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Assessment of Disease State, Disease Control and the Related Complications among Patients Suffering from Diabetes Mellites

Running Title: Diabetes prevalence, control, and complications

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ABSTRACT: Research has shown that people with diabetes mellitus are more vulnerable to infectious diseases than people without the condition. People with diabetes mellitus are more likely than non-DM people to get infections, especially urinary tract infections. The prevalence of infections, overall glycemic control, pathogens, and antibiotic resistance among individuals with chronic diabetes were assessed in this cross-sectional investigation. The SPSS version 29 was used to conduct statistical analyses. The data were analyzed using both descriptive and inferential statistics. For this study, information was gathered about the patients' comorbidities, glycemic levels, presence and kind of urinary infections, bacteria found in cultures and sensitivity tests, and antibiotics recommended to treat such infections. Among the studied individuals, it was observed that diabetes was poorly controlled among female patients, and the frequency of uncontrolled diabetes episodes was also high in female patients. Different type of bacteria were present in the urine of diabates patients with uncontrolled diabates and poor glycemic control patients.

INTRODUCTION

Impairment in the immune system, poor metabolic control, and incomplete bladder emptying due to autonomic neuropathy often contribute as additional and enhanced risks of developing urinary tract infections (UTIs) especially among chronic disease patients. Diabetes mellitus (DM) is considered as one of the most challenging health problems of the 21st century, worldwide. It affects every aspect of life, including quality of life (QoL), employment and even causing early deaths [1,2]. Uncontrolled hyperglycemia is associated with long-term damage with deleterious effects on various systems including the genitourinary system among DM patients [3]. DM patients are prone to have various kinds of infections more than non-diabetics. This high

incidence rate of infections is attributed in altering immune functions like polymorphonuclear leucocyte function, adhesion phagocytosis, chemotaxis and impaired antioxidant system [4,5].

DM has long been recognized as a predisposing factor for UTI episodes among DM patients [6-9]. Different studies are evident in literature that report prevalence of UTIs among DM patients. According to their findings, UTIs prevalence is quite high among diabetics than non-diabetics. A study found that the risk of UTIs for diabetic patients was two folds higher than that of non-diabetics [10,11]. Another study reported that the prevalence of UTIs among diabetic patients was 51% higher than non-diabetics. Furthermore, UTIs prevalence is significantly associated with age and is more common in patients aged >55 years. A study observed that the prevalence of UTIs with >55 years of age was 68.6% [8]. Low urinary concentration of interleukin-8 and interleukin-6 in diabetics has been shown to correlate with lower urinary leucocyte cell count which may contribute to the increasing incidence and worse outcomes in UTIs among DM patients [11,12].

Persistent uncontrolled hyperglycemia potentially causes nerve damage which further affects the ability of the urinary bladder to sense the presence of urine in it so it allows urine to stay in the bladder for a long time thus increasing the probability of getting UTIs [13,14]. A high concentration of urine may act as good media for pathogens and may enhance the growth of pathogenic bacteria in the urinary tract [15,16]. Gram-negative bacteria more commonly cause UTIs than gram-positive bacteria. Escherichia coli (E. coli) is the most common gram-negative pathogen that causes UTIs. A study reported that Escherichia coli contributes 56% of the UTIs followed by Klebsiella pneumoniae 35%, Proteus mirabilis 25%, Pseudomonas 9.5%, and Candida albicans 7.3% [9]. Enterobacter, Proteus mirabilis, Staphylococcus aureus are also among commonly isolated pathogens in the urine of DM patients [17-23].

Antimicrobial resistance (AMR) is one of the major healthcare concerns regarding treatment of UTIs among DM patients. AMR develops when pathogens like bacteria, viruses, fungi, and parasites no longer respond to the antimicrobial drugs. In the last 4 decades, the prevalence of multidrug-resistant pathogens has risen alarmingly among DM patients [24-29]. According to World Health Organization (WHO), bacteria that cause common community-acquired infections (CAIs) and healthcare-associated infections (HAIs) e.g., UTI, Pneumonia, etc, have very high rates of antibiotic resistance. Inapposite diagnosis and inadequate treatment of UTI can further lead to serious complications. Although, most of the countries have their guidelines regarding antibiotics usage and infection control but still healthcare providers are not fully compliant with them. This study determined prevalence of UTIs, glycemic status, pathogen types and antibiotic resistance pattern among chronic DM patients.

