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### ABSTRACT

Diabetes mellitus (DM) is a clinical disease correlated with a deficiency of insulin secretion or action. It is one of the leading causes of morbidity and mortality worldwide. The global burden of diabetes is rising due to increasing obesity and population aging. Urinary tract infections (UTI) are common microbial infections known to affect the different parts of the urinary tract accounting for major antibacterial drug consumption. About 150 million UTI cases were diagnosed every year. Urinary tract infections are the most important and most common site of infections in a diabetic patient. Diabetic patients have been found to have a 5-fold frequency of acute pyelonephritis at autopsy than non-diabetics. Most of the urinary tract infections in patients with diabetes are relatively asymptomatic. The presence of this syndrome predisposes to much more severe infections, particularly in patients with acute ketoacidosis, poor diabetic control, diabetic complications such as neuropathy, vasculopathy, and nephropathy. The Gram-negative aerobic bacilli are the large group of bacterial pathogens that cause UTI with few species of Gram-positive bacteria. However, some fungi, parasites, and viruses have also been reported to invade the urinary tract. Urinary tract infection affects women more than men due to several factors such as proximity of the genital tract to the urethra, anatomy of the female urethra, sexual activity, menopause, and pregnancy. Other possible risk factors of UTI include allergy, obesity, diabetes, past history of UTI, contraceptive use, catheter use, and family history.

**Keywords:** *Diabetes mellitus, urinary tract infections, risk factors, pathogenesis, antibiotic resistance.*

### 1. INTRODUCTION:

Diabetes mellitus is related to immune system dysfunction, which makes the afflicted individuals prone to frequent infections, especially infections of the genital and urinary tract. Diabetic patients have more than twice the opportunity of developing genitourinary tract infections (Abu-Ashour *et al.*, 2017). Few researches have shown that the cause could be due to dysfunctional bladders contracting poorly may make static pools of urine that serve as favorable media for microbial growth. Other studies suggest that urine of hyperglycemic patients encourages increased bacterial load and colonization in the urinary tract (Njunda *et al.*, 2013). These and other causes make the genitourinary system where UTI can be a cause of severe life-threatening complications such as emphysematous pyelonephritis, emphysematous cystitis, and renal papillary necrosis, which are common in a diabetic patient that leads to kidney failure in these patients (Casqueiro *et al.*, 2012).

The bacterial strains, mostly *E. coli*, can cause UTI in both females and males, while *Staphylococcus saprophyticus* have been found to cause UTI mostly in younger females and can also occur secondary to blood-borne infections (Anuja and Shah 2015). Others include *Pseudomonas aeruginosa*, *Klebsiella spp*, *Proteus mirabilis*, *Morganella spp*, and *Enterobacter spp*. Also implicated are *Enterococcus faecalis* and *Staphylococcus aureus* (Rubin *et al.*, 1992). Urinary tract infections in older males and females with the indwelling catheter are mostly occurring as a result of *Proteus spp* and *P. aeruginosa* (Cheesbrough M. 2010). These bacteria that cause UTI initially proliferate at the opening of the urethra and ascend to the bladder, while some may reach to the kidneys from the bloodstream (Gupta *et al.*, 2011). Infections of fungi are common among patients with exhausting diseases and structural abnormalities of the urinary tract, which are infrequent causes of UTIs in healthy persons (Fisher *et al.*, 2011). However, bacterial pathogens are the highest cause for the

majority of UTI incident in diabetic patients, determination of *Candida* spp. in urine cause a diagnostic challenge (Fisher, JF 2011).

It is very important to investigate diabetic patients for UTI for suitable diagnosis, whole treatment, and avoidance of progression to kidney complications and, finally, severe renal failure. However, there are controversies regarding the clinical pattern, incidence, and microbiology of UTIs in diabetic persons as compared to those non-diabetic ones (Aswani *et al.*, 2014). The aim of this study was to study the correlated between UTIs and diabetes mellitus, study many important factors that may play an achievable role in the incidence the UTIs in diabetic patients. Hence, this study would help assess the frequency of UTIs in the diabetic population and enable the diabetologists to predict the clinical and microbiological patterns of UTI in their patients.

