Urinary Tract Infection: Prevalence, Risk Factors, Bacterial Etiologies and Antimicrobial Resistance Profile among Egyptian Diabetic Patients

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Abstract — Diabetic patients are more prone to infections due to impaired immune status. One of the most frequent infections in diabetic patients is urinary tract infection (UTI). The aim of the work was to study the prevalence and associated risk factors of UTI among diabetic patients attending the outpatient clinics of Menoufia University hospital, and to assess the pattern of antimicrobial sensitivity of isolated organisms. A pre-designed questionnaire was used to collect information about age, sex and residence, smoking habits, and type and duration of diabetes. Laboratory investigations including blood analysis for glucose level, HBA1c, leukocytic count, urine culture and antimicrobial sensitivity testing were done. The prevalence of UTI was 51.3%, and the most significant risk factors associated with infection were older age, being female, BMI > 30, duration of diabetes > 10 years, together with uncontrolled diabetes. Residence, smoking, and type of diabetes were found to be insignificantly associated with UTI. Age, duration of diabetes, and HBA1c were found to be independently associated with UTI. Common isolated organisms in order of frequency were E. coli, Klebsiella, and Coagulase negative staph. More than 50% of isolates were resistant to one or more antibiotic on antimicrobial antibiotic sensitivity testing. The study concluded a high prevalence of UTI among studied patients. Proper control of diabetes with regular screening for HBA1c and UTI among diabetic patients is needed.

Index Terms— Egyptian, infection, risk, urinary.

I. INTRODUCTION

Diabetes mellitus (DM) is one of the top ten causes of death worldwide [1]. The incidence and prevalence of diabetes are increasing as by 2025, the number of diabetic patients is expected to double. [2] This number is expected to be 593 million by 2035 [3]. Diabetic patients have a high burden of the increased susceptibility to bacterial infections, increased risk for hospitalization, and increased mortality due to infection [4]. The most common infection among diabetic patients is urinary tract infection (UTI) [5], which contribute to the overall medical costs [6] and is a leading cause of end-stage renal disease [7]. It was reported that diabetes is associated with longer hospitalization, bacteremia, and septic shock in patients having UTI. In addition, it was found that UTI mortality is five times higher in diabetic patients aged 65 and older, as compared to control patients [8].

A lot of abnormalities in the host system predispose to the development of UTI among diabetic patients [9]. These factors include the immunologic deficiencies such as imperfect migration, phagocytic alteration of chemotaxis in polymorpho-nuclear leukocytes [3]. These factors make the diabetic patients at increased risk of acute pyelonephritis, renal abscess, and pyelitis. [10] Risk factors for UTI among diabetic patients include glycosuria, low immunity, and bladder dysfunction [11]. The most common pathogen isolated from urine of diabetic patients with UTI is Escherichia coli, other aggressive pathogens include Klebsiella spp., Proteus spp., Enterobacter spp., and Enterococci [12]. In Egypt Diabetes is a growing health problem with a prevalence of type 2 diabetes of 15.6% among adults aged 20 - 79 years [13]. In an Egyptian study done in 2015, the prevalence of UTI among 500 diabetic patients studied was 52.2%, and Escherichia coli was the most prominent uropathogen isolated [14]. This study aimed to assess the prevalence and associated risk factors of UTI among diabetic patients attending the outpatient clinics of Menoufia university hospital. And to determine the antimicrobial sensitivity patterns of isolated organisms.

II. SUBJECTS AND METHODS

A. Study Design

A cross-sectional study was done on 922 diabetic patients who attended the outpatient clinic of the Internal Medicine Department at Menoufia University Hospital from January to April 2019.

B. Sampling methodology

Patients were chosen by systematic random sample (every other day) for all attendances at that day. Total of 1345 patients attended the clinic at the time of the study. All patients, who agreed to participate in the study after explaining its purpose, were the study participants.

C. Exclusion criteria

Exclusion criteria were: Diabetic patients on antibiotics for the last two weeks, pregnancy, hospital staff, medical personnel, medical students, patients who could not speak or listen or who had mental health problems, and all emergencies and critically ill patients. After exclusion, a total of 922 patients were the study group.

