Original Article

Effect of Diabetes Mellitus on the Spectrum of Uropathogens and the Antimicrobial Resistance in Patients with Urinary Tract Infection

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ABSTRACT

Patients with diabetes mellitus frequently experience urinary tract infections (UTIs). In the present study, we looked at how glycemic control affects diabetic patients' rates of UTI, the causing pathogens, the presence of multi-drug-resistant (MDR) and extensively drug-resistant organisms, and the infections' relation to diabetes. Diabetes patients' midstream urine samples were included, after collecting and identifying the organisms, disc diffusion antibiotic sensitivity tests were conducted. The HbA1c was measured for all patients. A total of 500 diabetic patients provided urine samples for this study, and 189 (37.2%) of them had UTIs. Compared to 59 patients with managed glycemia, 130 individuals in the uncontrolled glycemic group experienced the most UTI cases. In both diabetic groups, females had a significantly higher prevalence of UTI than males (88.4% and 11.6%, respectively). The most common bacterial isolate, *E. coli*, displayed 58.4% MDR. Regardless of age or gender, glycemic control in diabetes patients is essential for decreasing UTI rates.

Keywords: Antibacterial resistance, Diabetes mellitus, Glycemia, MDR, UTI, XDR

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1. Introduction

Urinary tract infection (UTI) is one of the most frequent microbial diseases seen in clinical practice affecting patients of all ages (1). Every year, UTIs result in about 100,000 hospitalizations, mostly among women, the elderly, and people with multiple sclerosis, HIV, diabetes, and spinal cord injuries. Additionally, UTIs account for about seven million office visits and one million visits to the emergency departments (2). Diabetes mellitus (DM) is a set of metabolic diseases that are defined by hyperglycemia brought on by abnormalities in insulin production, insulin action, or both (3). As a result, those with DM are more prone to recurrent infections, particularly infections of the genitourinary tract. Genitourinary tract infections are more than twice as likely to occur in diabetic patients (4). The DM is a major threat to public health in developed and developing countries, where it affects more than 366 million people and is expected to reach 552 million by 2030 (5, 6). Increased adhesion of microorganisms to uroepithelial cells, granulocyte malfunction, and altered intracellular calcium metabolism are a result of the altered host responses in diabetic individuals. This makes these individuals more susceptible to acquiring UTI (7, 8), which are characterized by the presence of more than 10^5 organisms per milliliter of midstream urine (MSU) (9). Due to nerve damage brought on by high blood glucose levels, the bladder's capacity to detect urine may be compromised, resulting in urine remaining in the bladder for extended periods of time and a higher risk of infection in diabetes patients (10, 11). Another reason is that elevated urine glucose levels promote bacterial growth (12). Furthermore, the decreased production of cytokines such as IL-6 and other pro-inflammatory cytokines in diabetic patients' urine (13) may indicate abnormalities of the host defense system, which may raise the risk of contracting an infection. This is because prolonged DM reduces blood circulation. *Escherichia coli*, *Klebsiella spp*., *Proteus spp*., *Pseudomonas aeruginosa*, *Enterococcus spp*., *Staphylococcus aureus*, and coagulase-negative staphylococci are the bacteria most frequently linked to UTI in diabetics (14, 15). The correct identification of the causing bacteria and the use of efficient antibiotics for them are essential for the management of UTI in diabetics. Treatment and infection control continue to be made more difficult by the emergence of resistant bacterial strains in hospitals. Antibiotic resistance has continuously developed as a result of the excessive and inadequate use of antimicrobial drugs. Due to the fact that infections caused by multi-drug-resistant (MDR) strain commonly result in mortality, it has grown to be a significant global issue in recent years (16). The extensively drug-resistant (XDR) is the inability to be affected by at least one agent in all but two or fewer antimicrobial categories, while MDR is the inability to be affected by at least one agent in three or more antimicrobial categories (17, 18). Furthermore, increased control of glycemia in diabetic patients may help reduce UTIs. In addition, accurate screening for UTIs in diabetes patients is crucial to enable timely treatment and minimize consequences. Therefore, the present investigation aimed to detect uropathogens and antibiotic sensitivity patterns and to determine the status of MDR/XDR organisms causing UTI in diabetic patients. The findings will be helpful in the establishment of a strategy to track the emergence of resistant strains and determine the prevalent bacterial agent responsible for UTIs.

