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## The Outcome of Urinary Tract Infections among Diabetes Mellitus Patients in Ibb City, Yemen

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### Abstract

Urinary tract infections (UTIs) are the major health problem of patients with diabetes mellitus (DM) in Yemen, due to treatments of UTIs are usually empirical without a urine culture, which guide to use an inappropriate therapy. So, the current study was designed to examine the microbial pathogens that caused UTIs in DM patients at Nasser hospital in Ibb city-Yemen. A case-control study was conducted by collecting one hundred and thirty urine samples from DM patients (100) and 30 healthy individuals kept as normal control (NC). All urine samples of DM patients and NC individuals were analyzed by direct examination and inoculated in different standard bacteriological media and biochemical tests for the diagnosis species of microbial pathogens (bacteria and fungi) were performed. The microscopic examinations of urine showed that the white blood (W.B.Cs) or pus cells, Red blood cells (R.B.Cs), epithelial cells, glucosuria, and bacteriuria were significantly increased in DM patients than NC ones. There were non-significant differences of fasting blood sugar (mean=175 ± 46.4 mg/dl) among DM patients. The incidence of microbial growth that caused UTIs in DM patients were (38%), including 10% in T1DM and 28% in T2DM, which was highly significant than those in NC (7%). Our findings showed a higher incidence of Gram-negative bacteria (60.5%) than gram-positive bacteria (34.2%) and fungi (5.3%). Gram-negative species include *Escherichia coli* (18.4%), *Klebsiella pneumoniae* (13.1%), *Neisseria gonorrhoeae* (10.5), *Pseudomonas aeruginosa* (7.9%), *Proteus mirabilis* (5.3%), and *Salmonella typhi* (5.3%) while *Staphylococcus aureus* (15.8%), *Streptococcus spp* (10.5%) and *Staphylococcus spp* (7.9%) belong to gram-positive bacteria. The fungal isolates were of *Candida albicans*. Our results demonstrated that *Escherichia coli* and *Staphylococcus aureus* were more prevalent pathogens that caused UTIs in DM patients.

**Keywords:** Diabetes mellitus, Urinary tract infections, Microbial pathogens, Yemen.

## INTRODUCTION

Diabetes mellitus (DM) is a highly prevalent worldwide health problem, with an expected prevalence of 593 million by 2035, particularly of type 2 diabetes mellitus (T2DM). Asia and Africa are designated as the greatest potential regions for this disorder. An association between urinary tract infections (UTIs) and DM was first recognized in an autopsy series reported in the 1940's (Lahelma *et al.*, 2004; Vaag, 2006; Janifer *et al.*, 2009; Guariguata *et al.*, 2014).

DM causes changes in host defense mechanisms and neuropathy which impair bladder emptying and the presence of diabetic cystopathy and micro-vascular disease in diabetics' patients' kidneys. So, DM is a major risk factor for the higher incidence of UTIs in these patients, due to several mechanisms including: the presence of glycosuria, neutrophil dysfunction and increased adherence of the bacteria to uroepithelial cells, older ages, metabolic control, diabetic nephropathy, autonomic neuropathy and vascular complications (Boyko *et al.*, 2002; Hakeem *et al.*, 2009; Mnif *et al.*, 2009).

UTIs are the most common infections among patients with DM and responsible for morbidity and mortality, due to cystitis, pyelonephritis, impaired leucocyte function, recurrent vaginitis, emphysematous complications and renal/perinephric abscesses, particularly, when glycemic control is poor and if UTIs are unrecognized or untreated in these patients (Patterson and Andriole, 1997; Mahesh *et al.*, 2011; Prakasam *et al.*, 2012; Alkhyat and Al.Maqtari, 2014; Schneeberger *et al.*, 2014).

Other risk factors for UTIs among patients with and without DM were identified as: Obesity, female sex and prostate syndrome in men, glycosuria, low immunity and bladder dysfunction, UTIs are a relatively common problem that occurs in all age groups and observed most commonly among women than men, because of profound physiological, hormonal and anatomical changes during pregnancy (Nicolle, 2005; Funfstuck *et al.*, 2012; Hamdan, 2015; Rohini *et al.*, 2017).