D. Study instrument

A pre-designed questionnaire was used to collect

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information about age, sex and residence, smoking habits, and type and duration of diabetes. Patients’ height and weight were measured, and the body mass index (BMI) was calculated as weight divided by the square of the height (in kilograms per square meter) [15].

E. Laboratory investigations

Blood analysis: Venous blood samples were taken from all patients and collected samples were investigated for: random blood glucose, total leukocytic count, serum creatinine, and glycated hemoglobin (HbAlc). HbAlc was quantified spectrophotometrically using HbAlc test kits. HbAlc levels less than 7 % were considered good metabolic control and above 7.5 % considered as poor control according to the American Diabetes association [16].

Urinalysis: Urine samples were obtained from all patients by clean voided midstream technique into 20 ml calibrated sterile screw-capped containers. The sample container was labeled with the sample number, date and time of collection and transferred to the microbiology laboratory of the medical college of Menoufia University for the culturing, isolation, biochemical test and drug-resistance test. Until culture time, urine samples were stored at 2–8°C in refrigerator.

Uropathogens identification of urine samples: Urine samples were cultured on blood agar, MacConkey agar and Cysteine Lactose Electrolyte Deficient Agar (CLED) and the plates were incubated at 37°C for 24 h. Significant bacteriuria was defined as urine cultures grew >105 colony-forming unit/ml midstream urine [17].

Antimicrobial sensitivity testing: Antimicrobial sensitivity testing of all isolates was done on sensitivity test agar using disc diffusion methods following the definition of the National Committee of Clinical Laboratory Standards (NCCLS). [18] The antimicrobial agents tested were Ampicillin (AMP), Amoxicillin (AMC), Ciprofloxacin (CIP), Gentamycin, Co-trimoxazole, Amikacin, Nalidixic acid, Penicillin, Cefotaxime. The antimicrobial discs were tested in the following concentrations: Gentamycin (10 μg), Co-trimoxazole (25 μg), Amikacin (10μg), Nalidixic acid (30 μg), Penicillin (10 μg), Cefotaxime (30 μg), AMP (10 μg), AMC (10 μg), and CIP (5 μg).

Diameter of the zone of inhibition around the disc was measured to the nearest millimeter using a metal caliper and the isolate were classified as sensitive and resistant according to NCCLS [18].

F. Statistical analysis

Data were coded, tabulated and analyzed using (SPSS) version 20 (Armonk, NY: IBM Corp.). Qualitative data was expressed as numbers and percentages, and Chi-square test ($\chi^2$) was applied to test the relationship between variables. Quantitative data was expressed as mean and standard deviation (Mean ± SD), and Student-t-test was used to study association between normally distributed quantitative variables. Stepwise binary logistic regression analysis was done for the risk factors Two-sided. A p-value of <0.05 was considered as statistically significant.

III. RESULTS

A total of 922 patients were the study participants, their mean age was (51.08 ±11.79 years), 50.9% (No=469) were females, and 42.9% (No.=396) had a rural residence. The prevalence of UTI among the studied patients was 51.3%.

Table 1 shows that a significant relationship was found between patients who had UTI and who had not according to their age, gender BMI, and the duration of DM. Patients with UTI had a significantly longer age compared with those without UTI (p=0.028). Female patients had a significant higher percent of those having UTI compared to males (54.12% vs. 47.44%) (p=0.042). Patients with a BMI higher than 30 had a significant higher percent of those having UTI (52.43% VS. 47.5%) (p ≤0.001). Patients who had DM for more than 10 years had a significant higher percent of those having UTI compared with those who had disease duration less than 10 years (72.73% vs. 27.27%) (p ≤ 0.001). A non-significant difference was found between patients who had UTI and who had not according to their residence and type of diabetes (p > 0.05).