2. Materials and Methods

2.1. Population and Study Design

This cross-sectional study was carried out between March 2021 and June 2022 on diabetic patients aged ≥ 15 years who were referred to a Non-hospital Medical Laboratory in Qazvin, Northwest Iran. Out of 500 examined samples, 189 patients with positive UTIs were included in the research. Pregnant women and non-diabetic patients were omitted from the study. Diabetic patients who used antimicrobials for two weeks before and during data collection and who were hospitalized for more than 48 h with complaints of difficulty urinating, nausea, pain or pressure in the back or lower abdomen, burning sensation during urination, bloody, dark, cloudy, or strange-smelling urine, fatigue, and trembling were included. Moreover, HbA1c for All patients was conducted. Based on the obtained results, patients were categorized as controlled and uncontrolled.

2.2. Ethical Consideration

This research was supported by the Deputy of Research and Technology, Qazvin University of Medical Sciences, Qazvin, Iran, grant number 401000175. The Ethics Committee of the Metabolic Diseases Research Center, Research Institute for Prevention of Non-Communicable Diseases, Qazvin University of Medical Sciences, Qazvin, Iran, provided the ethical approval for the study (IR.QUMS.REC.1401.210). The research was conducted following the Helsinki Declaration and was approved by the Local Ethics Committee. Before supplying urine samples and participating in the research, patients were given a letter of information and a permission form. Patients' information, including name, gender, and, age was obtained.

2.3. Processing and Collection of Urine Samples

Each diabetes patient received instruction on how to gather a midstream, clean-catch urine sample. Consequently, 10 to 15 ml of MSU samples were collected in labeled, dry, leak-proof, and sterile containers. When rapid processing was not possible, the specimen was kept between 4 and 6°C, and when there was a delay of more than 2 h, boric acid (1.8% w/v) was added to the urine as a preservative. The presence of bacteria, a positive leukocyte esterase, and a white blood cell count (WBC) of >5 per high power field (HPF) were diagnostic for a urinary tract infection. Pyuria was defined as WBC higher than 10/HPF, and hematuria as red blood cell greater than 5/HPF. Two medical microbiologists performed both culture and antimicrobial susceptibility tests. All isolates were identified on the basis of cultural, biochemical, and morphological characteristics as per Bergey's Manual of Systemic Bacteriology (19). All urine samples were inoculated with 10 μL of urine using a calibrated inoculation needle, and each sample was inoculated on freshly prepared differential and selective culture media, including blood agar, mannitol salt agar, MacConkey agar, and eosin methylene blue (Oxoid, Basingstoke, UK). All plates were incubated for 18-24 h at 35 ± 2 for observable growth. After an overnight incubation at 35 ± 2, the plates were examined for signs of growth and colony features. Bacterial colonies differing in size, shape, and color were selected from these plates and separately sub-cultured for further characterization and identification. These biochemical tests included motility, Gram's reaction, indole tests, methyl red, Voges–Proskauer, citrate utilization, utilization of carbohydrates (e.g., glucose, sucrose, mannitol, lactose, and fructose), oxidase, catalase, coagulase if a single bacterium was isolated at a concentration of $\geq 10^5$ cfu/mL of urine, the culture was considered significant for UTI.

