

Urinary Tract Infection in Patients with Diabetes Mellitus

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ABSTRACT

Background: urinary tract infections (UTI) are one of the most common types of bacterial infection in patients with diabetes mellitus (DM). There are certain aspects to diabetes that makes it a risk factor for getting urinary tract infection and additionally, diabetes may also predispose to certain complications.

Methodology: in this paper we aim to carry out a systematic review on observational (nonrandomized) studies on PUBMED. **Aim:** to evaluate the prevalence, pathogenesis, diagnosis, management and complications of UTI in patients with DM. **Conclusion:** the proper management of UTI in diabetics is crucial, as prompt diagnosis and correct use of antibiotics is vital for treatment. Future research in this regard will hopefully decrease the burden of UTI in diabetic patients.

Keywords: Urinary tract infections, diabetes mellitus, UTI in DM, risk factors of UTI, diagnoses of UTI, treatment option of UTI in diabetic patient, complication of UTI in diabetic patient

INTRODUCTION

Urinary tract infection (UTI) can be roughly classified based on anatomy as upper UTI and lower UTI, or both. UTI can be symptomatic or asymptomatic, but is defined as presence of bacteriuria with a quantitative count of more than or equal to 10^5 colony forming unit of bacteria per milliliter⁽¹⁾. The most common causative pathogen for both uncomplicated and complicated UTIs is *Escherichia coli*⁽²⁾. Other organisms that cause UTI are *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Proteus mirabilis*, *Enterococcus faecalis*, group B *Streptococcus*, *Pseudomonas aeruginosa*, *Candida* spp, and *Staphylococcus aureus*⁽³⁾. National Ambulatory Medical Care Survey reported UTI to be the most common bacterial infection worldwide⁽¹⁾. Among the most common risk factors of UTI are female anatomy, sexual activity, urinary tract abnormalities like vesicoureteral reflux, blockage anywhere in the urinary tract, catheter use, and a suppressed immunity state such as diabetes^(4,5).

Diabetes mellitus (DM) is a group of metabolic disorders characterized by high blood sugar levels over a prolonged period. DM is classified as type I or type II based on the pathology. Type I results due to failure of the pancreas to produce insulin, while type II is resistance of insulin by the cells of body⁽⁶⁾. Both types of DM can have acute or chronic complications. Some acute ones include

hyperosmolar hyperglycemia, diabetic ketoacidosis, coma or death, and chronic ones are nephropathy, ophthalmopathy, foot ulcers, and cardiovascular diseases^(6,7). It was recorded in 2015 that worldwide 415 million people had diabetes, 90% of which was type II DM. This number is estimated to rise to 552 million in 2030⁽⁸⁾. It was reported to be the cause of 1.5 to 5 million deaths each year, and budgets a global economic cost of 612 billion US dollars for its management⁽⁹⁾. There is an increased risk of UTI in patients with DM, especially DM type II, therefore in this study we aim to review the literature for prevalence, pathology, complications, and management of UTI in diabetics.

METHODOLOGY

We carried out a systematic review on observational (nonrandomized) studies by evaluating 37 articles, after exclusion, using search on PUBMED (January 1983 to December 2016) to identify the prevalence, pathogenesis, management, and complication of UTI in patients with DM type II. The keywords used for the search were: *Urinary tract infections, diabetes mellitus, UTI in DM, risk factors of UTI, diagnoses of UTI, treatment option of UTI in diabetic patient, complication of UTI in diabetic patient*

Prevalance of UTI in Patients with DM vs. Patients without DM

Many studies have stated the general incidence of UTI among patients with DM. An observational study

of all patients with in the UK general practice research database noticed that the incidence rate of UTI was 46.9 per 1,000 person-years among diabetic patients versus 29.9 for patients without diabetes ⁽¹⁰⁾. An American database study during 2014 found that a UTI diagnosis was more common in subjects with diabetes compared to those without diabetes (9.4% vs 5.7%, respectively) ⁽¹¹⁾. Another study done in America with over 70,000 patients with DM type II found that 8.2% were diagnosed with UTI in 1 year (12.9% of female and 3.9% of male, with increasing incidence with age) ⁽¹²⁾. 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 bacteriurea was reported to have an increased prevalence in diabetics by about 8% to 25%, and was also found to have amplified occurrence with in patients with longer duration of diabetes ⁽¹³⁾.

