MULTIDRUG RESISTANT PROFILE OF UROPATHOGENIC *Escherichia coli*(UPEC) ISOLATED FROM DIABETIC PATIENTS IN SOME HOSPITALS OF BAUCHI METROPOLIS, NIGERIA

ABSTRACT

Background: Urinary Tract Infection (UTI) is a common pathogenic inflammatory, distressing and occasionally life-threatening condition that affects people of all ages and gender, with difficulty in treatment due to high rate of antibiotic resistance. Diabetic patients are more prone to urinary tract infection due to their immunocompromised system and hyperglycemia level compared to non- diabetic patients. *Escherichia coli* is the primary cause of UTIs in humans both in diabetic and non-diabetic patients. Antibiotics are becoming less and less effective, therefore there is an urgent need to curtail this problem in order to have good administration of antibiotics to patients for effective treatment.

Aim: The aim of this study was to isolate uropathogenic *Escherichia coli* from diabetic patientsanddetermine its antibiotic-resistantpattern

Methods: A total of 288 study participants were enrolled in the study, (194 diabetic and 94 non diabetic patients). Clean catch mid-stream urine samples were collected from all the participants in sterile containers. Each urine sample was streaked onto CLED (cysteine lactose electrolyte deficient agar), incubated at 37^0C for 24h and the isolates were identified using standard methods. Data obtained were analyzed statistically.

Results:A total of 64 UPEC was isolated from diabetic patients and 35 UPEC ~~was isolated~~ from non-diabetic patients. Age group of 31-40 had high frequency of occurrence in both the study participants, while age group of 10-20 and ≥ 71 years had the least. There was no significant difference between age group and the number of isolates as $p > 0.05$. Highest frequency of UPEC was found within the female than their male counterparts. Type2 patients have high frequency of isolates compared to type 1 patients in both the study participants. In the present study, 52 UPEC isolates from diabetic patients and 27 UPEC isolates from non-diabetic patients were resistant to 2 or more antimicrobial agent (multidrug resistance). The highest resistance was observed against ampicillin and piperacillin-tazobactams, while the least resistant in imipenem.

Conclusion: The study established that UPEC infection was more prevalent in diabetic than non-diabetic patients, and also more prevalent in the middle age group, female gender and type2 diabetic patients. High rate of multidrug resistance was observed in both the study participants, and this signals a tremendous problem in prescription of antibiotics to patients. The emergence of multi resistant strains of UPEC has added to the need of urgent development of more control measures and policies to the use of antibiotics.

Keywords: UPEC (uropathogenic *E. coli*), diabetic patients, non-diabetic patients, multidrug resistance.

1. INTRODUCTION

Urinary Tract Infection (UTI) which is defined as the presence and active multiplication of microorganisms within the urinary tract is one of the commonest bacterial infections seeking treatment in clinical practice [1]. 250 million people globally experience urinary tract infections (UTIs), it is one of the most common diseases in humans with a variety of etiological factors [2]. As stated by [3] , the infection is named after the affected urinary organ or part and is known as cystitis (bladder infection) and pyelonephritis (kidney infection). The symptoms of bladder and

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kidney infections differ, with cystitis causing painful and frequent urination and pyelonephritis causing high fever and flank pain [3].

Diabetes mellitus (DM) is an ever-growing heterogenic disorder altering the metabolic abilities of the body, primarily characterized by persistently high glucose levels (hyperglycemia) resulting from defects in insulin secretion attenuating every bodily function [4,5]. It is among the most common non-communicable diseases in emerging and developed nations[6], it has a number of effects on the genitourinary system [7]. According to [8], Diabetes Mellitus (DM) has become a significant public health issue worldwide and has emerged as a significant socio-economic burden for developing nations.

UTIs are classified based on the type of infection (upper or lower UTI), the presence or absence of symptoms (symptomatic or asymptomatic), the tendency to recur (single episode or recurrent UTI), and the presence or absence of complicating factors (uncomplicated or complicated UTI) [9,10,11,12,3,2]. Similarly, risk of UTI increases with age, poor metabolic control, various impairments in the immune system and incomplete bladder emptying due to autonomic neuropathy[13].

The common symptoms of UTI include burning micturition, urgency, dysuria, cramping in the lower abdomen, mental irritability, back or flank pain, chill, nausea, fever, vomiting, fatigue, and weakness [14]. According to [15], it is very important to screen diabetic patients for UTIs for timely diagnosis, complete treatment, and prevention of progression to renal complications and ultimately severe renal failure.