2.4. Testing for Antimicrobial Susceptibility

The antibiotic susceptibility test (AST) was done using the disk diffusion method based on the Clinical and Laboratory Standard Institute (CLSI 2022) guideline. For Gram-negative organisms, the bacterial inoculum was generated by suspending newly grown bacteria in 2 ml of sterile nutrient broth and incubating for 3 to 4 h at 35 ± 2. The turbidity of the tube was matched to the 0.5 Mc Farland Standard. The inoculum was subsequently streaked throughout the entire Muller-Hinton agar (MHA) plate. For Streptococcus spp, bacterial inoculum was generated by suspending newly grown bacteria in 2 ml of sterile Brain Heart Infusion broth containing yeast extract and then matching the turbidity of the tube to 0.5 Mc Farland turbidity standards. Then, 5% blood was added as it was streaked onto an MHA plate. Eighteen antimicrobial disks, including amikacin (30 µg), tobramycin (10 µg), cefoxitin (30 µg), ceftazidime (30 µg), erythromycin (15 µg), cephalexin (30 µg), cephalothin (30 µg), cefazolin (30 µg), nalidixic acid (30 µg), trimethoprim-sulfamethoxazole (25 µg), amoxicillin (30 µg), imipenem (10 µg), ceftriaxone (30 µg), gentamicin (10 µg), vancomycin (30 µg), norfloxacin (10 µg), nitrofurantoin (300 µg), and tetracycline (30 µg), were put onto inoculation plates and incubated overnight at 35ºC. The zone diameter criteria were used to measure the diameter of the zone of inhibition and to determine the level of sensitivity to each antibiotic (CLSI, 2022).

Limitation

A detailed comparison among diabetic patients with and without UTI concerning the glycemic control is not possible due to the small number of diabetic patients with controlled glycemia that were analyzed in the present research and the absence of historical data on the non-UTI diabetic patients. Additionally, the biochemical aspect is only used to identify the isolates. To pinpoint the location of drug-resistance genes, MDR strains should undergo genotypic analysis. Nevertheless, despite these drawbacks, we offered sufficient proof that glycemia control in diabetic patients may help in lowering the incidence of UTI in these vulnerable patients, particularly in older participants.

Statistical Analysis

Descriptive statistics were used to measure the characteristics of the study. Pearson Chi-square was used to determine significant differences between proportions. A *P*-value of < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS (version 16) statistical software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Participant Characteristics

Between March 2021 and June 2022, this study was carried out on urine samples from 500 diabetic individuals. A total of 311 (62.2%) out of the 500 tested samples were sterile urine samples. In the current study analysis, 189 (37.8%) additional samples tested positive for uropathogens with a colony count greater than 10^5 CFU/mL of urine. Patients with controlled glycemia (HbA1c<8) and patients with uncontrolled glycemia (HbA1c≥8) were divided into two groups in the study population, and Table 1 summarizes their key characteristics. In the uncontrolled glycemic group (n=130, 68.8%), there were significantly more individuals

with UTI than in the managed glycemic group (n=59, 31.2%). In comparison to diabetic patients with unregulated glycemia, the mean age of diabetic patients with managed glycemia was significantly reduced [P<0.01; Table 1].

3.2. Urinary Tract Infections and Etiology of Isolates

In the current study, 167 (88.4%) of the participants with UTIs were females, compared to only 22 (11.6%) (P<0.0001) in males. The obtained results demonstrated that females have a substantially greater prevalence of UTIs than males. It is noteworthy to mention that both patient populations with controlled and uncontrolled glycemia exhibit this gender distribution trend. It is important to note that, in contrast to the group with managed glycemia, there is a definite aging-related rise in UTI incidence in patients with uncontrolled glycemia, as 52.3% of UTI cases were detected in women over the age of 46 (Table 2). Despite the small number of males with UTI in this research, the same pattern was seen in both genders, particularly in the managed glycemic group. The UTI cases by age ranges revealed an obvious increase in UTI cases with age in the uncontrolled glycemia category (P=0.017), in contrast to the regulated glycemia group, where there was no trend in UTI cases by age (Figure 1). The prevalence and distribution of Gram-negative and Gram-positive bacteria recovered from clinical specimens for both managed and uncontrolled glycemia categories are displayed in Table 3. These pathogens, isolated from both males and females, were clinically significant. In patients with uncontrolled glycemia, *E. coli* was the most common pathogen identified from urine samples, as indicated in Table 3. *E. coli* was really isolated from 91.2% of the cases of UTI in females and 8.8% of UTI cases in males. According to Table 3, *E. coli* was the most common pathogen in both groups of patients with managed and uncontrolled glycemia (67.4% and 32.6%, respectively). In the uncontrolled glycemic category, *K. pneumoniae* strain was the second most common pathogen after *E. coli*; however, *S. saprophyticus* was discovered in 4.8% of the UTI cases. The most common uropathogens were *E. coli* and *K. pneumoniae*, which account for 78.8% of the UTI cases (Table 3).

