Comparative study of emphysematous pyelonephritis and pyelonephritis in type 2 diabetes: a single-centre experience

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Abstract

Purpose Emphysematous pyelonephritis (EPN) patients with type 2 diabetes (T2D) have severe complications and high morbidity with poor prognosis as compared to Pyelonephritis. The aim was to study clinical features, microbiological profile, complications of EPN and pyelonephritis in T2D patients.

Methods This was a hospital-based prospective study done on 200 T2D patients with upper UTI. Various clinical, biochemical parameters and urine examination and culture were monitored. Patients were followed up for 6 months with respect to number of UTIs, glycemic control and renal parameters.

Results Pyelonephritis was present in 180(90%) and EPN in 20(10%) of upper UTI patients. Longer duration of diabetes, presence of nephropathy, chronic kidney disease (CKD), hypertension (HTN), history of symptomatic UTI in a prior year, renal calculi and obstruction increase the risk of EPN. Patients with EPN commonly present with vomiting, flank pain altered sensorium and renal tenderness. Complications like diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar state (HHS), multiorgan dysfunction syndrome (MODS), acute kidney injury (AKI) and hypotension occur frequently in EPN as compared to pyelonephritis in T2D patients. Patients with EPN had poor glycemia and lower estimated glomerular filtration rate (eGFR) as compared to pyelonephritis. Bacteriuria was present in 90% and 66.7% of EPN and pyelonephritis patients respectively. *E. coli* was the most common isolate in both UTI groups. A significant number of EPN patients develop recurrent UTI. Patients with EPN have an improvement in glycemia on follow up, but renal parameters do not improve on follow up, while as pyelonephritis patients have an improvement in glycemia and renal parameters with intensive treatment. Recurrent UTI in upper UTI patients leads to worsening of glycemia and renal parameters.

Conclusion Complications frequently occur in EPN patients as compared to pyelonephritis.

Keywords Urinary tract infections · Type 2 diabetes · Emphysematous pyelonephritis · Pyelonephritis

Introduction

Patients with Type 2 Diabetes (T2D) are at increased risk of infections, with the urinary tract being the second most frequent

site [1, 2] and good diabetic control has been recommended as a means of mitigating this risk. [3] Urinary tract infection (UTI) is second only to lower respiratory tract infection among patients with diabetes, as a cause of sepsis. [4]

UTI is an inflammatory response of the urothelium to bacterial invasion, which is usually free of bacteria. UTI is frequently associated with bacteriuria and pyuria. UTI commonly affects women of all ages and varies dramatically in their presentation and sequelae. UTI is a common cause of morbidity and can lead to significant in-hospital mortality. The spectrum of UTI ranges from asymptomatic bacteriuria (ASB) to lower UTI (cystitis) and upper UTI. Acute pyelonephritis is a bacterial infection of the renal parenchyma that can be organ- and/or life-threatening and often leads to renal scarring. [5] Serious complications of UTI include emphysematous pyelonephritis (EPN), renal abscesses and renal papillary necrosis, are all encountered more frequently in T2D than in the general population. [6, 7]

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S Yu, et al. found the prevalence of UTI in patients with diabetes in United States database was 8.2%. UTI was diagnosed in 12.9% females and 3.9% males. [8] Diabetes also results in three times more hospitalizations for acute pyelonephritis among women (10.86/10,000) than for men (3.32/10,000). [9]

EPN is an acute, necrotizing infection affecting renal parenchyma, collecting system as well as surrounding tissue, with a hallmark presence of gas within these structures. [10, 11] EPN is a life-threatening infection with a mortality rate as high as 80% in earlier studies. [12] However, in recent years, the mortality of EPN patients has decreased to 25% (1%–46%). [13]

Symptoms of UTI are similar in patients with and without diabetes, though some patients with diabetic neuropathy may have altered clinical signs. The most common pathogens isolated from the urine of T2D with UTI are *Escherichia coli* (*E. coli*), followed by *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., and *Enterococci*. [14] Patients with diabetes are more prone to have resistant pathogens as the cause of their UTI. A urine culture should be obtained in all cases of diabetes with suspected UTI before initiation of treatment.

Patients with T2D and UTI usually present with hypo- or hyperglycemia, or hyperglycemic hyperosmolar state (HHS), or even diabetic ketoacidosis (DKA). [15] Diabetic patients are more likely to suffer from acute kidney injury (AKI) compared with non-diabetics as a result of upper UTI. [16] An episode of acute pyelonephritis may lead to abscess formation (eg, nephric, perinephric); sepsis; or sepsis syndrome, septic shock, and multiorgan dysfunction syndrome (MODS).

