

# A Literature Review on Urinary Tract Infection due to Diabetes Mellitus and Development of Antimicrobial Resistance

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**Abstract:** *Diabetes mellitus (DM) is a chronic metabolic disorder and one of the major causes of morbidity globally. It is estimated that the risk of DM will be greatly increased in the future. Diabetes mellitus is associated with various types of infections notably skin, mucous membrane, soft tissue, urinary tract, respiratory tract, and surgical and/or hospital - associated infections. The reason behind this frequent association with infections is an immunocompromised state of diabetic patients because uncontrolled hyperglycemia impairs the overall immunity of diabetic patients via the involvement of various mechanistic pathways that lead to the diabetic patient as immunocompromised. There are specific microbes that are associated with each type of infection and their presence indicates specific types of infections. For instance, E. coli and Klebsiella are the most common causative pathogens responsible for the development of urinary tract infections. Studies on this correspondence are very rare at the international level and practically non-existent in the national territory; therefore, this work aims to identify the different microbes involved in urinary tract infections in individuals and assess their behavior toward the available antibiotics.*

**Keywords:** Urinary Tract Infection, Diabetes Mellitus, Antimicrobial Resistance

## 1. Introduction

There are 425 million people with diabetes mellitus in the world. By 2045, this figure will grow to over 600 million. Diabetes is a chronic disease in which the sugar level in the blood increases. Diabetes is one of the prime causes of global morbidity. The occurrence of diabetes mellitus is tripled with many millions of new cases. The top ten countries with the highest number of diabetic patients according to the World Health Organization (WHO) are America, India, Bangladesh, Italy, Brazil, Russia, Pakistan, China, Japan, and Indonesia. In industrial countries, there is a high chance of early onset of diabetes in adults. In the general population, urinary tract infections are one of the most frequent bacterial infections with an estimated rate of occurrence of 17.5/1000 person in a year.

According to an American study directed at a health service database of 70, 000 patients with type 2 diabetes, in that 8.2% were diagnosed with urinary tract infection within 1 year of incidence increases with age. In another database study, 89, 790 matched pairs of patients with and without type 2 diabetes mellitus were found to suffer from urinary tract infections, which are very common in diabetic patients as compared to that non-diabetic patients. Urinary tract infections' frequent occurrence leads it to be positioned among the top ten concurrent or complicating illnesses throughout the life course of the management of DM. It also reported that up to 50% of women during their period of life at least had one urinary tract infection. More severe instances of urinary tract infections appeared to be associated with Type 2 diabetes mellitus.

A proposed cohort study of 12 months proved that like Type2DM patients Type 1DM patients are also at higher risk of urinary tract infections as well as skin, soft tissues infections, and lower respiratory tract infections, with distinguished increased risks of similar infections in both types 1 and type 2 diabetes. Type 2DM and Type 1DM are also mostly involved with impairment in the innate and adaptive immune system, eventually leading to an increased risk of infections.

