Comparison of agents and sensitivity profile in urinary tract infection in diabetic and non-diabetic patients

Comparison dos agentes e perfil de sensibilidade em infecção do trato urinário em pacientes diabéticos e não diabéticos

Debora da Silva Krenke¹, Simão Augusto Lottenberg², Marines Dalla Valle Martino³, Jacyr Pasternak⁴

ABSTRACT

Objective: To study diabetic and non diabetic patients in UTI, regarding the prevalence of broad spectrum beta-lactamase producing pathogens and quinolone resistance. Methods: Inclusion criteria for this study was the presence of positive urine culture and fasting glucose equal to or above 126 mg/dl and below 100 mg/dl. We managed to include 494 patients, 210 diabetics and 284 non-diabetics. Results: Escherichia coli was the most frequently found pathogen in both diabetic and non-diabetic groups, and significantly more frequent in non diabetic patients (p = 0.0001) – 60% to 31% when compared to their diabetic counterparts. Candida albicans infecting the urinary tract was found in 30% of diabetics and in 16% of non-diabetics (p = 0.003). Broad spectrum beta-lactamase production was more frequent in diabetic patients (12%) than in non-diabetics (4%) (p = 0.03). Quinolones resistance was more common in diabetics (40%) when compared to non-diabetics (14%) (p = 0.0001). Escherichia coli is one of the pathogens more frequently found in patients with UTI. Conclusion: Diabetics have a greater likelihood of developing fungal urinary tract infection by Candida albicans, have more broad spectrum beta-lactamase producing Escherichia coli and more quinolone-resistant pathogens.

Keywords: Diabetes mellitus; Urinary tract; Urinary tract infections; Drug resistance, bacterial
INTRODUCTION

Diabetes mellitus (DM) is a set of metabolic disorders that underutilize glucose, thus resulting in hyperglycemia(1).

The most common test used to measure blood glucose level is fasting glucose. According to the Sociedade Brasileira de Diabetes, the result of such test is considered normal when the glucose rate varies from 70 to 110 mg/dl. If the result is between 110 and 125 mg/dl, the individual is considered as having inadequate fasting glucose level. Thus, it becomes necessary to order an exam called glucose tolerance oral test(2).

If we have a result equal to or above 126 mg/dl, in at least two consecutive tests, than diabetes mellitus is confirmed, which also happens when random glycemia (tested at anytime) is equal to or above 200 mg/dl in the presence of symptoms(3).

Diabetic patients usually have a greater occurrence of certain infections, including urinary tract infection (UTI). Experimentally, there is a reduction in neutrophil activity, and high urinary glucose levels inhibit the phagocytic function of leucocytes, thus increasing bacterial adherence to uro-epithelial cells(3).

Among the patients with neuropathy, the most important factor seems to be bladder dysfunction, there is a reduction in bladder filling sensation and also a reduction in the detrusor reflex activity(3).

A recent study showed that in the relation between UTI and metabolism control in the diabetic patient, high levels of glycosylated hemoglobin represented a significant risk factor for bacteriuria in women with type 2 diabetes mellitus(4).

DM has been considered a predisposing factor for UTI, especially in women, in whom the prevalence of asymptomatic bacteriuria is four fold higher when compared to women without diabetes(5). The same is not true for men with diabetes, in whom the prevalence of bacteriuria is similar to that in the general population. In patients aged over 65 years, the prevalence of UTI tends to be equal in both sexes(6).

In a major intra-hospital bacteremia study, diabetes was present in more than 60% of cases, and the urinary tract was the most frequent site of infection(9).

Etiological agents that most frequently caused this type of infection in the general population are enterobacteria, such as Escherichia coli, Klebsiella pneumoniae, Proteus spp, Enterobacter spp; and among Gram-positive cocci, the most frequent was Staphylococcus spp, with emphasis to the Staphylococcus saprophyticus and the Enterococcus spp(7). Unusual bacteria, such as Acinetobacter spp and group B streptococci are the most common in diabetic patients. Enterobacter spp, Enterococcus spp and Pseudomonas aeruginosa must be considered in hospitalized patients(3).

Diabetic patients are under the risk of developing fungal UTI, especially Candida albicans(8). Most infections by Candida spp are asymptomatic. Local complications are not frequent, however they can be potentially severe in diabetic patients and include pneumaturia, fungal ball formation, calyceal invasion, perinephric abscess and papillary necrosis. These complications result in bacteria that ascend the urinary tract, especially in the presence of poorly controlled diabetes(6).