Higher glucose concentrations in urine may promote the growth of pathogenic bacteria. [17, 18] Impairments in the immune system, including humoral, cellular, and innate immunity may contribute to the pathogenesis of UTI in diabetes. [19, 20] Factors that increase the risk of UTI in diabetes include age, metabolic control, diabetic nephropathy, autonomic neuropathy and vascular complications. [21]

Diagnosing and managing acute pyelonephritis is not always straightforward. Wide variation exists in the clinical presentation. Treatment of UTI in patients with T2D depends on several factors, including: presence of symptoms, severity of systemic symptoms, if infection is localized in the kidney, presence of urologic abnormalities, accompanying metabolic alterations, and renal function. [18] The management of a patient with EPN involves; fluid and electrolyte resuscitation, acid-base balance, diabetic control, and an antibiotic regimen. [22] Timely administration of appropriate antibiotics and early PCD are of paramount importance. [23]

Given the seriousness of the upper UTI in patients with diabetes, there is an urgent need to focus this issue through comprehensive research. Moreover, there is a scarcity of literature on this issue. Furthermore, the studies which are following the patients for a substantial period of time are very limited. So the present study tried to address the aforementioned gap in the literature. This study has advantages over existing studies, as patients have

been followed up for a considerable period of 6 months. Moreover in this prospective study, we have analyzed the clinical features, microbiological profile and complications of pyelonephritis and EPN in T2D patients and the influence of upper UTI on glycemic and renal parameters on follow up.

Materials and methods

This was a hospital-based prospective study of adult T2D patients with upper UTI attending the Endocrinology department of tertiary care hospital in North India. The study was approved by the Institutional ethical committee.

Study subjects

The study recruited consecutive two hundred (200) upper UTI patients admitted in the Endocrinology department and they were followed up for 6 months. This study was conducted for 3 years, from December 2015 to December 2018. Informed consent was sought from all the recruited subjects and the study was conducted in accordance with the Declaration of Helsinki. All patients were interviewed at baseline using a standardized questionnaire, which included number of UTIs within the previous year and the treatment for same and urinary tract surgery. Moreover, this questionnaire also collected information about the socio-demographic profile of the patients. A detailed physical examination of the subjects were carried, based on a study protocol. The eligibility criteria for including subject in the study were: both male and female T2D patients with upper UTI and having age > 30 years. The exclusion criteria were (i) Other type of diabetes, (ii) Immunocompromised states- HIV, malignancy, patients on steroids and transplant recipients, (iii) Lower UTI, (iv) Recent hospitalization/surgery, (v) Use of antimicrobial drugs within the previous 14 days and (vi) Recent urinary instrumentation.

Detailed study design

Clinical and biochemical parameters

Clinical parameters including duration of diabetes, complications of diabetes, drug therapy, clinical symptomatology especially urinary complaints (fever, dysuria, hematuria, increased frequency, nausea/vomiting, flank pain, altered sensorium and renal tenderness) and comorbidities [hypertension (HTN), obesity, hypothyroidism, chronic kidney disease (CKD), coronary artery disease (CAD) and others] were recorded. Patients were followed for 6 months with regard to number of UTIs (urine examination or culture documented) and any treatment received for the same. Complete blood count (CBC), renal function test (KFT), fasting (FBG) and 2 h postprandial blood glucose (PP), 24 h urinary protein estimation and Glycosylated Hemoglobin (HbA1c) were

estimated at baseline. HbA1c was measured by column chromatography (Bio-Rad, Richmond, CA). Ultrasonography (USG) of the abdomen and pelvis was done in all admitted patients. Blood culture and non-contrast computed tomography (NCCT) abdomen were done as per requirement.

Upper UTI patients were divided into pyelonephritis and EPN. Acute pyelonephritis was said to be present when the patient complained of fever ($>38.3^{\circ}\text{C}$) with chills and rigors, flank pain, nausea, and vomiting and USG was suggestive of combination of enlarged kidney, presence of collection and/or perinephric stranding. The diagnosis of EPN was based on the clinical features and documentation of gas within the renal parenchyma, collecting system, or perinephric tissue on NCCT abdomen. The severity of EPN was graded as per the Huang classification. According to this classification, class 1 EPN is defined as gas in the collecting system only, class 2 as gas in the renal parenchyma with no extension to the extrarenal space, class 3A as extension of gas or abscess to the perinephric space, class 3B as extension of gas or abscess to the pararenal space and class 4 as bilateral EPN or EPN in a solitary kidney.

