Recent Studies on Urinary Tract Infections in Diabetes Mellitus

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Abstract

Diabetes mellitus (DM) is one of the common endocrine disorder characterised by increased levels of glucose in the blood. DM is an important medical and public health issue world widely. The incidence has been exponentially increased globally. Evidence revealed that diabetics are more prone to infections than non-diabetic patients. UTI is one of the infections that occurs more frequently among DM patients. UTIs are considered as complicated and carry worst outcome when it occurs in DM patients. Many studies concluded that uncontrolled DM is significantly associated with more UTIs. Majorly E.coli followed by Klebsiella pneumoniae are the most common causative agents of UTIs among DM patients and cystitis is the most prevalent type of UTI. Resistance pattern of antibiotics is highly variable but the majority of the pathogens showed resistance against ampicillin, trimethoprim/sulfamethoxazole and cefotaxime while prescribing patterns showed that cephalosporins were the most commonly prescribed antibiotics followed by penicillin.

Keywords: Diabetes mellitus; Urinary tract infections; Antibiotic resistance; Antibiotic prescribing patterns

Diabetes Mellitus: General Background

Diabetes mellitus (DM) is one of the most challenging health problems of the 21st century. It's considered as the 5th leading cause of death in developed countries. It affects every aspect of patients' life, including quality of life (QoL), employment and even causing premature death [1,2].

Global burden of DM

The global prevalence of DM continues to increase at an alarming rate from 4.7% (108 million DM patients) in 1980 to 8.5% (422 million DM patients) in 2014 [3]. In lower and middle-income countries the prevalence of DM has risen faster than higher-income countries over the past decade. Furthermore, DM caused around 1.5 million deaths in 2012. Uncontrolled DM caused an additional 2.2 million of deaths by increasing the risks of different diseases like cardiovascular, renal and other diseases. Of these 3.7 million deaths, 43% are early deaths and occurred before the age of 70 years. Percentage of early deaths attributed to diabetes is higher in lower and middle-income countries than in higher-income countries. In Asia, it is estimated that Asians have a higher risk of developing DM and to have potentially worse prognosis than non-Asians. The number of DM patients are expected to be double or more than double by 2025 [4]. According to the report of Global estimates of diabetes prevalence 2013, the prevalence of DM was about 17.5% and has a similar prevalence in the Asian-Pacific Region countries i.e. Singapore, Brunei, Korea and Japan.

Literature Review

DM and infections

Studies have shown that diabetic patients are prone to have various kind of infections more than non-diabetics. This high incidence rate of infections is attributed to altered immune functions like polymorphonuclear leukocyte function, adhesion phagocytosis and chemotaxis. Particularly acidosis can further depress polymorphonuclear leucocyte function [5,6]. In diabetic patients, there is an impaired antioxidant system involved in bactericidal activity [7]. Poor glycaemic control has been shown by various studies to be a risk factor for developing different infections [8,9].

Elevated sugar level leads to altered immune function in diabetic patients which is significantly associated with various innate and adaptive immune system defects, which may lead to an increase in the risk of getting UTI [6,10]. Hyperglycaemia also associated with elevated levels of inflammatory markers [11,12]. All these changes make diabetic patients prone to have more infections such as UTI, RTI, skin and soft tissue infections (SSTIs).

Common infections among patients with DM

Studies have shown that diabetic patients are prone to have various kinds of infections more than non-diabetics. This high incidence rate of infections is attributed to altered immune functions like polymorphonuclear leukocyte function and adhesion phagocytosis and chemotaxis. Particularly acidosis can further depress polymorphonuclear leucocyte function. In diabetic patients, there is an impaired antioxidant system involved in bactericidal activity [6]. So for appropriate recovery from infections blood glucose levels should be closely monitored and controlled in diabetic patients [13]. 14 years follow up study demonstrated that out of 4748 diabetics 83.8% (3980) patients had an event of hospitalisation due to infection. Furthermore, diabetic patients displayed an increasing trend of hospitalisation within the study period (1996-2009) with a 4% annual increase [14]. Muller et al. described that incidence of different types of infection is higher among DM patient than non-diabetics. Upper respiratory tract infections (URTIs) are most common infections i.e. 9.1% and 7.7%, while Lower respiratory tract infections (LRTIs) were 5.7% and 5.6% among type 1 DM and type 2 DM respectively. Furthermore, UTIs are 9.6% and 6.9% among type 1 DM and type 2 DM respectively, followed by skin and soft tissue infections, as shown in **Table 1.**

