Infection and Drug Resistance

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ORIGINAL RESEARCH

Prevalence of Bacterial Urinary Tract Infection and Antimicrobial Susceptibility Patterns Among Diabetes Mellitus Patients Attending Zewditu Memorial Hospital, Addis Ababa, Ethiopia

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Background: Urinary tract infection (UTI) is caused by colonization and growth of microorganisms within the urinary system. Diabetic patients are more prone to bacterial UTI due to impaired host defense and high glucose concentration in urine. Surveillance of uropathogens and their antibiogram is a key to patient management.

Methods: A hospital-based cross-sectional study was conducted from May to July, 2018. Urine samples were collected for culture and identification based on the standard protocol. An antimicrobial susceptibility test (AST) was done for all isolates using the Kirby–Bauer disk diffusion method. Data were entered into Epi-data version 3.2.1 and exported to the Statistical Package for the Social Science (SPSS) version 20.

Results: Out of 225 participants, significant bacteriuria was reported in 9.8% of the cultures. Five species of bacteria were isolated and *E. coli* (63.6%) was the leading uropathogen, followed by *K. pneumoniae* (13.6%). Duration of diabetes, previous history of UTIs and symptomatic UTI were found to be strongly associated with significant bacteriuria. Gram-negative bacterial isolates showed high sensitivity to nitrofurantoin and meropenem (100%). In contrast, a high level of resistance to ampicillin, doxycycline and cefuroxime (100%) and to amoxicillin-clavulanate (94.4%) was observed. Gram-positive bacteria showed high level of resistance to penicillin (100%). Multiple-drug resistance (MDR) was high for Gram-negative bacteria (100%).

Conclusion: Previous history of UTIs and duration of diabetes were found to be important factors that increase the prevalence of UTI among diabetes patients. This study also showed a high prevalence of drug resistance to doxycycline, amoxicillin-clavulanate, cefuroxime and penicillin for both Gram-negative and Gram-positive bacteria. Since therapeutic selection for empirical treatment and management should be based on knowledge of the local bacterial profile and antimicrobial response, we suggest physicians take this high resistance profile in to consideration when prescribing antimicrobials against the pathogens in question.

Keywords: UTI, antibiotic susceptibility, diabetes mellitus, significant bacteriuria

Background

Urinary tract infection is caused by colonization and growth of microorganisms such as bacteria, fungi and viruses within the urinary tract (UT).[1,2] However, UTI due to virus and fungi has a low incidence.[1] The primary etiological agents of UTIs are Gram-negative bacteria; however, Gram-positive bacteria may also be involved in UT infections.[3,4] The common uropathogens are *Escherichia coli*, *Staphylococcus*

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saprophyticus, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus* species, *Pseudomonas aeruginosa*[1,2,5–7] and group B *streptococcus*.[2] The most common cause of UTI in men and women with and without DM is *E. coli*. Some reports have noted that a lower proportion of UTIs is caused by this organism in diabetic patients as compared with age-matched non-diabetic patients.[8]

Under normal circumstances, the UT is resistant to long-term colonization and growth of microorganisms.[9] This resistance emanates from various physiological processes, one of which is emptying out urine that flushes out harmful microbes that temporarily colonize urine in the bladder.[3,5,9,10] Additionally, innate immunity such as cytokines, chemokines,[3,5] secretory immunoglobulin,[5,9] mucous production, prostatic secretion, barrier formation and high concentration of urea[3] prevent persistent microbial colonization and infection of the UT. Nevertheless, structural and functional abnormality that blocks urine flow[11] and other risk factors that damage host immunity may lead to UTI.[6] When such damage occur, the UT can be struck by uropathogens like *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*, which possess virulent factors that enable them to colonize urinary epithelial cells.[10]

Due to their anatomic and physiologic nature, UTI is more common in women than men.[1,12] Nearly half of all women have been affected by this infection at least once in their lifetime.[13] Other important risk factors that enhance UTI include: diabetes mellitus (DM), hypertension, allergies, catheterization, use of diaphragms, birth control pills and spermicidal agents, age, delays in micturition, abuse of antibiotics and other immune suppressive conditions.[6]

Chronic diseases are emerging as one of the leading causes of worldwide morbidity and mortality. Among these, DM is one of the dominant non-communicable, chronic and endocrine diseases.[14,15] According to estimates from the 2017 International Diabetics Federation, 451 million (8.4%) people, globally, between 18–99 years of age were living with DM and 5 million people aged 20–79 years of age died due to this disease. However, the number of people with DM is projected to rise to 693 million (9.9%) by 2045. From the African region, in 2017, Ethiopia had the highest number of people (2.6 million) with diabetes, with a 5.2% national prevalence.[16] Similarly, a higher prevalence of DM was also found in a retrospective study between January 2010 and December 2013 in Addis Ababa.[14]

Host immune system abnormalities due to DM such as impaired migration, chemotaxis, phagocytosis and intracellular killing potential of polymorphonuclear cells, local complications related to neuropathy like impaired bladder emptying and higher glucose concentration of urine in diabetic patients enhance UTI. Patients with DM have a higher prevalence of asymptomatic bacteriuria (ASB) and a higher incidence of symptomatic UTIs, which more often lead to complications compared with those without DM.[17] It appears that the increased prevalence of urinary tract infections in diabetic patients is not the result of a difference in the bacteria but is due to changes in the uro-epithelial cells leading to an increased adherence of *E. coli* expressing type 1 fimbriae. Hypothetically, these changes are in the glycosylation of the infected cells.[18] Research shows that UTI is more common,[19–21] severe and produces more serious outcomes in patients with DM.[22–24]