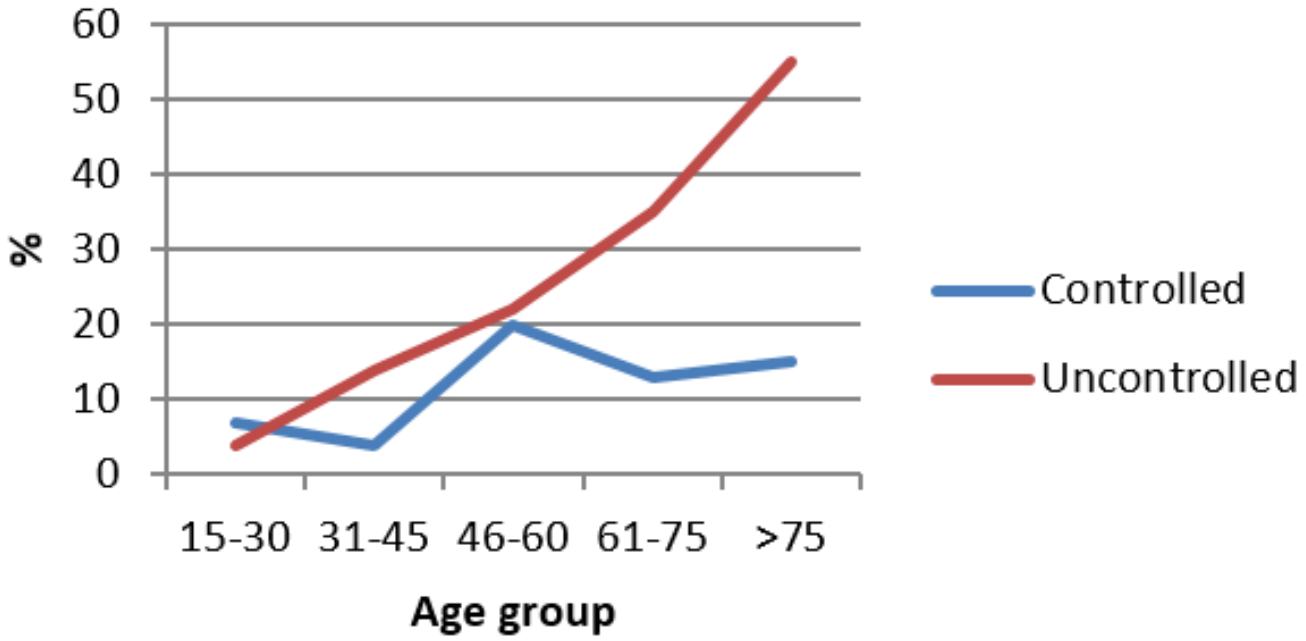

Figure 1: Distribution of UTI infections according to glycemic status and age ranges of diabetic patients.

Table 1: Characteristics of the study patients with controlled and uncontrolled glycemia.

	Controlled glycemic group			Uncontrolled glycemic group		
Number of patients	Male	N= 8	59 (31.2%)	Male	N= 14	130 (68.8%)
	Female	N= 51		Female	N= 116	
Mean age (years ± SD)	62.5±16.5					

Table 2: Sex and age distribution of patients with positive UTI included in this study.

Glycemic status	Patients age groups	Gender		Total
		Male	Female	
Controlled	18-30	1	6	7
	31-45	2	2	4
	46-60	2	18	20
	61-75	1	12	13
	>75	1	14	15
	Total	7	52	59
Uncontrolled	18-30	0	4	4
	31-45	2	12	14
	46-60	1	21	22
	61-75	5	30	35
	>75	7	48	55
	Total	15	115	130

3.3. Antimicrobial Susceptibility Pattern of Gram-Negative Bacterial Isolates

The findings of testing for antibiotic resistance of the most common Gram-negative and Gram-positive infections were examined and displayed in Tables 4 and 5, respectively. Gram-negative isolates were more susceptible to nitrofurantoin (81.5%), followed by amikacin (70.9%), among the examined common antibiotics, whereas they were also more resistant to amoxicillin (88.4%). Table 4 displays the results.

