admission was 9.3% (78 mmol/mol). Mean duration of DM was 13.9 ± 8.5 yr. E.coli was the predominant uropathogen for both (67.3% in DM and 61.8% in non-DM group). Most isolated microorganisms were sensitive to nitrofurantoin (87.0% in DM, vs 83.6% in non-DM group, P = 0.265). Mean DM duration of higher than 10,5 years showed greatest risk of multidrug resistance (MDR) (AUC = 0.58, sensitivity of 63.7% and specificity of 50%, P = 0.019). Diabetic patients with UTI had poor glycemic control and long-standing DM. Nitrofurantoin was the most appropriate antimicrobial agent for empirical use. The MDR was higher in patients with DM lasting longer than 10.5 years.

Keywords: Urinary tract infection, diabetes mellitus, antibiotic resistance

Introduction

Urinary tract infections (UTIs) are common in patients with diabetes mellitus (DM) [1-3]. Immunologic dysfunction causing defective migration and chemotaxis in polymorphonuclear leukocytes, autonomic neuropathy resulting in incomplete bladder emptying, and poor metabolic control may contribute to the increased risk of UTI. Microorganisms may become more virulent in a high glucose environment, thus patients with DM are prone to severe UTI [4-5]. Other serious infectious complications, such as emphysematous cystitis and pyelonephritis, renal abscesses and renal papillary necrosis are more frequently seen in these patients as well.

Frequent prescription of antibiotics, including the ones with broad-spectrum, may result in development of antibiotic-resistant urinary pathogens. Since patients with DM are more prone to have resistant pathogens, they inevitably require longer and more potent antimicrobial treatment [6]. However, it is important to be sure that the appropriate antimicrobial agent is chosen.

The most common etiological agent for community-acquired UTI is Escherichia coli (E. coli), regardless of diabetic status [4,7]. The aim of this study was to investigate the impact of DM on the spectrum of uropathogens and antimicrobial drug susceptibility in DM patients with UTI in our region.

Material and Methods

Subjects

This retrospective study was performed at the outpatient endocrinology clinic of Baskent University, Faculty of Medicine, Adana Dr. Turgut Noyan Teaching and Medical Research Center, and eligible patients were recruited between January 2008 and December 2016. Patients with and without DM, and with a documented urine culture were included as study and control groups. The data in each enrolled patient's medical reports and their DM-related complications were evaluated thoroughly. Medications used for the treatment of DM were recorded, as

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well. UTI was defined as the presence of a positive urine culture accompanied by urinary symptoms, including dysuria, urgency, frequency, and/or abdominal discomfort. Individuals under 18 yr of age and those with a history of antibiotic use within 1 month of recruitment were excluded. Any accompanying condition that may interfere with immunity, such as active cancer or chronic renal failure requiring dialysis, were also excluded.

The study was approved by the Local Ethics Committee of Baskent University (Project No. KA 17/51).

Study protocol

Blood samples were drawn after 8-12 hr of fasting for the measurement of fasting glucose, which was determined by the enzymatic spectrophotometric method using an Aeroset autoanalyzer. Measurements of fasting sugar and glycated hemoglobin (HbA1c) were carried out for all patients with DM.

All urine samples were processed in the laboratory, following standard laboratory protocol. Mid-flow samples of urine (10 microlt) were taken and embedded in 5% sheep blood and MacConkey agar. Cultures were incubated for 18-24 hr at 37°C in an aerobic atmosphere. The plates with detectable growth were transported to the VITEK-1 automation system for performance of bacterial identification and antimicrobial susceptibility testing. The samples that exhibited positive pyuria but negative growth were incubated for an additional 24 hr. Bacterial growth was evaluated using the criteria published in the Clinical Microbiology Procedures Handbook [8]. Antibiogram tests were performed using the disc diffusion method following the CLSI criteria. Urine samples showing a colony count more than 105 cfu/mL were considered to be positive for UTI. The samples were considered as being contaminated if more than two clinical isolates were obtained from the same patient. Antibiograms were investigated and resistance rates were compared.

Statistical analysis

Data were analyzed using the SSPS statistical software (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.). The percentages in different categories were compared using Chi square test, and means were compared using Student's t-test. A P-value less than 0.05 was considered as significant. Receiver operating characteristic (commonly known as ROC) curve analysis was performed to determine DM duration for multidrug resistance (MDR) risk.