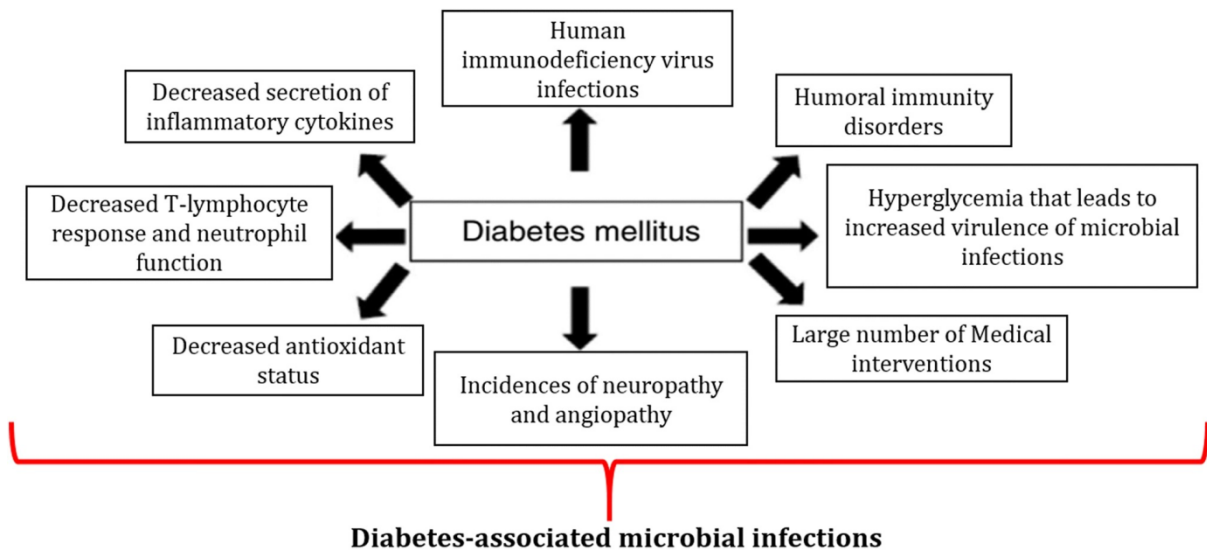
Several pieces of evidence have recommended that hyperglycemia is the assisting factor for bacterial infections, also leading to increased utilization of antibiotics. In addition to that, these types of infections accompany kidney injury either by direct invasion of the pathogen or endotoxin, leading to further complications. The spectrum of urinary tract infections in diabetes mellitus patients is asymptomatic bacteriuria to lower tract infections, severe urosepsis, and pyelonephritis. Emphysematous cystitis and pyelonephritis, renal papillary necrosis, and renal abscesses are some serious complications that occur in urinary tract infections. All these types of complications are very often found in Type2DM as compared to the general population.

The incidence of bilateral kidney infection was also found to be increased in patients with DM. Additionally; there are very high chances of bacteremia in diabetic patients having urinary tract infections in comparison to non-diabetic individuals.

## 2. Occurrence

It occurs when the body cannot produce insulin or is the inability to use the present insulin. Diabetes leads to the development of many other complications like nerve damage, kidney issues, vision problems, cardiovascular

illness, and various skin conditions. People with diabetes are very susceptible to urinary tract infections (UTIs) that acutely affect the kidney, urethra, urinary bladder, and ureters. It can also cause nerve damage to the urinary tract and lead to bladder problems. UTIs are ordinary types of infections that affect the urinary system.



There are some factors responsible for repeated urinary tract infections in diabetic patients. Various disabilities in the immune system, poor metabolic control, and higher concentrations of sugar in the urine give favorable conditions for the multiplication of microbes. Hyperglycemia is one of the main causes of disoriented immunity via the involvement of several mechanistic pathways.

Diabetes mellitus patients are at higher risk of developing asymptomatic bacteriuria, acute pyelonephritis, and other complications of urinary tract infections. *K. pneumonia* and *E. coli* are the most frequent causative agents for the incidence of symptomatic urinary tract infection and asymptomatic bacteriuria.

Similar bacteria are most likely to involve in urinary tract infections for both the individuals with and without diabetes mellitus but also extract complicated urinary tract infections. In diabetic patients associated bacteria, i. e., *Enterococcus* spp. (4%), *Staphylococcus* spp. (5%), *Klebsiella* spp. (6%), and *E. coli* (71%). *Enterococcus* spp. were more frequently found than *Klebsiella* spp. and *Staphylococcus* spp. in patients without diabetes mellitus. The degree of other species such as *Proteus* spp., *Pseudomonas* spp. and other bacteria such as *Streptococcus B* were found adjacent in both groups of individuals (Table 1).

Bacteria are responsible for urinary tract infection in patients with and without diabetes mellitus after matching.

Adopted from (Malmartel and Ghasarossian 2016)

Bacteria	Patients with diabetes N = 124 (%)	Patients without diabetes N = 246 (%)	P value	Patients with uncontrolled diabetes N = 100 (%)	Patients with controlled diabetes N = 24 (%)	P value
<i>Escherichia coli</i>	88 (71)	169 (69)	0.74	72 (72)	16 (67)	0.79
<i>Enterococcus</i> spp.	5 (4)	25 (10)	0.07	5 (5)	0	–
<i>Klebsiella</i> spp.	8 (6)	11 (4)	0.57	5 (5)	3 (13)	0.17
<i>Proteus</i> spp.	3 (2)	10 (4)	0.56	3 (3)	0	–
<i>Staphylococcus</i> spp.	6 (5)	6 (2)	0.23	4 (4)	2 (8)	0.3
<i>Pseudomonas</i> spp.	1 (1)	11 (4)	0.07	1 (1)	0	–
Other bacteria	13 (10)	14 (6)	0.14	10 (10)	3 (13)	0.7

