A Prospective study of Emphysematous Pyelonephritis in Patients with Type 2 Diabetes

Abstract

Introduction: Emphysematous pyelonephritis (EPN) is a necrotizing infection of the renal parenchyma. There is a lack of studies on follow up of EPN patients. The study aimed to explore the effect of EPN in patients with type 2 diabetes (T2D) on glycemic and renal parameters on follow up, and factors suggesting the failure of medical treatment. **Methods:** This was a hospital-based prospective study done over a period of 3 years on newly diagnosed consecutive 20 patients of emphysematous pyelonephritis (EPN) with T2D. Study analyzed the clinical, laboratory, radiological, microbiological findings, complications, treatment modality, and outcome. All patients were followed up for 6 months with respect to the number of urinary tract infections (UTIs), glycemic control, and renal parameters. **Results:** Most of the patients were postmenopausal females with longer duration of diabetes and complicated by triopathy. Fever and renal angle tenderness were the most common clinical finding. The majority of our patients 12 (60%) had EPN (class 1 and 2). Severe hyperglycemia was present in 19 (95%), hyperosmolar hyperglycemic state (HHS) in 5 (25%), diabetic ketoacidosis (DKA) in 3 (15%), and acute kidney injury (AKI) in 15 (75%). Bacteriuria was present in 90% and bacteremia in 30%. *E. coli* was the most common organism isolated (80%). The survival rate was 90%, with failure of medical treatment in 30%. Renal obstruction and worsening azotemia predicted the failure of medical management. The significant number (11, 55%) of patients developed recurrent UTI on follow up. Factors that increased the risk of recurrent UTI in EPN were chronic kidney disease, poor glycemia, and renal obstruction. The recurrent UTI patients had significantly higher glycosylated hemoglobin A1c (HbA1c) at follow up than at baseline, but renal parameters did not differ. **Conclusions:** We recommend early aggressive medical treatment of EPN. Altered sensorium, renal obstruction, and deteriorating renal function may suggest the failure of medical treatment.

Keywords: *Emphysematous pyelonephritis, Gas forming organism, Necrotizing pyelonephritis, Type 2 diabetes, Urinary tract infection (UTI)*

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Introduction

Infections are common in patients with diabetes, and some of these infections occur almost exclusively in T2D patients, with the urinary tract being the most frequent site,[1,2] and good diabetic control has been recommended as a means of decreasing this risk.[3] UTI in patients with diabetes is often given less importance, more attention being paid to macrovascular and microvascular complications. Awareness of the disease, knowledge of the spectrum of bacteria and their sensitivity to antibiotics, and the common complications of UTI will help to reduce morbidity and mortality.

Emphysematous pyelonephritis (EPN) is an acute, necrotizing infection affecting renal parenchyma and collecting system as well as surrounding tissue with a hallmark of the presence of gas within these structures.[4,5] Kelly and MacCallum[6] in 1898 reported the first case of EPN, although the term "emphysematous pyelonephritis" was first applied by Schultz and Klorfein (1962).[7] Gas formation in EPN is due to pathogenic bacteria causing mixed acid fermentation in a hyperglycemic environment in tissues that are ischemic. This results in tissue destruction and encourages purulent infection and inhibition of the removal of locally produced gas.[8]

EPN is commonly associated with diabetes especially in females, debilitated immune-deficient individuals, and patients harboring obstructed urinary system with infective nidus.[9] EPN is a life-threatening infection with a mortality rate as high as

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80% in earlier studies.[10] However, in recent years, the mortality rate among EPN patients has sharply decreased to 25% (1%–46%).[11]

Four factors have been implicated in the pathogenesis of EPN: (i) gas-forming bacteria; (ii) a high tissue glucose level (favoring rapid bacterial growth); (iii) impaired tissue perfusion (diabetic nephropathy can lead to additional compromise of regional oxygen delivery in the kidney, which results in tissue ischemia and necrosis, as well as nitrogen released during tissue necrosis); and (iv) a defective immune response due to an impaired vascular supply.[8] Although a high tissue glucose level could provide a favorable environment for the growth of gas-producing bacteria in patients with diabetes, hyperglycemia results in renal vasculopathy, renal neuropathy, and leukocyte dysfunction.[12]

