

# Risk Factors for Symptomatic Urinary Tract Infection in Women With Diabetes

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ON BEHALF OF THE DIABETES WOMEN  
ASYMPTOMATIC BACTERIURIA UTRECHT  
STUDY GROUP

either type 1 or type 2 diabetes during a period of 18 months.

**OBJECTIVE** — Women with diabetes have urinary tract infections (UTIs) more often than women without diabetes. The aim of the present multicenter study was to evaluate which clinical characteristics are associated with the development of a symptomatic UTI during an 18-month follow-up period.

**RESEARCH DESIGN AND METHODS** — Patients with either type 1 or type 2 diabetes who were between 18 and 75 years of age were included. Follow-up results were available for 589 of the 636 women included in this study. All patients were interviewed, their medical history was noted, and at least one uncontaminated urine culture was collected at the moment of study entry.

**RESULTS** — Of the 589 women, 115 (20%) developed a symptomatic UTI, 96 (83%) of whom were prescribed antimicrobial therapy. A total of 34 women (14%) with type 1 diabetes developed a UTI. The most important risk factor for these women was sexual intercourse during the week before entry into the study (44% without vs. 53% with sexual intercourse, relative risk [RR] = 3.0,  $P = 0.01$ ). A total of 81 (23%) women with type 2 diabetes developed a UTI. The most important risk factor for these women was the presence of asymptomatic bacteriuria (ASB) at baseline (25% without vs. 42% with ASB,  $RR = 1.65$ ,  $P = 0.04$ ).

**CONCLUSIONS** — Risk factors for developing a UTI are the presence of ASB for women with type 2 diabetes and sexual intercourse during the week before entry into the study for women with type 1 diabetes.

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An increased prevalence of urinary tract infections (UTIs) and asymptomatic bacteriuria (ASB) has been described in women with diabetes compared with women without diabetes (1–6). Because UTI complications (e.g., bacteremia, renal abscesses, and renal papillary necrosis) occur more often in diabetic patients, it is important to recognize UTIs in this patient

group (1,2). However, the risk factors for developing a UTI have not been defined in women with diabetes, and it is unknown whether ASB precedes symptomatic bacteriuria in these patients. Therefore, we decided to investigate which risk factors (including ASB) are associated with an increased risk of symptomatic UTI development in a large group of women with

## RESEARCH DESIGN AND METHODS

The recruitment of the patients has been described elsewhere (6). Briefly, all patients were interviewed, and data were obtained from the hospital files using a standardized questionnaire. We performed two urinary cultures to diagnose ASB in 417 of the 636 patients and did not find any significant differences between these 417 patients and the whole study group. At the moment of study entry (i.e., the initial clinical visit), all patients were given a standard form with a return envelope and were asked to mail the form to the investigator (S.E.G.) if they developed a symptomatic UTI (e.g., symptoms of dysuria, increased frequency of urination, and lower abdominal or flank pain) or used antimicrobial agents for any reason during the 18 months after inclusion. Furthermore, the treating physician asked the patient if she had developed a symptomatic UTI or had taken antimicrobials in the time between her inclusion into the study and the outpatient clinic visits for routine examination at 9 and 18 months after inclusion. Antimicrobial therapy was usually prescribed by a general practitioner after diagnosing a UTI in symptomatic women by means of urinary diagnostic tests (urine culture or microscopic analysis or leukocyte esterase on dipstick testing). The development of secondary complications (e.g., retinopathy, neuropathy, and macrovascular diseases) during this period was also recorded by the treating physician. Finally, the investigator phoned all patients (or the general practitioner of the patient, if the patient had moved) for whom these follow-up data were incomplete. HbA<sub>1c</sub>, creatinine, and urinary albumin values were determined at baseline and at the end of the follow-up period. Follow-up results were available for 589 women (93% of the study population). Reasons for inadequate follow-up included the following: impossibility of reaching the patient ( $n = 41$ ), known death (two by cardiovascular causes, one by breast carcinoma, and one by pneumonia), renal-pancreatic transplantation ( $n = 1$ ), and patient refusal ( $n = 1$ ). Clinical characteris-

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**Abbreviations:** ASB, asymptomatic bacteriuria; CFU, colony-forming units; RR, relative risk; UTI, urinary tract infection.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Clinical characteristics of the study population

Characteristics	All women	Type 1 diabetic women	Type 2 diabetic women
n	589	241	348
ASB	148 (25)	49 (20)	99 (28)
Baseline age (years)	51.9 ± 15.0	40.9 ± 13.4	59.4 ± 11.3
Diabetes duration (years)	13.7 ± 11.3	19.2 ± 13	9.8 ± 7.8
UTI previous year before study entry	126 (20)	48 (19)	78 (22)
Symptomatic UTI during follow-up	115 (20)	34 (14)	81 (23)
Cystitis	111 (19)	32 (13)	79 (23)
Pyelonephritis	3 (0.5)	1 (0.4)	2 (0.6)
Bacteremia	1 (0.2)	1 (0.4)	—
Baseline creatinine (μmol/l)	80 ± 36	81 ± 50	79 ± 21
Microalbuminuria at baseline*	28 (6)	5 (3)	23 (9)
Macroalbuminuria at baseline*	34 (8)	14 (8)	20 (8)
Baseline HbA <sub>1c</sub>	8.4 ± 1.6	8.4 ± 1.6	8.5 ± 1.7

Data are n (%) or means ± SD. \*436 women were assessed at baseline.

tics (e.g., age, percentage with type 1 diabetes, and percentage with ASB at the moment of inclusion) between patients with complete follow-up and those without follow-up did not differ significantly ( $P > 0.6$ ).