The increased risk of UTI among diabetic patients, coupled with the increase in the incidence of DM worldwide in recent years, may impose a substantial burden on medical costs.[23] In addition, the high rates of antibiotic prescription, including broad-spectrum antibiotics, for UTI in this group of patients may further induce the development of antibiotic-resistant urinary pathogens[25.] Moreover, the inappropriate use of antibiotics often results in increased resistance of UT pathogens to the most commonly used antimicrobial drugs.[26] Appropriate antibiotic use in patients with a complicated UTI seems to reduce length of hospital stay and therefore has a favorable effect on patient outcomes and health care costs.[27]

Studies regarding UTI in DM patients are limited in Ethiopia, particularly in the study area. Therefore, this study was designed to determine bacterial profile and antimicrobial susceptibility patterns among DM patients attending Zewditu Memorial Hospital (ZMH) in Addis Ababa, Ethiopia, with the aim of generating reliable information on which to base treatment of diabetic patients with UTIs in this area.

Methods and Materials

Study Setting

The study was conducted from May to July, 2018 at Zewditu Memorial Hospital, Addis Ababa, Ethiopia. Addis Ababa is the capital city of Ethiopia. According to the 2007 census report,[28] Addis Ababa city had a total population of 2,738,248, with a growth rate of 2.1%. Based on this figure, the central statistical agency of

Ethiopia estimated that the population of Addis Ababa was projected to reach around 3.95 million in 2018. ZMH is one of the biggest hospitals in Ethiopia and is located in central Addis Ababa. It was built, owned and operated by the Seventh-Day Adventist Church, but was later nationalized during the Derg regime in 1976. It provides all-round health care services and is the leading hospital providing antiretroviral treatment (ART) and addressing other chronic diseases, including DM.

Study Design and Participants

A hospital-based cross-sectional study was conducted to determine the prevalence of urinary tract bacterial infection and antimicrobial resistance patterns of bacterial uropathogens among diabetes mellitus patients at Zewditu Memorial Hospital, Addis Ababa, Ethiopia.

Source Population

The source population was all diabetic patients visiting ZMH.

Study Population

Diabetic patients who came for follow-up at ZMH were included.

Inclusion Criteria

The study involved DM patients above 18 years and those who came to ZMH for follow-up during the study period and were willing to participate.

Exclusion Criteria

DM patients who had been taking antibacterial drugs for the previous two weeks, pregnant DM women and DM patients previously exposed to catheterization were excluded from the study.

Operational Definition

Asymptomatic bacteriuria: the presence of significant bacteriuria ($\geq 10^5$cfu/mL) in urine culture without signs and symptoms of urinary tract infection.

MDR: non-susceptibility to at least one agent in three or more antimicrobial categories.

Symptomatic bacteriuria: the presence of significant bacteria in urine culture ($\geq 10^5$cfu/mL) accompanied by at least two complaints of UTI symptoms such as dysuria, urgency for urination, frequent urination, suprapubic pain, flank pain, fever and chills.

Sample Size and Sampling Technique

Sample size was calculated by applying the single population proportion formula, $n=(Z\alpha/2)^2 \times p\ (1-p)/d^2$), where, n = sample size, z = statistic for a level of confidence, d = margin of error, and p = expected or proportional prevalence, 95% confidence level with a margin of error of 5% and 17.8% prevalence from a previous study[29] conducted at Gondar University Hospital. The calculation resulted in 225 samples. Therefore, 225 study participants were selected using a systematic random sampling technique via the lottery method from DM patients' follow-up records, and data and urine sample were collected when they came for follow-up during the study period. Hospital DM follow-up records showed that the total DM patients attending ZMH for treatment follow-up during the sample collection period was 750.

Data Collection and Laboratory Methods

Clinical Examination

After obtaining an informed consent from the patients, socio-demographic data and clinical data were collected from patient using pre-structured questioners by nurses.

Specimen Collection

A freshly voided midstream urine sample (10–20 mL) was collected in a wide-mouthed sterile, dry and leak-proof container after instructing the enrolled DM patients to clean their genitals with soap and water.[4]

Culturing and Identification Procedure

Urine specimens obtained from DM patients were inoculated onto MacConkey agar (HKM, China) and Blood agar (Biomark, India)[30] using a calibrated loop (0.001mL). Cultures were incubated in an aerobic atmosphere at 37°C for 24 hours. A positive urine culture was defined as a colony count of $\geq 10^5$CFU/mL for midstream urine.[31] A Stuart scientific colony counter was used for counting. All positive cultures were further identified by their colony characteristics and Gram staining. Further identification was done using different biochemical tests, including catalase, mannitol salt agar and PYR test for Gram-positive bacteria and mannitol utilization, hydrogen sulphide production (H_2S), indole production, citrate utilization, lysine iron agar test, gas production, hydrolysis of urea, and motility tests and carbohydrate metabolism for Gram-negative bacteria.[4]