The most common causative bacterial pathogens are *E. coli* (68%) and *Klebsiella pneumonae* (29%).[13] Traditionally, early nephrectomy was considered the treatment of choice.[14] With the availability of better imaging modalities, potent antibiotics, and image-guided drainage, an initial conservative approach is appealing.[15] In 1996, Chen *et al.*,[16] reported that antibiotic therapy combined with computed tomography-guided percutaneous catheter drainage (PCD) was an acceptable alternative to nephrectomy. Wan and Rullard[17] reported that thrombocytopenia, azotemia, and high urinary red blood cell counts are predictors of poor outcome in EPN. The severity of hematuria in patients with EPN probably reflects the degree of necrosis resulting from the infectious process and the presence of renal vein thrombosis. Altered consciousness, hypotension, severe proteinuria, and extension of infection to the perinephric space have also been associated with poor prognosis.[18] There are lack of studies on follow up of T2D patients with EPN and effect on glycemic and renal parameters.

In this prospective study, we analyzed the characteristics of 20 T2D patients with EPN for patient demographics, clinical, laboratory, radiological, microbiological findings, complications, treatment modality, and outcome and influence of EPN on glycemic and renal parameters on follow up, and the factors suggesting the failure of medical treatment.

Methods

This was a hospital-based prospective study of adult T2D patients attending the Endocrinology department of Sher-i-Kashmir Institute of Medical Science, Srinagar, Jammu and Kashmir, India. The study was approved by the Institutional ethical committee of the SKIMS (IEC/SKIMS/2015-235 dated 31 December 2015).

The study recruited consecutive 20 EPN patients admitted in the Endocrinology department, and they were followed for six months. The diagnosis of EPN was based on clinical features and documentation of gas within the renal parenchyma, collecting system, or perinephric tissue on non-contrast computed tomography (NCCT) abdomen. This study was conducted over a period of three years from December 2015 to December 2018. Informed consent was obtained from all the recruited subjects. All patients were interviewed at baseline using a standardized questionnaire, regarding the number of UTIs within the previous year and the treatment for the same, urinary tract surgery, marital status, and menopausal status in females. A detailed physical examination of the subjects was carried based on a study protocol and patients found to have any urogenital abnormalities, including, but not limited to cystocele (in females), recent hospitalization/surgery, use of antimicrobial drugs within the previous 14 days, and patients on prophylaxis for recurrent UTI, urinary tract surgery, and recent urinary instrumentation were excluded from the study. The eligibility criteria for including subjects in the study were: Both male and female T2D patients of age >30 years. Exclusion criteria included i) type 1 diabetes, ii) gestational diabetes, iii) secondary diabetes, iv) immunocompromised states- HIV, malignancy, patients on steroids and transplant recipients, and v) Catheterized patient.

Clinical parameters including duration of DM, 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 six months with regards to the 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 two-hour postprandial blood glucose (PP), 24-h urinary protein estimation, and glycosylated hemoglobin (HbA1c) were estimated at baseline and six months. HbA1c was measured by column chromatography (Bio-Rad, Richmond, CA) with whole blood collected in ethylenediamine tetra acetic acid (EDTA). Ultrasonography (USG) of the abdomen, blood culture, and non-contrast computed tomography NCCT abdomen were done in all patients. The severity of the 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.[18] Certain factors have been associated with poor outcome in EPN; these bad prognostic factors include thrombocytopenia, azotemia, hematuria, altered consciousness, shock [systolic blood pressure (BP) <90 mmHg] on initial presentation, severe

proteinuria, need for emergency hemodialysis, severe hypoalbuminemia (serum albumin <3 g/dl), polymicrobial infections, and extension of infection to the perinephric space.[18-21]

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 six 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.[22] 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.[23] Disks of commonly used drugs against Gram-positive and negative organisms were selected.