Urine examination and culture sensitivity

Voided, clean-catch and midstream urine samples were collected from patients in a sterile wide-mouth container for routine urine analysis and culture sensitivity at baseline and at 6 months. The study participants were educated on how to collect a “clean-catch” midstream urine specimen and the importance to avoid contamination. Samples were inoculated on Hichrome UTI agar media using a calibrated loop to determine colony-forming unit (CFU). The plates were incubated at 37°C aerobically for 24 h. The organisms were identified using standard cultural, morphological and biochemical techniques. [24] Antimicrobial sensitivity testing was carried out on Mueller Hinton Agar (MHA) plates with commercially available discs by the Kirby-Bauer disc diffusion method and interpreted according to Clinical and Laboratory Standards Institute (CLSI) criteria. [25]

Definitions

Pyuria (defined as ≥ 10 leukocytes/ mm^3) and hematuria (defined as ≥ 3 RBC/HPF) were detected by microscopic examination. For the diagnosis of Bacteriuria in women, a midstream urine count $\geq 10^5$ CFU/ml was considered diagnostic. [26] While for the diagnosis of Bacteriuria in men, a midstream urine colony count of $\geq 10^4$ CFU/ml was indicative. When the growth of 3 or more different microorganisms was seen, the urine specimen was considered to be contaminated. Obesity was defined as BMI ≥ 25 kg/m^2 , uncontrolled hypertension was defined as systolic blood pressure (SBP) of ≥ 140 or diastolic blood pressure (DBP) of ≥ 90 mmHg, optimal diabetes control when HbA1c $< 7\%$ and uncontrolled when

HbA1c $\geq 7\%$, proteinuria was defined as 24 h urinary protein ≥ 150 mg, glycosuria was defined as the presence of glucose in urine, leucocytosis as total leucocyte count (TLC) more than upper normal limit for the laboratory ($4\text{--}10 \times 10^3/\mu\text{L}$), AKI when creatinine increased by 0.3 mg/dl from baseline. DKA and HHS defined as per American diabetes association (ADA) guidelines. Severe hyperglycemia when blood glucose > 300 mg/dl. Cystopathy when the post-void residual urine was > 150 ml, and in presence of decreased bladder sensation. Shock and MODS were defined as per Infectious disease society of America (IDSA) guidelines. Estimated glomerular filtration rate (eGFR) was calculated by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration).

Management protocol

As per the protocol, the treatment included early vigorous fluid resuscitation, rapid control of glycemia, electrolyte management, initiation of empiric antibiotics, close clinical and biochemical monitoring and percutaneous drainage (PCD) (if required). Treatment with empiric antibiotics, using broad-spectrum antibiotics was initiated and patients who had septic shock received vancomycin to cover for Methicillin-resistant *Staphylococcus aureus* (MRSA). Treatment was tailored when culture results were available. The recommended duration of antibiotic treatment for UTI in diabetes was followed. Nephrectomy was carried out in patients refractory to antibiotics and PCD and/or clinical deterioration.

Follow up

Upper UTI patients were followed up for 6 months with respect to number of UTIs (urine examination or culture documented), any antibiotic treatment received for the same and hospitalizations. At the end of follow up these patients again underwent urine examination, urine culture sensitivity, FBG, PP, CBC, KFT, and HbA1c.

Statistical analysis

Quantitative variables were expressed as means $\pm$ SD while qualitative variables were expressed in terms of proportion. Descriptive and univariate analytic techniques were used to analyze the data. Categorical variables were compared employing Chi-square test and Fischer exact tests whereas continuous variables were compared by using Student's *t* test for independent observations. For paired or matched observations McNemar's test and paired Student's *t* test were used for categorical and continuous variables respectively. To study the joint effects and interactions of various independent variables, binary logistic regression analysis was carried out to calculate multivariate *P* value. *P* values < 0.05 were considered statistically significant. All the analyses were performed by the statistical software SPSS

Version 21 (IBM SPSS statistics for windows, version 21 Armonk NY: IBM Corp).

Results

Table 1 demonstrates the baseline characteristics of T2D patients with EPN and pyelonephritis. Out of a total 200 patients, only 20(10%) had EPN while 180(90%) had pyelonephritis. CT class 1 and 2 were present in 60% of EPN patients. Left side (55%) was slightly predominantly involved and bilateral disease was present in 10% of EPN cases. The mean age was 57.70 ± 7.69 years in EPN compared to 55.13 ± 9.64 years in pyelonephritis. Female gender, postmenopausal state and marital status were comparable between EPN and pyelonephritis patients. The mean duration of diabetes was higher in patients with EPN compared to pyelonephritis, 13.50 ± 4.12 and 10.45 ± 6.25 years respectively ($P = 0.035$). With respect to diabetic microvascular complications; nephropathy was significantly higher in patients with EPN compared to pyelonephritis ($P = 0.015$). With regard to comorbidities (like HTN, hypothyroidism, CKD, CAD and

dyslipidemia); HTN and CKD were frequently associated with EPN ($P < 0.05$). The presence of previous UTI did significantly influence the development of EPN as compared to pyelonephritis.