Results

Study population

A total of 1110 consecutive patients with urine culture were evaluated and 590 were excluded because of contaminated or sterile-inconclusive cultures. Five hundred-twenty samples were positive for uropathogens. Group 1 included 355 patients with DM and group 2 included 165 cases without DM. Mean age was higher in the DM group (63.9 ± 12.4 vs 59.6 ± 17.3 yr respectively, P = 0.001). Females showed a much higher prevalence of UTI in both groups (85.6% in DM vs 70.3% in non-DM, P = 0.000).

Mean duration of DM was 13.9 ± 8.5 yr. Mean HbA1c level on admission was 9.3% (78 mmol/mol). A total of 93 patients (26.2%) had diabetic retinopathy, 96 (27%) had neuropathy, 104 (29.3%) had nephropathy, 282 (79.4%) had DM-related macrovascular complications, and 159 (44.8%) had glucosuria. Of the 355 DM patients, 72.7% (n = 258) were on insulin, 52.4% (n = 186) were on oral hypoglycemic agents, and 1.4% (n = 5) were on glucagon-like peptide 1 agonist (Table 1).

Etiology of isolates

The prevalence and distribution of Gram-negative and Gram-positive bacteria and yeast isolated from the samples are shown in Table 2. Gram-negative and Gram-positive bacteria were present almost equally in both groups (P = 0.223). E. coli was the predominant uropathogen (67.3% in the DM group and 61.8% in the non-DM group), and the difference was insignificant (P > 0.05).

Antimicrobial susceptibility pattern

Antibiotic sensitivity/resistance patterns of both groups are presented in Table 3. There was no difference between groups as regard to most sensitive and resistant antibiotics in urinary tract infection. Both DM and non-DM groups demonstrated a high level of resistance to ampicillin (60.6%, n = 215 vs 69.1%, n = 114 respectively, P = 0.162), and a high percentage of patients in both groups were sensitive to nitrofurantoin (87.0%, n = 309 vs 83.6%, n = 138, P = 0.265).

Gram–negative isolates: Both DM and non-DM groups demonstrated a high level of resistance to ampicillin (69.4%, n = 193 vs 79.7%, n = 94 respectively, P = 0.52), whereas nitrofurantoin was the leading agent that they were sensitive to (93.5%, n = 260 vs 94.9%, n = 112, P = 0.42).

Gram-positive isolates: DM and non-DM groups were highly sensitive to nitrofurantoin (90%, n = 45 vs 68.8%, n = 22 respectively, P = 0.05). They were resistant to ciprofloxacin (54%, n = 27 vs 53.1%, n = 17 respectively, P = 0.97) and norfloxacin (52%, n = 26 and 53.1%, n = 17 respectively, P = 0.57). See Table 4 for details.

Ciprofloxacin resistance was observed in 42.9% (n = 223) of the total isolates (37.5%, n = 133 in the DM group vs 54.5%, n = 90 in the non-DM group).

MDR (≥ 2 antimicrobial agents) was observed in 68.7% (n = 347) of the isolated uropathogens in total (64.9% in the DM group and 76.7% in the non-DM group). The difference between the groups did not reach statistical significance (P = 0.08).

A reasonable HbA1c goal for adults is less than 7% (53 mmol/mol), according to the American Diabetes Association [9]. When we compared MDR in the patients with DM with HbA1c cut-off at 7% (53 mmol/mol), we found no significant difference between the HbA1c levels and the presence of MDR (P = 0.769). The mean HbA1c levels of patients with MDR was 9.1% (76 mmol/mol), whereas it was 9.4 (79 mmol/mol) in the MDR negative ones.

Utilizing the ROC curve, the mean DM duration of greater than 10.5 yr showed the greatest risk of MDR (Figure 1) (area under the curve = 0.58, sensitivity of 63.7% and specificity of 50%, P = 0.019).

Table 1. General characteristics of the study and control subjects

Characteristic	Group 1, DM	Group 2, non-DM	P
Number of patients, n (%)	355 (68.2)	165 (31.7)	
Mean age, years ± SD	63.9 ± 12.4	59.6 ± 17.3	0.001
Female/Male, n (%)	304/51 (85.6/14.4)	116/49 (70.3/29.7)	0.000
Fasting plasma glucose (mg/dL)	220.9 ± 107.9	96.0 ± 13.5	0.000
Duration of diabetes in yr	13.9 ± 8.5	-	
HbA1c, %	9.3 ± 2.3	-	
Glucosuria, n (%)	159 (44.8)	-	
Diabetes-related microvascular complications			
Diabetic retinopathy, n (%)	93 (26.2)	-	
Diabetic neuropathy, n (%)	96 (27)		
Diabetic nephropathy, n (%)	104 (29.3)		
Diabetes-related macrovascular complications*, n (%)	282 (79.4)	-	
Antidiabetic medication, n (%)			
Insulin	258 (72.7)	-	
OADs	186 (52.4)		
GLP-1 agonist	5 (1.4)		
Insulin + OADs	89 (25.1)		

*Ischemic heart disease, peripheral vascular disease, and cerebrovascular disease. DM: Diabetes mellitus; GLP-1: Glucagon-like peptide 1; OADs: Oral antidiabetic drugs.