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was done on Mueller–Hinton agar (Oxoid, England) using the Kirby–Bauer disk diffusion method based on Clinical and Laboratory Standard Institute (CLSI) guidelines.[32] When pure culture was obtained, a loopful of bacteria (3–5 pure colonies) was taken and emulsified in 5mL sterile normal saline and mixed gently until it formed a homogenous suspension. Then, the turbidity of the suspension was adjusted to the density of a McFarland 0.5 standard (Mary-l'Etoil, France). A sterile cotton swab was dipped into the suspension, and excess suspension was removed by gentle rotation of the swab against the surface of the tube in order to standardize the inoculum size. The swab was then used to distribute the bacteria evenly over the entire surface of Mueller–Hinton agar (Oxoid, England). The inoculated plates were left at room temperature to dry for 3–5 minutes. Next, selected antimicrobial disks were placed on the plate by a disk dispenser and incubated at 35°C–37°C for 16–18 hours.[4,30] The antimicrobial agents tested with respective concentrations were: nitrofurantoin (30 µg), ciprofloxacin (15 µg), doxycycline (30µg), ampicillin (10µg), vancomycin (30µg), co-trimoxazole (25µg), gentamycin (10µg), cefoxitin (30µg), penicillin (10 units), meropenem (10µg), ceftazidime (30µg), cefuroxime (5µg), cefepime (30µg), and amoxicillin-clavulanate (30µg). These antimicrobial agents were selected based on recommended drugs for treatment of UTIs from CLSI guidelines[32] and Ethiopian hospital treatment guidelines, 2014. Diameters of the zone of inhibition around the disks were measured using a digital caliper. The result was interpreted as sensitive, intermediate and resistant based on CLSI guidelines.[30] Multiple-drug resistance is defined as non-susceptibility of tested bacteria to at least one antimicrobial agent in three or more antimicrobial categories.[33] Positive results from urine culture and antimicrobial sensitivity test results were reported to the attending physicians for subsequent treatment and follow-up.

Quality Assurance

Completeness of the questionnaires was properly checked by applying a pre-test before the actual data collection. Collection and examination of the specimens were done following the standard operating procedures (SOPs) for urinalysis, culture and antimicrobial susceptibility patterns. Proper specimen labeling and matching with respective identification numbers was checked. Sterility and performance of culture media was tested prior to the actual work. Sterility of media was checked by incubating overnight at 37°C. In addition, *E. coli* (ATCC 25922), *K. pneumoniae* (ATCC 700603), *P. mirabilis* (ATCC 35699) and *S. aureus* (ATCC 25923) were used as reference strains. Training was given for data collectors, who were all nurses.

Data Analysis and Interpretation

The data were cleaned, edited and entered onto Epi-data version 3.2.1 and analyzed using SPSS version 20 statistical software for further analysis. Different variables were described and characterized by frequency distribution. Binary and multivariate logistic regressions were used and a *p*-value of less than or equal to 0.05 with a 95% confidence interval was considered to test statistically significant associations.

Results

Socio-Demographic Characteristics

A total of 225 diabetic patients with and without symptoms of UTI were investigated during the study period. Of these, 75 (33.3%) were males and 150 (66.7%) were females. The age of the patients ranged from 20 to 80 years, with a mean age of 45.52 years and a standard deviation (SD) of ±14.079. The majority of participants 158 (70.2%) were married. All study participants were from an urban area and the majority (206 (91.6%)) had type II diabetes mellitus. Nearly half of the study participants earned a monthly income of 1651–5250 Ethiopian birr. About 80% of the study participants were literate (Table 1).

Clinical Features of Urinary Tract Infection

Symptoms suggestive of UTI were observed in 97 (43.11%) of the study subjects. The most frequently observed complaints were flank/loin pain, which was observed among 90 (40%), frequent urination, 80 (35.56%), and urgent urination, 66 (29.3%). Fever, dysuria, suprapubic pain, nausea and vomiting were also observed among 52 (23.2%), 42 (18.7%), 38 (16.9%), 26 (11.6%) and 5 (2.2%) participants, respectively (Table 2).

Culture Results

Significant bacteriuria was observed in 22 of 225 (9.8%) urine samples cultured. Of these, 15 (68.2%) were from symptomatic and 7 (37.8%) were from asymptomatic UTI DM patients. Out of s total 22 positives, 3 (13.6%) were from males and 19 (86.4%) from females. Bivariate logistic regression analysis determined significant bacteriuria to be strongly associated with duration of diabetes, previous UTIs and current symptoms of UTI (p <0.05). The results of the study indicate that the chance of getting a UTI among DM patients who have had diabetes for more than 10 years was more than four times greater (COR; 4.364 [95% CI, 1.637–11.629]) than among DM patients who have had diabetes for 10 years or less. Similarly, DM patients with previous UTIs had a 4.709 times greater chance of developing a UTI (COR; 4.709 [95% CI; 1.873–11.842]) than those patients without previous UTIs; and those patients with a symptomatic UTI were at three times greater risk of having significant bacteriuria than asymptomatic patients (COR; 3.162 [95% CI, 1.235–8.094]).

However, other factors like gender, educational status, DM type, marital status, frequency of previous UTIs and fasting blood glucose levels were not statistically associated with significant bacteriuria. The odds of getting significant bacteriuria were not statistically significant between age groups (p >0.05), as significant bacterial isolates were distributed in all age groups of the study participants. However, the highest (20.0%) and the lowest (4.7%) prevalent significant bacteriuria were observed among the age groups ≥64 years and 50–64 years, respectively. Regarding marital status, the highest (14.3%) significant bacteriuria was isolated from single DM patients but this association was not statically significant (p >0.050). Similarly, 19/22 (86.4%) of the bacteria were isolated from female diabetics. Even though the risk of getting a UTI was higher (3.481 times) in female patients than in male patients, no statistically significant association was observed between gender and significant bacteriuria, albeit the failure was marginal (p = 0.051).

In multivariate logistic regression analysis, duration of diabetes and previous UTIs were significantly statistically associated with significant bacteriuria, with adjusted odds ratios (AORs) of (95% CI) 3.477 [1.266–9.554] and 3.645 [1.403–9.473], respectively. Symptomatic condition was not shown to have a significant association with AOR (95% CI) 2.354 [0.881, 6.294] (Table 3).