Urinary tract infection (UTI) is among the most common medical condition seen in all age groups with DM [13]. Diabetic patients are highly susceptible to UTI compared to non-diabetics[8]. Evidence from various epidemiological studies showed that UTI is more common in females with diabetes than in non-diabetic females[16], it is more common in diabetes because of a combination of host and local risk factors. Modification of chemical composition of urine in diabetes mellitus can alter the ability of urine and support the growth of microorganisms[7].

Recent epidemiological studies and analytical experimentation of patients with preexisting diabetes mellitus have authenticated their plausibility of developing UTIs that are potentially perilous with fatal manifestations [4]. Various impairments in the immune system, including humoral, cellular, and innate immunity may contribute to the pathogenesis of UTI in diabetic patients[5].

According to [3], bacteria are the primary cause of UTIs in humans and the most contributed bacterial pathogen of UTIs is *Escherichia coli* in diabetic and non-diabetic patients and others are *Klebsiellapneumonia*, *Staphylococcussaprophyticus*, *Proteusmirabilis*, *Enterococcusfaecalis*, Group-B *Streptococcus*, *Pseudomonas aeruginosa*, *Candida*spp, and *Staphylococcusaureus*[14,15,17].

However, among the bacterial species involved in UTIs, uropathogenic *Escherichia coli* strains (UPEC) are the most common. UPEC account for about 80% of uncomplicated UTIs, 95% of community-acquired infections, and 50% of hospital-acquired infections [18]. UPEC also remains the most frequent pathogen in complicated UTIs [19]. According to [2], UPEC is a heterogeneous group of extraintestinal pathogenic *E. coli* (ExPEC) that seem to originate from the gut.

Antimicrobial resistance is naturally occurring as a reaction of microbial organisms to the environment[20]. The emergence of multi-drug resistant (MDR) strains is escalating, causing urinary tract infections ~~increasing~~ to increaseboth in community and hospital settings [1,15,21]. Increasing cases of diabetes mellitus which consequently leads to more UTI cases and irrational

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use of antibiotics has led to the emergence of multi-drug resistant strains[22]. More so, studies in Africa have shown the need to have systematic screening of UTI in diabetic patients due to the increasing prevalence [22].

There is widespread concern about the high rates of resistance to antimicrobials used in the treatment of urinary tract infections, particularly in developing countries. Antibiotics, including the broad-spectrum ~~antibiotics~~, are frequently prescribed, which may lead to the development of antibiotic-resistant urinary pathogens. Patients with diabetes mellitus are more likely to have resistant pathogens, necessitating longer and more potent antimicrobial treatment. Improved glycemic control in diabetics may thus aid in the control of UTIs. Accurate screening for UTIs in diabetic patients is also critical to enable appropriate treatment and avoiding related complications [23].

Diabetes mellitus (DM) has now become a global health issue to health care professionals [8].Frequent prescription of antibiotics, including the ones with broad-spectrum, has result in development of antibiotic-resistant urinary pathogens. Since patients with DM are more prone to have resistant pathogens, they inevitably require longer and more potent antimicrobial treatment [23]. Therefore, improved control of glycaemia, timely diagnosis, complete treatment and screening for UTIs in diabetic patients is critical to prevent progression to renal complications and ultimately severe renal failure and other related complications.

2. MATERIALS AND METHODS

2.1 Study Area

The study area was conducted in Bauchi State, Nigeria. The study areas used for the collection of samples include; Abubakar Tafawa Balewa University Teaching Hospital (ATBUTH), Bauchi State, and Bauchi ~~state~~ State ~~specialist~~ Specialist ~~hospital~~Hospital.

2.2 Sample Collection

Each patient was informed to collect approximately 20 ml of midstream urine into a crew cap sterile calibrated urine container. Proper instructions and illustration were given to the patients in order to avoid contamination. At the point of collection, samples were labeled with name, sex and age of the patients. The samples were placed in an ice box and transported to the laboratory for further analysis, but in cases of delay, the urine samples were refrigerated at $4^{o}C$ to avoid the multiplication of bacteria [24].

2.3 Data Collection

A structured questionnaire and patient clinical sheet ~~was~~ wereused to ~~sought~~ seekfor demographic data and clinical details (clinical symptoms, previous antibiotic usage, risk factors/behaviours). Verbal/informed consent was obtained from each patient to be enrolled in this study.

