Treatment duration and prognostics in febrile urinary tract infection

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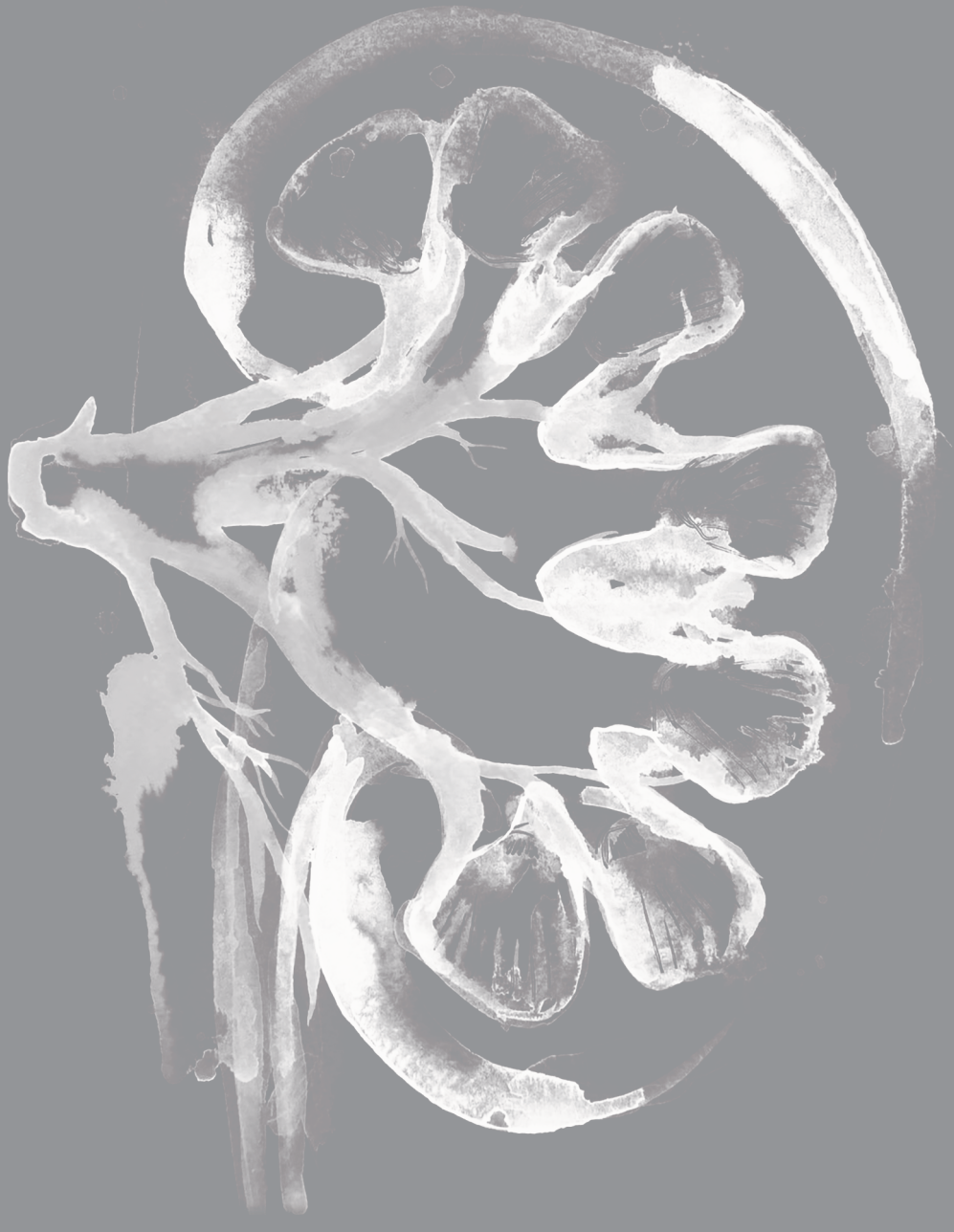

Chapter 4

Diabetes mellitus and the course of febrile urinary tract infection

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Abstract

Objective

Evaluate the impact of diabetes mellitus on the clinical presentation and microbiological and clinical outcomes of febrile urinary tract infection (UTI).

Research design and methods

A prospective observational multicenter cohort study including 858 adults with community-onset febrile UTI presenting at seven emergency departments and 35 primary care units. The effect of pre-existing diabetes on presentation, microbiological and clinical outcome was assessed and multivariable logistic regression performed to establish whether diabetes was an independent risk factor for a complicated course.