Basically, UTIs are infections caused by the presence and growth of microorganisms in urinary tract, due to the entrance of bacteria from the digestive tract into the opening of the urethra, began to multiply and caused infections. Women are more susceptible to UTIs than men, due to short urethra, inability of women to empty their bladder completely, absence of prostatic secretion, pregnancy and the proximity of vagina and anus, which resulted the easy contamination of the urinary tract with fecal normal flora (Okonko *et al.*, 2009; Haider *et al.*, 2010).

Variety of microorganisms, including fungi and viruses can cause UTIs, but bacteria are the most common pathogens, which are responsible for nearly 95 % of cases. *E. coli* is the more prevalent causative agent among bacteria and it is solely responsible for more than 80% of

these infections (Papazafiropoulou *et al.*, 2010; Pargavil *et al.*, 2011; AL-Kadassy *et al.*, 2016).

Importantly, bacterial infections are a major problem in DM patients; these infections are caused by number of bacteria which include: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus species*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterobacter*, group B *Streptococci*, *Enterococcus faecalis*, *Serratia species*. The prevalence of bacteriuria is higher in diabetic women than in non-diabetic women, various risk factors for bacteriuria in women with diabetes include sexual intercourse, age, degree of glycosuria and duration of metabolic control, macro albuminuria, high body mass index (BMI) and complications of diabetes (Andriol, 2002; Harding *et al.*, 2003; Pargavil *et al.*, 2011; Hoepelman *et al.*, 2003).

The most common etiological species of bacteriuria in diabetic women include *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, group B *Streptococcus*, *Staphylococcus saprophyticus*, the erroneous of current therapy for UTIs is usually use of empirical treatment without the a urine culture and susceptibility testing, so, antimicrobial resistance was increased worldwide for the most microbial pathogens that caused UTIs and treatments become a major health problem in these patients (Gupta *et al.*, 2001; Al-Haddad, 2005; Mordi, 2006; Ghenghesh *et al.*, 2009; Papazafiropoulou *et al.*, 2010; Chakupurakal *et al.*, 2011; Lucas *et al.*, 2015).

Indeed, the main risk factors of UTIs in developing country, including our country "Yemen" are : Poor or inadequate personal hygiene, lower socioeconomic of population, lower socioeconomic population, sexual activity, the use of certain contraceptive methods and increase antimicrobial resistance (Lucas *et al.*, 2015 , AL-Kadassy *et al.*, 2016).

Finally, Yemen is currently undergoing the rapid increase in the incidence of diabetes, in the year 2000, the prevalence of diabetes in the whole of Yemen increased from 4.7 to 6.57 % , in 2004, the total prevalence T2DM in the urban cities of Yemen was about 4.6 % (4.6 % of males and 2 % of females) and in 2008, the incidence of diabetes in Yemen had increased to 10.4 %. Furthermore, the prevalence of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) were found to be 2 and 2.2 %, respectively. Other reports indicated the UTIs were increased in Yemeni diabetic female: obese and BMI higher than male patients (Gunaid *et al.*, 1997; Gunaid, 2002; Kholood *et al.*, 2003; Al-Habori *et al.*, 2004; Al-Haddad, 2005; Gunaid and Assabri, 2008 ).

This study was aimed to determine the outcome of microbial pathogens that causing UTIs in DM patients and explore the association of risk factors (age, sex, duration of disease and blood glucose levels) with these patients , which attending to Nasser hospital, Ibb city, Yemen.