2.4 Inclusion/ Exclusion Criteria

The study ~~will~~ include diabetic and non-diabetic patients regardless ~~with~~ of thepresence of UTI symptoms. All other patients without these criteria ~~are~~ wereexcluded.

2.5Sample Size Determination

~~Sample size determination is the act of choosing the number of observations or replicates to include in a statistical sample. Sample size determination is the mathematical estimation of the number of subjects/units to be included in a study.~~

The number of samples ~~that was~~ collected ~~was~~ weredetermined using the formula of [25]. Prevalence of p= 0.25(25%) [26], based on previous study.

Using the formula

$n = (Z)^2 p(1-p)$

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d^2

Where;

n = Desired sample size

Z = 1.96 (The standard normal deviate, corresponds to the 95% confidence level).

p = Prevalence of previous study or related (0.25)

d = Degree of accuracy (5%)

Therefore $n = \frac{(1.96)^2 \times 0.25(1-0.25)}{(0.05)^2}$

$n = \frac{(1.96)^2 \times 0.25 \times (0.75)}{(0.05)^2}$

$n = \frac{3.8416 \times 0.1875}{0.0025}$

$n = \frac{0.7203}{0.0025}$

Sample size (n) =288.1

Approximately n=288

2.6 Blood Glucose Test

Plasma glucose (after an overnight fasting of eight or more hours) was determined using the glucose meter Accu-Chek Active system (Roche Diabetes Care, Basel, Switzerland), this was carried out within fractions for each participant. DM was diagnosed according to [27] criteria with symptoms of diabetes plus a fasting blood glucose level equal to or more than 126 mg/dl.

2.7 Sample Processing

2.7.1 Inoculation and Isolation of Bacteria from Urine Samples

Urine ~~S~~samples ~~was~~ were observed macroscopically for colour, blood tinge and turbidity. All the urine samples were aseptically inoculated using a sterile wire loop, a loopful of well-mixed uncentrifuged urine was aseptically inoculated unto Cysteine Lactose Electrolyte Deficient (CLED) agar by streak-plate method as described by [28,29,30]. The plates were incubated at 37°C for 18-24 hours.

2.7.2 Identification and Characterization of Isolates

The colonies were further identified based on colonial morphology and biochemical tests (Indole ~~test~~, Methyl Red ~~test~~, Vogues Proskauer ~~test~~, Citrate Utilization ~~test~~, ~~coagulase~~ Coagulase and ~~catalase~~ Catalase tests) as described by [28]. Colonies were observed for morphological features such as size, shape, edge consistency, margin, colour, opacity and ~~effect on media i.e. lactose or non-lactose fermenters~~lactose fermentation. In addition to these morphological features of the colonies, motility, Gram staining reaction, and biochemical tests ~~was used in identifying the isolates~~were then analysed. The isolates were maintained on Nutrient agar slants~~,~~ until required for further use [29].

2.8 Antimicrobial ~~susceptibility~~ Susceptibility ~~testing~~Testing of the UPEC Isolates

The susceptibility pattern of the isolates to commonly used antimicrobial agents ~~were~~ was determined using ~~as~~ the Kirby-Bauer disc diffusion techniques as described by [31]. A loopful of growth of each isolate on agar medium ~~will be~~was suspended in a sterile saline and then ~~was~~ diluted in steps of 1:10 to give turbidity equivalent to the 0.5 McFarland standards (a density of $1x10^8$ cells/mL) before inoculation. Muller-Hinton agar medium was prepared according to the manufacturer's instructions and ~~was~~ poured (about 25 ml of the media) into each of the sterile petri-plates, the plates ~~was~~ were allowed to solidify. After ~~the~~ adjusting the turbidity of the inoculum, a sterile cotton swab stick was dipped into the suspension, and pressed

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firmly against the inside wall of the tube; the swab was streaked over the surface of the solidified Muller-Hinton agar plates 3 times rotating the plate after each application to ensure an even distribution and allowed to stand at room temperature for 10 minutes [32].

Antibiotic discs of known concentration ~~of antibiotics~~ were aseptically placed using sterile forceps and then gently pressed down on the Muller-Hinton agar plates to ensure a firm contact. The plates were then inverted and incubated at 37^{o}C for 24 hours. The diameter of the zone of inhibition produced by each antibiotic disk was measured and interpreted according to Clinical and Laboratory Standard Institute [33] guidelines.