Table 2 shows the clinical characteristics of T2D patients with EPN and pyelonephritis. Based on symptomatology, EPN patients frequently had nausea/vomiting, flank pain, altered sensorium and renal tenderness ($P < 0.05$). Complications like AKI was frequently present in patients with EPN compared to pyelonephritis ($P < 0.001$). DKA and HHS also occurred frequently in EPN patients compared to pyelonephritis ($P < 0.05$). MODS, hypotension and renal obstruction also occurred frequently in patients with EPN.

Table 3 shows laboratory parameters of T2D patients with EPN and pyelonephritis. Patients with EPN had significantly higher mean fasting blood glucose (FBG) than pyelonephritis ($P = 0.034$). HbA1c was also considerably higher in patients with EPN than pyelonephritis ($P = 0.019$). Mean HbA1c was $12.06 \pm 2.23\%$ in EPN and $10.87 \pm 2.12\%$ in pyelonephritis patients. Renal parameters (serum creatinine and eGFR) and proteinuria were significantly associated with EPN ($P < 0.05$), with

Table 1 Baseline characteristics of T2D patients with EPN and pyelonephritis

ntd	EPN	Pyelonephritis	<i>P</i> value*	OR (95% CI)
Number of patients	20(10%)	180(90%)		
Age in yrs.	57.70 ± 7.69	55.13 ± 9.64	0.253	
Female Gender	18(90%)	142(78.9%)	0.239	
Post Menopausal	14(77.8%)	106(74.6%)	0.773	
Marital status	14(70%)	107(59.4%)	0.360	
Diabetes duration in years	13.50 ± 4.12	10.45 ± 6.25	0.035	
Diabetic Complication				
Retinopathy	11(55%)	72(40%)	0.196	2.75(1.20–6.27)
Nephropathy	8(40%)	31(17.2%)	0.015	
Neuropathy	11(55%)	82(45.6%)	0.422	
Treatment				
SGLT2I	2(10%)	8(4.4%)	0.275	
Comorbidity				
HTN	19(95%)	134(74.4%)	0.040	5.83(0.80–42.44)
Hypothyroidism	3(15%)	34(18.9%)	0.671	
CKD	6(30%)	20(11.1%)	0.017	2.26(1.21–6.79)
CAD	1(5%)	9(5%)	1.000	
History of symptomatic UTI in year prior to study entry	10(50%)	51(28.3%)	0.046	2.27(1.00–5.19)
Exam				
BMI	26.35 ± 5.89	26.11 ± 4.59	0.830	
Obesity (BMI ≥ 25 kg/m ²)	14(70%)	106(58.9%)	0.366	

SGLT2I Sodium-glucose co-transporter 2 inhibitors, *HTN* Hypertension, *CKD* Chronic kidney disease, *CAD* Coronary artery disease, *BP* Blood pressure, *BMI* Body mass index

Categorical variables [n (%)] and *Continuous variables* [mean $\pm$ SD]

* *P* value < 0.05 is considered statistically significant

Table 2 Clinical characteristics of T2D patients with EPN and pyelonephritis

Parameter	Total	EPN	Pyelonephritis	P value*	OR (95% CI)
Fever(>38.3 °C)	156(78%)	19(95%)	137(76.1%)	0.053	
Dysuria	154(77%)	13(65%)	141(78.3%)	0.179	
Frequency	114(57%)	5(25%)	109(60.6%)	0.002	0.25(0.09–0.66)
Nausea/ Vomiting	55(27.5%)	10(50%)	45(25%)	0.018	2.63(1.16–5.98)
Flank pain	64(32%)	17(85%)	47(21.6%)	0.000	12.04(3.66–39.61)
Altered sensorium	30(15%)	9(45%)	21(11.7%)	0.000	4.63(2.10–10.22)
Hematuria	5(2.5%)	1(5%)	4(2.2%)	0.450	
Renal tenderness	38(19%)	14(70%)	24(13.3%)	0.000	9.94(4.09–24.19)
Complications					
AKI	49(24.5%)	15(75%)	34(18.9%)	0.000	9.24(3.54–24.13)
Severe hyperglycemia	106(53%)	14(70%)	92(51.1%)	0.108	
HHS	21(10.5%)	5(25%)	16(8.9%)	0.026	2.84(1.14–7.02)
DKA	16(8%)	4(20%)	12(6.7%)	0.037	2.87(1.09–7.57)
MODS	16(8%)	4(20%)	12(6.7%)	0.037	2.87(1.09–7.57)
Hypotension	22(11%)	5(25%)	17(9.4%)	0.035	2.69(1.08–6.70)
Obstruction	17(8.5%)	5(25%)	12(6.7%)	0.005	3.58(1.48–8.66)