Bacterial Etiologies

A total of 22 bacterial uropathogens were isolated. Of these, 4 (18.2%) were Gram-positive bacteria and 18 (81.8%) were Gram-negative bacteria. *E. coli* was the most frequently isolated uropathogen [14 (63.6%)] followed by *K. pneumoniae* [3 (13.7%)] and *P. rettgeri* [1 (4.5%)]. Among Gram-positive bacteria, only *Enterococcus* spp. [2 (9.1%)] and coagulase negative staphylococcus (CoNs) [2 (9.1%)] were isolated (Figure 1).

Antimicrobial Susceptibility Testing

The antimicrobial susceptibility test was performed on all culture-positive urine samples using the disk diffusion method. Gram-negative bacterial isolates (n=18) were tested against 12 antibiotics while Gram-positive isolates were tested against 9 antibiotics (Tables 4 and 5, respectively). Sensitivity to Gram-negative isolates was highest for meropenem, with a rate of 18/18 (100%), nitrofurantoin 18/18 (100%) and gentamicin 16/18 (88.9%), whereas the highest level of resistance was observed for doxycycline, with a rate of 18/18 (100%), ampicillin 18/18 (100%), cefuroxime 18/18 (100%) and amoxicillin-clavulanate 17 (94.4%). *E. coli*, the most frequently isolated bacteria, was highly resistant to doxycycline (100%), ampicillin (100%) and amoxicillin-clavulanate (92.9%) (Table 4). Overall, Gram-positive bacterial isolates (n = 4) showed 100% sensitivity to six of the tested antibiotics, whereas a high level of resistance was observed to penicillin (100%) (Table 5).

Multiple Drug Resistance Patterns

The frequency of MDR was found in all Gram-negative bacteria (100%), whereas none of the Gram-positive bacteria showed MDR (Table 6).

Discussion

In the present study, the overall prevalence of UTIs in both symptomatic and asymptomatic diabetic patients was 9.8%. This rate is comparable to the rates reported from other studies in Ethiopia, such as in Debre Tabor (10.9%),[20] Hawassa (13.8%)[34] and Addis Ababa (10.9%)[35]), and in India (12.2%)[36] and Romania (10.7%).[37] However, much higher prevalence rates were reported in Bahir Dar (30.5%)[38] and Arbaminch (33.8%)[39] in Ethiopia, and in Sudan (19.5%),[40] India (22%),[21] Pakistan 52.76%),[41] Egypt (52.2%)[19] and Nepal (54.25%).[42] Inclusion of asymptomatic DM patients and

Table 1 Socio-Demographic Characteristics of Diabetes Mellitus Patients Investigated for Urinary Tract Infection at Zewditu Memorial Hospital, Addis Ababa, Ethiopia, May to July, 2018

Variables		Frequency	Percentage
Gender	Male	75	33.3
	Female	150	66.7
Marital status	Single	28	12.4
	Married	158	70.2
	Separated/divorced	39	17.3
Residence	Urban	225	100
	Rural	0	0
Educational status	No modern schooling	47	20.9
	Primary schooling	71	31.6
	Secondary schooling	71	31.6
	Above secondary schooling	36	16.0
Average monthly income in birr	≤1650	86	38.2
	1651–5250	111	49.3
	>5250	28	12.4

exclusion of catheterized DM patients, which is a known determinant factor that may increase the prevalence of UTIs,[19,42] could be reasons for detecting a lower prevalence of UTIs in our study compared to these other reports.

In the present study, 22 bacterial uropathogens belonging to five species were isolated. Gram-negative bacteria were more prevalent (81.8%) than Gram-positive bacteria (18.2%), as has been the case in most studies conducted elsewhere in the world. Our finding of high Gram-negative bacterial isolates in DM patients is in concordance with reports from Mekelle (83%),[43] India (92%)[44] and Sudan (87.2%).[40] However, relatively lower prevalence rates were reported from similar studies in Ethiopia, such as in Debre Tabor (41.9%)[20] and Bahir Dar (61.9%).[45]

Table 2 Frequency of Symptoms Suggestive of UTI in Diabetes Mellitus Patients in Zewditu Memorial Hospital, Addis Ababa, Ethiopia, May to July, 2018

Symptoms of UTI	Frequency	Percentage
Flank/loin pain	90	40.00
Frequent urination	80	35.56
Urgent urination	66	29.33
Fever	52	23.11
Dysuria	42	18.67
Suprapubic pain	38	11.56
Nausea	26	16.89
Vomiting	5	2.22

Generally, in the present study (63.6%) and in most other studies conducted elsewhere, such as Pakistan (60.0%),[24] India (67.6%),[46] Dessie (63%),[47] Sudan (54.6%)[40] and Romania (68.9%),[37] *E. coli* was the most frequently isolated uropathogen. This dominance of *E. coli* among UTI patients may not be surprising since it is the commonest flora of the gastrointestinal tract and bowel from which it ascends to the urinary tract and uses its well characterized virulence factors to colonize the urinary tract. The second leading bacterial isolate in our study was *K. pneumoniae* (13.7%), as was true for reports from Bahir Dar,[38] Dessie,[47] Sudan[40] and Nigeria.[22] In contrast, *Proteus* species, *Pseudomonas* species and CoNs were reported to be the second most abundant bacterial isolates from UTI in studies in Addis Ababa,[48] Bahir Dar[49] and Pakistan,[24] respectively.

In the present study, small proportions of *Enterococcus* spp. and CoNs were isolated, each with a rate of 9.1% among the overall bacterial isolates. The 9.1% prevalence rate for *Enterococcus* spp. was also reported in Sudan.[40] However, *S. aureus* and *S. saprophyticus* in Debre Tabor,[20] *S. saprophyticus* in Bahir Dar,[49] *S. aureus* in Arbaminch[39] and CoNs in Dessie[47] were the leading Gram-positive isolates, showing variations in the dominance of UTI bacterial isolates among the different geographic locations in Ethiopia.