Results

Of 858 patients, 140 had diabetes (93% type 2 diabetes). Patients with diabetes were older, more frequently male, and had a higher rate of cardiovascular and urinary tract comorbidities. Diabetes was not associated with longer fever duration or prolonged hospital admission. Patients with diabetes more often had bacteremia at presentation, ICU admission, recurrent UTI, asymptomatic bacteriuria and mortality during 30 days of follow-up. However, when adjusted for possible confounders, diabetes was not an independent risk factor for any of these complications, although women with diabetes were at increased risk of asymptomatic bacteriuria after one month. The higher prevalence of complications in diabetics was mainly explained by an increased prevalence of cardiovascular comorbidity and higher age.

Conclusions

Although it is widely held that patients with diabetes have a more complicated course of infections, our data show that diabetes is not independently associated with adverse outcomes in an unselected population of patients with febrile UTI. Cardiovascular comorbidity and increased age are the main risk factors for a complicated course.

Introduction

Diabetes mellitus affects about 6% of the population worldwide, and this number is expected to grow in the coming years.(1,2) Asymptomatic bacteriuria in diabetes - a common finding in up to one quarter of patients - predisposes to urinary tract infections(UTIs).(3,4) This increased risk of acquiring UTIs in diabetic patients is clear.(5,6) It is less clear whether UTIs in diabetic patients compared to non-diabetic patients follow a more complicated course, although various treatment guidelines reflect this perception.(7,8) In previous studies on diabetes and the outcome of febrile UTI, diabetes was associated with a higher rate of bacteremia and a longer duration of hospitalization and fever.(9-11) Two studies reported a higher mortality(10,12) and a recent meta-analysis demonstrated an increased hazard ratio for death from infection other than pneumonia (HR 2.39).(13) On the contrary, increased mortality was not associated with diabetes in a large review of hospitalizations due to pyelonephritis.(14)

However, these studies specifically focusing on urinary tract infections in diabetes are limited by small sample size, inadequate adjustment for confounding and varying inclusion criteria.

Therefore, this prospective observational cohort study was performed to evaluate the impact of diabetes on the clinical presentation of febrile UTI and its microbiological and clinical outcomes.

Research design and methods

We conducted a prospective observational multicenter cohort study including consecutive patients with febrile UTI from January 2004 until January 2011. Participating centers were 35 primary health centers and the emergency departments of 7 hospitals, all clustered in one area of the Netherlands. The local ethics committees approved the study and all participants provided written informed consent.

Inclusion criteria were age ≥ 18 years, fever (≥ 38.0°C) and/or a history of fever or shaking chills within 24 hours before presentation, at least one symptom of UTI (dysuria, perineal pain or flank pain) and a positive nitrite dipstick test or leucocyturia as defined by a positive leucocyte esterase dipstick test or the presence of more than five leucocytes per high-power field in a centrifuged sediment. Exclusion criteria were current treatment for urolithiasis or hydronephrosis, pregnancy, known allergy to fluoroquinolones,

receipt of hemo- or peritoneal dialysis, a history of kidney transplantation, or known presence of polycystic kidney disease. Patients were only included once in the study.

Procedures

Demographic and clinical data were collected at baseline, at 3-4 days and 28-32 days after enrollment. Microbiological data were collected at baseline and since August 2006 a second urine culture was obtained after 28-32 days. The presence of diabetes was included in the standard questionnaire at baseline, which was filled out by qualified research nurses or the clinical investigator by reviewing the medical record completed with a patient interview. When diabetes was newly diagnosed during admission, the patient was regarded as diabetic patient. In case the patient was lost to follow-up, mortality was assessed using interviews from patient's GP and/or hospital chart review and/or local governmental mortality registries. Blood and urine cultures were performed using standard microbiological methods. MIC breakpoints for resistance were based on EUCAST criteria (www.eucast.org).

