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Original Article

Association of serum triglycerides with urinary tract infections in type 2 diabetes mellitus patients

Jianmin Ren[1], Faming Zhao[1], Xiang Li[2], Jinbo Liu[1]

[1]*Department of Endocrinology, Qilu Hospital of Shandong University, Jinan, Shandong, P.R. China;* [2]*Department of Endocrinology, Boshan District Hospital, Zibo, Shandong, P.R. China*

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Abstract: Urinary tract infections (UTI) frequently occur in type 2 diabetes mellitus (T2DM) patients but associated risk factors have remained unclear. The purpose of this study was to investigate clinical characteristics of UTI and determine variables related to UTI patients of T2DM. This was an exploratory retrospective study. Hospitalized T2DM patients with (n=133) and without UTI (n=248) were enrolled in the present study. Medical records were obtained by clinical history and physical examinations. Clean-catch midstream urine specimens for urinary dipstick testing, sediment, and culture were collected. Pathogen distribution and antibiotic susceptibility characteristics were analyzed. Binary logistic analysis was performed to identify the relationship between UTI and variables of interest in Chinese patients with T2DM. There were a total of 133 T2DM patients with UTI, including 118 females, accounting for 88.73%. The most frequent UTI pathogens were *E. coli* (59.39%), followed by *E. faecalis* (6.77%) and *C. albicans* (6.01%). Antibiotic susceptibility testing for *E. coli* demonstrated that imipenem (100%) was the most effective agent, followed by amikacin (92.40%) and meropenem (89.87%). Many *E. coli* strains (50% or more) were resistant to ampicillin (84.81%), followed by levofloxacin (68.35%) and ciprofloxacin (56.96%). T2DM patients with UTI had longer hospital stays and higher serum triglyceride levels than T2DM patients without UTI ($p<0.05$). Binary logistic analysis revealed that UTI was associated with increased serum triglyceride levels in T2DM patients. This study's results reveal that UTI is most commonly encountered in female diabetic patients. These results also suggest, for the first time, that UTI is correlated with increased serum triglyceride levels in Chinese patients with T2DM.

Keywords: Type 2 diabetes mellitus, urinary tract infections, retrospective study, risk factors

Introduction

Prevalence of diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), has increased dramatically, worldwide, in recent decades. Following the trend of urbanization and lifestyle changes, the prevalence of diabetes is also high in China. In 2010, the Chinese Center for Disease Control and Prevention and Endocrinology Branch of the Chinese Medical Association investigated prevalence of diabetes in the adult Chinese population (≥ 18 years). According to American Diabetes Association (ADA) 2010 diabetes criteria, overall prevalence of diabetes and prediabetes was estimated to be 11.6% and 50.1% in the Chinese adult population, respectively [1]. These findings suggest that diabetes is an important public health problem in China. T2DM patients are at an increased risk of infections, with urinary tract infections the most frequent infection [2-4]. The spectrum of urinary tract infections (UTI) in diabetes patients ranges from asymptomatic bacteriuria (ASB) to cystitis, pyelonephritis, and severe urosepsis. Severe complications include renal papillary necrosis, perinephric abscess, and septicemia. All UTI types are more frequent in T2DM patients [5, 6]. However, UTI risk factors in diabetes patients are unclear, with various studies demonstrating differing results. The aim of this present study was to investigate clinical characteristics of UTI and to identify variables associated with UTI in Chinese patients with T2DM.

Patients and methods

Patients

In total, 133 hospitalized T2DM patients with UTI were enrolled, in the Department of En-

Table 1. Clinical characteristics of T2DM patients

	T2DM with UTI (n=133)	T2DM without UTI (n=248)	*P*-values
Age (years)	66.32±11.23	64.71±12.36	>0.05
Diabetes duration (years)	11.09±8.34	10.06±8.10	>0.05
Male/Female	15/118	41/207	>0.05
BMI (kg/m^2)	24.27±3.58	25.15±4.41	>0.05

T2DM: type 2 diabetes mellitus; UTI: urinary tract infection; BMI: body mass index.