EPN Emphysematous pyelonephritis, AKI Acute kidney injury, HHS Hyperglycemic hyperosmolar state, DKA Diabetic ketoacidosis, MODS Multiorgan dysfunction syndrome

Categorical variables [n (%)]

* P value < 0.05 is considered statistically significant

eGFR of 35.93 ± 17.59 and 50.11 ± 28.27 ml/min/1.73m² in patients with EPN and pyelonephritis respectively. Proteinuria was present in 70% of EPN patients and 39.4% of pyelonephritis patients ($P = 0.009$). On the basis of urine examination, glycosuria correlated significantly with EPN ($P < 0.05$). Urine culture was positive in 18(90%) of EPN and 120(66.7%) of pyelonephritis patients.

E. coli was most common isolated organism, present in 85% of EPN patients and 52.2% of pyelonephritis patients. *E. coli* in pyelonephritis was followed by *Enterococcus faecalis* in 6.1%, *Candida* spps (3.3%), *Klebsiella pneumonia* (2.6%), *Staphylococcus aureus* (1.7%), and *Enterococcus faecalis/E. coli* (0.6%). On the basis of USG finding (renal cyst, renal calculi and cystopathy) only renal calculi correlated with EPN ($P = 0.013$).

Out of 200 T2D patients with upper UTI, only 173 had complete follow up at 6 months. Table 4 shows various baseline and follow up parameters of T2D patients with upper UTI. Patients had lower mean FBG and blood glucose PP at follow up than baseline ($P < 0.001$), also HbA1c improved at follow up from $10.90 \pm 2.13\%$ to $10.38 \pm 2.02\%$ ($P = 0.004$) with intensive treatment. Renal parameters revealed that serum creatinine did not significantly improve at follow up, from 1.72 ± 1.13 mg/dl to 1.66 ± 1.25 mg/dl, while eGFR improved insignificantly ($P = 0.629$).

Out of 20 EPN patients, 19 and out of 180 pyelonephritis patients, 154 followed till 6 months, as shown in Table 5. Almost 50% of the EPN patients developed UTI during the

follow up duration and majority of them were having multiple episodes. Out of 19 EPN patients, 1 patient developed one episode, 4 patients two episodes, 3 patients three episodes and 1 patient four episodes. Out of 154 EPN patients, 53 developed UTI on follow up, 30 patients developed one episode, 20 patients two episodes and 3 patients three episodes. Overall prevalence of recurrent UTI was 35.8%, with 47.4% in EPN and 34.2% in pyelonephritis patients.

Table 6 shows the follow up of T2D EPN patients. Patients with EPN had significantly higher mean of FBG, PP and HbA1c at follow up than at baseline ($P < 0.05$) while renal parameters did not improve at follow up despite intensive treatment.

In pyelonephritis patients, glycemia and renal parameters improved on follow up with intensive treatment, as shown in Table 7.

Comparison of recurrent and non-recurrent UTI at baseline and follow up is shown in Table 8. Recurrent UTI (62 patients) had significantly higher HbA1c at follow up ($12.27 \pm 1.61\%$) than at baseline ($11.29 \pm 2.31\%$) ($P = 0.007$). Renal parameters significantly worsened at follow up, with eGFR worsening from 47.56 ± 21.10 to 41.33 ± 12.48 ml/min/1.73m² ($P = 0.048$). In non-recurrent UTI (111 patients), mean FBG, PP and HbA1c reduced at follow up from baseline ($P < 0.001$) with intensive treatment, HbA1c changed from $10.46 \pm 1.89\%$ to $9.32 \pm 1.74\%$ at follow up. Serum creatinine and eGFR did not improve significantly ($P > 0.05$) at follow up, with eGFR of 52.60 ± 20.54 and 54.17 ± 29.22 ml/min/1.73m² at baseline and follow up respectively.