Most of urinary tract infections are caused by *E. coli* majority of them are uncomplicated. Although, in diabetic patients, other strains are generally cultured. For example, a study stated that 47% of diabetic patients have urinary tract infections and there is a 68% chance of urinary tract infections in non - diabetic patients due to the commonly found uropathogen named *E. coli*. Other than *E. coli* diverse uropathogens were also found in diabetic patients, including *Proteus* spp., *Klebsiella* spp., *Enterococcus faecalis*, *Enterobacter* spp., and Group B *Streptococci*.

According to the study carried out by Kamoun et al urinary tract infections would be more frequent in diabetic patients; they are at the origin of the rise in bacterial adhesion, decline in cytokine secretion, and the presence of glycosuria. The study by Mehvish and Betty assessing the prevalence of urinary tract infections in diabetic patients showed that the occurrence of urinary tract infections in poor socioeconomic countries is 56.4% for diabetic patients and 43.6% for non - diabetic patients. In countries with high socioeconomic status, this frequency is 51.6% for diabetic patients and 48.4% for non - diabetic patients. These results from their

report show that urinary tract infections would occur more in diabetic patients as opposed to non diabetic patients.

Indeed, urinary tract infections are frequent both in hospitals and in community settings. In recent years, there has been an increase in the degree of resistance of germs that are responsible for urinary tract infections to antibiotics; this was because of the advent production of *Enterobacteriaceae* called extended - spectrum beta - lactamase.

Following the episode of bacterial multidrug resistance, the sensitivity towards these bacteria to antibiotics considerably reduced in diabetic patients, as seen in a study carried out at the Gondar University Hospital in Ethiopia on the prevalence of multidrug resistance of these bacteria to antibiotics it is found that occurrence of bacterial multidrug resistance in urinary tract infections in diabetic patients was 59.8%. Certainly, the resistance of bacteria to the antibiotics in general population and in diabetics in particular account for a public health problem today. The multidrug resistance of uropathogenic bacteria in diabetic patients exhibit that diabetes is involved in the alteration of the bacterial epidemiology of urinary tract infections and that leads to increased resistance to the antibiotics used to treat them.

There is a high frequency of urinary tract infections in women compared to that in men. In diabetic patients, 73.50% were women, whereas 26.50% were men. In non - diabetic patients, 54% were women and 46% were men. This is elucidated by the fact that urinary tract infection in women can be explained by several factors related to the physiological and anatomical nature of their urinary tract since the length of their urethra is much smaller (4 cm). Also, hormonal and physiological changes can elevate the occurrence of these infections. Men are comparatively more protected because of the anatomical structure of the urinary system. Faecal contamination is then reduced since there is a distance between his anus and his urinary meatus.

Due to age and the state of immunosuppression, urinary tract infection is very common in elderly patients and it is exaggerated by the frequency of severe and complicated forms of infection. Thus, among the diabetics, 42 (50.60%) were aged 60 years and above and 32 (38.55%) were aged between 40 and 59 years. This high incidence can be explained by many factors such as the aging of the urinary excretion system or a reduction of the muscular tone of the bladder walls, which involves a bladder stasis responsible for the augmentation of germs by declining the urinary excretion rate. In between the ages of 20 and 39 years, there is a severe sexual phase in men. This could disclose the fact that it is the age group where urinary tract infection is higher in non - diabetics.

The increasing pathophysiology of urinary tract infection and the strong colonization of the perineum by *Enterobacteriaceae* of digestive origin, and in particular *Escherichia coli*, associated with specific factors of uropathogenicity such as bacterial adhesins capable of binding to the urinary epithelium explain that the species *Escherichia coli* dominate the epidemiological profile. Gram - positive bacteria have an adhesion factor, which is lipoteichoic acid, which may explain why the species

*Staphylococcus aureus* is represented with a rate of 17.29%. The rate acquired for *Klebsiella pneumoniae* species (19.55%) is close to that found by other studies, thus indicating that it is a species frequently stumbled upon in urinary tract infections on diabetics.