Table 2. UTI pathogens in diabetic patients

	Number	Constituent Ratio
Gram negative bacteria	96	72.18%
E. coli	79	59.39%
K. pneumoniae	8	6.02%
P. mirabikis	3	2.26%
C. koseri	1	0.75%
P. vulgaris	1	0.75%
E. cloacae	1	0.75%
C. freundii	1	0.75%
S. liquefaciens	1	0.75%
S. marcescens	1	0.75%
Gram positive bacteria	22	16.54%
E. faecalis	9	6.77%
E. faecium	5	3.76%
Gram-positive corynebacterium	2	1.50%
S. saprophyticus	2	1.50%
S. aureus	2	1.50%
S. agalactiae	1	0.75%
E. gallinarum	1	0.75%
Fungus	15	11.28%
C. albicans	8	6.01%
C. tropicalis	4	3.01%
C. glabrata	3	2.26%

docrinology of Qilu Hospital Shandong University, from January 2010 to September 2014. Concurrently, 248 hospitalized T2DM patients, without UTI, were enrolled with matching ages and genders. According to World Health Organization (WHO) 1999 criteria, diabetes is defined by the following: (1) Presence of classic hyperglycemia symptoms (polyuria, polydipsia, polyphagia, and unexplained weight loss) and an abnormal blood tests with fasting plasma glucose (FPG) concentration ≥ 7 mmol/L (or 126 mg/dL) or ≥ 11.1 mmol/L (or 200 mg/dL) 2 hours after a 75 g glucose drink or a casual plasma glucose value ≥ 11.1 mmol/L (or 200 mg/dL); and (2) In patients without classic symptoms, diagnosis could also be made by two abnormal blood tests on separate days. Fasting was defined as no caloric intake for at least 8 hours. Casual was defined as any time of the day, not accounting for the last meal. UTI was defined as presence of classic genitourinary signs or symptoms (dysuria, urgency, frequency, fever, suprapubic tenderness, and costovertebral angle pain). Laboratory tests confirmed the diagnosis (at least 10^5 colony forming units/mL in a culture of clean-voided midstream urine and pyuria ≥ 10 white blood cells/high-powered field). ASB was defined by finding at least 10^5 colony forming units/mL of the same uropathogen in two consecutive clean-voided midstream urine specimens in the absence of signs or symptoms above. Exclusion criteria included recent hospitalization or urinary system surgery (within the past 6 months), known urinary tract abnormalities (polycystic kidneys and ureter malformations), known urinary tract obstruction, use of immunosuppressive medications or glucocorticoids, catheter use over the past 2 months, use of antimicrobial drugs in the past 14 days, and ages less than 18 years.

Methods

Medical records were obtained by clinical history and physical examinations. Body weight, in light clothing, and height, without shoes, were measured. BMI was also calculated. Urine and blood samples were collected after an overnight fast of at least 12 hours. In total, 30-40 mL clean-voided midstream urine from each patient was collected in the morning and samples were immediately sent to the clinical laboratory for analysis. Identification of pathogens and antibiotic susceptibility was assessed using the Biomerieux system (Vitek 2 compact, Biomerieux, France). Number of bacteria in the urine was estimated by streaking with a calibrated loop. Hemoglobin A1c (HbA1c) was assessed by high-pressure liquid chromatography (G8, Tosoh, Japan). Fasting C-peptide and insulin levels were assessed by chemiluminescence (Avdia Centaur CP, Siemens, Germany). Blood glucose and lipid levels were measured with an automatic biochemistry analyzer (c8000, Roche, Germany). Urinalysis was per-

Table 3. Frequent pathogen sensitivity for seven antibiotics

	E. coli	*K. pneumoniae*	*E. faecalis*	*E. faecium*
Imipenem	100%	87.5%	-	-
Amikacin	92.41%	100%	-	-
Meropenem	89.87%	87.5%	-	-
Penicillin G	-	-	100%	0%
Vancomycin	-	-	100%	100%
Linezolid	-	-	88.89%	100%
Nitrofurantoin	62.03%	77.5%	77.78%	40%

"-" indicates that this test was not performed.

formed with a urine analyzer (XL, Cobio, Germany).

Statistical analysis

Analyses were performed using SPSS (Statistical Package for the Social Sciences) 19.0 (SPSS, IL, USA) statistical package. All variables were tested for normal distribution of data. Data are presented as mean ± standard deviation or percentages. Differences between the studied groups were examined using Student's unpaired *t*-test or Mann-Whitney *U*-test for parametric and non-parametric data, respectively. Chi-square test was used for categorical data. Binary logistic analysis was performed to examine the relationship between UTI and variables. *P* values <0.05 were considered statistically significant.