Definitions

Pyuria (defined as ≥ 10 leukocytes/mm^3) and hematuria (defined as ≥ 3 RBC/HPF) were detected by microscopic examination. For the diagnosis of UTI in women, a midstream urine count $\geq 10^5$ CFU/ml was considered diagnostic.[24] whereas for the diagnosis of UTI 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 presence of glucose in urine, leukocytosis as total leucocyte count (TLC) more than upper normal limit for the laboratory (4–10 x 10^3/μL), thrombocytopenia as platelet count <1.2 lakh/ml, acute kidney injury (AKI) when creatinine increased by 0.3 mg/dl from baseline or absolute value ≥ 1.5 mg/dl after excluding CKD, hypotension when SBP <90 mmHg, anemia when Hb <10 g/dl, and hypoalbuminemia when serum albumin <3 g/dl. The estimated glomerular filtration rate (eGFR) was calculated by MDRD (modification of diet in renal disease). Shock and MODS were defined as per Infectious Diseases Society of America (IDSA) guidelines.

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 PCD (if required). We defined the conservative treatment of EPN as medical treatment alone or a combination of medical treatment and percutaneous nephrostomy (PCN). Treatment with empiric antibiotics, using broad-spectrum aminoglycosides, piperacillin/tazobactam, fluoroquinolones, or carbapenems 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 and deterioration on this protocol led to consideration for nephrectomy. The success of conservative treatment was defined as clinical resolution and disappearance/decrease in gas on follow-up imaging during hospitalization and after discharge from the hospital.

Follow up

The EPN patients were followed for 6 months with respect to the number of UTIs, any antibiotic treatment received for the same, and hospitalizations. At the end of follow-up these patients again underwent urine examination, urine culture sensitivity, 24-h urinary protein estimation, FBG, PP, CBC, KFT, and HbA1c.

Statistical analysis

Quantitative variables were expressed as means ± standard deviation (SD), whereas 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 Mc Nemar'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 20 (IBM SPSS statistics for windows, version 20 Armonk NY: IBM Corp).

Results

Table 1 demonstrates the baseline characteristics of T2D patients with EPN. Table 2 shows various clinical and laboratory parameters. The reason for altered sensorium was metabolic encephalopathy in five patients; with two patients of DKA and three patients of HHS. Two patients had septic encephalopathy. Table 3 shows the radiological characteristics of EPN patients. Table 4 shows the risk factors for recurrent UTI in T2D patients with EPN. Out of 20 T2D patients with EPN who were followed for 6 months, 11 patients again developed UTI during follow up with 14 episodes of UTI. The frequency of UTI was that 8 patients developed one episode and 3 patients had two episodes. Eight episodes were pyelonephritis including one had EPN whereas rest were lower UTI and all episodes received antibiotic

Table 1: Baseline characteristics of T2D patients with EPN

Characteristic	*n* (%)
Age in yrs	57.7±13.6
Females	18 (90)
Post Menopausal	14 (77.8)
Diabetes duration in years	13.5±4.1
Diabetic Complication	
Retinopathy	19 (95)
Neuropathy	11 (55)
Nephropathy	13 (65)
Treatment	
Insulin	20 (100)
Insulin dose Units/kg	0.56±0.34
Comorbidity	
HTN	19 (95)
Hypothyroidism	3 (15)
CKD	4 (20)
CAD	1 (5)
Dyslipidemia	8 (40)
History of symptomatic UTI in year prior to study entry	8 (40)
Exam	
Uncontrolled BP	8 (40)
BMI (kg/m^2)	26±5.8
Obesity (BMI ≥25 kg/m^2)	14 (70)

Categorical variables [*n* (%)] and Continuous variables [mean±SD]. *$P<0.05$ is considered statistically significant. HTN - Hypertension, CKD - Chronic kidney disease, CAD - Coronary artery disease, BP - Blood pressure, BMI - Body mass index