**MATERIALS AND METHODS**

This case-control study was approved by the institutional research committee and anonymity of patients was protected. Urine samples from DM patients (100) and NC individuals (30) at morning from midstream were collected in a sterile and dry container for each. All samples were labeled and subjected immediately to macroscopic and microscopic examination. Then bacterial culture were done for all DM patients and NC individuals in Nutrient, Blood and MacConkey, Cysteine lactose electrolyte deficient (CLED), Sabouraud dextrose (SDA) agars (HiMedia, India), then incubated aerobically at 37°C for 24–48 hours. The sub-culturing of bacterial isolates on a suitable media for confirmation and identification of bacteria in positive cultures based on known standard methods was done. These include Gram staining of smears, biochemical tests relevant to these isolates, included: Kligler iron agar (KIA), indole, motility, citrate and methyl red tests and the routine bench tests such as: catalase, oxidase and coagulase tests were done. Finally, the fasting blood sugar levels were detected according manufactured kit.

**RESULTS AND DISCUSSION**

Our findings showed that among one hundred DM patients, males were 37% and females were 63% and classified into four groups: Group I, 4-19 years, represented 6%; Group II, 20-39 years, represented 14%; Group III, 40-59 years, represented 61%; Group IV, 60-84 years, and represented 19%. While among thirty healthy individuals as NC; 40% were male and 60% females. Our results showed that DM significantly increased in older patients, 61% patients belong to age group 40-59 years. There was no significant difference among DM patients regarding the fasting blood sugar and mean value was 175 ± 46.4 mg/dl. T2DM was more significantly prevalent (71%) than T1DM (29%). DM was more prevalent among women (19% T1DM and 44% T2DM), than diabetic men (10% T1DM and 27% T2DM), as shown in Table 1.

**Table 1. Demographics characters of diabetes mellitus (DM) patients and Normal Control (NC).**

Characters	Diabetes mellitus (DM) patients			Normal Control (NC).		
	Male	Female	Total	Male	Female	Total
Ages and Sexes N (%)						
Group I:4-19 Years.	2 (2%)	4 (4%)	6 (6%)	2 (6.7%)	3 (10%)	5 (16.7%)
Group II:20-39 Years.	4 (4%)	10 (10%)	14 (14%)	1 (3.3%)	5 (16.7 %)	6 (20%)
Group III:40-59 Years.	21 (21%)* *	40 (40%)	61 (61%)	4 (13.3%)	6 (20%)	10 (33.3%)
Group IV:60-84 Years	10 (10%) *	9 (9%)	19 (19%)	5 (16.7%)	4 (13.3%)	9 (30%)
Total	37 (37%)	63 (63%) **	100 (100%)	12 (40%)	18 (60%)	30 (100%)
Types of diabetes mellitus N(%)						
Type 1 diabetes mellitus (T1DM)	10 (10%)	19(19%)	29 (29%)	-	-	-
Type 2 diabetes mellitus (T2DM)	27 (27%)	44(44%)	71 (71%)**	-	-	-
Total	37 (37%)	63(63%)	100 (100%)	-	-	-
Duration of diabetes mellitus	(Mean +SD) years					
Group I	2.3 ± 1.5			-	-	-
Group II	4.2* ± 3.6			-	-	-
Group III	5.1* ± 4.8			-	-	-
Group IV	7.3** ± 5.2			-	-	-
Fasting Blood Sugar Concentration	(Mean +SD) (mg/dl)					
Group I	176 ± 59.5			-	-	-
Group II	172 ± 46.3			-	-	-
Group III	174 ± 46.7			-	-	-
Group IV	178 ± 33.2			-	-	-
Mean	175 ± 46.4			-	-	-

\*P<0.05 , \*\*P<0.01

Our results of urine direct examination showed a significant difference between DM patients and NC