In the present study, duration of DM was shown to be an important risk factor for UTI development (p = 0.003),

Table 3 Isolation Rate of UTI in Diabetes Mellitus Patients Investigated for Urinary Tract Infection in Relation to Associated Factors at Zewditu Memorial Hospital, Addis Ababa, Ethiopia, May to July, 2018

Category	Significant Bacteriuria		Crude		Adjusted	
	Yes N (%)	No N (%)	P-value	Odds Ratio (95% CI)	p-value	Odd Ratio (95% CI)
Gender						
Male	3 (4.0)	72 (96.0)		1		
Female	19 (12.7)	131 (87.3)	0.051	3.481 [0.974–1.036]		
Total	22 (100%)	203 (100%)				
Age in years						
20–34	5 (9.4)	48 (90.6)		1		
35–49	9 (10.8)	74 (89.2)	0.792	1.168 [0.369–3.695]		
50–64	3 (4.7)	61 (95.3)	0.320	0.472 [0.107–2.075]		
>64	5 (20.0)	20 (80.0)	0.202	2.40 [0.625–9.210]		
Marital status						
Single	4 (14.3)	24 (85.7)		1		
Married	14 (8.9)	144 (90.1)	0.376	0.583 [0.177–1.922]		
Divorced	4 (10.3)	35 (89.7)	0.617	0.686 [0.156–3.012]		
Educational status						
No schooling	7 (14.9)	40 (85.1)	0.098	6.125 [0.718–52.259]		
Primary	9 (12.7)	62 (87.3)	0.131	5.081 [0.618–41.786]		
Secondary	5 (7.0)	66 (93.0)	0.382	2.652 [0.298–23.592]		
Above secondary	1 (2.8)	35 (97.2)		1		
Average monthly income in birr						
≤1650	14 (16.3)	72 (83.7)	0.118	5.250 [0.658–41.873]		
1651–5250	7 (6.3)	104 (93.7)	0.584	1.817 [0.214–15.409]		
>5250	1 (3.6)	27 (96.4)		1		
Type of DM						
Type 1 DM	3 (15.8)	16 (84.2)		1		
Type 2 DM	19 (9.2)	187 (90.8)	0.363	0.542 [0.145–2.029]		
Duration of DM						
≤10 years	6 (4.5)	126 (95.5)		1		1
>10 years	16 (17.2)	77 (82.8)	0.003	4.364 [1.637–11.629]	0.016	3.477 [1.266–9.554]
Fasting blood glucose						
<126 mg/dl	3 (5.4)	53 (94.6)		1		
≥126 mg/dl	19 (11.2)	150 (88.8)	0.209	2.238 [(0.636–7.868)]		
Previous history of UTIs						
No	8 (5.1)	148 (94.9)		1		
Yes	14 (20.3)	55 (79.7)	0.001	4.709 [1.873–11.842]	0.008	3.645 [1.403–9.473]
Frequency of previous UTIs						
Once	6 (15.8)	32 (84.2)		1		
Twice	2 (12.5)	14 (87.5)	0.757	0.762 [0.137–4.251]		
Three and above	6 (40.0)	9 (60.0)	0.066	3.556 [0.920–13.740]		

(*Continued*)

Table 3 (Continued).

Category	Significant Bacteriuria		Crude		Adjusted	
	Yes N (%)	No N (%)	P-value	Odds Ratio (95% CI)	p-value	Odd Ratio (95% CI)
Present symptoms of UTI						
Asymptomatic	7 (5.5)	121 (94.5)		1		1
Symptomatic	15 (15.5)	82 (84.5)	0.016	3.162 [1.235–8.094]	0.088	2.354 [0.881–6.294]

Abbreviation: mg/dl, milligram per deciliter.

as evidenced by the proportion of significant bacteriuria being observed more in those with a diabetic history of >10 years (17.2%) than in those who were diabetic for only <10 years (4.5%). This is likely to be because of the progressive nature of diabetes that may damage the genitourinary system (neuropathy) leading to a dysfunctional bladder thereby creating micturition abnormality, a condition important for the developments of UTIs.[19,50] In fact, previous studies from Egypt[19] and India[51] reached the same conclusion, that the longer the duration of DM, the higher the rate of UTIs observed. However, some studies from Iran[52] and Addis Ababa[26] reported no statistically significant association between duration of diabetes and UTIs.