Results

Clinical characteristics of T2DM patients with UTI

The total of 133 T2DM patients with UTI included 15 males (11.27%) and 118 females (88.73%). Average age and diabetes duration was 66.32±11.23 and 11.09±8.34 years, respectively. BMI was 24.27±3.58 kg/m^2. Of the 133 patients, 64 were ASB, accounting for 48.12% of diabetes patients with UTI (**Table 1**).

Pathogen distribution and antibiotic susceptibility assessment of T2DM patients with UTI

The most frequent UTI pathogens were *E. coli* (59.39%), *E. faecalis* (6.77%), and *C. albicans* (6.01%) (**Table 2**). Imipenem (100%) was the most effective agent against isolated *E. coli* strains, followed by amikacin (92.40%), meropenem (89.87%), piperacillin-tazobactam (77.22%), cefepime (75.95%), ertapenem (70.88%), cefotetan (69.62%), ceftazidime (63.29%), and nitrofurantoin (62.03%). Of the *E. coli* strains, 50% or more were resistant to ampicillin (84.81%), followed by levofloxacin (68.35%), ciprofloxacin (56.96%), cefazolin (51.90%), compound sulfamethoxazole tablets (TMP-SMX) (51.90%), and gentamicin (50.63%). Of the fungi strains, 100% were sensitive to fluconazole, voriconazole, amphotericin B, and fluorine cytosine (**Table 3**).

Variables associated with UTI in diabetes patients

Compared with T2DM patients without UTI, no differences in diabetes duration, BMI, FPG, fasting C-peptide, fasting insulin, HbA1c, TC, LDL-c, HDL-c, serum creatinine, blood urea nitrogen, and serum cystatin C levels, along with white blood cell count, neutrophil count, and neutrophil percentage were observed in diabetes patients with UTI (**Tables 1**, **4**). T2DM patients with UTI had longer hospital stays and higher serum triglyceride levels than T2DM patients without UTI ($p<0.05$). Mann-Whitney *U*-test was used to compare variables in routine urine examinations between T2DM patients with and without UTI. Results revealed that differences in urine nitrite levels were observed between the groups ($p<0.05$). Binary logistic analysis revealed that UTI was associated with serum triglyceride levels in T2DM patients (OR: 1.47, 95% CI: 1.12-1.94).

Discussion

Patients with diabetes mellitus, including type 1 and type 2, are at an increased risk of infection. Diabetic patients are more than twice as likely to be hospitalized for infection management than patients without diabetes. Skin and soft tissue infections, sepsis, pneumonia, and UTI are the most frequent infections encountered. Since 2006, UTI has been the most common infection, accounting for over 30% of all infection-related emergency department encounters in the USA [7]. T2DM patients with UTI, in the present study, were elderly and had a long duration of diabetes. Results from this study confirmed previous reporting that UTI

Table 4. Comparison of laboratory test data between groups (mean ± SD)

	T2DM with UTI (n=133)	T2DM without UTI (n=248)	*p*-values	OR	95% CI
Length of hospital stay (days)	13.29±6.75	11.08±3.97	<0.001	1.102	1.046-1.162
FPG (mmol/L)	8.88±4.16	7.99±3.58	0.171	1.049	0.980-1.122
Fasting C-peptide (ng/ml)	0.81±1.27	0.97±1.30	0.831	1.023	0.827-1.266
Fasting insulin (μIU/ml)	2.60±6.88	4.04±14.19	0.303	0.983	0.952-1.015
HbA1c (%)	5.63±4.36	5.81±4.53	0.373	0.974	0.921-1.031
Total cholesterol (mmol/L)	4.72±1.31	4.74±1.19	0.093	0.757	0.546-1.048
Triglyceride (mmol/L)	1.84±1.92	1.50±0.75	0.005	1.476	1.124-1.939
LDL-c (mmol/L)	2.58±1.12	2.57±1.21	0.092	1.342	0.953-1.889
HDL-c (mmol/L)	1.07±0.47	1.11±0.50	0.190	0.652	0.344-1.236
Serum creatinine (μmol/L)	81.89±72.75	77.59±61.96	0.349	0.996	0.987-1.005
Blood urea nitrogen (mmol/L)	6.47±5.75	5.77±4.50	0.124	1.083	0.978-1.199
Serum cystatin C (mg/L)	1.12±0.89	1.05±0.70	0.349	0.754	0.437-1.301
White blood cell count (*10^9/L)	7.30±3.30	7.56±3.99	0.644	0.938	0.713-1.233
Neutrophil count (*10^9/L)	5.10±3.10	5.28±3.72	0.915	0.983	0.725-1.334
Neutrophil percentage (%)	63.34±19.23	62.20±19.79	0.318	1.009	0.991-1.028