Definitions

A urinary tract disorder was defined as the presence of any anatomical or functional abnormality of the urinary tract excluding the presence of a urinary catheter or history of nephrolithiasis. These two variables were analyzed separately. Recurrent UTI was defined as two or more episodes of UTI in the last six months, or three or more episodes of UTI in the last year. The isolation of coagulase-negative staphylococci from the blood culture was considered to indicate contamination and thus absence of bacteremia. Adequate treatment was defined as appropriate antibiotic treatment, taking into account the causal uropathogen(s) in urine- and blood culture and its resistance pattern. Asymptomatic bacteriuria was defined as the growth of $\geq 10^5$ CFU/mL of a uropathogen in a midstream urine sample collected 28-32 days after enrolment without symptoms suggesting UTI (dysuria/flank pain/fever).(15) Recurrent UTI was defined as the growth of $\geq 10^3$ CFU/mL of a uropathogen in a midstream urine sample collected 28-32 days after enrolment plus ≥1 symptom suggesting UTI.(16,17) Due to logistic reasons, in 500 patients (58%) a urine culture at 28-32 days after inclusion could be obtained; outcomes of asymptomatic bacteriuria and recurrent UTI could only be assessed in these patients.

Data on bacteremia were missing in 51 patients because no blood cultures were performed at presentation. Survival data were lacking in four patients

due to loss to follow-up; those patients were excluded from analysis of 30-day mortality. All patients were relatively young (22, 24, 26 and 67 years), and three had no underlying illnesses except for a stroke in the medical history of a 67-year old male, so risk of mortality is low.

Statistical analysis

Descriptive analysis included means with standard deviation (SD) or medians with interquartile range (IQR), as appropriate. Comparison of groups was performed using the Mann-Whitney U-test or unpaired t-test for continuous variables and the Chi-squared test for categorical variables. Odds ratios and 95% confidence intervals were calculated. Factors included in the logistic regression models for adverse outcomes (bacteremia, asymptomatic bacteriuria, recurrent UTI and 30-day mortality) using Enter selection method were age, sex, comorbidities, bacteremia at presentation (for 30-day mortality), and receiving an adequate antibiotic treatment (for recurrent UTI) if the *p* value was <0.2. Interactions between paired variables were tested. A two-tailed *p*-value <0.05 was considered to indicate statistical significance. All analyses were performed using SPSS 20.0 (SPSS Inc, Chicago, IL, USA).

Results

Of 858 consecutive patients, 140 had diabetes (130 (93%) type 2 diabetes), of which 41 (30%) used insulin, and 19 (14%) were managed by diet only. Diabetic patients were older (median age 73 [IQR 60-81] vs 64 [IQR 42-77] years), more frequently male (48% vs 35%, *p* 0.006), more often presented at the emergency department (86% vs 76%, *p* 0.008) and had a higher rate of cardiovascular and urinary tract comorbidities compared to 718 patients without diabetes. Further baseline characteristics of the study population are summarized in Table 1.

Signs and symptoms

Patients with diabetes had comparable signs and symptoms at presentation compared to non-diabetic patients, except for systolic blood pressure (138 ± 25 mmHg vs 129 ± 22 mmHg, respectively) and flank pain (50% versus 65%, respectively). After correction for age (both continuous and in quartiles), diabetes no longer had a significant influence on the absence of flank pain in the diabetic patients.

Table 1. Baseline characteristics of 858 patients presenting with febrile UTI

Characteristic	All (n=858)	Diabetes (n=140)	No diabetes (n=718)	p-value
Age, median [IQR] years	66 [46-78]	73 [60-81]	64 [42-77]	<.001
Male sex	320 (37)	67 (48)	253 (35)	.006
Antibiotic pre-treatment	254 (30)	48 (34)	206 (29)	.189
Urologic history				
Urinary tract disorder*	210 (24)	48† (34)	162 (23)	.005
Indwelling urinary catheter	58 (7)	16 (11)	42 (6)	.016
Recurrent UTI‡	269 (31)	54 (39)	215 (30)	.044
Comorbidity				
Malignancy	91 (11)	19 (14)	72 (10)	.230
Heart failure	128 (15)	39 (28)	89 (12)	<.001
Cerebrovascular disease	112 (13)	25 (18)	87 (12)	.074
Chronic renal insufficiency	78 (9)	26 (19)	52 (7)	<.001
Chronic obstructive pulmonary disease	118 (14)	28 (20)	90 (13)	.023
Presentation				
At emergency department	662 (77)	120 (86)	542 (76)	.008
Shaking chills	489/783 (63)	79/125 (63)	410/658 (62)	.851
Dysuria§	613 (76)	102 (83)	511 (75)	.065
Flank pain	526/837 (63)	66/132 (50)	460/705 (65)	<.001
Fever duration at presentation, median hours [IQR]‖	30 [12-60]	36 [15-72]	29 [12-60]	.397
Heart rate >90 beats/minute	448/850 (53)	73/139 (53)	375/711 (53)	1.000
Systolic blood pressure, mean mmHg ± SD	130 ± 23	138 ± 25	129 ± 22	<.001
Diastolic blood pressure, mean mmHg ± SD	72 ± 14	72 ± 16	72 ± 14	.940

Data are presented in n (%) unless otherwise stated. UTI = urinary tract infection, IQR = interquartile range, SD = standard deviation.