2.9 Data Analysis

The data obtained was recorded in Microsoft ~~excel~~ Excel and analyzed ~~by~~ using Chi-square statistical analysis.

3. RESULTS AND DIS~~S~~CSUSION

3.1Characteristics of Participants Based on Blood Sugar Level (FBS)

In this study, patients who had ≥ 126 mg/dl of fasting blood sugar were considered ~~as~~ positive for diabetes mellitus, while those with fasting blood sugar (FBS) < 126 mg/dl were considered nondiabetics~~. As shown in table 1.~~ (Table 1)

Table 1: Distribution of Study Participants Based on Blood Sugar Level (FBS)

Blood glucose level (mg/dL)	No ~~(%)~~ of patients ~~Tested~~ tested (n=288)	Percentage (%)
High (Diabetic)	194	67.4
Normal(Non-diabetic)	94	32.6

Key: high= ≥ 126mg/dl, normal= < 126 mg/dl (WHO criteria for diabetic diagnosis), FBS-Fasting Blood sugar.

The amount of glucose in the bloodstream is referred to as blood glucose or blood sugar. Fasting blood glucose test is a simple test, accurate and inexpensive test that can screen for diabetes [27]. Diabetics have an impaired immune system, making them more susceptible to many illnesses, among these is urinary tract infection. Based on several researches, diabetic patients are more likely to develop UTIs than non-diabetic patients. ~~There are n~~Numer~~ous r~~easons that could explain the increased occurrence of UTI in diabetic individuals. Studies indicated that high glucose levels in urine promote the formation of uropathogens [34]. Higher glucose levels in renal parenchyma create a favourable environment for bacterial colonization, resulting in complications including emphysematous pyelonephritis [35]. Increased glucose levels may impair humoral, innate, and cellular immunity. Autonomic neuropathy can cause bladder dysfunction, resulting in urine retention and stasis.

Poor metabolic regulation causes hyperglycemia, which can lead to a decreased renal threshold for glucose reabsorption and glycosuria. Glycosuria provides a rich medium for bacterial species to thrive in the presence of decreased immunity. According to [36], elevated

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plasma glucose levels cause glucosuria, which promotes bacterial proliferation through an increase in cell count, implying neutrophil dysfunction.

Several researchers used fasting blood sugar to screen their study participants ~~from~~for diabetic mellitus. This follows the suites of [37] who conducted a research on pattern of organism causing urinary tract infections in diabetic and Non diabetic patients in Bangladesh, [38] who conducted their research on the Clinical profile of urinary tract infections in diabetics and non-diabetics, [39] who worked on the prevalence of urinary tract infections and their antimicrobial sensitivity among diabetic and non-diabetic patients in Zakho, Iraq~~,~~ [40] who conducted their research in Iraq also used fasting blood sugar to screen their study participants from diabetic mellitus, also [41] who conducted their research on diabetic patients in port Harcourt, Nigeria. All the above researchers used fasting blood sugar to screen their patients.

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3.2 Sociodemographic Variables of UPEC ~~infection~~ Infection Among Study Participants

In this study, the age range of 31-40 had the highest rate of *E. coli* infection in both the study participants, 28.1% in diabetic and 25.7% in non-diabetic patients. In this study, the female gender in both the study population has a ~~high~~ highestrate of occurrence compared with their male counterparts. In this study, married participants have higher rate of infection in both diabetic and non-diabetic patients. While the illiterates have a higher rate of infection in NDM patients than NDM patients. And also, Urban dwellers have high rate of occurrence of UTI in both DM and NDM patients than rural dwellers. As shown in table 2.