| Variable          | UTI (No. = 473) | No UTI (No. = 449) | Chi squared test | P-value |
|------------------|-----------------|-------------------|-----------------|---------|
| Age in years     | 51.36±10.42     | 49.78±11.47       | 2.19*           | 0.028   |
| Gender           |                 |                   |                 |         |
| Male             | 217(45.88%)     | 236(52.56%)       | 4.12**          | 0.042   |
| Female           | 256(54.12%)     | 213(47.44%)       |                 |         |
| Residence        |                 |                   |                 |         |
| Urban            | 231(48.83%)     | 221(49.22%)       | 0.01**          | 0.907   |
| Rural            | 242(51.17%)     | 228(50.73%)       |                 |         |
| Smoking          |                 |                   |                 |         |
| Present          | 71(15.01%)      | 53(11.80%)        | 2.03**          | 0.153   |
| Absent           | 402(84.99%)     | 396(88.20%)       |                 |         |
| BMI              |                 |                   |                 |         |
| < 30             | 248(52.43%)     | 295(65.70%)       | 17.34**         | <0.001  |
| > 30             | 227(47.57%)     | 154(34.30%)       |                 |         |
| Type of diabetes |                 |                   |                 |         |
| Type I           | 22(4.65)        | 17(3.78%)         | 0.43**          | 0.51    |
| Type II          | 451(93.35%)     | 432(96.22%)       |                 |         |
| Duration of diabetes mellitus | |                   |                 |         |
| < 10 years       | 129(27.27%)     | 236(52.56%)       | 61.59**         | <0.001  |
| > 10 years       | 344(72.73%)     | 213(47.44%)       |                 |         |

N.B.: * t-test; ** Chi-square test.

Patients diagnosed with UTI had a significant higher level of random blood glucose, total leukocytic count, serum creatinine, and HbA1c levels. Compared to patients without UTI (P ≤ 0.05) (Table 2).

| Variable          | UTI (No. = 473) | No UTI (No. = 449) | Test | P value |
|------------------|-----------------|-------------------|------|---------|
| Random blood glucose (mg/dl) | 378.9±79.9 | 244.1±48.1 | 30.84* | <0.001 |
| HbA1c (%)        |                 |                   |      |         |
| ≤ 7              | 207(43.76%)     | 229(51.00%)       | 4.84** | 0.027  |
| > 7              | 266(56.24%)     | 220(49.00%)       |      |         |
| Serum creatinine (mg/dl) | 1.27±0.52 | 0.8±0.12 | 18.69* | <0.001 |
| Total leukocytic count/1000 | 15.4±1.6 | 13.23±0.32 | 28.21* | <0.001 |

N.B.: * t-test; ** Chi-square test.
Binary logistic regression analysis was used to detect the independent predictors for UTI among the studied patients. The present study found that having an older age, a duration of DM more than 10 years, and having a higher level of total leukocytic count and HbA1c were independent predictors for (Table 3).

### TABLE 3: BINARY LOGISTIC REGRESSION ANALYSIS OF RISK FACTORS OF URINARY TRACT INFECTION AMONG DIABETIC PATIENTS

| Parameter                        | Wald  | p-value | Odd's ratio | CI 95%  |
|----------------------------------|-------|---------|-------------|---------|
| Age                              | 6.84  | 0.008   | 1.43        | 1.10-1.86 |
| Female sex                       | 1.37  | 0.242   | 1.18        | 0.91-1.53 |
| Random blood glucose              | 2.370 | 0.124   | 1.021       | 0.994-1.049 |
| Total leukocytic count            | 12.968 | <0.001  | 5.113-51.988 |
| BMI >30 Kg                       | 1.931 | 0.165   | 0.056       | 0.001-3.271 |
| Duration of diabetes mellitus >10 years | 7.345 | 0.021   | 2.95        | 2.25-3.89  |
| HbA1c                            | 4.56  | 0.032   | 1.34        | 1.03-1.73  |

Table 4 shows the antimicrobial sensitivity of different bacteria isolated from urine culture of the studied patients. E. coli was sensitive to all studied antibiotics except for CIP, with the highest sensitivity was to cefotaxime (80.3%) and the lowest was to AMP (27.8%). About the remaining isolated organisms, all showed sensitivity to all tested antibiotics.