Table 3 Laboratory parameters of T2D patients with EPN and pyelonephritis

Parameter	EPN	Pyelonephritis	<i>P</i> value*	OR (95% CI)
FBG in mg/dl	294.15 ± 94.84	247.00 ± 93.48	0.034	
Blood glucose PP	345.50 ± 77.10	307.00 ± 117.21	0.153	
HbA1c in %	12.06 ± 2.23	10.87 ± 2.12	0.019	
Uncontrolled diabetes (HbA1c ≥ 7%)	20(100%)	178(98.9%)	0.636	
Creatinine in mg/dl	2.24 ± 1.68	1.69 ± 1.01	0.034	
eGFR ml/min/1.73m ²	35.93 ± 17.59	50.11 ± 28.27	0.029	
Proteinuria	14(70%)	71(39.4%)	0.009	3.15(1.26–7.87)
Leucocytosis	12(60%)	74(41.1%)	0.106	
Urine examination				
Pyuria	19(95%)	168(93.3%)	0.774	
Hematuria	6(30%)	42(23.3%)	0.508	
Glycosuria	17(95%)	131(72.8%)	0.000	9.09(3.80–21.74)
Urine culture				
Positive urine culture	18(90%)	120(66.7%)	0.032	4.04(0.96–16.89)
Organism				
<i>E. coli</i>	17(85%)	94(52.2%)		
<i>Enterococcus faecalis</i>	1(5%)	11(6.1%)		
<i>Klebsiella pneumoniae</i>	–	4(2.6%)		
<i>Staphylococcus aureus</i>	–	3(1.7%)		
<i>Enterococcus faecalis/ E. coli</i>	–	1(0.6%)		
<i>Candida spp</i>	–	6(3.3%)		
Yeast	–	1(0.6%)		
<i>E. coli</i> vs Others	17(94.4%)	94(78.3%)	0.108	
USG				
Renal cyst	3(15%)	12(6.7%)	0.179	
Renal calculi	5(25%)	14(7.8%)	0.013	3.17(1.29–7.77)
Cystopathy	5(25%)	19(10.6%)	0.059	

FBG Fasting blood glucose, PP Post prandial, HbA1c Glycosylated hemoglobin, eGFR Estimated glomerular filtration rate
Categorical variables [n (%)] and Continuous variables [mean ± SD]

* *P* value < 0.05 is considered statistically significant

Table 4 Follow up of T2D patients with upper UTI

Variables	Baseline <i>n</i> = 173	Follow up <i>n</i> = 173	<i>P</i> value*
FBG in mg/dl	246.14 ± 92.37	198.47 ± 59.64	0.000
Blood glucose PP	305.76 ± 101.61	246.51 ± 69.58	0.000
HbA1c in %	10.90 ± 2.13	10.38 ± 2.02	0.004
Creatinine in mg/dl	1.72 ± 1.13	1.66 ± 1.25	0.399
eGFR ml/min/1.73m ²	48.80 ± 22.22	50.01 ± 28.62	0.629

FBG Fasting blood glucose, PP Post prandial, HbA1c Glycosylated hemoglobin, eGFR Estimated glomerular filtration rate

Continuous variables [mean ± SD]

* *P* value < 0.05 is considered statistically significant

Table 5 Follow up of T2D patients with upper UTI

Variables	EPN	Pyelonephritis
Recurrent UTI (UTI on follow up)	9(47.4%)	53(34.2%)
Number of Episodes		
0	10(52.6%)	101(65.6%)
1	1(5.3%)	30(19.5%)
2	4(21.1%)	20(13%)
3	3(15.8%)	3(1.9%)
4	1(5.3%)	0
Total	19(100%)	154(100%)

Categorical variables [n (%)]

Table 6 Follow up of T2D patients with EPN

Variables	Baseline <i>n</i> = 19	Follow up <i>n</i> = 19	<i>P</i> value*
FBG in mg/dl	299.21 ± 98.62	208.84 ± 41.91	0.001
Blood glucose PP	351.00 ± 75.07	280.16 ± 63.56	0.011
HbA1c in %	12.17 ± 2.23	11.32 ± 1.69	0.044
Creatinine in mg/dl	2.25 ± 1.72	1.95 ± 1.71	0.113
eGFR ml/min/1.73m ²	36.45 ± 17.91	39.82 ± 13.20	0.639

FBG Fasting blood glucose, PP Post prandial, HbA1c Glycosylated hemoglobin, eGFR Estimated glomerular filtration rate

Continuous variables [mean ± SD]

* *P* value < 0.05 is considered statistically significant

Discussion

UTI is more common, severe and carries worse prognosis in patients with T2D. In comparison to non-diabetics, epidemiological studies have shown that the relative risk of UTI in diabetics increases by a factor of 1.2–2.2. [27] The mean hospitalization rate in patients with acute pyelonephritis was found to be 3.4–24 times in diabetes as compared to general population. [9] The spectrum of causative organisms for acute pyelonephritis is similar as compared to non-diabetics. EPN is an uncommon necrotizing infection of the renal system predominantly seen in patients with diabetes, with the potential to cause high morbidity and mortality, particularly if the diagnosis and treatment are delayed. In this study, we analyzed the clinical features, microbiological profile and complications of EPN and pyelonephritis in T2D patients and influence of upper UTI on glycemic and renal parameters on follow up.