Major infections and most recurrent infections associated with DM are RTI (Pneumonia, Influenza, Tuberculosis), UTI (Asymptomatic bacteriuria, Fungal cystitis, Emphysematous cystitis, Bacterial pyelonephritis, Emphysematous cystitis and Perinephric abscess) Gastrointestinal and liver infections (H. pylori infection, Oral and oesophageal candidiasis, Hepatitis C, Hepatitis B), Skin and soft tissue infections (Foot infections, Necrotizing fasciitis, Fournier's gangrene), Head and neck infections (Invasive external otitis), Sepsis, Postoperative infections, Biliary tree infections, Peritonitis, Appendicitis and HIV infections [15]. Patients with moderately controlled glycemia i.e. HbA1c <8.0, are at higher risk of infection. Skin, mucus membrane and nail infections are common among diabetics. Skin infections are present in 20% of the patients.

Table 1 Incidence of infections in type 1 DM and type 2 DM are given below table.

Infections	Percentage of patients (%)	
	Type 1 DM	Type 2 DM
URTI*	9.1%	7.7%
LRTI*	5.7%	5.6%
UTI*	9.6%	6.9%
Skin and soft tissue infections	5.5%	4.2%
Fungal infections	6.5%	6.1%

*URTI: Upper respiratory tract infections, *LRTI: Lower respiratory tract infections,
*UTI: Urinary tract infections
Note: Table adopted from Muller et al. [29].

In the UK there is 6-7 times greater risk for hospitalisation in diabetic patients due to skin and soft tissue infections. Diabetic foot infections are common and need multidisciplinary team for management [16-18].

UTIs among patients with DM

Different studies have shown that prevalence of UTI is high among diabetic patients [19-21]. A study by Gillani et al. done in Malaysia on the diabetic patients with diabetic ketoacidosis (DKA) and concluded that out of 967 patients 679 patients (70.2%) had bacterial infections while UTI observed in 198 patients (29.2%) [22]. Chazan et al. concluded that UTIs are five times higher among diabetics than non-diabetics. While Hoepelman et al. found that the risk of UTI for diabetic patients was two folds higher than that of non-diabetics. UTIs are also more severe and carry worse outcomes in patients with DM [23,24]. Low urinary concentration of interleukin-8 and interleukin-6 in diabetics has been shown to correlate with lower urinary leukocyte cell count which may contribute to increased incidence and worst outcomes in UTI among diabetic patients [24,25]. Urine samples with a glucose concentration of more than 5.5mmol/dl showed significant bacterial growth than normal urine [25]. High concentration of urine may act as good media for uropathogens and may enhance the growth of pathogenic bacteria in the urinary tract. [26]. Various impairments in the immune system, poor metabolic control, and incomplete bladder emptying due to autonomic neuropathy may all contribute to the enhanced risk of UTIs in DM patients [23]. In diabetic patients, there is an increased adherence of bacteria to uroepithelial cells particularly E. coli expressing type-1 fimbriae which may show increase pathogenesis and prevalence of bacteriuria among diabetic patients [26,27]. Diabetes is considered as a risk factor for early clinical failure after 72hrs of antibiotic treatment in women with acute pyelonephritis [28]. Among diabetic women, relapse and reinfections are more common i.e. 7.1% and 15.9% respectively while 2.0% and 4.1% respectively in non-diabetic women [29]. UTIs are more common during pregnancy and occurrence of UTI during pregnancy is 56% while in second-trimester incidence is up to 50% among pregnant women. Hormonal changes physiological and mechanical changes (expansion of uterus, reduce bladder tone, reduce urine flow from ureter) during pregnancy may facilitate bacterial growth and make pregnant women more prone to UTIs [30,31]

Table 2 summarises some available literature reviews on journal articles related to the UTI in DM and prevalence of UTI among diabetic patients [32-44]. By looking at studies, all of them concluded that there is a high prevalence of UTIs among diabetic patients. Shah et al. [45] and Yadav et al. [20] found that 40.2% and 38% of DM patients have UTI respectively, while Ijaz et al. [44], Pargavi et al. [21], Hirji et al. [33] also stated high prevalence of UTIs i.e. 51%, 37% and 62% respectively whereas, Al-Rubeaan et al. [34] and Hamdan et al. [35] found 25.2% and 19.5% respectively as shown in **Table 2**. Incidence and prevalence rates are higher in females than in males [21,45]. Prevalence of UTI is higher in patients with uncontrolled glycaemia than patients with controlled glycaemia [19,45]. High sugar levels in urine make patients prone to UTIs [20]. UTIs are more common in age-group more than 55 years old [44].