The resistance of germs to beta - lactamines was very high found in many research papers. Kibret and Abera also discovered in their study the high rates of resistance to antibiotics such as AMX and cephalotin. In addition, Ejaz et al. acquired high resistance to CFM and TOB antibiotics. The resistance rates were 90.6% and 72% respectively. It is also noticed that bacteria were also very much resistant to the antibiotics of the aminoglycoside and tetracycline class, which is in unison with the work carried out by Kibret and Abera. Concerning phenicolates, the resistance rate found as 73.53%; these resistance rates are very high in comparison to those reported by other authors in the literature review. These dissimilarities in the sensitivity of germs to antibiotics, which vary broadly from one study to another, could be described by the variance in bacterial ecologies and the conditions of antibiotic use, which remain very fluctuating. There is very high resistance proportion against beta - lactamines and quinolones is found and could be explained by the known practice of self - medication, the illegitimate sale and use of drugs, and the expansion of clandestine health care units directed by unqualified health personnel who constantly prescribe antibiotics with the doses and durations that are non - compliant. This could also describe the fact that the bacterial species *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* are most multidrug - resistant.

The results of this study are of great importance to public health because the antibiotic resistance of uropathogens is not systematically sought in people suffering from diabetes.

*E. coli* (ESBL) was among the most common gram - negative isolate followed by *Pseudomonas auregonosa*, *Klebsiella pneumoniae* (ESBL), and *Klebsiella pneumoniae* cephalosporinase producers. These isolates were equally present in both groups. Both, *E. coli* and *K. pneumoniae* strains were the most common uropathogens. Similar observations were earlier reported and established the prevalence of ESBL - producing *E. coli* and *K. pn* species in diabetics and in non - diabetic subjects. These findings together may indicate a direct relationship between glycemic control and UTI with ESBL - producing strains.

Among the gram - positive, *Enterococcus* represented 5.9% of the isolated pathogens, whereas *staph epidermidis* was found in three of the cases and only about 1% of cases were assigned to candida species. *Enterococcus Spp* 0.93, and *Candida* 5.61 was found in a local study and 18.4%, 8% from other similar studies, correspondingly.

Gram - negative bacteria exhibited an alarming resistance to first - and second - line agent's trimethoprim - sulphamethoxazole, cephalosporins, amikacin, amoxicillin/clavulanic acid, and fluoroquinolones in this study. Our study indicates that these antibiotics cannot be used as an empirical treatment for UTI in DM patients due to the emergence of increasing antimicrobial resistance to

first - and second - line drugs. Therefore, emerging resistance to these antibiotics in diabetics may be considered while developing new guidelines. Although Gram - negative isolates were sensitive to carbapenems and antipseudomonal penicillins, these drugs cannot be recommended in outpatient settings due to their supervised drug administration protocols. Also, where fosfomycin and nitrofurantoin have shown intermediate to full susceptibility patterns, more than 50% of the isolated Gram - positive isolates were resistant to these antibiotics. This result questions the effectiveness of fluoroquinolone for the empiric treatment. Though, all the isolated uropathogens were susceptible to nitrofurantoin. This is consistent with earlier studies. Therefore, nitrofurantoin can be used as the drug of choice in the study area as a potential treatment for UTI.

Canagliflozin and Dapagliflozin, new antihyperglycemic molecules inhibiting renal glucose reabsorption and thus increasing glucosuria, were recently tested in clinical trials and were found to be associated with only a slight increase in UTI in T2D. This suggests that the contribution of glucosuria is limited in UTI and it does not explain its increased prevalence in diabetic patients. Nevertheless, there was a higher correlation between glucosuria and genital infection in Dapagliflozin - treated patients probably due to a greater effect of glucosuria in promoting the growth of fungal pathogens associated with genital infection as compared to bacterial pathogens typically associated with UTI. In a new report, James and Hijaz have reviewed recent publications on lower urinary tract symptoms (LUTS) and UTI in diabetic women and have concluded that aging and obesity are significantly associated with worsened LUTS. Glucosuria was also found to be associated with UTI and diabetic patients appeared to be at a higher risk for colonization with the virulent, extended - spectrum  $\beta$  - lactamase - producing *E. coli* and *Klebsiella* species in UTI. The obesity might be considered as a cofounder in the correlation between glycemic control and UTI as obesity rates are increasing regularly worldwide.

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