### 1.1 Urinary Tract Infection in Diabetic Women

The larger cases of UTI were found in women compared to men both in diabetic and non-diabetic individuals. The majority of the study done all over the world has concluded female predominance to UTI over (Geerlings *et al.*, 2008). The higher rate of occurrence UTIs among female patients is due to the short urethra and its proximity to the anus (Chhetri *et al.*, 2001), pregnancy, sexual activity, menopause (Schaeffer *et al.*, 2001), perineal contamination of the urinary tract with fecal micro-flora, and the absence of prostatic secretion (Pargavi *et al.*, 2011). According to a study that achieved at the University of Uyo Teaching Hospital in Nigeria, The majority of outpatients presenting with symptoms and signs of urinary tract infections in Uyo do not have Microbiological confirmed UTI as only about 30% of women with presenting signs of UTI had positive results for urine culture tests while only about 12% of men with these sign are culture positive for UTI (Abraham *et al.*, 2019). Urinary bladder dysfunction occurs in 26%–85% of diabetic females, depending on the duration of diabetic disease and the age extent of neuropathy, and thus should be considered in all diabetic patients with infections of the urinary tract (Frimodt-Møller C. 1980).

### 1.2 Pathogenesis

Several potential mechanisms unique to diabetes may contribute to the increased risk of UTI in patients with diabetes (Chen *et al.*, 2009).

Higher concentrations of glucose in the urine may promote the growth of harmful bacteria (Wang *et al.*, 2013). However, several studies did not find a relationship between HbA1c levels, which serves as a risk of UTI among diabetic patients, and a proxy for glycosuria; also, sodium-glucose cotransporter two inhibitors, which increase glycosuria, were not found to increase the rate of urinary tract infections (Boyko *et al.*, 2002). High renal parenchymal glucose levels make a favorable environment for the growth and proliferation of microorganisms, which might be one of the precipitating factors of pyelonephritis and the complications such as emphysematous pyelonephritis (Soo Park *et al.*, 2006). Various impairments in the immune system, including innate, humoral, and cellular immunity, may contribute to the pathogenesis of UTI in patients with diabetes (Geerlings SE *et al.*, 2000).

### 1.3 Risk factors

Asymptomatic Bacteriuria (ASB) is more predominant in women due to a short urethra that is in proximity to the moist, warm, vulvar, and perianal areas that are colonized with intestinal bacteria. ASB increases with age and is also associated with foreign bodies or urinary tract abnormalities (Colgan *et al.*, 2006; Nicolle LE 2014). Numerous studies have reported an increased incidence of ASB in diabetic patients, with estimations ranging from 8%–26% (Zhanel *et al.*, 1995). A meta-analysis of 22 studies, issued in 2011, found a point frequency of 12.2% of ASB among diabetic patients versus 4.5% in healthy control individuals (Schneeberger *et al.*, 2014). The point prevalence of ASB was higher in patients with a longer duration of diabetes, was higher both in men and women and was not correlated with glycemic status, as estimated by glycosylated hemoglobin A1c (HbA1c) (Renko *et al.*, 2011). A current prospective study of inpatients at an Indian hospital found a 30% prevalence rate of asymptomatic bacteriuria among diabetic patients (Aswani *et al.*, 2014).

Pyelonephritis was found to be 4.1 times more recurrent in pre-menopausal diabetic women than in non-diabetic women in a case-control study of a Washington State health group (Scholes *et al.*, 2005). In a Canadian study, diabetic women (type 2 and 1, identified by receipt of oral hypoglycemic or insulin therapy) were 6–15 times more commonly hospitalized (according to age group) for acute pyelonephritis than non-diabetic women, and also diabetic men

were hospitalized 3.4–17 times more than non-diabetic men (Nicolle *et al.*, 1996). A study of Danish detected that patients with diabetes mellitus were three times more likely to be hospitalized with pyelonephritis, as compared to subjects without diabetes (Benfield *et al.*, 2007).