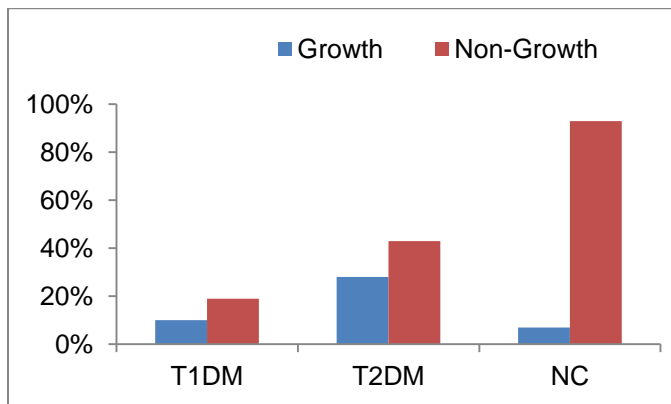
individuals, the mean numbers of WBCs, red blood cells and epithelial cells were higher in DM patients than in NC,

the percentages of glycosuria and bacteriuria in DM patients were 40% and 27% respectively (Table 2). Our results showed that 38% DM patients showed microbial pathogens growth including 10% in T1DM and 28% in T2DM, which was highly significant than those in NC (7%). (Figure 1).

**Table 2. Microscopic examination of urine in diabetes mellitus patients and healthy individuals.**

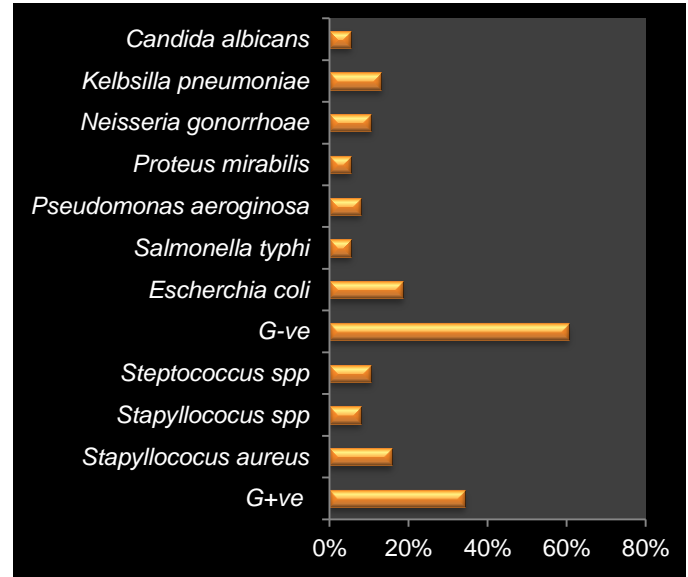
Tests	Diabetes mellitus patients	Healthy individuals
W.B.Cs.*103 cells (mean +SD)	5.3 ± 3.6**	2.4 ± 2.2
R.B.Cs*106 cells (mean +SD)	1.8 ± 1.5*	1.3 ± 1.1
Epithelial cells.(mean +SD)	4.8 ± 3.2**	2.2 ± 0.9
Glucosuria N(%)	40 (40%)**	5 (17%)
Bacteriuria N(%)	27 (27%)**	3 (10%)

\*P<0.05, \*\*P<0.01



**Fig. 1. Distribution of the percentages of microbial growth in DM (T1DM, T2DM) patients and normal control (NC).**

Our findings showed a higher incidence of Gram-negative bacteria (60.5%) than gram-positive bacteria (34.2%) and fungi (5.3%). Gram-negative species include *Escherichia coli* (18.4%), *Klebsiella pneumoniae* (13.1%), *Neisseria gonorrhoeae* (10.5), *Pseudomonas aeruginosa* (7.9%), *Proteus mirabilis* (5.3%), and *Salmonella typhi* (5.3%) while *Staphylococcus aureus* (15.8%), *Streptococcus spp* (10.5%) and *Staphylococcus spp* (7.9%) belong to gram-positive bacteria. The fungal isolates were of *Candida albicans*. Our results demonstrated that *Escherichia coli* and *Staphylococcus aureus* were more prevalent pathogens that caused UTIs in DM patients (Figure 2).