3.4. Antibiotic Susceptibility Pattern of Gram-Positive Bacteria Isolates

While Gram-positive isolates were more resistant to amoxicillin and imipenem, with respective resistance rates of 79.2% and 62.5%, they were particularly susceptible to gentamicin (83.3%), nitrofurantoin and tobramycin (both with 79.2%), and less so to both (83.2%). The outcomes are displayed in Table 5.

3.5. Pattern of Multi-drug-resistant/Extensively drug-resistant Pathogens in Diabetic Patients

E. coli had the highest MDR rate among the 13 distinct bacterial isolates, followed by *Klebsiella pneumoniae*. Diabetes patients had an incidence of MDR and XDR of 57.1% and 7.4%, respectively. Table 6 presents the outcomes.

Table 3: Pattern of microbial isolates from the urine sample

	Isolated organisms	Controlled glycemia		Uncontrolled glycemia		Frequency (%)	Total (%)
		Males No. (%)	Females No. (%)	Males No. (%)	Females No. (%)		
Gram negative bacteria	*Escherichia coli*	4 (3.2)	38 (30.4)	7 (5.6)	76 (60.8)	125 (66.1)	165 (87.3)
	Klebsiella pneumoniae	2 (8.3)	4 (16.7)	3 (12.5)	15 (62.5)	24 (12.7)	
	Citrobacter freundii	0 (0.0)	1 (25.0)	0 (0.0)	3 (75.0)	4 (2.1)	
	Enterobacter aerogenes	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)	2 (1.1)	
	Proteus mirabilis	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)	2 (1.1)	
	Serratia	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)	1 (0.5)	
	Pseudomonas aeruginosa	0 (0.0)	0 (0.0)	2 (50.0)	2 (50.0)	4 (2.1)	
	Acinetobacter	0 (0.0)	1 (33.3)	0 (0.0)	2 (66.7)	3 (1.6)	
Gram positive bacteria	*Staphylococcus aureus*	1 (20.0)	1 (20.0)	1 (20.0)	2 (40.0)	5 (2.6)	24 (12.7)
	S. saprophyticus	0 (0.0)	3 (33.3)	1 (11.1)	5 (55.6)	9 (4.8)	
	S.epidermidis	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)	1 (5.0)	
	E. faecalis	0 (0.0)	1 (20.0)	1 (20.0)	3 (60.0)	5 (2.6)	
	S. agalactiae	0 (0.0)	1 (25.0)	0 (0.0)	3 (75.0)	4 (2.1)	
	Total	7 (3.7)	50 (26.5)	15 (7.9)	117 (61.9)	189 (100)	189

Table 4: Antibiotic susceptibility pattern of gram negative bacterial isolates

Antibiotic used	Sensitive	Intermediate	Resistant
	No. (%)	No. (%)	No. (%)
Trimethoprim-sulfamethoxazole	64 (33.9)	6 (3.2)	119 (62.9)
Amoxicillin	7 (3.7)	15 (7.9)	167 (88.4)
Amikacin	134 (70.9)	14 (7.4)	41 (21.7)
Imipenem	113 (59.8)	4 (2.1)	72 (38.1)
Gentamycin	116 (61.4)	12 (6.3)	61 (32.3)
Nalidixic acid	71 (37.6)	18 (9.5)	100 (52.9)
Nitrofurantoin	154 (81.5)	10 (5.3)	25 (13.2)
Tobramycin	126 (66.7)	14 (7.4)	49 (25.9)
Cefazolin	114 (60.3)	6 (3.2)	69 (36.5)
Cephalothin	102 (54)	18 (9.5)	69 (36.5)
Cephalexin	61 (32.3)	12 (6.3)	116 (61.4)
Ceftriaxone	92 (48.7)	8 (4.2)	89 (47.1)
Cefoxitin	130 (68.8)	6 (3.2)	53 (28)
Ceftazidime	92 (48.7)	7 (3.7)	90 (47.6)