For klebsiella spp, the highest sensitivity was to AMC (90.1%) and the lowest was to AMP (46.5%). For P. aeruginosa, the highest sensitivity was to Nalidixic acid (90.9%) and the lowest was to Cefotaxime. For S. typhi, the highest sensitivity was to Cefotaxime (90.9%) and the lowest was to Nalidixic acid (27.2). For Proteus, the highest sensitivity was to Cefotaxime and Nalidixic acid with 100% sensitivity, and the lowest sensitivity was to Penicillin (20.3%). Regarding S. aureus, the highest sensitivity was to CIP and Nalidixic acid with 100% sensitivity, followed by Cefotaxime with 88.4% sensitivity and its sensitivity to all remaining antibiotics was 50%. Enterococcus organism showed 100% sensitivity to AMC and Nalidixic acid and showed the lowest sensitivity to Co-trimoxazole with 41.6% sensitivity. As for Coagulase negative staph, it showed 100% sensitivity to AMC, AMP and Cefotaxime, and its lowest sensitivity was to amikacin (31.4%).

As shown in Table 4, the reported high rate of antibiotic resistance (> 50%) of different isolated organisms is as follows: E. coli: CIP (100%), AMP (72.1%), amikacin (68.3%), and Co-trimoxazole (50.8%). Klebsiella spp.: AMP and amikacin (53.4%). Coagulase negative staph: amikacin (68.5%). Proteus: CIP and Co-trimoxazole (59.3%), AMP (69.4%), and Penicillin (79.6%). Enterococcus: Co-trimoxazole (58.3%). P. aeruginosa: gentamycin (54.5%), AMC (63.6%), and Cefotaxime (81.8%). S. typhi: amikacin (63.6%), Nalidixic acid (72.7%), Co-trimoxazole (81.8%) and Penicillin (81.8%).

### TABLE 4: FREQUENCY OF ISOLATED ORGANISMS FROM URINE CULTURES OF THE STUDIED PATIENTS AND THEIR ANTIMICROBIAL SUSCEPTIBILITY PATTERN

| Isolated bacteria | No. (%) | Sensitivity | AMC | AMP | Co-trimoxazole | Cefotaxime | Amikacin | Nalidixic acid | Penicillin | Cefotaxime |
|-------------------|---------|-------------|-----|-----|----------------|------------|----------|---------------|------------|-----------|
| E. coli           | 183(38.69%) | 13(2.33%)   | 0.000% | 0.000% | 0.000%        | 0.000%      | 100.00%  | 100.00%       | 100.00%    | 100.00%   |
| Klebsiella spp    | 101(21.35%) | 7(0.00%)    | 100.00% | 100.00% | 100.00%       | 100.00%     | 100.00%  | 100.00%       | 100.00%    | 100.00%   |
| Coagulase negative staph | 70(14.8%) | 13(2.33%)   | 0.000% | 0.000% | 0.000%        | 0.000%      | 0.000%   | 0.000%        | 0.000%     | 0.000%    |
| Proteus           | 59(12.47%)  | 13(2.33%)   | 0.000% | 0.000% | 0.000%        | 0.000%      | 0.000%   | 0.000%        | 0.000%     | 0.000%    |
| S. aureus         | 26(5.00%)   | 13(2.33%)   | 0.000% | 0.000% | 0.000%        | 0.000%      | 0.000%   | 0.000%        | 0.000%     | 0.000%    |
| Enterococcus      | 12(2.54%)   | 13(2.33%)   | 0.000% | 0.000% | 0.000%        | 0.000%      | 0.000%   | 0.000%        | 0.000%     | 0.000%    |
| P. aerogenosa     | 11(2.33%)   | 13(2.33%)   | 0.000% | 0.000% | 0.000%        | 0.000%      | 0.000%   | 0.000%        | 0.000%     | 0.000%    |
| S. typhi          | 11(2.33%)   | 13(2.33%)   | 0.000% | 0.000% | 0.000%        | 0.000%      | 0.000%   | 0.000%        | 0.000%     | 0.000%    |
| Total             | 473(100.00%)| 226(47.7%)  | 72(15.07%)| 80(16.91%)| 23(4.82%)| 30(6.30%)| 125(26.71%)| 115(24.04%)| 147(30.82%)|

N.B.: R = Resistant; S = Sensitive; AMP: Ampicillin; AMC: Amoxicillin; CIP: Ciprofloxacin.