### Definitions

ASB was defined as the presence of  $\geq 10^5$  colony-forming units (CFU) per milliliter of one or two of the same microorganisms in a culture of clean-voided midstream urine from a patient without fever or symptoms of a UTI (7).

Diabetes was defined according to the 1985 World Health Organization criteria as a fasting glucose concentration of  $\geq 7.8$  mmol/l, a 2-h glucose concentration of  $\geq 11.1$  mmol/l, or the use of glucose-lowering medication (tablets or insulin) (8). Peripheral neuropathy was defined as at least one positive test result of a standardized vibration, temperature, or monofilament test or (when these tests were not performed) the presence of at least four of the following symptoms: complaints of pain, burning, pricking, numbness, or tingling sensations in the feet; an absence of ankle jerks; disturbances in pinprick or light-touch sense; and feet abnormalities (deformations, callus, ulcer, or fissure) (9). Hypertension was defined as systolic blood pressure  $>160$  mmHg, diastolic blood pressure  $>95$  mmHg, or the use of antihypertensive drugs (10). Albumin excretion was measured in 24-h urine samples and defined as normoalbuminuria when albumin excretion was  $<30$  mg/24 h, microalbuminuria when albumin excretion was 30–300 mg/24 h or when the patient used

ACE inhibitors, and macroalbuminuria when albumin excretion was  $\geq 300$  mg albumin/24 h. Patients with microalbuminuria who had received ACE-inhibition therapy from their treating physician, sometimes resulting in normoalbuminuria, were included. Therefore, we decided to include all patients with ACE inhibition therapy in the microalbuminuria group.

Lower UTI (cystitis) was defined as the presence of complaints of dysuria, frequency of urination, urgency of urination, and/or abdominal discomfort. Upper UTI (pyelonephritis) was defined as the above complaints and/or the presence of fever ( $>38.3^\circ\text{C}$ ) and flank or low-back pain (11). The relative increase in creatinine, albumin, and HbA<sub>1c</sub> was defined as the difference between the values after 18 months and the baseline values divided by the baseline values and multiplied by 100.

### Urine culture

Two screening methods were used simultaneously: first, a Uricult dipslide (Orion Diagnostica, Espoo, Finland) was dipped in freshly voided midstream urine; and second, a direct preparation was made (i.e., some urine was put on a slide and viewed with a  $40\times$  objective microscope). If at least  $10^5$  CFU/ml grew on the dipslide or if  $>5$  leukocytes or  $>10$  microorganisms were seen on the slide, the urine (stored at  $4^\circ\text{C}$ ) was plated onto blood agar and MacConkey plates, and the results were read after 24 h. Causative microorganisms were identified using the Vitek automated identification system (bioMérieux, Den Bosch, the Netherlands). All urine samples were plated

using quantitative loops at the Bosch Mediecentrum in 's-Hertogenbosch and the Diaconessenhuis in Utrecht, the Netherlands. Patients with *Lactobacilli*,  $\alpha$  streptococci, *Staphylococcus epidermidis*, and other contaminants were not included. Only uropathogens defined as *Enerobacteriaceae*, *Staphylococcus aureus*, *Staphylococcus saprophyticus*, and *Enterococci* were included. No results were noted if more than three different microorganisms grew on the plate and the urine was regarded as contaminated.

### Statistical analysis

Risk factors for the incidence of a UTI were investigated using the Cox proportional hazard analysis, which resulted in a hazard ratio as the approximation of the relative risk (RR). All analyses were performed on women with type 1 diabetes and type 2 diabetes separately. A two-tailed  $P$  value  $<0.05$  was considered statistically significant. The statistical software SPSS (release 9.0) for Windows was used.

**RESULTS** — Baseline characteristics of the study population are shown in Table 1. Of the total study population ( $n = 589$ ), 115 women (20%) developed a symptomatic UTI, 96 (83%) of whom received antimicrobial therapy. A total of 17% of the diabetic patients did not receive antimicrobial therapy, because the general practitioner treated them with additional fluid intake or cranberry juice. Among the patients who developed a UTI, the mean number of UTIs was 1.9 per patient; 67 patients developed one UTI, 28 patients developed two UTIs, 8 patients developed three UTIs, and 12 patients developed more than four UTIs. Five of these patients with more than two UTIs may have had a recurrence with the same microorganism, because they developed the second UTI within 2 weeks of the first UTI. The first UTI during follow-up was used in all analyses. The cystitis-to-pyelonephritis ratio was 37:1. The mean duration between the moment of study inclusion and development of a UTI was 7 months. A total of 45% of the type 1 diabetic and 25% of the type 2 diabetic women ( $P < 0.001$ ) had had sexual intercourse the week before study entry. This difference is the result of the lower mean age of women with type 1 diabetes compared with women with type 2 diabetes (40.9 vs. 59.4 years), because younger women more often had sexual intercourse the week before study entry (mean ages with and without sexual intercourse were 44.5 and 55.4 years, respectively,  $P < 0.001$ ).