MATERIALS AND METHODS

This study was conducted after the permission and approval from the concerned authorities, and the records of patients who were admitted with DM were reviewed. Convenient sampling technique was used to obtain the required sample size. The sample size was calculated online using an online sample size calculator, www.raosoft.com. The study inclusion criteria included adult patients aged ≥ 18, with diagnosed DM from at least 1 year and had at least one prescription medication regarding DM treatment. Patients' collected data was kept strictly confidential. Patients' socio-demographic characteristics like gender, age, marital status and clinical data DM status, UTI status, type of UTI, prescribed antibiotics were analyzed using SPSS version 29.0 as descriptive statistics. Categorical data were presented as frequency and percentage while continuous data were reported as mean ± standard deviation. The Chi-square test was used to find the association of glycemic control with UTI. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 451 DM patients were studied. Gender distribution was not equal between males and females, and the female patients were 317 (70.3%) while the male patients were 134 (29.7%). The mean age of the DM patients was 57.62 (±9.77) years. There were more elderly (≥50 years-old) patients i.e., 395 (87.6%) than non-elderly (<50 years-old) 56 (12.4%). The majority of the patients were married i.e., 403 (89.4%) and 314 (69.6%) of the studied patients had type 2 DM. The studied patients were also analyzed and classified according to their glycemic control i.e., good control vs poor control. Patients with good control (HbA1c <6.5%) were 209 (46.3%) and with poor control (HbA1c ≥ 6.5%) were 242 (53.7%). There was a high prevalence of UTIs among the studied cohort of DM patients. In the current study out of 451 DM patients, 165 (36.6%) patients had UTIs. These results are shown in table 1.

Variables	N	%
Gender		
Male	134	29.7
Female	317	70.3
Age		
< 50 Years	56	12.4
≥ 50 Years	395	87.6
Marital status		
Single/Unmarried	48	10.6
Married	403	89.4
Education		
< Secondary	244	54.1
Post-Secondary	207	45.9
Type of DM		
Type 1	137	30.4
Type 2	314	69.6
Comorbidities other than DM		
Yes	294	65.2
No	157	34.8
Glycemic control		
Yes (HbA1c < 6.5%)	209	46.3
No (HbA1c ≥ 6.5%)	242	53.7
Obese/Over weight		
Yes	178	39.5
No	273	60.5
UTIs		
Yes	165	36.6
No	286	63.4
DM diagnosis (years)		
< 5 Years	135	29.9
≥ 5 Years	316	70.1

Table 1: Demographic and clinical characteristics of the study patients (n=451)

The prevalence of UTIs was higher among female patients 117 (70.9%) than the male patients (23.8%). The prevalence of UTIs among the married patients was higher 148 (89.7%) than the single/unmarried 17 (10.3%). All of the demographic and clinical characteristics of the DM patients suffered from UTIs are presented in table 2.

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Variables	N	%
Gender		
Male	48	29.1
Female	117	70.9
Age		
< 50 Years	26	15.8
≥ 50 Years	139	84.2
Marital status		
Single/Unmarried	17	10.3
Married	148	89.7
Education		
< Secondary	97	58.8
Post-Secondary	68	41.2
Type of DM		
Type 1	29	17.6
Type 2	136	82.4
Comorbidities other than DM		
Yes	101	61.2
No	64	38.8
Glycemic control		
Yes (HbA1c < 6.5%)	28	17.0
No (HbA1c ≥ 6.5%)	137	83.0
Obese/Over weight		
Yes	87	52.7
No	78	47.3

Table 2: Demographic and clinical characteristics of the patients with UTIs (n=165)

Among the reported UTIs, cystitis (37.6%) and asymptomatic bacteriuria (29.1%) were the most common types followed by pyelonephritis (15.8%), urosepsis (10.9%), and prostatitis (6.7%). These results are presented in figure 1.