* defined as any functional or anatomical abnormality of the urinary tract except urinary catheter and history of nephrolithiasis.

† prostatic hypertrophy (20), malignancy of the urinary tract (6), neurogenic bladder (5), status after nephrectomy (3), and other anatomical or functional disorders of the urinary tract (14)

‡ defined as ≥ 3 UTIs in the past 12 months or ≥ 2 UTIs in the past 6 months

§ not recorded in patients with an indwelling urinary catheter

‖ recorded in 660 patients

Microbiological outcome

In 809 patients (94%), a urine culture was performed at baseline. *Escherichia coli* was the most common isolated uropathogen in both diabetic and non-diabetic patients (Table 2). *Klebsiella* spp. (9% vs 4%), *Enterococcus* spp. (11% vs 3%) and *Staphylococcus* spp. (5% vs 2%) were isolated more frequently in diabetic patients. Also urine culture of diabetic patients more frequently revealed more than one uropathogen (11% vs 4%). A comparable distribution

Table 2. Uropathogens isolated from urine culture at inclusion

Uropathogen	Diabetes (n=133)	No diabetes (n=676)
Escherichia coli	69 (52)	393 (58)
Proteus spp.	5 (4)	23 (3)
Klebsiella spp.	12 (9)	28 (4)
Pseudomonas aeruginosa	4 (3)	18 (3)
Enterococcus spp.	14 (11)	19 (3)
Staphylococcus spp.	6 (5)	10 (2)
Candida spp.	0 (0)	2 (0,3)
Other	14 (11)	89 (13)
None/ contaminated	23 (17)	121 (18)

Data are presented as n (%). Urine culture was not performed in 49 patients.

of uropathogens among diabetic and non-diabetic patients was seen in an analysis excluding patients with an indwelling urinary catheter (n =753).
Resistance patterns of *E. coli* urinary isolates were comparable between diabetic and non-diabetic patients: amoxicillin-clavulanic acid (17% vs 12%), trimethoprim-sulfamethoxazole (25% vs 30%) and ciprofloxacin (19% vs 12%), even when only patients without indwelling catheter and without antibiotic pre-treatment were analyzed (data not shown).
Baseline blood cultures were performed in 807 patients (94%). Diabetic patients more often had bacteremia (29% vs 20%). Also in patients with low bacterial counts in their urine culture ($< 10^5$ CFU/mL), bacteremia was more prevalent in diabetic patients versus non-diabetic patients (22% vs 16%, respectively). In the latter comparison patients with a urinary catheter or patients who had received antibiotic pre-treatment were excluded (Table 4).

Clinical outcome

Upon presentation, diabetic patients were more frequently admitted to the hospital (81% vs 64%). Moreover, they were more frequently admitted to the intensive care unit during hospitalization (6% vs 3%). However, when admitted, fever duration and length of hospital stay were comparable. Diabetic patients were more often bacteremic at presentation (30% vs 22%). After one month, diabetic patients had a higher rate of asymptomatic bacteriuria (13% vs 9%; OR 1.5, 95% CI 0.8-3.0), recurrent UTI (9% vs 3%; OR 2.9, 95% CI 1.2-7.2) and mortality (6% vs 2%; OR 3.3, 95% CI 1.3-8.0), although absolute numbers were low (Table 3). In a subgroup analysis of diabetic patients, use of insulin was not associated with any of the adverse outcomes.