Table 2: Baseline characteristics and parameters of T2D patients with EPN

Parameter	*n* (%) patients
Fever(>38.3°C)	19 (95)
Nausea/Vomiting	10 (50)
Flank pain	17 (85)
Altered sensorium	7 (35)
Hematuria	1 (5)
Renal tenderness	14 (70)
Hypotension (systolic BP <90 mmHg)	6 (30)
Diagnosis	
DKA	3 (15)
HHS	5 (25)
Bacteremia	6 (30)
AKI	15 (75)
MODS	4 (20)
Parameter	
FBG (mg/dl)	294±94
Blood glucose PP	345±77
HbA1c in %	12.0±2.2
Uncontrolled diabetes HbA1c ≥7%	20 (100)
Creatinine (mg/dl)	2.2±1.0
eGFR (ml/min/1.73m^2)	28.6±12.1
Proteinuria	12 (60)
Leucocytosis	12 (60)
Thrombocytopenia	6 (30)
Anemia	7 (35)
Hypoalbuminemia	4 (20)
Urine examination	
Pyuria	19 (95)
Urine culture	
Positive urine culture	18 (90)
Organism	
E. coli	16 (80)
K. pneumoniae	1 (5)
Enterococcus faecalis	1 (5)
USG	
Renal cyst	3 (15)
Renal calculi	6 (30)
Obstruction	5 (25)
Cystopathy	6 (30)

Categorical variables [*n* (%)]and Continuous variables [mean±SD]. *$P<0.05$ is considered statistically significant. EPN - emphysematous pyelonephritis, AKI - acute kidney injury, FBG-fasting blood glucose, PP - post prandial, HbA1c-glycosylated hemoglobin, eGFR - estimated glomerular filtration rate

treatment. On multivariate analysis, the factors, which were found to correlate with recurrent UTI on follow up in T2D patients with EPN were a presence of CKD, renal obstruction and higher HbA1c with risk ratio (RR) for CKD of 2.06 (1.20–2.83) and 1.91 (1.11–2.71) for renal obstruction. Table 5a shows various baseline and follow up parameters of T2D patients with EPN. Patients with EPN had lower mean FBG, PP, and HbA1c at follow up than baseline ($P < 0.05$). HbA1c significantly decreased from 12.0% ± 2.2% to 9.1% ± 1.4% at follow up. Renal parameters revealed that the serum creatinine reduced significantly at follow up, with a creatinine of 1.5 ± 1.0 mg/dl at follow up and 2.2 ± 1.0 mg/dl at baseline, while eGFR increased significantly ($P < 0.001$) at follow up. *E. coli* was still the most common organism at follow up. T2D patients with EPN who were followed up for 6 months, were further subdivided based on recurrent and non recurrent UTI, for comparison at baseline and follow up. Table 5b reveals that the EPN T2D patients with recurrent UTI (11 patients) had significantly higher HbA1c at follow up (13.1 ± 1.2%) than at baseline (11.7 ± 1.8%) ($P = 0.04$). Renal parameters were not significantly different at follow up, whereas bacteriuria, leukocytosis, pyuria, and glycosuria significantly reduced at follow up ($P < 0.05$). Mean FBG, PP, and HbA1c reduced at follow up from baseline in EPN T2D patients with non recurrent UTI (9 patients) ($P < 0.05$). HbA1c changed from 11.8 ± 1.6% to 9.0 ± 1.2% at follow

up ($P < 0.001$). Serum creatinine reduced significantly at follow up, whereas eGFR increased significantly ($P = 0.041$) at follow up from 46.2 ± 15.0 to 59.5 ± 10.1 ml/min/1.73m^2. Proteinuria, bacteriuria, leukocytosis, pyuria, hematuria, and glycosuria significantly reduced at follow up from baseline in non recurrent UTI patients.

Table 6 reveals the CT class, treatment modality, and outcome in T2D patients with EPN. One patient of nephrectomy died, whereas one patient managed with

Table 3: CT Characteristics of EPN

Variables	*n* (%) patients
CT Class	
Class 1	6 (30)
Class 2	6 (30)
Class 3a	5 (25)
Class 3b	1 (5)
Class 4	2 (10)
Side	
Right	7 (35)
Left	11 (55)
Bilateral	2 (10)

medical and PCD also died. So, survival with PCD was 75%, whereas PCD prevented nephrectomy in 75% of cases. Three patients received hemodialysis. Two patients of AKI received hemodialysis, and one patient with acute on chronic kidney disease also received same.

Table 7 shows the factors, which predict the failure of medical management (antibiotic) in T2D patients with EPN on multiple logistic regression analysis. The factors, which predicted the failure of medical management and the requirement of PCD or nephrectomy were altered sensorium, renal obstruction, and worsening of renal function.