Table 2 Summary of Related Studies on prevalence of UTI, pathogen involved and antibiotics sensitivity among diabetic patients; Prevalence of UTI among diabetic patients.

Author	Study Design/Setting/Duration of Study (t)	Diagnostic tool	Conclusion
Shah et al. [45]	Retrospective Study n=348 t=12 months	Urine analysis reports	Prevalence of UTI=40.2% Females=52.9% Males=47.1%
Yadav et al. [20]	Prospective Study n=100 t=10months	Urine analysis	Prevalence of UTI is 38% in diabetic patients. UTI seen more common in females i.e. 63.16% while male's contribution was 36.84% among studied subjects. The High sugar level is the main cause of prevalence of UTI among the diabetic patients.
Ijaz et al. [44]	Descriptive, cross-sectional study n=292 t=6months	Urine analysis	Prevalence of UTI among diabetic patients is 51%. Prevalence of UTI is more common in patient more than 55 years that is 68.6%.
Pargavi et al. [21]	Prospective Study n=200 t= unavailable	Microscopic examination of the urine	Prevalence of UTI=37% Females=43% Males=30% *Escherichia coli*=56% *Klebsiella pneumonia*=35% *Proteus mirabilis*=85%
Sewify et al. [19]	Retrospective n=722 t=3years	Urine analysis	The prevalence of UTI is high in patients with uncontrolled glycaemia (78.2%) than patients with controlled glycaemia (21.8%)
Hirji et al. [33]	Prospective study n=135620 1 year	Oxford Medical Indexing System	This study revealed that 62% diabetic patients got UTI upon 1 year follow up.
Al-Rubeaan et al. [34]	Prospective hospital based study n=1000 t=6months	Urine analysis	This study found prevalence of UTI was 25.2% Males: 7.2% Females: 41.2% Prevalence of UTI in high in diabetics with BMI above 30 kg/m2.
Hamdan et al. [35]	Retrospective Cross sectional study n=200 t=6months	Urine analysis	Prevalence of UTI among diabetic patients was 19.5% 17.1% diabetics have symptomatic UTI while 20.9% diabetic have asymptomatic UTI.

Uropathogens in DM anti-microbial resistance patterns

Generally, urine is considered sterile and germ-free. Different studies found that most uropathogens responsible for UTIs colonise the colon and perianal region. Faecal pathogens that ascend with the opening of urethra, stick to the wall of urethra, multiply and move up towards the bladder and causing signs and symptoms. Mostly uropathogens comes via ascending rout via urethra and reside towards the bladder [31]. A variety of gram-positive bacteria, gram-negative bacteria and fungi may cause UTIs. According to Pargavi et al. *Escherichia coli* (*E. coli*) (56%), *Klebsiella pneumonia* (35%) and *Proteus mirabilis* (85%) are the most common uropathogens found in diabetic patients [21]. A study from July 2006 to June 2009 in Sabah General Hospital revealed that the incidence of UTI in patients with the peak occurring in patients aged 60 years and above. Infection was more common in females and in ethnic Kadazan's. *E. coli* (38.2%), *Klebsiella* (15.0%), *Pseudomonas* (9.5%), *Candidaalbicans* (7.3%), *Enterobacter, Proteus mirabilis*, *Staphylococcus aureus* were also more commonly isolated [46]. *E. coli* was isolated from 77% (90 cases), *Klebsiella spp*. 8.5% (10 cases), *Proteus spp*. 3.4% (4 cases), *Staphylococcus epidermidis* 3.4% (4 cases), *Staphylococcus saprophyticus* 3.4% (4 cases), *Streptococcus spp*. 2.5% (3 cases), *Enterococcus spp* 1.7% (2 cases), and *Citrobacter spp*. 0.85% (1 case) [36]. A retrospective study done by Dash et al. found that

Gram-negative aerobic rods are causative agent in 78.2% (*E coli* most common i.e. 68.8%) cases while Gram-positive *cocci* and *Candida species* are responsible for 20.8% and 1% respectively. *E. coli* is 94.7%. [37]. Most common bacteria isolated from urine sample were E coli 57.90% (most common), *Staphylococcus aureus* 21.05%, *Klebsiella species* 15.79%, *Enterococcus species*, 2.63% and *Pseudomonas species* 2.63% [20]. *E.coli* found in 75.8% patients was the most common uropathogen, *P.aeruginosa* in 72.5%, *Proteus* in 69.8%, *S.aureus* in 67.8% patients [44]. *E. coli* was the highest uropathogen followed by *Streptococcus sp.*, *Acinetobacter* and *Klebsiella* pneumonia. On the other hand Meropenem showed no resistance to *E coli,* Amikacin exhibit 3% resistance while amoxicillin (94%) and ciprofloxacin (79%) showed the highest resistance [38].