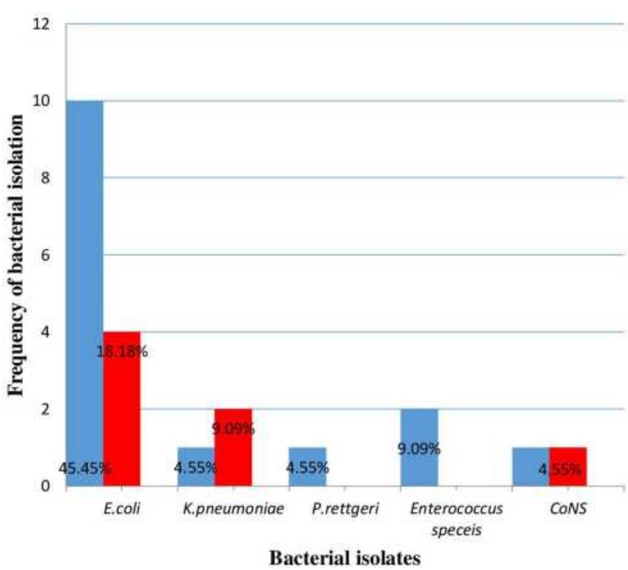

Figure 1 Distribution of bacterial uropathogens isolated from symptomatic and asymptomatic urinary tract infections among diabetic patients at Zewditu Memorial Hospital, Addis Ababa, Ethiopia, May to July, 2018. The bar graph shows the frequency of bacterial isolation versus types of bacterial isolates. The vertical axis indicates the frequency of bacterial isolation and the horizontal axis indicates types of bacterial isolate. Blue indicates symptomatic UTIs and red indicates asymptomatic UTIs among diabetes mellitus study subjects. A total of 22 bacteria were isolated, of which 18 were Gram-negative and 4 were Gram-positive. *E. coli* was the most frequently isolated uropathogen, with a total of 14 isolates; 10 were isolated from symptomatic UTI DM patients and 4 from asymptomatic UTI DM participants. *K. pneumoniae* was the second most frequently isolated pathogen, accounting for 1 symptomatic UTI DM participant and 2 asymptomatic UTI DM participants. Of the total 22 isolates, 15 were isolated from symptomatic UTI DM participants and the remaining 7 isolates were from asymptomatic UTI DM participants.

Another identified risk factor associated with significant bacteriuria in this study was previous history of UTIs. Sixty-nine of the study participants had a history of previous UTIs. However, 14 of the 22 (63.63%) participants with significant bacteriuria were among those who had a previous history of UTIs. In fact, the likelihood of developing significant bacteriuria was 4.709 times greater among participants with a history of UTIs than those without (p <0.05). Other in-country studies have reported the same trend of a higher rate of significant bacteriuria among those with a previous history of UTIs.[26,29,53] However, two studies, from Hawassa[34] and Arbaminch,[39] reported a contradictory finding, whereby they found a statistically significant association of significant bacteriuria among DM patients with no history of UTIs. Possibly these lstudies introduced real biases during recruitment of participants.

Only 97/225 (43.1%) of the participants in our study had symptoms of UTI. However, the majority (15/22; 68%) of participants with significant bacteriuria were those with symptoms (p <0.05). This is not unexpected, as was the case in other studies,[26,35] because long duration of DM and delayed medical intervention are likely to result in renal defects that, in turn, lead to occurrence of UTI symptoms. In contrast, our finding disagrees with the studies conducted in Hawassa,[34] Sudan[40] and Italy,[8] where symptomatic UTI had no significant association with significant bacteriuria. The difference might be due to respondent bias in accurately describing the symptoms characterizing symptomatic UTI.

Of the three variables described above that were found in bivariate analysis to have had significant associations with significant bacteriuria in this study,

Table 4 Antimicrobial Susceptibility Patterns of Gram-Negative Bacteria Isolated from Diabetes Mellitus Patients Investigated for UTI at Zewditu Memorial Hospital, Addis Ababa, Ethiopia, May to July, 2018

Antimicrobial Agents	Bacterial Isolates							
	E. coli (n = 14)		*K. pneumoniae* (n = 3)		*P. rettgeri* (n = 1)		Total (n = 18)	
	S N (%)	R N (%)	S N (%)	R N (%)	S N (%)	R N (%)	S N (%)	R N (%)
Meropenem	14 (100)	0 (0)	3 (100)	0 (0)	1 (100)	0 (0)	18 (100)	0 (0)
Nitrofurantoin	14 (100)	0 (0)	3 (100)	0 (0)	1 (100)	0 (0)	18 (100)	0 (0)
Co-trimoxazole	4 (28.6)	10 (71.4)	1 (33.3)	2 (66.7)	0 (0)	1 (100)	5 (27.8)	13 (72.2)
Gentamicin	12 (85.7)	2 (14.3)	3 (100)	0 (0)	1 (100)	0 (0)	16 (88.9)	2 (11.1)
Ciprofloxacin	6 (42.9)	8 (57.1)	0 (0)	3 (100)	1 (100)	0 (0)	7 (38.9)	11 (61.1)
Doxycycline	0 (0)	14 (100)	0 (0)	3 (100)	0 (0)	1 (100)	0 (0)	18 (100)
Amoxicillin-clavulanate	1 (7.1)	13 (92.9)	0 (0)	3 (100)	0 (0)	1 (100)	1 (5.6)	17 (94.4)
Ampicillin	0 (0)	14 (100)	0 (0)	3 (100)	0 (0)	1 (100)	0 (0)	18 (100)
Cefuroxime	0 (0)	14 (100)	0 (0)	3 (100)	0 (0)	1 (100)	0 (0)	18 (100)
Cefotaxime	8 (57.1)	6 (42.9)	1 (33.3)	2 (66.7)	1 (100)	0 (0)	10 (55.6)	8 (44.4)
Ceftazidime	10 (71.4)	4 (28.6)	0 (0)	3 (100)	1 (100)	0 (0)	11 (61.1)	7 (38.9)
Cefepime	11 (78.6)	3 (21.4)	2 (66.7)	1 (33.3)	1 (100)	0 (0)	14 (77.8)	4 (22.2)

Abbreviations: N (n), number; R, resistance; S, sensitivity.

only previous history of UTIs and current symptoms of UTI were found by multivariate analysis to be persistently associated with significant bacteriuria. Surprisingly, however, this finding contradicted reports from Sudan,[40] whereby duration of diabetes and previous history of UTIs had no significant association with significant

Table 5 Antimicrobial Susceptibility Patterns of Gram-Positive Bacteria Isolated from Diabetic Mellitus Patients Investigated for UTI at Zewditu Memorial Hospital, Addis Ababa, Ethiopia, May to July, 2018