Table 5: Antibiotic susceptibility pattern of Gram positive bacteria isolates

Antibiotic used	Sensitive	Intermediate	Resistant
	No. (%)	No. (%)	No. (%)
Trimethoprim-sulfamethoxazole	13 (54.2)	0 (0)	11 (45.8)
Amoxycillin	5 (20.8)	0 (0)	19 (79.2)
Amikacin	17 (70.8)	0 (0)	7 (29.2)
Imipenem	9 (37.5)	0 (0)	15 (62.5)
Gentamycin	20 (83.3)	0 (0)	4 (16.7)
Nalidixic acid	10 (41.7)	1 (4.2)	13 (54.1)
Nitrofurantoin	19 (79.2)	0 (0)	5 (20.8)
Tobramycin	19 (79.2)	2 (8.3)	3 (12.5)
Cefazolin	14 (58.3)	0 (0)	10 (41.2)
Cephalothin	18 (75.0)	1 (4.2)	5 (20.8)
Cephalexin	15 (62.5)	2 (8.3)	7 (29.2)
Ceftriaxone	17 (70.8)	1 (4.2)	6 (25.0)
Cefoxitin	18 (75.0)	1 (4.2)	5 (20.8)
Ceftazidime	14 (58.3)	0 (0)	10 (41.7)
Norfloxacin	17 (70.8)	0 (0)	7 (29.2)
Tetracycline	18 (75.0)	1 (4.2)	5 (20.8)
Erythromycin	15 (62.5)	2 (8.3)	7 (29.2)
Vancomycin	16 (66.7)	2 (8.3)	6 (25.0)

Table 6: Pattern of MDR & XDR pathogens in diabetic patients

Bacterial isolates	Diabetic Patients			Total isolates
	Sensitive (%)	MDR (%)	XDR (%)	
Escherichia coli	45 (36.0)	73 (58.4)	7 (5.6)	125
Klebsiella pneumoniae	5 (20.8)	14 (58.4)	5 (20.8)	24
Citrobacter freundii	0 (0)	3 (75.0)	1 (25.0)	4
Enterobacter aerogenes	0 (0)	2 (100)	0 (0)	2
Proteus mirabilis	1 (50.0)	1 (50.0)	0 (0)	2
Serratia	0 (0)	1 (100)	0 (0)	1
Pseudomonas aeruginosa	1 (25.0)	2 (50.0)	1 (25.0)	4
Acinetobacter	2 (66.7)	1 (33.3)	0 (0)	3
Staphylococcus aureus	2 (40.0)	3 (60.0)	0 (0)	5
S. saprophyticus	6 (66.7)	3 (33.3)	0 (0)	9
S.epidermidis	0 (0)	1 (100)	0 (0)	1
E. faecalis	2 (40.0)	3 (60.0)	0 (0)	5
S. agalactiae	3 (75.0)	1 (25.0)	0 (0)	4
Total	67 (35.5)	108 (57.1)	14 (7.4)	189

4. Discussion

Patients with diabetes are more likely to develop a UTI, especially women. In this study, we examined diabetic individuals with controlled and uncontrolled glycemia to see if there were any variations in the bacteriologic patterns of UTI and patterns of antibiotic susceptibility of the bacteria involved. The uncontrolled diabetic patients showed a significantly higher overall rate of UTIs; these people were at double risk compared to the controlled diabetic group. The uncontrolled diabetes group also showed a considerably greater prevalence of UTIs in females. Based on an analysis of our findings, 37.8% of the 500 diabetic individuals we received tested positive for uropathogens. According to reports, this frequency is higher than the typical 20–30% found in diabetes individuals (20-22). In addition, the majority of UTI infections in our study (68.8%) were discovered in diabetic patients with uncontrolled glycemia, in line with earlier studies that revealed this tendency when comparing diabetic patients (thought to have uncontrolled glycemia) with nondiabetic individuals with normal glycemia. In addition, our findings revealed that women made up the bulk of UTI cases (88.5%), supporting earlier research (23). The UTI prevalence is higher in adult women than in men, including among diabetics. It is noteworthy to mention that this gender distribution pattern was remarkably comparable in diabetic groups with managed and uncontrolled glycemia, indicating that glycemic control has an effect on how UTIs are distributed by gender (Table 2). Similar findings were reported in other research that compared diabetes and nondiabetic adult subjects and found no significant differences in the