Chaudhary et al. revealed that *E. coli* contribute 55% of cases of UTI in diabetic patients. Imipenem was 95% effective for Gram-negative organism while Vancomycin is 100% effective for gram-positive *cocci* [32].

Table 3 summarises some available literature reviews on journal articles related to uropathogens involved in UTI and anti-microbial resistance pattern of different uropathogens among diabetic patients. *E coli* is the most common uropathogens among all diabetic patients followed by *Klebsiella pneumoniae, Staphylococcus aureus, Enterococcus* species, *Pseudomonas* species *Candida* species and others. Most of the uropathogens

Table 3 Uropathogens involved in UTI and anti-microbial resistance patterns.

Author	Study Design/ Setting/Duration of Study (t)	Diagnostic tool	Conclusion
Keah et al. [36]	Retrospective cross sectional n= 225 t=1 yr.	Urine culture and sensitivity	*E. coli*=77% *Klebsiella spp.*=8.5% *Proteus spp.*=3.4% *Staphylococcus epidermidis*=3.4% *Staphylococcus saprophyticus*=3.4% *Streptococcus spp.*=2.5%, *Enterococcus spp*=1.7% *Citrobacter spp.*=0.85% Resistance: Following is the resistance profile of different antibiotics; Ampicillin 63% Amoxycillin-clavulanate 3.7% Cefuroxime 1% Cephalexin 3.8% Sulphamethoxazole-Trimethoprim 40.1% Norfloxacin 8.6% Fosfomycin 1% and Pipemidic Acid 14.3%.
Dash et al. [37]	Retrospective study n=1670 t=2.5yrs	Urine culture and sensitivity	Gram-negative aerobic rods are responsible for 78.2% (*E coli* 68.8%) cases. While Gram-positive cocci responsible for 20.8% and *Candida* spp. 1% cases of UTI among diabetics. *E.coli* is 94.7% resistant to ampicillin, 63.7% to Augmentin, 51.9% to Co-trimoxazole, 9.8% to Nitrofurantoin, 66.7% to Cefaclor, 58.2% to Cefpodoxime, 53.4% to Ciprofloxacin, 47.1% to Ofloxacin, 15.9% to Gentamicin and 5.8% to Amikacin.
Yadav et al. [20]	Prospective Study n=100 t=10months	Urine culture and sensitivity	Most common bacteria isolated from urine sample were *Escherichia coli* 57.90% (most common) *Staphylococcus aureus* 21.05%, *Klebsiella species* 15.79%, *Enterococcus* species, 2.63% and *Pseudomonas* species 2.63%. Gram-positive bacteria were more sensitive to Gentamycin, Vancomycin, Linezolid, Teichoplanin, Cotrimoxazole, Ampicilin while Gram negative bacteria showed more sensitivity to Polymyxin B, Nitrofurantoin, Carbapenems, Cefazolin and Gentamycin.
Ijaz et al. [44]	Descriptive, cross-sectional study n=292 t= 6months	Urine culture and sensitivity	*E.coli found* in 75.8% patients was the most common uropathogen, *P.aeruginosa* in 72.5%, Proteus in 69.8%, *S.aureus* in 67.8% patients. Most of above uropathogens are resistant to Augmentin while Gentamicin shown maximum sensitivity.
Chaudhary et al. [32]	Prospective study n=125 t=6months	Urine culture and sensitivity	UTIs are frequent in patients with diabetes most frequent uropathogen was *E. coli* (51%) Imipenem 95% effective for Gram negative organism while Vancomycin is 100% effective for gram-positive cocci.
Pargavi et al. [21]	Prospective Study n=200 t=Not available	Urine culture and sensitivity	Among all uropathogens *E. coli* were most common following *Klebsiella pneumoniae* and *Proteus mirabilis*. Antibiotic susceptibility tests revealed that Ofloxacin, Nalidixic acid and Ciprofloxacin were most effective against above mentioned uropathogens while Ampicillin, Gentamicin and Carbenicillin were poorly effective against above mentioned pathogens.
Shill et al. [38]	Retrospective study n=78 t=6months	Urine culture and sensitivity	*E. coli* was the highest uropathogen followed by *Streptococcus* sp., *Acinetobacter* and *Klebsiella pneumonia*. Resistance pattern observed among studied subjects are Amoxicillin: 78% Ciprofloxacin: 72.8% Cephradine 60.4% Cefixime 51.2% Ceftriaxone 50.9 Nitrofurantoin 50.9% Cefepime 45.4% Gentamicin 44.9% Amikacin 23.6% Meropenem 9% So meropenem shown least resistance while Amoxicillin shown highest resistance
Hamdan et al. [35]	Cross sectional study n=200 t=6months	Urine culture and sensitivity	*E. coli* was the most frequent isolate followed by *K. pneumonia*. Multi-drug resistance was observed in 28.2% of the total isolates. 97% of the Gram-negative bacteria were sensitive to cephalexin, while all Gram-negative organisms showed 100% sensitivity to gentamicin.