In a study conducted at the Pisa Hospital, there was no significant difference between diabetic and non-diabetic patients regarding the pathogen and antimicrobial resistance, and Escherichia coli, Enterococcus spp and Pseudomonas spp were the most prevalent pathogens responsible for UTI(9). Another study showed that UTI by Klebsiella spp is the most frequent in patients with diabetes when compared to those non-diabetic patients(10).

Asymptomatic bacteriuria is associated with the risk of developing symptomatic UTI, however, as it happens in other situations, there is no indication to treat asymptomatic bacteriuria in diabetic individuals(6).

In the general population, treatment must be based on the urine Gram study or in results of previous bacterial cultures. Most uropathogens are sensitive to fluoroquinolones; ciprofloxacin and levofloxamine are good options, especially for outpatients. For patients with acute pyelonephritis, endovenous fluoroquinolones, ceftriaxone or combination therapies, such as ampicillin plus gentamycin are advocated(3).

In more severe patients, we must consider alternatives such as imipenem, ticarcillin/clavulanate and piperacillin/tazobactam, especially if one suspects of infection by resistant microorganisms such as Pseudomonas spp(3).

Regarding fungal infections, the mere presence of asymptomatic candiduria usually does not determine specific treatment. Correcting risk factors, such as glycemia control and removal of urinary catheters, can result in remission of candiduria. But symptomatic candiduria is an indication for treatment(6).

A recent comparative study between diabetic and non-diabetic patients, both with febrile UTI, showed that diabetic patients had a higher incidence of Escherichia coli resistant to fluoroquinolones(11).

Members of the Enterobacteriaceae family-broad spectrum beta-lactamase producers (BSBL) are resistant to penicillin, cephalosporin and aztreonam(12).

Some studies have shown that diabetes mellitus is a risk factor for finding BSBL producing Escherichia coli and Klebsiella pneumoniae in UTI(12-13).

UTI complications (bacteremia, renal abscess, renal papilla necrosis) and resistance (BSBL and fluoroquinolones), occur more frequently among diabetic
patients, when compared to their non-diabetics (12–14), hence the importance of studying the characteristics of UTI agents and sensitivity in this group of patients.

**OBJECTIVE**

To compare positive urine cultures of diabetic and non-diabetic patients in regards of:
- agents identified;
- the sensitivity profile regarding quinolones and BSBL production.

**METHODS**

A quantitative, retrospective, descriptive-exploratory study, carried out at the clinical pathology laboratory of a large private hospital in the city of São Paulo.

The selection of the population was based on their glycemia, glycosylated hemoglobin and urine cultures.

Inclusion criteria were:
- patients with positive urine culture;
- patients with glycemia above 126 mg/dl and below 100 mg/dl;
- patients with glycosylated hemoglobin above 7%.

For urine cultures, we used manual techniques to identify the microorganisms (chromogenic agar) and automatic ones (Vitek System).

BSBL production was determined by the plate diffusion disc method (Muller-Hinton) with combined discs (ceftazidime + clavulanic acid) and its correspondent (ceftazidime). Reading and interpretation was carried out as follows:
- Positive BSBL: when the halo between the antibiotic combined with clavulanic acid is 5mm than its correspondent.
- Negative BSBL: when the halo between the antibiotic combined with clavulanic acid is < 5mm larger than its counterpart.

In order to determine serum glycemia we used the Vitro system, peroxidase-oxidase colorimetric method.

In order to determine glycosylated hemoglobin values we used the automatic method by means of the D-10 BIO RAD equipment, HPLC (high definition liquid chromatography) methodology.

The patients were divided into two groups – those who had positive urine cultures, glycemic values above 126 mg/dl and glycosylated hemoglobin higher than 7; and those who had positive urine cultures and glycemic levels below 100 mg/dl.

The criterion used to classify the patient as being diabetic or not was data survey in the electronic medical chart of each patient, where we searched for diabetes mellitus diagnosis and the use of oral hypoglycemic agents.

The chi-squared test ($\chi^2$) was applied to statistically analyze the results (BioEstat 2.0).

**RESULTS**

In a total of 494 patients with UTI, 210 (43%) were diagnosed as diabetics (127 women and 83 men) and 284 (57%) as non-diabetic (220 women and 64 men).

The uropathogen most frequently isolated in diabetic and non-diabetic patients was *Escherichia coli*, 65 (31%) and 172 (61%), respectively (p = 0.0001). *Enterococcus* spp was found in 16% versus 10% (NS), *Klebsiella pneumoniae* was isolated in 8% versus 8% (NS), *Pseudomonas aeruginosa* was isolated in 8% versus 5% (NS), *Candida albicans* in 7% versus 1% (0.0032) in diabetic and non-diabetic patients, respectively (Table 1).