Table 3. Relation between diabetes mellitus and clinical and microbiological outcome of 858 patients presenting with febrile UTI

Outcomes	All (n=858)	Diabetes (n=140)	No diabetes (n=718)	Univariate OR[5] [95% CI]	Multivariate OR[5] [95% CI]
Clinical					
Hospital admission	575 (67)	114 (81)	461 (64)	2.4 [1.6-3.8]	-
Hospitalization duration (days), median [IQR]	6 [4-9]	6 [4-11]	6 [4-8]	-	-
ICU admission	32 (4)	9 (6)	23 (3)	2.1 [0.9-4.6]	-
Bacteremia at presentation	185/807 (23)	40/134 (30)	145/673 (22)	1.6 [1.0-2.3]	1.2 [0.8-1.8]
Defervescence[1] (days), median [IQR]	2 [1-3]	2 [1-3]	2 [1-3]	-	-
30-day mortality	21/854 (2)	8 (6)	13/714 (2)	3.3 [1.3-8.0]	2.0 [0.7-5.8]
Microbiological[2]					
30-day asymptomatic bacteriuria[3]	49/500 (10)	12/92 (13)	37/408 (9)	1.5 [0.8-3.0]	1.1 [0.5-2.5]
30-day recurrent UTI[4]	21/500 (4)	8/92 (9)	13/408 (3)	2.9 [1.2-7.2]	2.2 [0.7-6.8]

Data are presented in n (%) unless otherwise stated. UTI = urinary tract infection, OR= odds ratio, CI = confidence interval, IQR = interquartile range, ICU = intensive care unit

[1] recorded in 667 patients: 105 (75%) diabetic patients and 562 (78%) non-diabetic patients

[2] of 500 patients with a urine culture performed after 30 days

[3] defined as the growth of a uropathogen $\geq 10^5$ in a midstream urine sample without symptoms of UTI

[4] defined as the growth of a uropathogen $\geq 10^3$ in a midstream urine sample plus ≥1 symptom(s) of UTI

[5] univariate and multivariate OR of risk factor diabetes mellitus for the corresponding outcomes

Multivariate analysis

After adjusting for possible confounders, independent risk factors for bacteremia were age (OR 1.0, 95% CI 1.0-1.0) and chronic renal insufficiency (OR 1.9, 95% CI 1.1-3.1) but diabetes was not (OR 1.2, 95% CI 0.8-1.8). Risk factors for 30-day mortality were age (OR 1.1, 95% CI 1.1-1.2) and heart failure (OR 3.2, 95% CI 1.2-8.9). Diabetes was not a significant risk factor for mortality (OR 2.0, 95% CI 0.7-5.8). Similarly, bacteremia was not associated with mortality (OR 1.6, 95% CI 0.6-4.4). None of the variables we studied were independently associated with recurrence of UTI during 30 days of follow-up (Table 3).

Also, diabetes was not independently associated with asymptomatic bacteriuria after one month (OR 1.1, 95% CI 0.5-2.5). Only having an indwelling catheter was significantly associated (OR 8.0, 95% CI 3.6-17.7). Potential interactions between variables (e.g diabetes mellitus and sex) were additionally tested, but they did not significantly change the models, except for asymptomatic bacteriuria. Of female diabetic patients, 15% had asymptomatic bacteriuria after one month compared to 4% in female non-diabetic patients (OR 4.3, 95% CI 1.5-11.9). In male, 11% of diabetic patients had asymptomatic bacteriuria compared to 17% in non-diabetic (OR 0.6, 95% CI

Table 4. Relation between urine bacterial load and bacteremia in adults with febrile UTI

CFU/mL urine	% bacteremia diabetic patients	% bacteremia non-diabetic patients
$<10^3$	1/1 (100%)	1/9 (11%)
10^3-10^4	1/2 (50%)	2/17 (12%)
10^4-10^5	0/7 (0%)	7/36 (19%)
$>10^5$	19/59 (32%)	65/277 (23%)
Total	21/69 (30%)	76/343 (22%)

Analysis performed in all patients with positive urine culture; patients pretreated with antibiotics or patients with indwelling urinary catheter were excluded from analysis.

0.2-1.7). So, there is an important interaction between diabetes and sex for the risk of asymptomatic bacteriuria (adjusted OR 0.1, 95% CI 0.02-0.7 for male diabetic patients).

Conclusions

In this prospective observational multicenter cohort study, diabetes mellitus was not independently associated with increased mortality or a complicated outcome of febrile urinary infection compared to non-diabetic patients. The prevalence of adverse outcomes was higher in diabetic patients, but mainly attributable to concurrent illnesses, especially cardiovascular comorbidities, and a higher age of the diabetic population. This is in line with the fact that most of the diabetic patients had type 2 diabetes.