#### 1.4 The Pathogens and Antibiotic Resistance

*Escherichia coli* (*E. coli*) are the most common pathogens isolated from the urine of diabetic patients with UTI, other Enterobacteriaceae such as *Proteus* spp., *Klebsiella* spp., *Enterobacter* spp., and Enterococci (Geerlings *et al.*, 2002). *Escherichia coli* is the notable causative pathogens of UTI in both diabetic and non-diabetic people, followed by coagulase-negative *Staphylococci* (CONs), *Enterococcus* species (spp.), *Candida albicans*, and non-albicans *Candida* spp (Woldemariam *et al.*, 2019; Bollestad *et al.*, 2018). *Staphylococcus aureus* also constitutes the most pathogens responsible for UTI in diabetic patients, since those patients are classified as immunocompromised, and the bacteria *S. aureus* are opportunists. Moreover; the several virulence factors featured by *S. aureus* they have the ability to resist the most common antibiotics used to treat UTI as the drug of choice, pointing to the beta-lactam group of antibacterial antibiotics, they usually named Methicillin-resistant *S. aureus* (MRSA) (Martin *et al.*, 2014; Budiman *et al.*, 2018). Patients with diabetes are more prone to have resistant pathogens as the cause of their UTI, comprising fluoroquinolone-resistant uropathogens (Wu *et al.*, 2014), extended-spectrum  $\beta$ -lactamase-positive Enterobacteriaceae (Inns *et al.*, 2014; Colodner *et al.*, 2004), vancomycin-resistant Enterococci (Papadimitriou-Olivgeris *et al.*, 2014), and carbapenem-resistant Enterobacteriaceae (Schechner *et al.*, 2013). This might be due to many factors, including numerous courses of antibiotic therapy that are administered to these patients, frequently for asymptomatic or only mildly symptomatic UTI, and catheter-associated UTI and increased incidence of hospital-acquired, which are both associated with resistant pathogens. Type 2 diabetes is also a predisposing factor for fungal urinary infection (Sobel *et al.*, 2011).

## 2. MATERIALS AND METHODS

Approximately all studies in this review were used the same materials and methods for determining diabetes mellitus and UTIs in the selective persons of each study.

### 2.1 The Collection of samples

Almost in all studies, blood samples were collected from the patients visiting the hospital or any health location to select the diabetic patients included in this researches. Then, urine samples were collected as an aseptic technique as possible in a sterile universal tube. The collected samples were transported to the laboratories within 30 minutes of collection. If they could not, then the urine specimens were stored at 4 °C to prevent bacterial growth in the urine.

### 2.2 Laboratory Analysis

#### 2.2.1 Macroscopic Examination

Tektook *et al.* (2017) achieved routine urinalysis for each sample to determine the turbidity, color; specific gravity; reaction; Sugar and Ketone bodies as well as Albumin.

#### 2.2.2 Microscopic Examination

Depending on a cross-sectional study carried out in Uyo Teaching Hospital by Abraham *et al.* (2019), Ten millimeters of midstream urine was centrifuged for 5 minutes at 1,500rpm. The urine deposits were placed on a glass slide, covered with a coverslip, and examined by using 10x and 40x objectives to quantify the number of red blood cells, white blood cells, epithelial cells, calcium oxalate crystals, and cast present for possible detection of pyuria or bacteriuria. Gram stain was used to differentiate Gram-negative uropathogens from Gram-positive ones.

#### 2.2.3 Bacterial Isolation, Culture, and Colony Counts

According to a hospital laboratory-based cross-sectional study of (Narayani *et al.*, 2018), bacteria were isolated from urine samples and cultured on Mac-Conkey agar and blood agar by the Semi-Quantitative method. Sample with more than 10<sup>5</sup> colony-forming units (CFU)/mL bacteria were considered as positive. Isolation and identification of the microorganisms were done following standard laboratory protocol as per the American Society of Microbiology (ASM) (Isenberg, 2002). Antibiotic sensitivity tests of isolates were tested by the Kirby-Bauer disc diffusion method. The antibiotic discs used were ciprofloxacin, amoxicillin, ceftazidime, cotrimoxazole, cefotaxime, cefixime, gentamicin, cephalixin, ofloxacin, vancomycin, and nitrofurantoin. Results were read according to

Clinical Laboratory Standards Institute (CLSI) guidelines (2014).

In a prospective cross-sectional study of (Borowczyk *et al.*, 2017), antimicrobial sensitivity (susceptibility) or resistance also was performed by the Kirby–Bauer disk diffusion susceptibility test while it was calculated in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria (2014).