In a total of 65 UTI caused by *Escherichia coli* in diabetic patients, 8 (12%) were BSBL positive; while for non-diabetic patients, in a total of 172 positive cultures for *Escherichia coli*, 7 (4%) were BSBL positive (p = 0.032). The same comparison was made for UTI caused by *Klebsiella pneumoniae*, in which patients had 17 and 22 urine cultures positive for *Klebsiella pneumoniae*; of these, 4 (24%) and 5 (23%) were BSBL positive in diabetic and non-diabetic patients, respectively (NS) (Table 2).

Quinolone resistance was present in 40% of diabetics and in 14% of non-diabetics with UTI caused by *Escherichia coli* (p = 0.0001) (Table 3).

UTI caused by different species of *Candida* spp presented the following results: *Candida albicans* 42%
versus 22% (NS) and Candida non-albicans in 58% versus 78% (NS), in diabetic and non-diabetic patients, respectively (Table 4).

Table 4. Urinary tract infection caused by Candida albicans and Candida non albicans in diabetic and non diabetic patients

<table>
<thead>
<tr>
<th></th>
<th>Diabetics</th>
<th>Non-Diabetics</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N %</td>
<td>N</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>14</td>
<td>42</td>
<td>2</td>
</tr>
<tr>
<td>Candida non albicans</td>
<td>19</td>
<td>58</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>100</td>
<td>9</td>
</tr>
</tbody>
</table>

**DISCUSSION**

In the present investigation we tried to determine the bacteriological and sensitivity profiles regarding quinolone and BSBL production of UTI pathogens in diabetic and non-diabetic patients.

In the general population, most UTI are caused by *Escherichia coli* and affect mainly women at 40 years of age because of sexual activity and pregnancy. Prevalence in women is also due to the length of their urethra and the close proximity between the vaginal vestibule and the anus. In our study, we found a significant prevalence of UTI caused by *Escherichia coli* in non-diabetic patients when compared to their diabetic counterparts. The difference of age among the women in the groups may explain the marked prevalence of *Escherichia coli* causing UTI in non-diabetics when compared to the diabetic patients. This difference could have been higher, since many of the patients with UTI were not included, since the inclusion criteria for both diabetics and non-diabetics selected only those who had UTI and a positive glycemia test, and this excluded many women aged below 40 years.

Another important factor to be taken into account would be the fact that diabetic patients had higher incidence of UTI caused by unusual bacteria. In our study there was a significant difference between diabetic and non-diabetic patients as to the infection caused by other types of bacteria. In a recent study about febrile UTI in diabetic patients there was a significant difference concerning infections caused by *Escherichia coli*, when 100% of the urine cultures of non-diabetic patients (control group) grew *Escherichia coli*, that number being 83% in diabetics; and in the remaining 17% grew microorganisms different from *Escherichia coli*.

We also found a significant difference regarding the bacteriological profile of these patients, which was the high prevalence of *Candida albicans* in diabetic patients when compared to non-diabetic. In a study carried out in Prague, on diabetes and candidiasis, they concluded that diabetic patients are under a higher risk of developing fungal UTI. In this same study, there were different species of *Candida* spp, and 60% were *Candida albicans*. In our investigation, when we compared the frequency of UTI caused by *Candida albicans* and *Candida non-albicans*, there was no significant prevalence of *Candida albicans* concerning the UTI in diabetic and non-diabetic patients.

As to the resistance of microorganisms responsible for UTI, some studies have shown that DM is a risk factor for the development of BSBL producing *Escherichia coli* and *Klebsiella* spp. In our results, UTI caused by BSBL positive *Escherichia coli* was significant in diabetic patients, when compared to their non-diabetic counterparts. As for the infections caused by BSBL positive *Klebsiella pneumoniae*, there was no significant difference.

Quinolones are considered as first choice drugs for patients with UTI, however, an article published showed an increase in quinolone resistance in diabetic patients with UTI caused by *Escherichia coli*. In our study, a reasonable number of diabetic patients with UTI caused by *Escherichia coli* were resistant to quinolones, and only a minority of the non-diabetic patients had such resistance.

**CONCLUSION**

In our study, UTI caused by *Escherichia coli* was most frequently present in a group of non-diabetic patients.

UTI caused by *Candida albicans* was higher in diabetic patients when compared to non-diabetics. Another important piece of data was that BSBL producing and quinolone-resistance *Escherichia coli*, was higher in diabetic patients when compared to non-diabetics.

**REFERENCES**