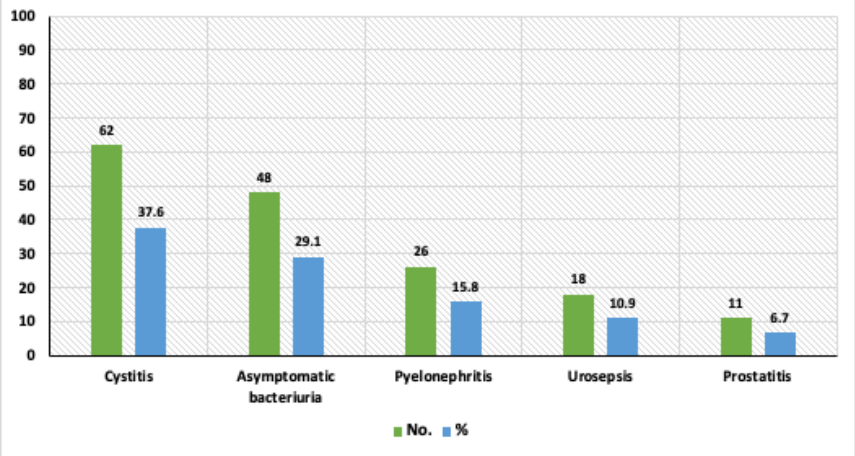

Figure 1: Common pathogen types among the reported UTIs

The DM patients with poor glycemic control 137 (62.6%) had more frequent episodes of UTIs than the DM patients with good glycemic control 28 (12.1%). The obtained results showed that a statistically significant (p<0.05) association was present between glycemic control and the risk of getting UTIs. According to the obtained results, DM patients with poor glycemic control had higher risk of getting UTIs than DM patients with poor glycemic control. These results are presented in table 3.

Glycemic status	Good	Poor	*p*-Value
	N (%)	N (%)	
UTI	28 (12.1)	137 (62.6)	0.043
No UTI	204 (87.9)	82 (37.4)	

Table 3: Prevalence of UTIs and its association with glycemic status

Escherichia coli was the most common gram-negative bacteria which identified from the urine of DM patients suffering from UTIs. Escherichia coli was found in 37 (22.4%) of the studied DM patients with UTI followed by Klebsiella pneumoniae 22 (13.3%), Pseudomonas aeruginosa 8 (4.8%) and Proteus mirabilis 5 (3%). On the other side, among the gram-positive bacteria, Enterococcus spp. was the most common 18 (10.9%), followed by Streptococcus agalactiae 15 (9.1%), Staphylococcus aureus 9 (5.5%) and Staphylococcus epidermidis 8 (4.8%). Other than bacteria, Candida spp. were 21 (12.7%), Trichosporon spp. 4 (2.4%) and unknown pathogens were 18 (10.9%). These results are presented in table 4.

Pathogen type	N	%
Gram-negative bacteria		
Escherichia coli	37	22.4
Klebsiella pneumoniae	22	13.3
Pseudomonas aeruginosa	8	4.8
Proteus mirabilis	5	3.0
Gram-positive bacteria		
Enterococcus spp.	18	10.9
Streptococcus agalactiae	15	9.1
Staphylococcus aureus	9	5.5
Staphylococcus epidermidis	8	4.8
Candida spp.	21	12.7
Trichosporon spp.	4	2.4
Unknown pathogens	18	10.9

Table 4: Pathogens isolated from urine of DM patients with UTIs

Antibiotics resistance pattern among two most common gram-negative bacteria i.e., Escherichia coli and Klebsiella pneumoniae, causing UTIs among DM patients were also observed. Escherichia coli had the highest resistance to nalidixic acid (52%) while the least resistance to imipenem (2%), gentamicin (8%), and nitrofurantoin (11%). Klebsiella pneumoniae had the highest resistance (83%) against ampicillin and cefoperazone (35%), while the least resistance against nitrofurantoin (8%) and imipenem (9%). These results are presented in figure 2.