### 3. RESULT AND DISCUSSION:

#### 3.1 RESULT

The higher cases of UTIs were found in females compared to males both in non-diabetic and diabetic patients. The majority of the studies achieved all over the world have concluded females predominance to UTIs over males (Akbar, 2001; Bonadio *et al.*, 2006; Boroumand *et al.*, 2006 and Geerlings, 2008). According to Table 1, which belongs to the study of (Abraham *et al.*, 2019), we also observed that the prevalence of UTI was higher in females 37 (25.9%) than in males 26 (11.5%) with a highly significant P-value (0.0001). In table 2, which demonstrated the association of certain risk factors with pyelonephritis, we found that the study of (Scholes *et al.*, 2005) considered the diabetes mellitus as a risk factor for pyelonephritis as well as other factors such as UTIs, chlamydial infection, sexually transmitted diseases (STD), sexual intercourse, hypertension, and Any antibiotic use. The majority of studies concluded that the Gram-negative bacteria were highly predominant in diabetic people with UTIs when compared to Gram-positive bacteria. Furthermore, *E. coli* and *Klebsiella* species were the most prevalent bacterial infections | those groups of people (Kolawole *et al.*, 2009; Inabo *et al.*, 2006; Kehinde *et al.*, 2011; Abraham *et al.*, 2019). Also, another study which was achieved in Iraq showed that *E. coli* and *Klebsiella pneumoniae* were the major pathogens in diabetic patients (table 3) (Tektook *et al.*, 2017 ). According to the study of (Narayani *et al.*, 2018), the antibiotic susceptibility pattern of *E. coli* and *K. pneumoniae* was showed in Table 4 as an example of the resistance of bacteria in diabetic patients. Moreover, they found that all *K. pneumoniae* isolates were multidrug-resistant (MDR) in diabetic, whereas 66.6% were MDR in non-diabetic patients. Likewise, *S. aureus* showed 100% MDR in diabetic patients, whereas in non-diabetic patients, 75% were found as MDR strain. There are several studies were had similar results in

case of bacterial resistance such as ((Maharjan *et al.*, 2015; Puri *et al.*, 2006 and Jha and Bapat, 2005; Borowczyk *et al.*, 2017).

#### 3.2 DISCUSSIONS

Urinary tract infections (UTI) are common bacterial infections known to affect the different parts of the urinary tract accounting for large antimicrobial drug consumption (Dias Neto *et al.*, 2003). About 150 million UTI cases were identified every year (Akram *et al.*, 2007). UTIs are mainly defined as the colonization of a varied population of microorganisms colonizing in the urinary tract. From a microbiological viewpoint, UTI can occur anywhere, including the kidneys, bladder, ureters, and urethra (Hackett G 2005).

The larger susceptibility to infection in diabetic patient is due to the hyperglycemic environment that favors immune dysfunction (the reduced response of T cells, damage to the neutrophil function, humoral immunity, depression of the antioxidant system), gastrointestinal and urinary dysmotility, micro- and macroangiopathies, neuropathy, decrease in the antibacterial activity of urine, and the greater number of medical interventions required in these patients (Casqueiro and Alves 2012; Muller *et al.*, 2005). The Gram-negative bacilli, a class of bacteria, were highly prevailing in the UTI among diabetic patients when compared to Gram-positive bacteria, particularly cocci. Among the Gram-negative bacterial species, *Escherichia coli* were the most predominant uropathogenic, followed by *Klebsiella pneumoniae*. *Staphylococcus aureus* was the most prevalent Gram-positive cocci (Oluremi *et al.*, 2011).

Antibiotic is the cornerstone for treating bacterial infection. Emergence in resistance of bacteria against antibiotics are the main barrier against infection. According to a current study established in China, The effective drug against *S. aureus* was found to be vancomycin (susceptibility of 50%) and gentamicin (susceptibility of 50%) in diabetic patients, while in non-diabetic patients, the most effective drugs found to be gentamicin (susceptibility of 100%) followed by ofloxacin, ciprofloxacin, and vancomycin, (75.0 % each). *S. aureus* was highly resistant to cephalixin, amoxicillin, cotrimoxazole, ofloxacin, and ciprofloxacin (100% each) followed by ceftazidime (50.0%) in diabetic patients. In the non-diabetic group also, it was highly resistant to amoxicillin (75.0%) followed by ceftazidime and cotrimoxazole (50.0 %)(Narayani *et al.*, 2018).