In our study, females (90%) outnumbered males (10%). Pyelonephritis was present in 90% and EPN in 10% of upper UTI patients. Longer duration of diabetes, presence of nephropathy, CKD, HTN, history of symptomatic UTI in a prior year, renal calculi and obstruction increase the risk of EPN. Complications like DKA, HHS, MODS, AKI and hypotension

frequently occur in patients with EPN, as compared to pyelonephritis.

UTI is more common in females with diabetes. [28, 29] The increased occurrence in women is presumably because of their increased susceptibility to UTI due to short urethra. One Indian study revealed pyelonephritis and EPN is common in 6th decade of life with a mean age of 57.4 ± 8.5 years and with female predominance. [30] Study by Boyko EJ, et al., [27] Chiță T, et al., [31] and Janifer J, et al., [32] revealed that diabetes of longer duration was related to substantial increases in the risks of UTI. Longer duration of diabetes leads to increased prevalence of chronic diabetic complications. The association between nephropathy and UTI has been studied in the literature especially regarding the increased albumin excretion rate, with microalbuminuria or macroalbuminuria being incriminated as risk factors for the occurrence of UTI. [28]

Urinary tract obstruction has been reported to occur in 25–40% of EPN patients, [22] while in our study renal obstruction was present in 25% of EPN and 6.7% of pyelonephritis patients. Calculi causing obstructive form a nidus of infection, causing stagnation or reflux of urine in the ureteral system and ascending infection. UTI induced AKI occurred in approximately 40% of diabetic patients in a study by Robbins SL, et al. [33]

In our study, EPN patients commonly presented with vomiting, flank pain altered sensorium and renal tenderness. Clinically EPN presents with nonspecific features of upper UTI including fever, flank pain, nausea, vomiting, altered sensorium, shock, AKI and disseminated intravascular coagulation. The study by Kumar et al. revealed more or less similar clinical symptomatology. [30] Costovertebral angle tenderness is considered the commonest physical finding. [10, 30, 34] Huang and Tseng reported thrombocytopenia (46%), renal impairment (35%), altered consciousness (19%) and shock (29%) in their study population of EPN. [34] Aswani SM, et al., [35] and another study [36] also showed fever and dysuria to be common symptoms.

In our study, EPN patients had poor glycemia and lower eGFR as compared to pyelonephritis. Studies [31, 35, 37] have shown individuals with poor glycemic control were more likely to suffer from UTI. In contrast, other studies [29] including a study by Geerlings SE, et al., [28] in 636 women with diabetes have reported no relationship between UTI and glycemic control. Hyperglycemia leading to elevated urinary or tissue glucose levels impair neutrophil function as studied by Balasoiu D, et al., [38] Fatima et al. [39] in her study reported all diabetes patients with UTI had poor glycemic control at presentation.

In our study, bacteriuria was present in 90% and 66.7% of EPN and pyelonephritis patients respectively. *E. coli* was the most common isolate in both UTI groups. *E. coli* was predominantly seen in EPN patients as compared to pyelonephritis. Kumar et al. in their study also revealed a higher prevalence of bacteriuria in EPN (92.3%) as compared to non-EPN (87.3%)

Table 7 Follow up of T2D patients with pyelonephritis

Variables	Baseline <i>n</i> = 154	Follow up <i>n</i> = 154	<i>P</i> value*
FBG in mg/dl	239.60 ± 90.26	197.17 ± 61.45	0.000
Blood glucose PP	300.18 ± 103.21	242.36 ± 69.35	0.000
HbA1c in %	10.75 ± 2.07	10.26 ± 2.03	0.014
Creatinine in mg/dl	1.69 ± 1.03	1.48 ± 0.8	0.046
eGFR ml/min/1.73m ²	48.80 ± 29.28	54.68 ± 22.25	0.047

FBG Fasting blood glucose, PP Post prandial, HbA1c Glycosylated hemoglobin, eGFR Estimated glomerular filtration rate

Continuous variables [mean ± SD]