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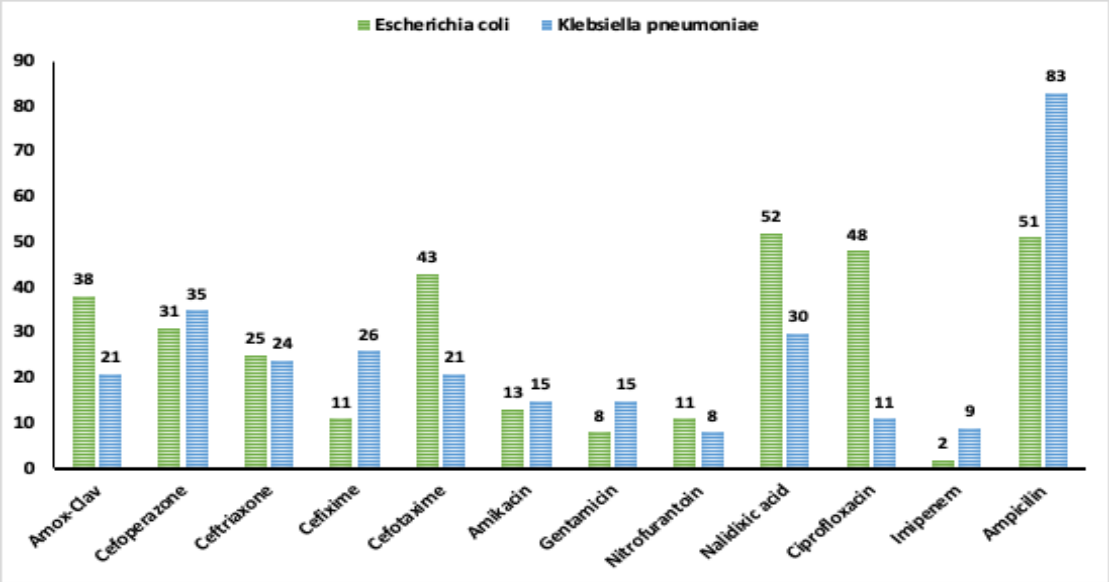

Figure 2: Antibiotics resistance pattern of two most common gram-negative bacteria

DISCUSSION

DM often causes various impairments in the immune system (low urinary concentration of interleukin-8 and interleukin-6, lower urinary leucocyte cell count), poor metabolic control and incomplete bladder emptying among DM patients. And due to autonomic neuropathy, these all factors usually contribute to the enhanced risks of UTIs in DM patients [10]. Inapposite diagnosis and inadequate treatment of UTIs can further lead to serious complications especially among chronic disease patients like DM. Thus, this study determined UTIs prevalence, glycemic status, pathogen types, and antibiotic resistance pattern among chronic DM patients.

Prevalence of UTIs has been determined in numerous studies performed in various countries across the globe. In literature, previous studies done in 2015 (38%), in 2011 (37%) and in 2016 (35%) showed a higher prevalence of UTIs which is in accordance to our study [30-32]. Whereas, there was a high prevalence of UTIs reported in other studies in 2014 (51%), and in 2012 (62%) as well. Few studies found less prevalence of UTIs than this study. These studies conducted in 2013 (25.2%) and in 2015 (19.5%), respectively [32, 33]. Similar to the majority of the studies present in literature, this study also showed a high prevalence of UTIs among the studied DM patients.

In line with previous studies, this study results also showed a higher prevalence of UTIs among female DM patients compared to males. In terms of gender, females are more prone to acquire UTIs than males. Women are vulnerable to UTIs due to their anatomy and reproductive physiology. The short urethra, urethra closer to the perirectal area where pathogen colonizes easier, absence of bacteriostatic prostatic secretions and sexual intercourse may force bacteria enter into the female bladder [24]. A study done in 2014 found 62.5% prevalence of UTIs among females and 37.5% among males [25]. Another study in 2014 also showed similar results to our study. They found 51.37% prevalence of UTIs among females while 48.63% in males. In women, there are high chances of UTIs during childbearing age that could be due to sexual intercourse or the use of contraception (e.g., diaphragm and spermicides).