Table 2. Distribution of urinary pathogens isolated from urine cultures between the groups

Pathogens	Group 1, DM n (%)	Group 2, non-DM n (%)	Total n (%)
Gram-negative microorganisms			
Escherichia coli	239 (67.3)	102 (61.8)	341 (65.6)
Klebsiella	33 (9.3)	12 (7.3)	45 (8.7)
Pseudomonas aeruginosa	3 (0.8)	2 (1.2)	5 (1.0)
Citrobacter	3 (0.8)	2 (1.2)	5 (1.0)
Gram-positive microorganisms	9.3 ± 2.3	-	
Streptococci	32 (9.0)	22 (13.3)	54 (10.4)
Coag. negative Staph	15 (4.2)	9 (5.5)	24 (4.6)
Staphylococcus aureus	3 (0.8)	1 (0.6)	4 (0.8)
Yeast	96 (27)		
Candida	12 (3.4)	2 (1.2)	14 (2.7)
Others	15 (4.2)	13 (7.9)	28 (5.4)

DM: Diabetes mellitus.

Table 3. Antibiotic sensitivity/resistance pattern of both groups

Antimicrobials		Group 1 (DM)/ (n,%)	Group 2 (Non-DM)/ (n,%)	Total
Ampicillin	S	113 (31.8)	40 (24.2)	153 (29.4)
	R	215 (60.6)	114 (69.1)	329 (63.3)
Amoxicillin clavulanic acid	S	186 (52.4)	85 (51.5)	271 (52.1)
	R	51(14.4)	33 (20.0)	84 (16.2)
Ampsul	S	156 (43.9)	73 (44.2)	229 (44.0)
	R	78 (22.0)	43 (26.1)	121 (23.3)
Ciprofloxacin	S	138 (38.9)	53 (32.1)	191 (36.7)
	R	133 (37.5)	90 (54.5)	223 (42.9)
Gentamycin	S	260 (73.2)	114 (69.1)	374 (71.9)
	R	63 (17.7)	39 (23.0)	102 (19.6)
Trimethoprim-Sulphamethoxazole	S	175 (49.3)	66 (40.0)	241 (46.3)
	R	129 (36.3)	70 (42.4)	199 (38.3)
Norfloxacin	S	200 (56.3)	74 (44.8)	274 (52.7)
	R	135 (38.0)	85 (51.5)	220 (42.3)
Nitrofurantoin	S	309 (87.0)	138 (83.6)	447 (86.0)
	R	24 (6.8)	18 (10.9)	42 (8.1)
Cefepime	S	66 (18.6)	26 (15.8)	92 (17.7)
	R	67 (18.9)	46 (27.9)	113 (21.7)
Ceftriaxone	S	61 (17.2)	25 (15.2)	86 (16.5)
	R	69 (19.4)	45 (27.3)	114 (21.9)
Amikacin	S	60 (16.9)	29(17.6)	89 (17.1)
	R	1 (0.3)	3 (1.8)	4 (0.8)
Penicilin	S	28 (7.9)	17 (10.3)	45 (8.7)
		20 (5.6)	16 (9.7)	36 (6.9)

S: Sensitive, R: Resistant, Ampsul: ampicillin sulbactam (Significant features are marked with bold)

Table 4. Antibiotic sensitivity/resistance pattern of Gram-negative and Gram-positive bacteria isolated from our patients