### IV. DISCUSSION

The present study showed that the prevalence of UTI among the studied diabetic patients was 51.3%. This prevalence is going on with other studies done in Egypt and showed also high prevalence of UTI among diabetic patients. [14], [19] Patients with diabetes have a 10-fold increased risk of UTI when compared to non-diabetics in a previous study [20]. Prevalence of UTIs infection and asymptomatic bacteriuria in diabetic patients ranges from 11% to 68% in some of international studies [21], [22]. This high prevalence among diabetic patients could be attributed to the autonomic neuropathy in those patients that leads to bladder dysfunction, incomplete bladder emptying and stagnation of urine that constitutes a favorable medium for microbial growth [6], [23]. Also, diabetic patients have impaired immune system functions as leucocyte adherence, chemotaxis, and phagocytosis, impaired neutrophil function, low levels of prostaglandin E, thromboxane B2, leukotriene B4, decreased T cell-mediated immune response, etc. leading to increased risk for infection in general, and especially UTIs. In addition, high glucose level in the urine favors the growth of bacteria as enriched media. Study of Akter et al., found that different species of bacteria have been colonizing the urinary tract of diabetic patients due to low immunity, glucosuria, bladder dysfunction, and depletion of local urinary cytokines [24].

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In the present study, the prevalence of UTI was associated significantly with increasing mean age, and this was in accordance with other studies [25]. On the other hand, other studies did not find any relationship between age and increased risk of UTI among diabetic patients [26].

This study showed a significantly high prevalence of UTIs among diabetic females compared to diabetic males (54% vs. 45%, P < 0.042). This finding agrees with many other studies [25], [26], [27]. Anatomically, women have shorter urethra than men. In addition, bacteria from rectum can easily travel up to the urethra and cause urinary tract infections [28]. Risk factors like pregnancy, frequent sexual intercourse, shorter urethra and perineal colonization of common pathogens like Escherichia coli and S. aureus also increase the risk of UTI infections in female compared to males [29].

A Canadian study demonstrated that diabetic females were 6–15 times more frequently hospitalized for acute pyelonephritis than non-diabetic females, and diabetic males were hospitalized 3.4–17 times more than non-diabetic males. Asymptomatic bacteriuria was reported to have an increased prevalence in diabetics by about 8% to 25% and was also found to have amplified occurrence among patients with longer duration of diabetes [23].

In the present study, there was a significant increase in the risk of UTI among patients with diagnosed diabetes more than 10 years. This may be attributed to the long-term effects of diabetes like impaired immune system and neuropathy. Previous studies detected similar increase in the risk for patients with diabetes >15 years [27]. Long standing diabetes may develop cystopathy, nephropathy, and renal papillary necrosis, that predispose to UTI [30]. On the other hand, another study has found that the duration of diabetes did not influence the risk of UTI in diabetic patients [26].

This study revealed that a none-significant association was detected between the type of diabetes and increased infection risk. A previous study has found that people with diabetes, particularly T1DM, are at increased risk of serious infections, but the risk for UTI was higher among T2DM [31]. Another study has found that 64.2% of T1DM patients had positive urine culture with bacteriuria and pyuria, and 77.7% of T2DM patients had positive urine culture and pyuria. The study revealed that Escherichia coli was the most common isolated uropathogen [19].

HbA1c reflects average plasma glucose over the previous six to eight weeks [16]. Concentrations of blood levels of HbA1c among diabetes mellitus (DM) patients are increased when there is poor glycemic control causing renal disease and predisposition to UTI [32]. HbA1c values reflect poor glycemic control and may be a proxy indicator for screening for UTI among women with diabetes mellitus [33].