**Fig. 2. The outcome of urinary tract infections (UTIs) among diabetes mellitus patients.**

## DISCUSSION

DM is a metabolic disorder resulting from a defect in insulin secretion and insulin action or both. Insulin deficiency leads to chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. Most of DM cases occur as a result of rise in developing countries, so, these countries will bear the brunt of DM epidemic to the extent of 77% of the global burden in the 21st century. International Diabetes Federation Association (IDFA) in 2011 estimated 366 million people suffer from DM and the number is expected to rise to 552 million by 2030 (Conget, 2002; Cho *et al.*, 2006; Nandeshwar *et al.*, 2010; Megerssa *et al.*, 2010).

UTIs are documented as an inflammatory response of the uro-epithelium by bacterial invasion that are usually associated with bacteriuria and pyuria. UTIs are the second most common site for bacterial infection in human, bacterial virulence factors play a subsidiary part in the genesis of disease, which occur in the presence of anatomic or function abnormalities in the kidney, bladder or collecting systems: obstruction to normal urine flow, including (renal, ureteric and bladder calculi and benign prostatic hypertrophy), cystic renal disease, specific diseases like, DM, abnormalities in host defense mechanisms and those infections that follow surgery or procedures done in urinary tract (Sibi *et al.*, 2011; Natesan and Thasneem, 2017).

In diabetic patients, screening for UTIs is very important to enable doctors to properly treat it and to prevent the development of possible complications,

including bacteremia, renal abscess and renal papillary necrosis. In general, UTIs are frequent causes of morbidity and mortality in diabetic patients, which due to immunologic defects contribute to the increased risk for infection: impaired neutrophil function, low levels of prostaglandin E, thromboxane B<sub>2</sub>, leukotriene B<sub>4</sub>, decreased T-cell-mediated immune response (Geerling, 2008).

Our results showed that UTIs were more prevalent in females than males of DM patients, also, the duration of DM disease increased with older patients at 40-59 years. These results were in agreement with other studies that demonstrated that UTIs were more prevalent in female than men of DM patients. Also, our results are similar to many previous studies that indicated the older age, duration of DM disease and glucose levels in DM are risk factors for UTIs among diabetic patients (Patterson and Andriole, 1997; Hammar *et al.*, 2010; Emiru *et al.*, 2013; Al-Hadad, 2005; Alsamarai *et al.*, 2011). In addition, others suggested that in diabetic patients, specific risk factors for UTI are usually the duration of diabetes and the presence of long-term complications, such as neuropathy, rather than current glucose control (Geerlings *et al.*, 2000; Gorter *et al.*, 2010).

On the other hand our findings disagree with other reports that showed no association between duration of DM disease and UTIs, the susceptibility of diabetic patients to UTIs could be explained by diminished neutrophil response, lower urinary cytokines and leukocyte concentrations, which might facilitate the adhesion of microorganisms to uroepithelial cells, also, sexual intercourse was reported as a risk factor for UTIs in women regardless of their DM status (Brown *et al.*, 2005; Lin *et al.*, 2012; Muller *et al.*, 2005; Geerlings *et al.*, 2000; Scholes *et al.*, 2005).

Our results showed that T2DM was more prevalent than T1DM. These results were similar with other reports, which illustrated that DM is the commonest metabolic abnormality in the world; T2DM is the commonest form of diabetes constituting nearly 90% of the diabetic population (Ramachandran and Snehalatha, 1999; Sharlin *et al.*, 2015). A study reported the prevalence of diabetes to be 34.80%, prevalence in women was calculated to be 31.20% and in males 40.40% (Muhammad *et al.*, 2013).

Our results about microscopic examination of urine showed that the white blood (WBCs) or (pus) cells, Red blood cells (R.B.Cs), epithelial, glucosuria and bacteriuria were increased in DM patients than NC individuals. These results were in agreement with others, who showed the conditions such as incomplete bladder emptying due to autonomic neuropathy and high glucose concentration in the urine allow urinary colonization by microorganisms, the presence of bacteria in urine "bacteriuria", evidenced that patients with diabetes have an increased risk of