Table 4: Risk factors for the recurrent UTI in T2D patients with EPN

Risk factors	Recurrent UTI	Non recurrent UTI	Univariate *P**	Multivariate *P**	RR (95% CI)
N	11	9			
Age in yrs	56.4±9.8	55.6±10.4	0.861		
Post Menopausal	9 (81.8)	5 (55.6)	0.215		
Diabetes duration in years	13.9±5.0	9.0±4.8	0.039	0.730	
Diabetic Complication					
Retinopathy	11 (100)	8 (88.9)	0.269	0.443	
Nephropathy	9 (81.8)	2 (22.2)	0.009		
Neuropathy	9 (81.8)	4 (44.4)	0.089		
Comorbidity					
HTN	11 (100)	8 (88.9)	0.269		
Hypothyroidism	2 (18.2)	1 (11.1)	0.666		
CKD	4 (36.4)	0 (0)	0.048	0.044	2.06 (1.20-2.83)
History of symptomatic UTI in year prior to study entry	6 (54.5)	2 (22.2)	0.152		
Parameter					
FBG (mg/dl)	281±100	258±96	0.608		
Blood glucose PP	351±138	322±80	0.584		
HbA1c in %	12.7±2.9	10.1±1.9	0.033	0.043	2.54(1.67–4.92)
Creatinine (mg/dl)	2.6±1.3	1.5±0.8	0.040	0.506	
eGFR (ml/min/1.73 m²)	40.6±20.9	56.1±22.6	0.003	0.888	
Proteinuria	9 (81.8)	3 (33.3)	0.031	0.078	
DKA	2 (18.2)	1 (11.1)	0.666		
HHS	4 (36.4)	1 (11.1)	0.205		
MODS	3 (27.3)	1 (11.1)	0.379		
AKI	10 (90.9)	5 (55.6)	0.077		
Bacterimia	3 (27.3)	3 (33.3)	0.776		
EPN grade 3-4	6 (54.5)	2 (22.2)	0.152		
Urine examination					
Pyuria	11 (100)	8 (88.9)	0.269		
Hematuria	1 (9.1)	0 (0)	0.265		
Glycosuria	10 (90.9)	9 (100)	0.365		
Organism					
E. coli	9 (81.8)	7 (77.8)	0.426		
Other	2 (18.2)	0 (0)	0.265		
USG					
Renal cyst	2 (18.2)	1 (11.1)	0.666		
Renal calculi	5 (45.4)	1 (11.1)	0.104		
Obstruction	5 (45.4)	0 (0)	0.022	0.042	1.91 (1.11-2.71)

Categorical variables [*n* (%)] and Continuous variables [mean±SD]. **P*<0.05 is considered statistically significant. HTN-hypertension, CKD-chronic kidney disease, BP- blood pressure, BMI-body mass index, HHS- hyperglycemic hyperosmolar state, DKA-diabetic ketoacidosis, MODS-multiorgan dysfunction syndrome, EPN-emphysematous pyelonephritis, AKI-acute kidney injury, FBG-fasting blood glucose, PP-post prandial, HbA1c-glycosylated hemoglobin, and eGFR-estimated glomerular filtration rate

Table 5a: Baseline and Follow up of T2D patients with EPN

Parameter	UTI at baseline *n*=20	UTI at follow up *n*=20	*P**
FBG (mg/dl)	294±94	209±49	<0.001
Blood glucose PP	345±77	269±58	<0.001
HbA1c in %	12.0±2.2	9.1±1.4	<0.001
Creatinine (mg/dl)	2.2±1.0	1.5±1.0	0.039
eGFR (ml/min/1.73m²)	28.6±12.1	51.8±20.2	<0.001
Proteinuria	12 (60)	4 (20)	0.011
Bacteriuria	18 (90)	4 (20)	<0.001
Pyuria	19 (95)	4 (20)	<0.001
Glycosuria	19 (95)	7 (35)	<0.001
Organism			
E. coli	16 (80)	4 (20)	
Other	2 (10)	0 (0)	

Categorical variables [*n* (%)] and Continuous variables [mean±SD]. *P<0.05 is considered statistically significant. FBG-fasting blood glucose, PP-post prandial, HbA1c-glycosylated hemoglobin, eGFR-estimated glomerular filtration rate

Table 5b: Follow up of T2D patients with symptomatic UTI on the basis of recurrent UTI