The present study found a significant association between uncontrolled diabetes in the form of elevated random blood glucose level and HbA1c and increased risk of UTI. This result goes with finding from previous studies [27]. Hyperglycemia contributes to the colonization of different kind of microorganisms in the urinary system [27]. The longer the duration and the greater the severity of diabetes were found to increase the chance to develop UTI [34].

Different results regarding effect of HbA1C was detected by a previous study that found that HBA1c >8 was not found to be associated with UTI [27].

Among the studied diabetic patients, the most commonly isolated in order of frequency were: E. coli (39%), Klebsiella (21%), Coagulase negative staph (15%), and Proteus (12.5%). Other less frequently isolated organisms were Pseudomonas aeruginosa, S. aureus, and Enterococcus.

Both gram positive and gram-negative bacteria are implicated as common causes of UTI, and E. coli was found to be the most common causative agent in both DM and non-DM patients [35]. E-coli was encountered as the leading organism causing UTI in diabetic patients in other studies [27].

There is evidence that strains of multi drugs resistant (MDR) E. coli increased in both diabetic and non-diabetic [12], [36]. In the present study, the antimicrobial resistance patterns of bacteria isolated from UTIs differed for different bacteria and antibiotics, but there is markedly resistance of organisms to tested antibiotics. This observed increase of antibiotic resistance is a world-wide phenomenon that occurs due to the abuse of antibiotics.

Irrational drug use such as: long-term use, low-dose antibiotic use due to lack of protocol for antibiotic use, and empiric therapy due to lack of laboratory facility to determine sensitivity, are the possible reasons for resistance [37]. This resistance was found to be a leading cause of recurrent infections and complicated UTIs [37].

The emergence of resistant bacterial strains occurs due to indiscriminate usage of antibiotics as multiple courses of antibiotic therapy that are administered to asymptomatic or only mildly symptomatic UTI [38]. This leads to the increased resistance to commonly used antimicrobials. [38]

Patients with diabetes are more likely to have resistant organisms causing the UTI, including extended-spectrum β-lactamase Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, fluoroquinolone-resistant uropathogens, and vancomycin-resistant Enterococci. Type II diabetes was found to serve as a risk factor for fungal UTI [39].

This study revealed that K. pneumoniae was the second most commonly isolated organism. This finding is in agreement with a recent report from Nepal [36]. Other aggressive pathogens are highly prevalent in diabetic UTIs, such as fungal infections, Klebsiella, Gram negative rods, enterococci, group B streptococci, Pseudomonas, and Proteus mirabilis [12]. Misuse and overuse of antimicrobials is one of the world’s most pressing public health problems. Infectious organisms adapt to the antimicrobials designed to kill them, making the drugs ineffective. People infected with antimicrobial-resistant organisms are more likely to have longer, more expensive hospital stays, and may be more likely to die because of an infection [40].

Limitations: One of the limitations of this study is collecting data from a tertiary care hospital that cannot be representative to all Egyptian diabetic patients. Another limitation was the use of antibiotics that were available in the market and not all antibiotics used in the clinical practice.

V. CONCLUSION

The prevalence of UTI infection among diabetic patients was 51.3%. The most significant risk factors associated with infection were the older age, being female, BMI > 30,
duration of diabetes > 10 years together with the uncontrolled diabetes. Residence, smoking, and type of diabetes was found to be insignificantly associated with UTI. Age, duration of diabetes, HBA1c were found to be independently associated with UTI. the common isolated organisms in order of frequency were E. coli, Klebsiella, and Coagulase negative staph, with more than 50% of isolates resistant to one or more antibiotic on antimicrobial antibiotic sensitivity testing. This study calls for proper control of diabetes with regular screening for HBA1c and for infection especially UTI. Patients should be educated about the appropriate antibiotic use based on culture results. Implementation of stewardship program to rationalize the antibiotic use is needed.

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ETHICAL APPROVAL
The study was reviewed and approved by the Research Ethics Committee of Menoufia University. Verbal and written consents were obtained from all participants.

COMPETING INTERESTS
The authors declare that they have no competing interests.

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