OR: odd ratio; HbA1c: glycated hemoglobin A1c; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; FPG: fasting plasma glucose; CI: confidence interval; SD: standard deviation.

was more common in female than male diabetic patients (88.73% vs. 11.27%). In women, several risk factors, including sexual intercourse, short urethra, and higher UTI recurrence, were associated with increased incidence of UTI [8, 9].

ASB is defined as the isolation of a specified quantitative bacterial count in an appropriately collected urine specimen from an individual without symptoms or signs of urinary tract infection. This present study demonstrated that ASB was usually encountered in T2DM patients with UTI. Meta-analysis revealed that prevalence of ASB was 12.2% among diabetes patients and was higher in patients with longer diabetes durations [10]. These results indicate that clinicians should pay more attention to routine urine examinations.

In this study, the most common pathogen in T2DM patients with UTI was *E. coli* (59.39%). Antibiotic susceptibility characteristics demonstrated that more than 50% of *E. coli* was resistant to ampicillin (84.81%), levofloxacin (68.35%), and ciprofloxacin (56.96%). These drugs are the most commonly used in clinical treatment for UTI. Therefore, initial empirical therapy and streamlining should be adjusted once microbiological results become available. Although imipenem (100%), amikacin (92.40%), and meropenem (89.87%) have demonstrated high antibiotic susceptibility, high costs and adverse drug reactions have limited their use clinically.

A novel finding of the present study was that fungal infections were the second most common pathogens (11.28%), following only *E. coli*. All fungal infection agents were candida species. Candida UTIs have usually occurred in hospitalized patients with indwelling bladder catheters [11]. T2DM is also a risk factor for fungal UTI [12]. This study's findings demonstrate that these candida species are highly sensitive to fluconazole, voriconazole, amphotericin B, and fluorine cytosine.

Many studies have assessed UTI risk factors in diabetes patients, with inconsistent results. Poor glycemic control and longer diabetes duration have been reported to increase UTI risk [13], but compared with T2DM patients without UTI, no differences were observed in FBG, HbA1c, and diabetes duration in T2DM patients with UTI in the present study. Thus, this study suggests that poor glycemic control and diabetes duration may not be associated with UTI in diabetic patients. Age and gender-matched T2DM patients, with and without UTI, were enrolled in the present study. Findings demonstrated that serum triglyceride levels were

associated with UTI in T2DM patients. Triglycerides were significantly associated with microvascular complications of diabetes [14]. Random clinical trials have demonstrated that fenofibrate treatment reduces diabetic retinopathy and diabetic nephropathy progression [15, 16]. Studies have also demonstrated that incomplete bladder emptying due to autonomic neuropathy contributes to UTI pathogenesis in diabetic patients. Further investigation into plausible mechanisms involved is needed.

This present study has some limitations. First, this was only a cross-sectional study. Long-term prospective studies are needed to classify the effects of antibiotic drugs on UTI pathogens in diabetics. Second, there were few patients. More T2DM patients with UTIs should be enrolled in future studies with more UTI risk factors considered.

In conclusion, the findings of the present study confirm that female diabetic patients with UTI are more common than male patients and UTI is associated with serum triglyceride levels in Chinese patients with T2DM.

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Disclosure of conflict of interest

None.

Address correspondence to: Jinbo Liu, Department of Endocrinology, Qilu Hospital of Shandong University, 107 W. Wenhua Road, Jinan, Shandong, P.R. China. Tel: +86-18560085019; E-mail: sanpiliu@163.com

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