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Table 2: Distribution of UPEC Isolates in Diabetic and Non-Diabetic Patients According to Demographic Variables

Patients Details(Variables)	No of Samples Collected N=288	No (%) of UPEC in DM Patients (n=64)	No (%) of UPEC in NDM Patients (n=35)	P-value
Age (years)				
10-20	10	5(7.8)	2(5.7)	0.99
21-30	30	11(17.2)	7(20)	
31-40	38	18(28.1)	9(25.7)	
41-50	76	14(21.9)	8(22.9)	
51-60	68	9(12.5)	6(17.1)	
61-70	55	5(7.8)	3(8.6)	
≥71	11	2(3.1)	1(2.9)	
Gender				
Female	168	36(56.3)	20(57.1)	0.93
Male	120	28(43.8)	15(42.9)	
Marital status				
Single	14	10(15.6)	5(14.3)	0.62
Married	216	42(65.6)	20(57.1)	
Divorce	28	8(12.5)	8(22.9)	
Widow	30	4(6.3)	2(5,7)	

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Education				
Literate	189	40(62.5)	19(54.3)	0.42
Illiterate	99	24(37.5)	16(45.7)	
Residence				
Rural	70	21(32.8)	11(31.4)	0.88
Urban	218	43(67.2)	24(68.6)	

Key: UPEC= uropathogenic *E. coli*, DM= Diabetic Mellitus, NDM= Non-Diabetic Mellitus

The age distribution of patients with UPEC isolates was examined across different age groups. Among patients aged 10-20 years, 7.8% of diabetic patients and 5.7% of non-diabetic patients were infected with UPEC. In the 21-30 age group, the prevalence was 17.2% for diabetics and 20% for non-diabetics. For the 31-40 age group, UPEC was found in 28.1% of diabetic patients and 25.7% of non-diabetic patients. In the 41-50 age range, the prevalence was 21.9% in diabetics and 22.9% in non-diabetics. For patients aged 51-60, UPEC was observed in 12.5% of diabetic patients and 17.1% of non-diabetic patients. Among those aged 61-70, 7.8% of diabetic patients and 8.6% of non-diabetic patients had UPEC isolates. For patients aged 71 and above, UPEC was present in 3.1% of diabetic patients and 2.9% of non-diabetic patients. The chi-square test for this variable resulted in $p = 0.99$, indicating no significant association between age and UPEC prevalence.

The gender distribution showed that among female patients, 56.3% of diabetic patients and 57.1% of non-diabetic patients were infected with UPEC. For male patients, 43.8% of diabetics and 42.9% of non-diabetics had UPEC isolates. The chi-square test for gender resulted in $p = 0.93$, suggesting no significant relationship between gender and UPEC prevalence.

The marital status of patients was categorized as single, married, divorced, or widowed. Among single patients, UPEC was found in 15.6% of diabetic patients and 14.3% of non-diabetic patients. In married patients, the prevalence was 65.6% in diabetics and 57.1% in non-diabetics. For divorced patients, 12.5% of diabetics and 22.9% of non-diabetics had UPEC isolates. Among widowed patients, UPEC was present in 6.3% of diabetic patients and 5.7% of non-diabetic patients. The chi-square test for marital status resulted in $p = 0.62$, indicating no significant association between marital status and UPEC prevalence.

The residence of patients was classified as rural or urban. Among rural residents, UPEC was found in 32.8% of diabetic patients and 31.4% of non-diabetic patients. For urban residents, the prevalence was 67.2% in diabetics and 68.6% in non-diabetics. The chi-square test for residence resulted in $p = 0.88$, indicating no significant association between residence and UPEC prevalence. The education level of patients was divided into literate and illiterate categories. Among literate patients, 62.5% of diabetic patients and 54.3% of non-diabetic patients were infected with UPEC. For illiterate patients, the prevalence was 37.5% in diabetics and 45.7% in non-diabetics. The chi-square test for education resulted in $p = 0.42$, showing no significant relationship between education level and UPEC prevalence.

UTIs are more common and severe in patients with DM. they are also frequently caused by resistant pathogens [42]. Urinary tract infection is the most common~~est~~ bacterial infection with a high rate of morbidity and financial cost~~.~~ ,The Uropathogenic *E. coli* (UPEC) ~~is~~ beingthe

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most commonest etiological agent of UTI in diabetic and non-diabetic patients. UPEC associated UTIs among diabetic and non-diabetic patients have been reported in previous studies [37,35,36]. The most frequently isolated microorganism from urine sample of this study is *E. coli*. The risk of developing urinary tract infection in diabetes is higher due to abnormalities in the host defense defence and high glucose in urine, the occurrence and infection with UPEC have probably been increased in diabetic patients because hyperglycemia suppresses the level of the immune system among this category of people [43].