The finding of this study also showed that a large number of patients' compliance with their medication was not good. As UTIs are considered as a severe complication when it comes to DM patients. Studies performed by Dielubanza *et al.,* 2014 and Schmiemann *et al.,* 2010 recommended that there should be culture and sensitivity tests perform before and after antibiotic therapy [20,21] in DM patients, which is not possible in every patient at every time. Our study results showed that 34.3% of physicians were non-compliant to culture test in the studied DM patients. A study done by Kahan *et al.,* reported that the patients' adherence rate for the treatment of UTIs was 40.5% [23]. However, a study was done in Taiwan by Jan *et al.,* 2007, showed more compliance (72.1%) towards the medication than our study for the treatment of UTIs among DM patients [22].

Prevalence of UTIs among elderly and non-elderly was nearly equal with slightly higher in non-elderly patients. In elderly patients, loss of estrogen causes a change in the vaginal flora, loss of lactobacilli in the vaginal flora results in periurethral colonization. Further complications could arise due to decreased bladder capacity and increased urine production, decreased lower urinary tract sensory threshold and decreased voided volume [26]. Regarding the age factor, two other studies [25,27] also reported similar results to our study results. Chaudhary *et al.,* 2014 assessed the age association with the UTIs and concluded that 31-40 years age group had a higher prevalence of UTIs followed by 41-50 years age group [25]. Njunda *et al.,* also found a high prevalence of UTIs (27.2%) among the age group of 41-60 years [27]. Unlike this study, Ijaz *et al.,* showed that the prevalence of UTIs was higher (68.6%) among patients >55 years of age than 41-55 years' age group (42.9%) [8].

Poor metabolic control may suppress the immune system. Furthermore, high urine glucose concentration shows significant bacterial growth than normal urine. The results of this study showed that the majority of patients had cystitis (37.6%) followed by asymptomatic bacteriuria, pyelonephritis, urosepsis and prostatitis. Similarly, other studies also reported cystitis as the most prevalent type of UTIs among the DM patients [14,28]. In this study, the prevalence of cystitis was higher than other types of UTIs. The bladder is a storehouse for urine where pathogens can enter and colonize much easier than other parts of the urinary tract system. Most of UTIs cases 137 (83%) in this study were found in patients with poor glycemic control. Whereas, only 28 (17%) of cases of UTIs were found in patients with good glycemic control. Those patients with poor glycemic control had more risk of getting UTIs than good glycemic control patients ($p<0.05$). The high concentration of sugar in the urine acts as a good media for the growth of pathogen in urine [12]. Similarly, other studies also stated a high prevalence of UTIs in patients with uncontrolled DM [6,29].

Escherichia coli is one of the common bacteria found in fecal flora, which makes it the most common causative agent for UTIs [24]. The results of this study showed that from gram-negative bacteria, Escherichia coli was the most common pathogen identified from the urine of DM patients infected with UTIs. After Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa and Proteus mirabilis were more abundant in DM patients' urine from gram-negative class. From gram-positive bacteria, Enterococcus spp., Streptococcus agalactiae, Staphylococcus aureus and Staphylococcus epidermidis were more frequent. In this study, though Escherichia coli was most common pathogen but interestingly its proportion was less than other studies done by Chaudhary *et al.,* (51%) and Ijaz *et al.,* (75.8%) among DM patients. Another study reported that the most common bacteria isolated from urine samples were Escherichia coli 57.90% (most common) followed by Staphylococcus aureus 21.05%%, Klebsiella species 15.79%%, Enterococcus species, 2.63% and Pseudomonas species 2.63% [7]. In literature, gram-negative aerobic rods are responsible for 78.2% of UTIs cases and gram-positive cocci are responsible for 20.8%, while Candida spp. are responsible for 1% of cases of UTIs among DM patients [30]. Another study also reported that Escherichia coli and Klebsiella pneumoniae are the most common pathogens reported among DM patients suffering from UTIs [31].