Table 4 Prescribing patterns of antibiotics for UTI among diabetic patients.

Author	Study Design/ Setting/Duration of Study (t)	Outcome Scales	Conclusion
Ramanath et al. [39]	Prospective cross sectional study n=136 t=9 months	Prescription analysis	Prescribing trends for in-patients was Ceftriaxone 68% (most common) Cefotaxime 12.2% and Ciprofloxacin 7.3% While for out-patients Ciprofloxacin 28.4%, Norfloxacin 22.1% and Nitrofurantoin 18.9% prescribed.
Naik et al. [40]	Retrospective observational study t=6months n=47	Prescription analysis among pregnant	For UTI most commonly prescribed antibiotic was Ceftriaxone followed by Cefotaxime. All of the studied pregnant women were also treated with Cefotaxime and Ceftriaxone
Gorter et al. [41]	Retrospective study (n=7063)	Prescription analysis	Prescribing pattern of antibiotic was significantly different between diabetic patients and non-diabetics.
Teng et al. [42]	Retrospective study n=105 t=3months	Prescription analysis	In prescribing trend of antibiotic for UTI there is no significant difference between public and private clinics in Malaysia.
Chneeberger et al. [43]	Retrospective study n=10,366 t=7years	Dutch registration database	96.1% antimicrobial prescribed for patients with UTI by GPs. Norfloxacin for uncomplicated UTI was not according to National Dutch guidelines.

are resistant to Amoxicillin, Ampicillin and Co-trimoxazole while majority of them are susceptible to Ciprofloxacin, Nitrofurantoin, Gentamicin, Amikacin and Imipenem.

Prescribing patterns of antibiotics for UTI among diabetic patients

Gorter et al. compared antibiotic prescribing pattern of antibiotics for UTI among diabetic patients and non-diabetics and found that prescribing pattern of antibiotic was significantly different between diabetic patients and non-diabetics [41]. Teng et al. found that prescribing rate of antibiotics for UTI was 57.1%, with no significant difference between public and private clinics in Malaysia. Penicillin 40%, Cotrimoxazole 38.5%, Cephalosporins 13.3%, Macrolides 3.3%, Quinolones 1.7% and Tetracyclines 3.3% prescribed for patients with UTIs [42]. Upon prescription analysis it's found that treatment for uncomplicated UTI in diabetic patients with Norfloxacin is not according to national Dutch guidelines [43] as shown in **Table 4.**

Above table summarise some available literature reviews on journal article related to the UTI in DM and prescribing pattern.

Conclusion

DM is a chronic disorder and causing a number of abnormalities and metabolic disorders in DM patient. Different studies concluded that DM is responsible for an increased number of infections and UTIs are also included among those infections. UTIs are more frequent and are likely to have a more complicated course in DM patients. Overall, the prevalence of UTI among DM patients is high. Different studies confirmed that uncontrolled DM is significantly associated with more UTI. Furthermore, the prevalence among females was higher than males. Cystitis is the most prevalent UTI type. Most common uropathogen identified from the urine of DM patients is *E. coli* followed by *Klebsiella pneumoniae.* Resistance pattern of antibiotics is highly variable but most of the bacteria showed resistance against ampicillin, TMP/SMX and cefotaxime. Prescribing patterns showed that cephalosporins were the most commonly prescribed antibiotics followed by penicillin.

Registration of study

The study was registered with the Malaysian National Medical Research Register (NMRR). NMRR ID: NMRR-17-901-35420.

Ethical approval of the study

This article does not contain any studies with human or animal subjects performed by any of the authors. All the aspects and protocols of this study have been reviewed by CRC and MREC. With the permission and approval from committee, the study was started.

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