The age distribution of patients with UPEC isolates was examined across different age groups. Among patients aged 10-20 years, 7.8% of diabetic patients and 5.7% of non-diabetic patients were infected with UPEC. In the 21-30 age group, the prevalence was 17.2% for diabetics and 20% for non-diabetics. For the 31-40 age group, UPEC was found in 28.1% of diabetic patients and 25.7% of non-diabetic patients. In the 41-50 age range, the prevalence was 21.9% in diabetics and 22.9% in non-diabetics. For patients aged 51-60, UPEC was observed in 12.5% of diabetic patients and 17.1% of non-diabetic patients. Among those aged 61-70, 7.8% of diabetic patients and 8.6% of non-diabetic patients had UPEC isolates. For patients aged 71 and above, UPEC was present in 3.1% of diabetic patients and 2.9% of non-diabetic patients

In this study, the age range of 31-40 had the highest rate of *E. coli* infection in both the study participants, 28.1% in diabetic and 25.7% in non-diabetic patients. This is in agreement with previous researches done by [39,41] who all reported the high rate of urinary tract infection in this range: reported high-rate UTI in that age range. While this study is not in agreement with the reports of [44], who conducted his research in Sudan reported high rate in the age range 44 and above, [45] reported age range of 40-49 have the highest range of infection and also [46] from Kebbi Nigeria who reported high rate of frequency in the age range of 61-65. High rate of occurrence of UTI infection in this age range (31-40) may be attributed to the fact that people are more sexually active at this age range, and also difference might be due to the competent immune system and high treatment-seeking behavior at a young age [47].

The gender distribution showed that among female patients, 56.3% of diabetic patients and 57.1% of non-diabetic patients were infected with UPEC. For male patients, 43.8% of diabetics and 42.9% of non-diabetics had UPEC isolates.

In this study, the female gender in both the study population has a high rate of occurrence compared with male counterparts. This could be attributed to the fact that the female gender anatomical structure, short urethra, close proximity of the urethra to the anus, decreases of normal vagina flora, in general, lifestyle habits of women are some of the predisposing factors that can increase the occurrence of UTI in females than males regardless of diabetic status [48,43]. The result is in disagreement with the reports of [46,45] who reported a higher rate of infection in males than their female counterparts.

The marital status of patients was categorized as single, married, divorced, or widowed. Among single patients, UPEC was found in 15.6% of diabetic patients and 14.3% of non-diabetic patients. In married patients, the prevalence was 65.6% in diabetics and 57.1% in non-diabetics. For divorce divorced patients, 12.5% of diabetics and 22.9% of non-diabetics had UPEC isolates. Among widowed patients, UPEC was present in 6.3% of diabetic patients and 5.7% of non-diabetic patients

In this study, married participants have higher rate of infection in both diabetic and non-diabetic patients. This may be attributed to the fact that they are sexually active at this status, while the widows have the lowest rate of infection in both the study population. This is in accordance with the report of [16].

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The education level of patients was divided into literate and illiterate categories. ThisAmong literate patients, 62.5% of diabetic patients and 54.3% of non-diabetic patients were infected with UPEC. For illiterate patients, the prevalence was 37.5% in diabetics and 45.7% in non-diabetics.

Literate have high rate of infection in DM compared to NDM patients. While illiterate have high rate of infection in NDM patients than NDM patients.

The residence of patients was classified as rural or urban. Among rural residents, UPEC was found in 32.8% of diabetic patients and 31.4% of non-diabetic patients. For urban residents, the prevalence was 67.2% in diabetics and 68.6% in non-diabetics. Urban dwellers have high rate of occurrence of UTI in both DM and NDM patients than rural dwellers. This may be attributed to the fact that the study was conducted in the city and most of the study participants live in urban areas.

3.3 Clinical Profile of UPEC Infection Among Participants Investigated in the Study

In this study, the rate of occurrence of UPEC infection based on the history of UTI is higher in ~~first~~ first-time encounters of UTI in both diabetic and non-diabetic patients. In this study, history of antibiotic usage shows a higher rate in DM than NDM patients in those ~~that~~ whodid not use antibiotics, while slightly higher in those ~~that~~ whouse antibiotics in NDM than DM patients. ~~As shown in table 3.~~ (Table 3)

Table 3: Distribution of UPEC Infection According toClinical Variables of Patients

Clinical Variables	No of Samples Collected (n=288)	No (%) of UPEC in DM (n=64)	No (%) of UPEC in NDM (n=35)	*p*
History of UTI				
Yes	84	10 (15.6)	9 (25.7)	0.22
No	204	54 (84.4)	26 (74.3)	
History of Antibiotic Treatment				0.89
Yes	23	5 (7.8)	3 (8.6)	
No	265	59 (92.2)	32 (91.4)	
Types of Diabetes				
Type 1	92	16 (25)	N.A	-
Type 2	196	48 (75)	N.A	
Duration of Diabetes				
< 5 years	113	35 (54.7)	N.A	-
≥ 5 years	175	39 (60.9)	N.A	

Key: N.A = non-applicable, DM = Diabetic Mellitus

Comment [A73]: This is more of Methodology. Not needed here. Apply to other segments before and after, please.