prevalence of bacteriuria in males and females (21, 22). Conversely, it was shown that bacteriuria is more common in diabetic women with uncontrolled glycemia (22) while still comparing nondiabetic with diabetic women patients. There is little data regarding the specifics of UTIs in diabetic men because the majority of prior studies on UTIs in diabetes patients were conducted in women (22, 24). In this investigation, we were able to demonstrate that postmenopausal women had a larger chance of developing an acutely symptomatic UTI due to diabetes than younger women. Our findings showed a strong relationship between age and UTI in the group with uncontrolled glycemia, and the majority of UTI cases were in older age groups (Figure 1). In contrast, although having fewer patients, the managed glycemia group showed a nearly equal proportion of UTI infections across all age groups, regardless of gender (Table 2). Because most patients with controlled glycemia are younger than older patients, they are more likely to stick to their medication and lead healthy lifestyles, which may account for the large age difference between the two groups as well as the association with UTI. There are many investigations on DM in terms of treatment, prevention, new substances, and new strategies for reducing the side effects of DM in patients (6, 25-27). In the current investigation, *Klebsiella* and *E. coli* were the most common pathogens found in urine specimens from both males and females. These species were collectively involved in 78.8% of UTI cases and were similarly prevalent in both groups of people with managed and uncontrolled glycemia. Similar findings have been previously published and supported the species' dominance in both diabetic patients and healthy participants (21-23, 28). As first-line antibiotics are utilized in medical centers and may aid doctors in the proper use of antimicrobial drugs in patients with diabetes, our study also sought to identify the resistance pattern for these antibiotics. According to the findings of the present research, female diabetic patients had a higher prevalence of UTIs than male diabetic patients. The primary etiological agent of UTI was *E. coli*. Additionally, it was found that as people age, the disease's prevalence rises and vice versa. *E. coli*, which had MDR, had a high level of resistance among uropathogenic bacteria. The increased prevalence of MDR strains in the population may be the cause of the rise in UTIs brought on by MDR *E. coli*. The importance of the present study lies in identifying common pathogens in diabetic patients with UTI in controlled and uncontrolled glycemia for the first time, as well as the pattern of antibiotic resistance, to provide clinicians with useful data on the use of antibiotics in diabetic patients. Therefore, a bigger diabetes population study is anticipated to provide more validation. A critical problem in hospital wards is the high prevalence of MDR/XDR strains found in this investigation. These results highlight the need for an organized campaign to inform and influence prescribers of antibiotics to adopt based on evidence prescribing to prevent antibiotic misuse and, consequently, antimicrobial resistance.

Abbreviations

Diabetes mellitus: DM, urinary tract infection: UTI, multi-drug-resistant: MDR, extensively drug-resistant: XDR, midstream urine: MSU, Antibiotic susceptibility test: AST

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Authors' Contribution

Designed the study: S.G.K.

Performed the study, writing the manuscript and statistical analysis: S.S, M.B, H.S, and S.R.

Project consultants: F.M, and V.C

Ethics

The Ethics Committee of the Metabolic Diseases Research Center, Research Institute for Prevention of Non-Communicable Diseases, Qazvin University of Medical Sciences, Qazvin, Iran provided the ethical approval for the study (IR.QUMS.REC.1401.210). In addition, the committee approved the utilization of human samples within this study. Also, it should be noted that biological samples are handled by the authors in the present study. The adopted methods for handling human samples were carried out in accordance with relevant guidelines and regulations provided in the Declaration of Helsinki. The research protocol was approved by the Research Ethics Committee at the Qazvin Medical University, Iran**.** Informed consent was obtained from all patients included in the current study.

Conflict of Interest

The authors declare no conflict of interest

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