PATHOGENESIS OF UTI IN PATIENTS WITH DM

Generally, UTIs begin when pathogens that normally reside in the gastrointestinal tract pollute the periurethral area and are able to colonize the urethra. From urethra, they migrate to the bladder and invade and colonize the superficial umbrella cells by expression of pili and adhesins. Host inflammatory responses and neutrophil infiltration come to play, but some bacteria escape the immune system, either by invading the host cell or through morphological changes resulting in resistance to neutrophils. These bacteria may undergo multiplication and formation of biofilm ⁽¹⁴⁾. The proteases and toxins produced by these bacteria induce host cell damage, releasing essential nutrients further promoting bacterial survival and ascent to the kidneys, where they may colonize resulting in pyelonephritis. If left untreated, the pathogen may the tubular epithelial barrier in kidney and can eventually end up as bacteremia ⁽¹⁵⁾.

The increased risk of getting a UTI in DM can be explained by the following mechanisms. Diabetic neuropathy leads to a dysfunctional bladder, thus creating the chance for UTI development. Autonomic neuropathy involving the genitourinary tract causes dysfunctional voiding and urinary retention, which leads to decreased bacterial clearance by micturition, thus facilitating bacterial growth. Bladder dysfunction may be found in 26%–85% of diabetic women. The higher glucose

concentration of glucose in the urine in patient with DM amplifies bacterial reproduction, which creates a positive atmosphere for infections. However, some studies have not found an association between HbA1c level or glycosuria, leading to a risk of UTI among diabetic patients ⁽¹⁶⁾. In case of pyelonephritis too, the high renal parenchymal glucose levels create a favorable environment for the growth and multiplication of microorganisms, sometimes also leading to renal complications such as emphysematous-pyelonephritis. Impaired immune responses (humoral, cellular, and innate immunity) play a role in a DM patient's reduced capacity to defend against bacterial proliferation. Reduced urinary interleukin-6 and -8 levels were noticed in patients with diabetes with asymptomatic bacteriurea, compared to those without diabetes. Dapagliflozin (a drug used by patients with DM) was associated with a slight increase in UTI ^(16,17).

DIAGNOSIS

The diagnosis of UTI must be suspected in any patient DM presents with symptoms consistent with UTI, which are: frequency, dysuria, urgency, and suprapubic pain for lower UTI. The symptoms for upper UTI include those of lower UTI along with fever, chills, costovertebral angle pain or tenderness ⁽⁷⁾. Some patients with DM type II and UTI may present with hypo- or hyperglycemia, non-ketotic hyperosmolar state, or even ketoacidosis, which requires a prompt exclusion of infectious factors, containing UTI ⁽¹⁸⁾. A midstream urine specimen should be examined, in case of suspicion, to look for the leukocytes. Pyuria can either be detected by urine dipstick leukocyte esterase test, or by microscopic examination (10 or more leukocytes/mm³). An absence of pyuria on microscopic analysis may suggest colonization ⁽¹⁹⁾. A dipstick test shows the presence of urinary nitrite, therefore, a positive test indicates the presence of bacteria, while a negative test can indicate absence of bacteria, or may indicate some gram-positive bacterial species that lack the ability to reduce nitrate to. Sometimes hematuria and proteinuria can also be a common finding ⁽²⁰⁾.

Obtaining a urine culture should be directed in all cases of suspected UTI in diabetic patients. The ideal method is from voided, clean-catch, mid-stream urine ⁽¹⁸⁾. A culture may also be obtained through a sterile urinary catheter inserted, or by suprapubic aspiration in a patient for whom specimen cannot be collected, such as in patients with altered sensorium or neurologic/urologic. In the case of patients

with long-term indwelling catheters, the desired method of obtaining a urine specimen for culture is collecting a specimen from the freshly placed catheter, since there is formation of biofilm on the catheter ⁽²¹⁾.