Comment [A74]: How?

Comment [A75]: Please verify validity of this statement

Comment [A76]: Same as above in Table 2

The history of urinary tract infections (UTI) was examined in relation to UPEC prevalence.Among patients with a history of UTI, 15.6% of diabetic patients and 25.7% of non-diabetic patients were infected with UPEC. For those without a history of UTI, the prevalence was 84.4% in diabetics and 74.3% in non-diabetics. The chi-square test for this variable resulted in p = 0.22, indicating no significant association between UTI history and UPEC prevalence.

In this study, DM patients with no previous history of UTI had higher rate of ~~contracting –~~the UTI compared with those who had a previous history of the UTI

In this study, the frequency of UTI was higher among duration of DM greater than 5 years compared to those patients of DM duration less than 5 years. This is in agreement with the studies conducted by [21,44] from Sudan found high rate of infection present in ≥5 years of DM duration. It is very well known that patients with a longer duration of DM have an increased prevalence of chronic diabetic ~~chronic -~~complications, which may lead to an increased presence of UTI [42]. In many of these patients, autonomic neuropathy results in dysfunctional voiding and urinary retention. [40]

The history of antibiotic treatment was also analyzed. Among patients with a history of antibiotic treatment, 7.8% of diabetic patients and 8.6% of non-diabetic patients had UPEC isolates. For those without such history, the prevalence was 92.2% in diabetics and 91.4% in non-diabetics. The chi-square test for this variable resulted in p = 0.89, indicating no significant association between antibiotic treatment history and UPEC prevalence.

Various studies have demonstrated that different outbreak of urinary tract infection in ~~type~~ Type 2 diabetic patients. Factors such as immune system disorders, weakening of white blood cells, poor blood supply, bladder dysfunction due to nephropathy and glucosuria can cause urinary tract infections in type 2 diabetic patients [5]. Dysuria is a complication of urinary tract infection in diabetic patients due to organ damage and even death due to the complexity of pyelonephritis. Also, these patients experience urinary retention, urgency, and incontinence during the night due to increased urination to excrete excess glucose. In this study, type 2 DM patients have high rate of infection compared to ~~type1~~ Type1 DM patients, ~~type~~ Type 2 has a prevalence of 25% while type 1 has a prevalence of 25% in this study. This is similar to a study conducted by [49] where high rate of infection was observed in type 2 DM patients.

3.4 Prevalence of UPEC isolates according to MDR pattern in diabetic and non-diabetic patients

~~In this study, antibiotics of known concentration were used to screen UPEC isolates that are resistant to antibiotics.~~ Ampicillin and piperacillin-tazobactam have the highest rate of resistance in DM and NDM patients, while the resistance was observed in imipenem, ceftriaxone and ceftazidime. While the other antibiotics have moderate rate of resistance to the isolates.

Table 4: Distribution of UPEC isolates according to MDR pattern in diabetic and non-diabetic patients

Antibiotics(µg)	No (%) of UPEC isolates and MDR pattern n=64-for DM, n=35 for NDM	
.		
	No (%) Resistant isolates in Diabetic (n=52)	No (%) Resistant isolates in non diabetic (n=27)
Ampicillin (10)	48(92.3)	22(81.5)

Comment [A77]: Statement like this are not to be made this way in discussion section. This is more of a methodology. RECAST.

Comment [A78]: Can you briefly highlight the possible reason for this?

Comment [A79]: Please check for the official format for reporting statistical results.