Clinical symptoms of febrile UTI were comparable between diabetic and non-diabetic patients, apart from the observation that diabetic patients experience less flank pain, as was reported previously.(9) This might possibly be explained by diabetic neuropathy, although diabetes had no significant influence on the absence of flank pain in the diabetic patients after correction for age.

The lack of flank pain in a substantial part of the study population shows once more that flank pain has a low predictive value in the identification of complicated UTI, whereas presence of fever effectively excludes the presence of a non-complicated UTI. Therefore, the determination of fever in patients with suspected UTI should be the starting point in further diagnostic and therapeutic steps, because that is the most reliable distinction between cystitis/urethritis and UTIs associated with tissue invasion.

Although diabetic patients had a nearly similar clinical presentation except for flank pain, they more often had bacteremia. Interestingly, bacteremia did not affect duration of fever and hospitalization. The higher rate of bacteremia might be partly due to presentation later in the course of UTI, as suggested by a longer fever duration before inclusion. Another explanation could be that their immune response is less efficient. Various in vitro, animal and a few patient studies investigated the host response in diabetes,(18,19) which seems to be altered and could predispose diabetic patients to e.g. recurrent infection. Of these, several mechanisms could explain our clinical findings. Firstly, although the systemic cytokine response to infection seems not to be altered,(18,20) a lower pro-inflammatory cytokine amount was found in urine from diabetic patients with asymptomatic bacteriuria,(18) possibly reflecting an attenuated local immune response. This could be the explanation why in this study, like another study(21), less virulent uropathogens, such as *Enterococcus* spp., more often were cultured in diabetic patients. However, these differences also could be due to more frequent usage of antibiotics or more hospital admissions of diabetic patients, as *Enterococcus* spp. are frequent causative micro-organisms of nosocomial infections.(22,23) Secondly, even when the same uropathogen is involved, there could be a better adhesion of bacteria on the uroepithelium by their type 1 fimbriae, as was shown in *E. coli*, especially in poorly controlled diabetic patients.(24) In our study, we did not systematically collect the level of control of diabetes at presentation. As a consequence, this findings could not be confirmed within our group of diabetic patients. However, considering the similar clinical presentation in both groups, this phenomenon might be more responsible for the acquisition of UTI and not associated with different presentation or outcome of UTI. Lastly, more bladder voiding problems are encountered in diabetic patients due to autonomic dysfunction,(25) which leads to stasis of urine and possibly higher risk of bacterial growth and lack of bacteriologic cure.(26,27)

Our findings support previous reports on the lack of an association between diabetes per se and an increased mortality in urinary tract infection. Age and comorbidity, especially heart failure in our study, were more predictive of mortality and should be accounted for, as was also demonstrated in a study of elderly patients with urosepsis.(28) Another study of 206 elderly patients with febrile UTI did show a higher mortality in diabetic patients, but here no correction was made for comorbidity.(10) A retrospective cohort study comparing diabetic persons with age and sex matched controls found a higher risk ratio for death due to infectious diseases, but did not report

febrile UTI specific mortality and did not take into account possible differences in comorbidities between diabetic persons and controls.(29) Similarly in other infections, such as community-acquired pneumonia, a higher risk of death in diabetic patients was assumed to be associated with a higher incidence of acute kidney injury and acceleration of underlying cardiovascular disease.(20) Therefore, when diabetes patients have cardiovascular or renal complications of disease, these conditions will be the main determinants of outcome in infections.

Diabetes mellitus was not an independent risk factor for asymptomatic bacteriuria after one month in our study population. However, there was an significant interaction between diabetes and sex, showing an increased risk of asymptomatic bacteriuria in women with diabetes compared to men. This is supported by previous research, which showed that women with diabetes have a higher risk of asymptomatic bacteriuria compared to healthy women(19,30-32). The results in men however are not supported by a recent meta-analysis, which demonstrated also a higher prevalence of asymptomatic bacteriuria in men with diabetes compared to healthy men.(32) Our study do not find support for an increased duration of antimicrobial treatment of febrile UTI in diabetic compared to non-diabetic patients, since clinical and microbiological outcomes after one month did not differ significantly between both groups, and diabetic and non-diabetic patients were treated alike.

In conclusion, our data show that diabetes is not independently associated with adverse outcomes in an unselected population of patients with febrile UTI, although it is widely held that patients with diabetes have a more complicated course of infections. Cardiovascular comorbidity and increased age are the main risk factors for a complicated course of febrile UTI.

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