The most common pathogens isolated from urine of diabetic patients with UTI are *Escherichia coli*, other *Enterobacteriaceae* such as *Klebsiella spp.*, *Enterobacter spp.*, *Proteus spp.*, and *Enterococci*. Patients with diabetes are more likely to have resistant organisms causing the UTI, including extended-spectrum β -lactamase-positive *Enterobacteriaceae*, carbapenem-resistant *Enterobacteriaceae*, fluoroquinolone-resistant uropathogens, and vancomycin-resistant *Enterococci*. Type II diabetes may also serve as a risk factor for fungal UTI ⁽²⁰⁾.

CURRENT LINES OF MANAGEMENT OF UTI IN PATIENTS WITH DM

Treatment of UTI in patients with DM type II depends on factors like: existence of the symptoms; whether infection is localized only in the bladder as in lower UTI, or also comprises the kidney as well, making it upper UTI; severity of systemic symptoms, presence of urologic abnormalities, renal function, and accompanying metabolic alterations ⁽²²⁾. Generally, management of UTI in type II DM patients is comparable to that of UTI in non-diabetic patients. Antibiotic choice is made fshould also be guided by local susceptibility patterns of uropathogens. Treatment should also involve correction of metabolic complications caused by the infectious process ⁽²³⁾.

Only to symptomatic cases must be treated because asymptomatic bacteriuria is a common finding, and antibiotic treatment in such cases does not do much benefit, instead serves mostly to increase bacterial resistance. Treatment should be tailored according to severity of infection and culture results ⁽²²⁾.

Since a patient with DM is already takes other drugs for the chronic condition, the choice of antibiotics in such patients should also take into consideration due to the likely drug interactions between antidiabetics and/or antihypertensive agents with the antimicrobials. Some antibiotics may also cause impaired glucose homeostasis that may worsen the state of the patient ⁽²³⁾. Most chronic DM patients have affected kidneys, and therefore dosage adjustment is required in diabetic patients with renal impairment for some antimicrobials agents are crucial. One such example is aminoglycosides. These

should be used with caution in patients with renal failure due to their nephrotoxic effect. Nitrofurantoin should be avoided in patients with renal failure too, due to peripheral neuropathy that is associated with the drug accumulation ⁽²⁴⁾.

COMPLICATIONS

Diabetes mellitus is a major risk factor for urinary tract infections and is also associated with increased risk of certain complicated UTIs such as emphysematous pyelitis (EP), emphysematous pyelonephritis (EPN), xanthogranulomatous pyelonephritis (XGP), emphysematous cystitis (EC), renal or perirenal abscess, and renal papillary necrosis (RPN) ^(25, 26). Unfortunately, patients with diabetes generally have worse outcomes of UTI when compared to those without diabetes. Diabetes is concomitant with longer hospitalization, azotemia, bacteremia, and septic shock. Diabetes was found to be risk factor for early clinical failure after 72 hours of antibiotic treatment in women with community-onset acute pyelonephritis ⁽²⁷⁾. The mortality rate from UTI is 5 times higher in patients with aged diabetes; as compared to elderly control patients. Relapse and reinfection are also more common in patients with DM. About 67% of episodes of emphysematous cystitis 90% of cases of emphysematous pyelonephritis occur in patients with diabetes mellitus. Additionally, renal and perinephric abscesses occur far more frequently in diabetic patients as well. Urosepsis and bacteremia are also more frequent in patients with diabetes ⁽²⁸⁾. Emphysematous difficulties in the kidney or the bladder are likely to be due to the existence of organisms that hastily ferment glucose and produce carbon dioxide ⁽²⁶⁾. If there is impaired tissue perfusion, as in diabetic patients, there is impaired transport of metabolic end products. Diabetes mellitus is a risk factor for the progress of renal abscess in association with ascending infection ⁽²⁹⁾.

CONCLUSION

Urinary tract infections frequently occur in diabetic patients due to an impaired immune status and increased glucose content of the urine, among other reasons. This makes UTI very important to investigate. Complicated cases of UTI may be infrequent but are more common in diabetics with far more severe consequences, and so warrant further investigation. The proper management of UTI in diabetics is crucial, as prompt diagnosis and correct

use of antibiotics is vital for treatment. Future research in this regard will hopefully decrease the burden of UTI in diabetic patients.

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