Parameter	EPN baseline (recurrent UTI) *n*=11	EPN follow up (recurrent UTI) *n*=11	*P**	EPN baseline (non recurrent) *n*=9	EPN follow up (non recurrent) *n*=9	*P**
FBG (mg/dl)	260±97	244±47	0.627	235±51	186±36	0.011
Blood glucose PP	320±134	300±37	0.638	297±57	237±46	0.025
HbA1c in %	11.7±1.8	13.1±1.2	0.044	11.8±1.6	9.0±1.2	<0.001
Creatinine (mg/dl)	2.3±1.6	2.2±1.5	0.881	1.7±0.5	1.2±0.5	0.049
eGFR (ml/min/1.73m²)	38.4±25.5	43.1±21.1	0.618	46.2±15.0	59.5±10.1	0.041
Proteinuria	9 (81.8)	4 (36.4)	0.034	3 (33.3)	0 (0)	0.065
Bacteriuria	11 (100)	3 (27.3)	<0.001	7 (77.8)	1 (11.1)	0.005
Pyuria	11 (100)	3 (27.3)	<0.001	8 (88.9)	1 (11.1)	0.001
Glycosuria	11 (100)	4 (36.4)	0.002	8 (88.9)	3 (33.3)	0.018
Organism						
E. coli	10 (90.9)	3 (27.3)		6 (66.7)	1 (11.1)	
Other	0 (0)	0 (0)		2 (22.2)	0 (0)	

Categorical variables [*n* (%)]and Continuous variables [mean±SD]. *P<0.05 is considered statistically significant. FBG-fasting blood glucose, PP-post prandial, HbA1c-glycosylated hemoglobin, eGFR-estimated glomerular filtration rate

Table 6: Computed tomography class, Treatment and Outcome in T2D patients with EPN

CT Class	Medical alone	Medical and PCD	Nephrectomy	Survival	Dead
Class 1 and 2 *n*=12	12	0	0	12	0
Class 3 and 4 *n*=8	2	4	2	6	2

Table 7: Variables predictive of failure of medical management (Antibiotic) in EPN on multiple logistic regression analysis

Variables	*P**	Odds ratio (95% CI)
Altered sensorium	0.044	3.26 (1.02-12.45)
Obstruction	0.024	6.00 (1.26-21.54)
Shock	0.556	1.05 (0.91-1.21)
MODS	0.417	2.14 (0.41-11.17)
Worsening renal function	0.040	5.62 (1.07-19.37)
Thrombocytopenia	0.725	1.33 (0.27-6.65)

*P<0.05 is considered statistically significant

Discussion

EPN is an uncommon necrotizing infection of the renal system predominantly seen in patients with diabetes. Predisposing factors encompass urinary tract obstruction, end-stage renal disease, immunosuppression, and rarely polycystic renal disease. Four key factors have been proposed including uncontrolled tissue glucose level favoring bacterial growth, renal tissue ischemia and necrosis secondary to compromised renal perfusion, immunodeficiency, and diabetic neuropathy.[8,13,18] The first step in managing a patient with EPN is fluid and electrolyte resuscitation, acid-base balance, diabetic control, and an antibiotic regimen.[12] Timely administration of appropriate antibiotics and early PCD are of paramount importance.[25]

The mean age of our study population was 57.7 ± 7.6 years (range: 30–68 years) with female preponderance (M:F = 1:9), which was similar to the results of other studies[26-29] who also revealed female predominance. The increased occurrence in women is

presumably because of their increased susceptibility to UTI due to short urethra.[13]

Clinically EPN presents with nonspecific features of upper UTI including fever, flank pain, nausea, vomiting, altered sensorium, shock, AKI, and disseminated intravascular coagulation. In our study fever and flank tenderness were the most common manifestations at presentation. Renal tenderness, hypotension, and altered sensorium were present in 70%, 30%, and 35%, respectively. DKA was present in 15%, HHS in 25%, bacteremia in 30%, AKI in 75%, and MODS in 20%. Costovertebral angle tenderness is considered the commonest physical finding.[4,13,16,18,29] Huang and Tseng[18] reported thrombocytopenia (46%), renal impairment (35%), altered consciousness (19%), and shock (29%) in their study population. Shokier *et al.*,[13] found deranged renal function (80%), shock and coma (15%) in their patients. Our study displayed a similar trend of clinical manifestations as shown by Sokhal AK *et al.*,[29] HTN induces ischemia due to arteriosclerosis and glomerulosclerosis.[30] In our study, HTN was seen in 95% of patients.