Antimicrobial Agents	Bacterial Isolates					
	Enterococcus spp. (n = 2)		Coagulase Negative *Staphylococcus* (n = 2)		Total (n = 4)	
	S N (%)	R N (%)	S N (%)	R N (%)	S N (%)	R N (%)
Nitrofurantoin	2 (100)	0 (0)	2 (100)	0 (0)	4 (100)	0 (0)
Ciprofloxacin	1 (50)	1 (50)	2 (100)	0 (0)	3 (75)	1 (25)
Doxycycline	0 (0)	2 (100)	2 (100)	0 (0)	2 (50)	2 (50)
Ampicillin	2 (100)	0 (0)	ND	ND	2 (100)	0 (0)
Vancomycin	2 (100)	0 (0)	ND	ND	2 (100)	0 (0)
Co-trimoxazole	ND	ND	2 (100)	0 (0)	2 (100)	0 (0)
Gentamicin	ND	ND	2 (100)	0 (0)	2 (100)	0 (0)
Cefoxitin	ND	ND	2 (100)	0 (0)	2 (100)	0 (0)
Penicillin	ND	ND	0 (0%)	2 (100)	0 (0)	2 (100)

Abbreviations: ND, not done; N, number; R, resistance; S, sensitivity; SPP, species.

Table 6 Multi-Drug Resistance Patterns of Gram-Negative Bacterial Isolates from Midstream Urine Samples Among Diabetes Mellitus Patients at Zewditu Memorial Hospital, Addis Ababa, Ethiopia, May to July, 2018

Antimicrobial Agents	Bacterial Isolates and Their Resistance to Different Classes of Antimicrobials		
	E. coli **(n = 14) Resistance, n (%)**	***K. pneumoniae*** **(n = 3) Resistance n (%)**	***P. rettgeri*** **(n = 1) Resistance n (%)**
Cotr, Cip, Dox, Amp, AMC, Cetz, Cef, Cft, Cep, Gen	1 (7.14)	0	0
Cotr, Cip, Dox, Amp, AMC, Cetz, Cef, Cft, Cep	2 (14.29)	1 (33.33)	0
Cotr, Cip, Dox, Amp, AMC, Cetz, Cef, Cft	0	1 (33.33)	0
Cotr, Cip, Dox, Amp, AMC, Cetz, Cef	1 (7.14)	0	0
Cotr, Cip, Dox, Amp, AMC, Cef, Cft	2 (14.29)	0	0
Cotr, Cip, Dox, Amp, AMC, Cef, Gen	1 (7.14)	0	0
Cotr, Cip, Dox, Amp, AMC, Cef,	1 (7.14)	0	0
Cotr, Dox, Amp, AMC, Cef, Cft	1 (7.14)	0	0
Cotr, Dox, Amp, AMC, Cef	1 (7.14)	0	1 (100)
Cip, Dox, Amp, AMC, Cetz, Cef	0	1 (33.33)	0
Dox, Amp, AMC, Cef,	3 (21.42)	0	0
Dox, Amp, Cef	1 (7.14)	0	0
Total	14 (100)	3 (100)	1 (100)

Abbreviations: Cotr, co-trimoxazole; Gen, gentamicin; Cip, ciprofloxacin; Dox, doxycycline; Amp, ampicillin; AMC, amoxicillin-clavulanate; Cetz, ceftazidime; Cef, cefuroxime; Cft, cefotaxime; Cep, cefepime.

bacteriuria in multivariate analysis. Moreover, in reports of other studies in Ethiopia, multivariate analysis showed previous history of UTIs to have had statistically significant associations with significant culture positive bacteria in diabetic patients.[34,53] However, other variables, such as gender in Harar[53] and educational status in Hawassa,[34] were equally important in this association but were not even significant by bivariate analysis in our study.

Regarding antimicrobial sensitivity test results, the Gram-negative uropathogens were highly sensitive to meropenem (100%), nitrofurantoin (100%) and gentamicin (88.9%). The latter two antimicrobials were also shown previously to be highly effective against Gram-negative bacteria with sensitivities of 95.5% and 73.3% for nitrofurantoin and gentamicin, respectively, in Dessie, Ethiopia.[47] A 100% sensitivity to nitrofurantoin was also recorded from a study in Arbaminch[39] and Gondar.[29]

In contrast, high level resistance was exhibited by the Gram-negative isolates against a number of tested antimicrobials that are commonly used against bacterial UTI: ampicillin (100%), doxycycline (100%), cefuroxime (100%), amoxicillin-clavulanate (94.4%), co-trimoxazole (72.2%) and ciprofloxacin (61.1%). The most disturbing observation in this connection is that all Gram-negative isolates had shown resistance to more than at least one antimicrobial in three classes tested (100% MDR level). Such high levels of resistance among uropathogens against these same antimicrobials seems widespread both in Ethiopia (eg 91.4% against ampicillin and 79.2% against amoxicillin-clavulanate,[38] 100% against co-tromoxazole, greater than 75% against amoxicillin-clavulanate,[53] and between 60% to 100% against ampicillin[29,34–36]) and elsewhere in the world.[36] Still more studies have confirmed that detection of high MDR among Gram-negative uropathogens is common both in Ethiopia and elsewhere.[20,34,47,49,53] The remarkably higher prevalence of resistance, including MDR, against these commonly prescribed antibiotics may be due to: their wider availability and ease of access outside treatment centers and, thus, indiscriminate use of the drugs without prescription;[54] fake drugs, sub-standard or expired drugs circulating that are likely to be used for self-treatment; frequent use of broad-spectrum antibiotics as prophylactics; and lack of laboratory tests for both AST and pathogen identification.[4]