		Gram-negative isolates (n,%) (E.coli Klebsiella Pseudomonas aeroginosa Citro-bacter ssp.)		Gram-positive isolates (n,%) (Streptococci Coag. Negative Staph Staphylococcus aureus)	
Antimicrobials		**Group 1 (DM)/ (n,%)**	**Group 2 (Non-DM)/ (n,%)**	**Group 1 (DM)/(n,%)**	**Group 2 (Non-DM)/(n,%)**
Ampicillin	S	83 (29.9)	22 (18.6)	29 (58)	14 (43.8)
	R	193 (69.4)	94 (79.7)	12 (24)	13 (40.6)
Amoxicillin clavulanic acid	S	172 (61.9)	77 (65.3)	12 (24)	3 (9.4)
	R	36 (12.9)	23 (19.5)	8 (16)	7 (21.9)
Ampsul	S	143 (51.4)	65 (55.1)	8 (16)	3 (9.4)
	R	65 (23.4)	35 (29.7)	8 (16)	3 (9.4)
Ciprofloxacin	S	105 (37.8)	33 (28)	21 (42)	14 (43.8)
	R	104 (37.4)	69 (58.5)	27 (54)	17 (53.1)
Gentamycin	S	226 (81.3)	90 (76.3)	22 (44)	16 (50)
	R	52 (18.7)	27 (22.9)	10 (20)	7 (21.9)
Trimethoprim-Sulphamethoxazole	S	156 (56.1)	53 (44.9)	12 (24)	6 (18.8)
	R	120 (43.2)	63 (53.4)	7 (14)	3 (9.4)
Norfloxacin	S	168 (60.4)	54 (45.8)	23 (46)	13 (40.6)
	R	108 (38.8)	64 (54.2)	26 (52)	17 (53.1)
Nitrofurantoin	S	260 (93.5)	112 (94.9)	45 (90)	22 (68.8)
	R	16 (5.8)	4 (3.4)	4 (8)	8 (25)
Cefepime	S	55 (19.8)	22 (18.6)	-	-
	R	67 (24.1)	43 (36.4)	-	-
Ceftriaxone	S	54 (19.4)	21 (17.8)	0 (0.0)	1 (3.1)
	R	68 (24.5)	43 (36.4)	0 (0.0)	0 (0.0)
Amikacin	S	59 (21.2)	27 (22.9)	-	-
	R	1 (0.4)	2 (1.7)	-	-
Penicilin	S	1 (0.4)	1 (0.8)	27 (54)	16 (50)
		0 (0.0)	0 (0.0)	20 (40)	16 (50)

S: Sensitive, R: Resistant, -:Not tested, Ampsul: ampicillin sulbactam (Significant features are marked with bold)

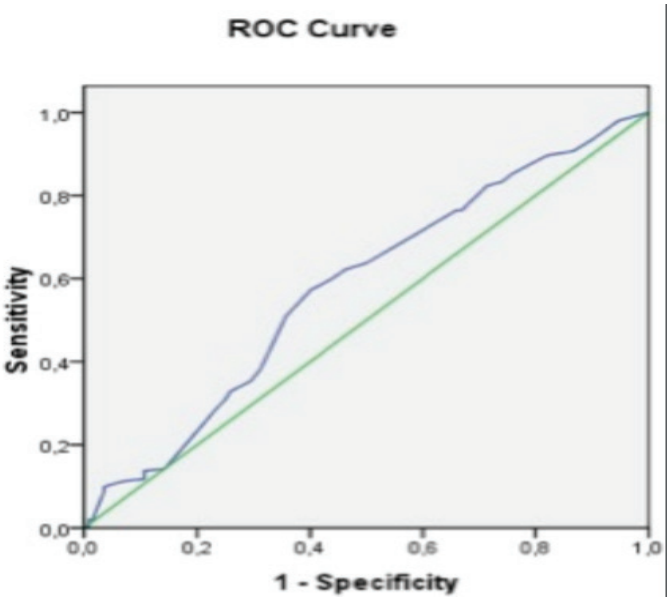

Figure 1. Diagonal segments are produced by ties

Discussion

UTIs are more common and severe in patients with DM. They are also frequently caused by resistant pathogens. In this study, we investigated the impact of DM on the spectrum of uropathogens and antimicrobial drugs' susceptibility in patients with UTI in our region. E. coli was the predominant uropathogen, followed by Streptococci, in the DM and non-DM groups. A high number of isolates were sensitive to nitrofurantoin in both groups, and MDR rates were higher in DM patients with long standing disease status.

Patients who have high HbA1c levels and increased duration of DM are at high risk for UTI [3,7,10-13]. High renal parenchymal glucose levels provide a favorable environment for the growth of microorganisms. Uncontrolled DM is more commonly associated with complicated UTI, like pyelonephritis and emphysematous cystitis [14]. In a meta-analysis of 22 studies on asymptomatic bacteriuria in patients with DM, it was shown that the mean duration of the DM was longer in patients with asymptomatic bacteriuria. In that meta-analysis, HbA1c was also found to be slightly higher in the DM subjects with asymptomatic bacteriuria, although the difference was not statistically significant [15]. Tseng et al have concluded that patients with HbA1c above 8.1% (65 mmol/mol) have higher prevalence of UTI [16]. In addition, HbA1c below 6.5% (48 mmol/mol) appeared to significantly decrease the risk of UTI. Sewify et al also found that most UTI cases have had uncontrolled glycemia [10].