asymptomatic bacteria and UTIs, bacterial infections were the most common infections in diabetic patients. Other study showed that Patients with diabetes have a 10-30 fold increased risk of UTIs when compared to non-diabetics (Goswani *et al.*, 2001; Hong, 2006; Bonadio *et al.*, 2006). Other researchers reported that about half of adult diabetic women have higher incidence of bacteriuria and asymptomatic UTIs at some stage throughout their life and tend to increase with age (Raz and Stamm, 1992; Geerlings, 2008; Janifer *et al.*, 2009). Previous studies documented that there is a relationship between bacteriuria and positive urine culture, T2DM patient's urine culture was positive in patient with bacteriuria. Patients with UTIs more likely to have leukocyturia, while a normal leukocyte count predicted the absence of UTI in 96% of the women (Lerman-Garber *et al.*, 2000; Tahir and Uddin, 2009).

Other studies revealed that the microscopic examination of urine samples have pus cells or W.B.Cs, RBCs, epithelial cells and *Schistosoma haematobium*, respectively positive in DM patients and they found a heavy and appreciable bacterial growth in patients with bacteriuria, while no appreciable bacterial growth in other patients without bacteriuria from all collected urine samples among diabetic pregnant women (El-Sokkary, 2011; Fareid, 2012). These findings about the presence of bacterial growth in DM patients were in agreement with many studies that reported a high prevalence of UTIs in DM patients than those non-diabetics ones, particularly, T2DM patients (Jackson *et al.*, 2004; Boyko *et al.*, 2005; Hirji *et al.*, 2012; Fu *et al.*, 2014).

Finally, our results showed a higher incidence of Gram-negative bacteria than gram-positive bacteria and fungi. UTIs are more common in diabetic females because of a combination of host and local risk factors, the principal causative agents accounting for 85% of cases of UTI are enteric G-ve bacteria. Other studies reported that the most frequent fungal infection is caused by *Candida albicans*, also UTIs can be caused by viruses (Numazaki *et al.*, 1973; Davies *et al.*, 1979; Tolk *et al.*, 1980; Gruneberg, 1980; Goswami *et al.*, 2001; Mansoor *et al.*, 2015). A previous study in Pakistan reported the incidence of *Escherichia coli* (80%), followed by *Staphylococcus aureus* (6%), *Klebsiella sp.* (6%), *Pseudomonas sp.* (4%) and *Proteus sp.* (4%) in UTIs (Ashraf, 2014).

Many studies reported that *E. coli* remains the most common etiological agent of UTIs. *E. coli* is a bacterium of the digestive tract; it can spread, especially, in women for anatomical reasons: down to the anus and then back in the urinary tract by multiplying and causing UTIs. Moreover, *E. coli* and G+ve bacteria, included: *Staphylococcus aureus*, *Staphylococcus spp.*, were found to be the common uropathogen in diabetic patients than those without diabetes. Additionally, these findings are consistent with

others, who reported that UTIs cause considerable morbidity and mortality in patients with DM, the successful management of UTIs in diabetic patients depends on the proper identification of the types of pathogenic bacteria and the selection of effective antibiotics against them (Goswami *et al.*, 2001; Salvatore *et al.*, 2011; A-Ameri *et al.*, 2014; Abdulla *et al.*, 2015; Chentouf *et al.*, 2015).

## CONCLUSION

Our findings indicated that UTIs were more prevalent among diabetics than non-diabetics individuals and more frequent in T2DM than T1DM patients. Also, UTIs were more frequent among diabetics' women than men. The G+ve bacteria are the most microbial pathogens that caused UTIs in DM patients, particularly, *Escherichia coli* is the commonest pathogen isolated in DM patients with UTIs followed by G+ve bacteria *Staphylococcus aureus* and *Candida albicans*. There were non-significant differences for fasting blood sugar, so we recommended to perform glycosylated haemoglobin (HbA1C) which serves as an estimator for the levels of blood glucose and it correlate with microbial infections in DM patients. Finally, an ongoing screening of UTIs should be encouraged for an updated knowledge about the uropathogens that causing infections and to inform about the emerging antibiotic resistance in different areas in our country "Yemen".

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## CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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