Antibiotic resistance is a large global health problem both for community and hospital-acquired infections (WHO 2011). This problem is challenging in low-income countries because of the irrational uses of antibiotics, high prevalence of infection, poor infection prevention practices, and over-the-counter availability of antibiotics. Hence the emerging occurrence of antibiotic resistance (Alemu *et al.*, 2012; Abera *et al.*, 2014) and DM in Ethiopia is a reason for concern for health care providers. According to the Iraqi study which shown that UTIs are higher among type II diabetic patients (81%) rather than type I (19%); this is correlated with the differences in the aetio-pathogenesis of each; since type I is an autoimmune disease characterized by dysregulation of the immune system and elevation of cellular infiltration at the  $\beta$ -cells of Langerhans cells in addition to autoantibodies, while type II is a metabolic syndrome characterized by miss control of glucose which may facilitate the bacterial growth (Wolde Gebre M 2013).

#### 4. CONCLUSIONS:

Based on the mentioned studies, it was concluded that diabetic patients are at high risk of infections. The most frequent infection is urinary tract infection, affecting mostly the women, the most common causative organism being *E.coli*. Therefore, Stepping-up the prevention and early detection of UTIs in this group of women seems to be the best way to avoid future complications as well as performing urine culture, and constant surveillance of UTI on DM patients is necessary.

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**Table 1. Prevalence of UTI in correlated with gender**

Gender	No. of Examined samples	No. of Samples with positive culture (%)	Odds Ratio	P-value
Female	143	37 (25.9)	2.7	0.0001*
Male	227	26 (11.5)	1	
Total	370	63 (17.0)	-	

\*Statistically significant, ( $\chi^2(1)=12.91$ ;  $P=0.0001$ ;  $OR=2.7$ )



**Table 2.** Association of certain risk factors with pyelonephritis

Variable	Case group, % (n = 242)	Control group, % (n = 546)	Odds Ratio	P-value
Diabetes	6.6	1.6	4.2 (1.8–9.7)	<0.001
Chlamydial infection	12.8	7.9	1.7 (1.0–2.8)	0.03
Other STD	28.1	30.8	0.9 (0.6–1.2)	>0.2
Any previous UTI	69.4	49.7	2.3 (1.7–3.2)	<0.001
Ever had sexual intercourse	98.8	91.2	7.6 (2.4–24.7)	<0.001
Hypertension	9.9	6.4	1.6 (0.9–2.8)	0.09
Any antibiotic use in the previous 30 day	15.8	8.1	2.1 (1.3–3.4)	<0.01

**Table 3.** Bacterial types causing UTIs in Diabetic patients

Type of Bacteria	No. of Isolates (%)	Type of D.M	
		I	II
<i>Escherichia coli</i>	15 (28,5)	2	13
<i>Klebsiella pneumoniae</i>	13 (24,5)	1	12
<i>Proteus mirabilis</i>	9 ( 17 )	2	7
<i>Streptococcus agalactiae</i>	7 (13 )	2	5
<i>Pseudomonas aeruginosa</i>	6 (11 )	2	4
<i>Staphylococcus aureus</i>	3 (6)	1	2
Total (%)	53 (100)	10 (19)	43(81)

**Table 4. Antibiotic Resistance of *E. coli* and *K. pneumoniae***

<b>Antibiotic</b>	<b>Resistance of <i>E. coli</i></b>		<b>Resistance of <i>K. pneumoniae</i></b>	
	<b>Diabetic No. (%)</b>	<b>Non- diabetic No. (%)</b>	<b>Diabetic No. (%)</b>	<b>Non- diabetic No. (%)</b>
Amoxicillin	81 (81.8)	64 (82.0)	3 (100)	5 (83.3)
Cefotaxime	39 (39.3)	23 (29.4)	0	2 (33.3)
Cefixime	36 (36.3)	26 (33.3)	0	2 (33.3)
Cotrimoxazole	33 (33.3)	32 (41.0)	0	3 (50.0)
Ciprofloxacin	42 (42.2)	29 (37.1)	3 (100)	1 (16.6)
Ofloxacin	48 (48.4)	30 (38.4)	3 (100)	2 (33.3)
Nitrofurantoin	3 (3.0)	9 (11.5)	0	2 (33.3)
Gentamicin	6 (6.0)	7 (8.9)	3 (100)	2 (33.3)