Escherichia coli displayed relatively high antimicrobial resistance rates against most of the tested antibiotics. Escherichia coli had the highest resistant to Nalidixic acid followed by ampicillin, ciprofloxacin, cefotaxime and Amox-Clav. Interestingly, resistance patterns of this study are slightly different from a similar study done in 2014 which also reported resistance patterns of Escherichia coli. It is reported in their study that Escherichia coli was 69% resistant to ampicillin, 23% resistant to cefotaxime, 23% resistant to ciprofloxacin, 24% resistant to ampicillin/sulbactam and 3% resistant to piperacillin/tazobactam. Similar to our study there were low resistance patterns observed against imipenem (0.3%) and meropenem (0.2%). Likewise, a study in 2015 also reported no resistance of Escherichia coli against gentamicin but the highest resistance was reported against ampicillin (28%) [32].

Another study reported that ciprofloxacin had relatively low resistance (31%) while gentamicin had 32.7% resistance followed by ceftriaxone (36.3%) and amoxicillin-clavulanic acid (36.3%). Cefoperazone/sulbactam had maximum resistance (39.8%) [8]. Another study evaluated that Escherichia coli was 94.7% resistant to ampicillin, 63.7% to amoxicillin-clavulanic acid, 51.9% to co-trimoxazole, 9.8% to nitrofurantoin, 66.7% to cefaclor, 58.2% to cefpodoxime, 53.4% to ciprofloxacin, 47.1% to ofloxacin, 15.9% to gentamicin and 5.8% to amikacin [31]. A study reported that cephalothin showed maximum (5.8%) resistance followed by TMP/SMX (48%), ciprofloxacin and ampicillin/sulbactam (34%), cefotaxime (28%), ceftazidime (26%) and amoxicillin/clavulanic acid (20%). Nitrofurantoin and amikacin showed minimum resistance [6].

In literature there was a variation of resistance pattern of Klebsiella pneumoniae observed among different studies conducted among DM patients. In our study, Klebsiella pneumoniae was the second most common pathogen found in this study. It

showed 83% resistance against ampicillin, 35% against cefoperazone and 30% resistance against Nalidixic acid. Sewify *et al.,* found nearly similar patterns of resistance to amoxicillin/clavulanate (24%) and amikacin 2%. Klebsiella pneumonia was 47% resistant to TMP/SMX. They found 42% ampicillin/sulbactam resistance while our study showed 21% resistance against Klebsiella pneumoniae [6]. In Sudan, Hamdan *et al.,* (2015) showed Klebsiella pneumoniae was 27.2% resistant to ampicillin, 0% resistant to gentamicin, 11.1% resistant to amoxicillin-clavulanic acid and 22.2% resistant to TMP/SMX [32].

Limitations of the study

This was a retrospective study and like other retrospective studies, evidence quality could be lower than the prospective studies. Another limitation could be misclassification bias. Despite limitations, the findings of this study suggest that an antimicrobial stewardship program is recommended to conduct in the hospitals to highlight the recent updates about resistance patterns of pathogens. Further studies are also encouraged to determine reasons and factors leading to non-adherence to medications among DM patients. A larger study would be beneficial to determine more precise prevalence of UTIs, antimicrobial susceptibility, types of pathogens involved, and antibiotic resistance among DM patients.

CONCLUSION

High prevalence of UTIs among DM patients confirmed that DM was uncontrolled and resulted in frequent episodes of UTIs among them. Undeniably, UTIs are more frequent and are complicated illnesses among DM patients. Overall, the prevalence of UTIs among the studied DM patients was 36.6%. Besides, the prevalence among females was higher than males. Cystitis was the most prevalent UTIs type found in the studied cohort of DM patients. The most common pathogen isolated from the urine of DM patients was Escherichia coli followed by Klebsiella pneumoniae. Resistance patterns of the antibiotics were highly variable but most of the bacteria showed resistance against ampicillin, and some of cephalosporins.

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