Comment [A80]: Please effect in other segment. Type NOT type

Comment [A81]: This is confusing

Amoxicillin-clavulanate (30)	39(75)	11(40.7)
Ceftriaxone (30)	16(30.8)	08(29.6)
Cefuroxime (30)	31(60.0)	16(59.3)
Ceftazidime (30)	17(32.7)	08(29.6)
Kanamycin (30)	42(80.8)	21(77.8)
Amikacin (30)	39(75)	20(74.1)
Gentamicin (10)	42(80.8)	19(70.4)
Streptomycin (10)	38(73.1)	18(66.7)
Ciprofloxacin (5)	27(51.9)	13(48.1)
Levofloxacin (5)	26(50)	11(40.7)
Nalidixic acid (30)	47(90.4)	21(77.8)
Ofloxacin (5)	28(53.8)	10(37.0)
Piperacillin tazobactam (100)	48(92.3)	22(81.5)
Imipenem (10)	10(19.2)	03(11.1)

Key DM- Diabetic mellitus, NDM- ~~non~~ non-diabetic mellitus, UPEC-Uropathogenic *E.coli*, MDR-multidrug resistance.

The presence of multidrug resistance in this study could be attributed to the dissemination of antibiotic resistance among UPEC isolates. UPEC can be seen as one of the most common~~est~~ pathogens causing UTI in immunocompromised patients such as diabetics. In this study, a high rate of MDR was encountered in UPEC isolate of both DM and NDM patients. Ampicillin has ~~resistant~~ resistancerate of 92.3% and 81.5% in diabetic and non-diabetic patients respectively. This is in agreement with studies of [50,43]. Other drugs that were resistance were piperacillin-tazobactam, nalidixic acid.

Quinolone and fluoroquinolone resistance of UPEC isolates were correlated with previous studies that resistance rate of diabetic UPEC to ciprofloxacin [50]. Resistance to fluoroquinolone among diabetic urinary *E. coli* isolates were 89.5% and non-diabetic urinary *E. coli* isolates were 50% have been reported. Common and overuse of quinolones and fluoroquinolone worldwide in the treatment of UTIs led to increased resistance in UPEC. [2].

On the other hand, imipenem, ceftriaxone, and ceftazidime ~~was~~ werefound to show the least resistance among the drugs used. This is in agreement with the reports of [51,35,43]. The isolates resistant to three or more classes of antibiotics were termed ~~as~~ MDR. Diabetes can be a factor associated with MDR *E. coli.* in this study, high rates of MDR *E. coli* in both diabetic and non-diabetic patients was observed as with the reports of [43,51]. The rapid development of resistance could be attributed to the irrational use of antibiotics and practices of self-medication among the general population thereby causing a problem in antibiotic therapy especially in developing countries due to lack of awareness and lack of effective implementation of the policy that regulates the use of antibiotics [52].

4. CONCLUSION

Comment [A82]: This table/result did not clearly depict the title. Moreover, this is not how to report MDR result. THIS IS NEEDS TO BE GIVEN DELIGENTLY CONSIDERED.

Comment [A83]: Cite an article to back this up because your work can't confirm this because you didn't compare with your species.

Comment [A84]: Drug(s) CANNOT be resistant, but a bacteria does. Please recast.

Comment [A85]: This is not clear

Comment [A86]: How can E. coli be diabetic? This is serious.

Comment [A87]: 1- Now compare this statement with your ABRACT (Result).
2-This should have come earlier.

Comment [A88]: How and ref?

Comment [A89]: The result and discussion sections needs a major revisitations.

~~In conclusion,~~ UPEC isolates were higher ~~UPEC isolates were high in diabetic~~ in diabetic patients than non-diabetic patients. it could be observed that most of the UPEC isolates from both ~~the~~ groups exhibited a remarkable rate of antibiotic resistance to commonly prescribed antibiotics for UTI irrespective of diabetic status. The study revealed ~~that~~ a high rate of multidrug resistance from both the study participants, this reaffirms ~~for~~ the need ~~of~~ forproper diagnosis and drug administration in the treatment of urinary tract infection especially in diabetic patients due to their immunological status.

Comment [A90]: For the conclusion to be valid, the MDR result needs to be validated and reflect some of the major values/percentages in the conclusion.

CONSENT AND ETHICAL APPROVAL

Ethical approval was granted by~~;~~ ~~-~~Abubakar Tafawa Balewa University Teaching Hospital, Ministry of Health Bauchi State Government Ethical Steering Committee. More so, written informed consent was obtained from all patients prior to specimen collection.

Comment [A91]: Move this to the beginning segment of Materials and Methods and state the Approval reference number.

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