* *P* value < 0.05 is considered statistically significant

Table 8 Follow up of T2D patients with upper UTI on the basis of recurrent UTI

Variables	Recurrent UTI baseline <i>n</i> = 62	Recurrent UTI follow up <i>n</i> = 62	<i>P</i> value*	Non-recurrent UTI baseline <i>n</i> = 111	Non-recurrent UTI follow up <i>n</i> = 111	<i>P</i> value*
FBG in mg/dl	262.92 ± 100.49	245.13 ± 52.87	0.243	236.77 ± 86.57	172.41 ± 45.81	0.000
Blood glucose PP	320.35 ± 136.95	306.05 ± 41.96	0.439	297.61 ± 74.53	213.26 ± 59.03	0.000
HbA1c in %	11.29 ± 2.31	12.27 ± 1.61	0.007	10.46 ± 1.89	9.32 ± 1.74	0.000
Creatinine in mg/dl	1.92 ± 1.08	2.30 ± 1.04	0.048	1.50 ± 0.81	1.43 ± 0.76	0.507
eGFR ml/min/1.73m ²	47.56 ± 21.10	41.33 ± 12.48	0.048	52.60 ± 20.54	54.17 ± 29.22	0.658

FBG Fasting blood glucose, PP Post prandial, HbA1c Glycosylated hemoglobin, eGFR Estimated glomerular filtration rate

Continuous variables [mean ± SD]

* *P* value < 0.05 is considered statistically significant

but the difference was not significant and similarly *E. coli* was frequently detected in EPN group as compared to non-EPN in their study. [30] Sharma S, et al., [40] reported prevalence of bacteriuria in 43% patients of elderly T2D. *E. coli* was also the most common cause of UTI in diabetes from western and Indian studies. [29–32, 35, 40] *E. coli* is by far the most common causative organism for EPN, isolated in 47–90% of the patients; the other commonly involved organisms include *Proteus mirabilis*, *Klebsiella pneumoniae*, *Enterococcus* species, and *Pseudomonas aeruginosa*. [39]

In the present study, six patients had pyelonephritis due to *Candida*, while another study [35] also reported similar finding. The relative higher percentage of *Enterococcus faecalis* could be because the patients were hospitalized and higher rates of *Enterococcus* spp. have been reported in hospitalized patients. [41]

Follow up of T2D patients with upper UTI

In our study, the overall prevalence of recurrent UTI was 35.8%; with 47.4% in EPN and 34.2% in pyelonephritis patients. A significant number of EPN patients develop recurrent UTI. Patients with EPN have an improvement in glycemia on follow up but renal parameters do not improve on follow up despite a large number of patients had AKI, even with intensive treatment. In contrast, pyelonephritis patients have an improvement in glycemia and renal parameters with intensive treatment. Recurrent UTI in upper UTI patients leads to worsening of glycemia and renal parameters.

In the study conducted by Gorter KJ, et al. [42] relapses and reinfections were reported in 7.1% and 15.9% of diabetic women. In a Finnish study [43] of women ages 17 to 82 who had *E. coli* cystitis, 44% had a recurrence within 1 year. There is limitation of studies that followed UTI in patients with diabetes. The study has revealed that *E. coli* is not only the number one cause of UTI in women, but it also increases the likelihood of recurrent UTI. [44]

This study needs to be considered in light of strengths and limitations. Prospective nature and adequate sample size were

some of the strengths of the study. The present study had several limitations. First, it was a single-centre study; second, other risk factors like frequency of sexual intercourse and use of condoms were not analyzed and duration of follow up was short.

Conclusion

T2D patients with EPN present with poor glycemia and lower eGFR. Longer duration of diabetes, presence of nephropathy, CKD, UTI in a prior year, renal calculi and obstruction increase the risk of EPN. Complications like DKA, HHS, MODS, AKI and hypotension frequently occur in EPN patients as compared to pyelonephritis. UTI can be consequences of or lead to uncontrolled glycemia. A significant number of EPN patients develop recurrent UTI. Patients with EPN have an improvement in glycemia on follow up but renal parameters do not improve on follow up while pyelonephritis patients have an improvement in glycemia and renal parameters with intensive treatment. Recurrent UTI in upper UTI patients leads to worsening of glycemia and renal parameters. A high index of suspicion and early imaging studies are required to diagnose EPN in diabetics presenting with features of pyelonephritis, especially if blood glucose is poorly controlled. Long term prospective studies on upper UTI in T2D patients are required to identify risk factors that can help pinpoint modifiable factors amenable to a disease prevention strategy and improve the overall management. So in a nutshell, there is an urgent need for sensitizing the endocrinologist and nephrologist about the severity of complications in T2D patients with EPN. We also urge authorities to issue a guideline for special care of EPN patient with T2D.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest to be declared.

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