In our study, T2D patients with EPN had mean FBG of 294 ± 94 mg/dl, PP of 345 ± 77 mg/dl and HbA1c of 12.0 ± 2.2%. Renal parameters revealed serum creatinine of 2.2 ± 1.0 mg/dl, with mean eGFR of 28.6 ± 12.1 ml/min/1.73m². Fatima R *et al.*,[31] in her study reported all patients had poor glycemic control at presentation. In our study, *E. coli* 16 (80%) was the most commonly isolated organism in EPN patients followed by *K. pneumoniae* 1 (5%), and *Enterococcus* faecalis 1 (5%). Based on USG finding renal obstruction and cystopathy were present in 25% and 30%, respectively. *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 *P. mirabilis*, *K. pneumoniae*, *Enterococcus* species, and *P. aeruginosa*.[13,20,21,31]

Urinary tract obstruction has been reported to cause EPN in 25%–40% of patients,[12] whereas in our study renal obstruction was present in 25% of cases. Calculi causing obstructive form a nidus of infection, causing stagnation or reflux of urine in the urethral system and ascending infection. In our study, the left kidney was involved in 55% of patients and the right kidney was involved in 35% of patients. In EPN, left kidney is more frequently involved than the right. A recent meta-analysis has reported that 52% of patients had left-sided, 37.7% right-sided, and 10.2% bilateral EPN.[20] Huang *et al.*, have reported that 67% and 8% of the patients with EPN had left-sided and bilateral disease, respectively.[18] In the literature, bilateral EPN is reported to occur in up to 10% of patients.[32]

In our study, the factors, which were found to correlate with recurrent UTI on follow up in T2D patients with EPN were a presence of CKD, renal obstruction, and higher HbA1c. So, renal obstruction and hyperglycemia should be treated aggressively to prevent recurrent UTI. A significant number of patients 11 (55%) develop recurrent UTI on follow up till 6 months. The recurrent UTI patients had significantly higher HbA1c at follow up than at baseline, but renal parameters did not differ. Renal parameters improved at follow up in non recurrent UTI patients. There are limitations of studies, which followed EPN in patients with diabetes. Sokhal AK *et al.*,[29] in his study showed advanced age, higher BMI, renal impairment, thrombocytopenia, altered sensorium, and shock at presentation can be used as a score for poor prognosis.

The treatment of EPN has evolved over years from emergency surgery to more conservative approaches due to the availability of better imaging modalities, potent antibiotics, and image-guided drainage. In recent years, the mortality of EPN patients has decreased to 25% (1%–46%)[11] as compared to 80% in earlier studies.[10,33] A recent meta-analysis has shown that compared to emergency nephrectomy, PCD and medical management alone are associated with a significantly lower mortality rate.[20] In our study, the success rate of conservative treatment was 94.4%, with overall mortality was 10% with 50% occurring in the surgical group. The likely reasons for the remarkably low mortality in our study are early and aggressive fluid resuscitation, rapid glycemic control, use of empirical broad-spectrum antibiotics, whereas higher mortality in the surgical group can be explained by high-risk nature of patients. Sokhal AK *et al.*, in his study, demonstrated an overall mortality rate of 8% in the 74 patients of EPN.[29] In our study survival rate was 90% with failure of medical treatment in 30% and the factors, which predicted the failure of medical management and the requirement of PCD or nephrectomy were altered sensorium, renal obstruction, and worsening of renal function.

The present study had several limitations. First, it was a single-center study; second, the number of cases was too small to analyze other risk factors. The small number of patient sampling may explain the lack of statistical significance seen in various parameters.

Conclusions

Female T2D patients are predisposed to EPN. *E. coli* is the most frequently isolated pathogen. We recommend early aggressive medical treatment of EPN. Altered sensorium, renal obstruction, and deteriorating renal function may suggest a failure of medical treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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