E. coli, the leading uropathogen in the present study, was 100% sensitive to meropenem and nitrofurantoin, and 87.5% to gentamicin. In the contrast, a very high level of resistance was observed to doxycycline (100%), ampicillin (100%), cefuroxime (100%) and amoxicillin-clavulanate (92.9%). Such high sensitivity of *E. coli* to the former two antibiotics was also reported previously from Sudan,[40] where it was 100% and 86.3% sensitive to gentamicin and nitrofurantoin, respectively; and in Ethiopia, where it was observed to be 100% sensitive to nitrofurantoin in Addis Ababa[26] and Hawassa.[34] However, this pathogen has been found to exhibit very high resistance (100%) to ampicillin, which is also supported by the reports from Hawassa (100%)[34] and Bahir Dar,[49] Iran (86.6%).[55] In contrast, in our study the 92.2%, 100% and 100% resistance of *E. coli* to amoxicillin-clavulanate, ampicillin and doxycycline, respectively, disagrees with the report from Sudan,[40] in that amoxicillin-clavulanate (sensitivity rate, 90.9%), ampicillin (sensitivity rate, 72.7%) and, in Tehran,[56] doxycycline (sensitivity rate, 100%) were presented as effective drugs. The deterioration in the effectiveness of amoxicillin-clavulanate and ampicillin against *E. coli* from UTIs is a matter of concern, given the facts that the primary etiology of UTI infection for DM patients is this uropathogen and these antimicrobials are among the most commonly used drugs in Ethiopia.

In the present study, the overall percentage of antimicrobial sensitivity of Gram-positive bacterial isolates to the majority of the tested antibiotics was high. For instance, *Enterococcus* spp. were 100% sensitive to nitrofurantoin, ampicillin and vancomycin. Previous studies from Ethiopia and tSudan[20,29,40] also reported this high sensitivity rate for the former two antibiotics. Similarly, CoNs were highly sensitive (100%) to six of the tested antimicrobials, namely, nitrofurantoin, ciprofloxacin, co-trimoxazole, gentamicin, cefoxitin and doxycycline, which was also observed in previous studies in Ethiopia, where 100% sensitivity was reported to doxycycline,[20] gentamicin[34] and ampicillin.[40]

Mixed results were observed in regard to resistance among the two Gram-positive bacterial species isolated, *Enterococcus* spp. and CoNs. On the one hand, *Enterococcus* isolates were 100% resistant to doxycycline, but CoNs were 100% sensitive to this drug. On the other hand, resistance to ciprofloxacin was 50% for *Enterococcus* spp. while it was 0% to CoNs. Moreover, CoNs isolates were 100% resistant to penicillin, as was the case in other studies elsewhere.[34,53] Overall, Gram-positive isolates presented better options for empiric treatment than Gram-negative isolates since they were 100% sensitive to the majority of tested antimicrobial drugs except penicillin and doxycycline resistance for CoNs and *Enterococci*, respectively.

Conclusion

Significant bacteriuria was obtained from 9.8% of participants, and *Escherichia coli* (63.6%) was the leading uropathogen. Presence of previous urinary tract infections and duration of diabetes were found to be important factors responsible for increased prevalence of laboratory-confirmed urinary tract infection among the diabetes patients. Nitrofurantoin and gentamicin were effective against both Gram-positive and Gram-negative bacterial uropathogens in the current study, which may be used for empirical therapy when urine culture is unavailable. This study also showed a high prevalence of drug resistance to common antimicrobials, particularly to co-trimoxazole, ciprofloxacin, doxycycline, ampicillin, amoxicillin-clavulanate, cefuroxime and penicillin. The prevalence of MDR was also high for Gram-negative bacteria. Therefore, cautious use of antibiotic therapy and immediate treatment of urinary tract infections in DM patients is mandatory. Moreover, therapeutic selection for empirical treatment and management should be based on knowledge of the local bacterial profile and antimicrobial response, and there should be continuous monitoring and review of antimicrobial policy in hospitals and the country at large.

Limitations of the Study

The present study did not include non-diabetic patients as a control group, which makes it difficult to indicate how much DM may increase the prevalence of UTIs compared with non-DM patients. In addition, the present study did not address UTIs caused by bacterial pathogens that are difficult to culture in the ordinary culture media and anaerobic bacterial pathogens which might change the prevalence of UTIs.

Abbreviations

AAU, Addis Ababa University; ATCC, American type culture collection; ASB, asymptomatic bacteriuria; CLSI, Clinical Laboratory Standard Institute; CoNs, coagulase negative staphylococci; COR, crude odds ratio; DMIP, Department of Microbiology, Immunology and Parasitology; DM, diabetes mellitus; MSU, midstream urine; NDM, non-diabetes mellitus; PYR, pyrrolidonyl acrylamides, SPSS, Statistical Package for the Social Science; SB, symptomatic bacteriuria; UTI, urinary tract infection; WHO, World Health Organization; ZMH, Zewditu Memorial Hospital.

Data Sharing Statement

Data is available upon request.

Ethics Approval and Consent

Ethical clearance was obtained from the Research and Ethical Review Committee and was approved by the Department of Microbiology, Immunology and Parasitology, School of Medicine, Addis Ababa University. Ethical clearance was also secured from Addis Ababa Public Health Research and Emergency Management Directorate. Official permission was also obtained from ZMH. In addition, written informed consent was obtained from the study participants before the initiation of data collection and all participants were informed about the purpose of the study, and told that it was conducted in accordance with the Declaration of Helsinki. The individual results of investigations remained confidential. The laboratory findings of the study participants were communicated to the responsible health professional assigned to the diabetic clinic for the purpose of managing the cases accordingly.

Consent for Publication

Not applicable. This study does not contain any individual or personal data.

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Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis and interpretation or in all of these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article was submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest for this work.

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