It is very well known that patients with longer duration of DM have increased prevalence of diabetic chronic complications, which may lead to an increased presence of UTI. In many of these patients, autonomic neuropathy results in dysfunctional voiding and urinary retention [4]. Accordingly, the mean HbA1c was 9.3% (78 mmol/mol) in our study. Most of our diabetic patients had long-standing DM (mean duration of 13.9 yr).

Patients with DM carry a higher risk of UTI, particularly women. Age is a well-known risk factor for bacteriuria [12,13]. In our study, we confirmed that females showed a much higher prevalence of UTI in both groups and mean age was higher in the DM group. Wilke et al have also made a similar observation [3]. Compatible with our findings, they reported that the most important factors associated with UTI are older age, female sex, and high HbA1c values.

Gram-negative bacteria, particularly E. coli, are the most common pathogen isolated in patients with UTI, regardless of DM status [12,14,17]. In our study, the most frequent organism isolated was E. coli as well. The profile of isolated organisms from our patients' urine specimens were similar between both groups ($P > 0.05$). Similar conclusions were reported in previous studies [17-19].

The widespread use of antimicrobial agents may lead to the emergence of drug-resistant organisms; thus, a progressively increasing resistance to antimicrobial agents is seen for most of the microorganisms causing UTI. It is important to know the antibiotic susceptibility patterns of isolated organisms. Like our study, many studies have found no difference regarding the susceptible bacterial agents and antibiotic resistance patterns of UTI between patients with and without DM [10,17,20,21].

Our study also aimed to determine the susceptibility patterns of antimicrobial drugs, which may help us to use appropriate therapeutic choices in DM patients. Both of our groups exhibited a high level of resistance to ampicillin and a sensitivity to nitrofurantoin. Taking the Gram staining status of the organisms into account, Gram–negative isolates, including E. coli and Klebsiella pneumoniae, demonstrated a high level of resistance to ampicillin in both groups, which was in agreement with previous studies [7,17,20]. As Table 4 shows, most isolated microorganisms were sensitive to nitrofurantoin, regardless of DM status. Similarly, a high percentage of Gram-positive isolates were sensitive to nitrofurantoin as well. Such findings have been documented elsewhere [10,22-24]. Depending on this widely-validated information, we propose that nitrofurantoin can be used as a drug of choice for empiric treatment of UTI in patients with DM.

Although fluoroquinolones have been recommended as the drug of choice for empirical treatment of community-acquired UTI, an increasing trend in fluoroquinolone resistance is an important problem facing DM patients [20,25]. In our cohort, ciprofloxacin resistance was observed in %42.9 of total isolates. This rate was higher when compared with the studies by Meiland et al and Borowczyk et al [26,27].

In the presence of comorbidities, MDR isolates dominate as the etiological factor [28]. In our study, MDR ($\geq$ 2 antimicrobial agents) was observed in about 70% of the total isolates and 65%-75% of the patients in the DM and non-DM groups. There are conflicting reports about the prevalence of MDR in patients with DM. Hamdan et al reported that 28.2% of the total isolates were affected, vastly different from the 93.9% reported by Nigussie et al [22,24]. The high incidence of MDR in our study may be attributed to the irrational use of antibiotics in our country.

Patients with longer DM duration have increased prevalence of diabetic chronic complications, which may lead to an increase in UTI caused by resistant pathogens. Accordingly, we found that the greatest increase in MDR risk existed among the patients who had

DM for longer than 10.5 yr.

The retrospective design of this study may be considered as a limitation. However, the strict patient selection criteria we used and the inclusion of only out-patients with a relatively high number may help to counter that.

Conclusion

In this study, we determined that the susceptible microorganisms and the antibiogram patterns in patients with UTI and DM in our region are compatible with the current medical literature. We found no difference regarding the susceptible bacterial agents and antibiotic resistance patterns of UTI between patients with and without DM. The most frequently isolated agent was E. coli, regardless of the DM status. Isolated microorganisms were dominantly sensitive to nitrofurantoin. Diabetic patients with UTI had poor glycemic control and long-standing DM. The appearance of MDR was greater among the patients with DM who had the disorder for longer than 10.5 yr.

Conflict of interest
The authors declare that there are no conflicts of interest.
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Ethical approval
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