**Table 2—Risk factors for the development of a UTI in women with type 1 diabetes**

Risk factors	UTI-negative	UTI-positive	RR (95% CI)	P
n	241	207 (86)	34 (14)	
Age (years)	41.4 ± 13.1	40.3 ± 13.5	0.98* (0.96–1.01)	0.2
ASB	21 (43)	6 (18)	1.20 (0.45–3.18)	0.7
Sexual intercourse	90 (44)	18 (53)	2.98 (1.30–6.83)	0.01
Oral contraceptive use	55 (27)	13 (38)	2.41 (1.12–5.17)	0.02
Macroalbuminuria	12 (7)	2 (7)	0.70 (0.21–2.33)	0.6
Macrovascular complications	24 (12)	3 (9)	0.21 (0.05–0.92)	0.04
Peripheral neuropathy	63 (30)	8 (24)	0.47 (0.20–1.11)	0.08
HbA <sub>1c</sub> (%) at inclusion	8.3 ± 1.5	8.6 ± 1.5	1.03† (0.75–1.42)	0.9
HbA <sub>1c</sub> (%) after 18 months	8.4 ± 5.0	8.1 ± 1.2	1.27† (0.90–1.79)	0.2

Data are n (%) or means ± SD, unless otherwise indicated. \*Units per year; †units per %.

### Risk factors for the development of a UTI in women with type 1 diabetes

A total of 34 of the 241 women (14%) with type 1 diabetes developed a UTI. Risk factors for the development of a UTI in these women were sexual intercourse (in the week before study entry) and oral contraceptive use (Table 2). The presence of macrovascular complications at the moment of study entry protected these women against the development of a UTI (Table 2). When a multivariate Cox proportional hazard analysis was performed (for sexual intercourse, macrovascular complications, and oral contraceptive use), only sexual intercourse remained a significant risk factor (RR = 3.6, P = 0.004).

### Risk factors for the development of a UTI in women with type 2 diabetes

A total of 81 of the 348 women (23%) with type 2 diabetes developed a UTI. The only significant risk factor for the development of a UTI in these patients was the presence of ASB at the moment of study entry (Table 3).

In both patient groups, age, glycemic control (HbA<sub>1c</sub> levels), the presence of peripheral neuropathy, and macrovascular complications did not influence the risk of developing a UTI. In addition, the presence of postvoiding bladder residue did not increase the chance of developing a UTI.

**CONCLUSIONS** — We investigated which clinical characteristics predisposed diabetic women to the development of a symptomatic UTI during an 18-month follow-up. We found that sexual intercourse the week before study entry and oral contraceptive use in type 1 diabetic women and the presence of ASB in type 2 diabetic women significantly increased the risk of developing a UTI during this period.

Earlier case-control studies in young women without diabetes have demonstrated that sexual intercourse and diaphragm/spermicide or condom use are significantly associated with the presence of UTIs (12,13). A large prospective study of sexually active young women also showed that recent sexual intercourse and the use of diaphragms with spermicide were strong risk factors for UTI development (14). An association between sexual activity and bacteriuria has been previously described in women with type 2 diabetes (15). We found that sexual intercourse was the most important risk factor for UTI development in women with type 1 diabetes, but could not demonstrate that the use of diaphragm/spermicide combinations or condoms was associated with an increased risk of UTI, because these contraceptives were only used in a very small number of patients. Thus, it seems that women with type 1 diabetes have the same risk factors for developing a UTI as other young women. We also demonstrated that the presence of macrovascular complications was inversely correlated with the risk of developing a UTI in women with type 1 diabetes (RR <1). The protective effect of

the presence of macrovascular complications in type 1 diabetic women is difficult to explain. It might be possible that women with macrovascular complications have less sexual intercourse (the most important risk factor for UTI in women with type 1 diabetes) than women without this complication. This is supported by the multivariate analysis, in which only sexual intercourse remained as a significant risk factor.

In a 1-year follow-up study (16) of women without diabetes, it was demonstrated that women with ASB at study entry had a significantly higher chance of developing a symptomatic UTI than nonbacteriuric women. That study also showed that age was positively correlated with the presence of ASB at baseline, but not with the development of a UTI during follow-up (16). We found comparable results in women with type 2 diabetes. The only significant risk factor for the development of a symptomatic UTI in women with type 2 diabetes was the presence of ASB at the moment of study entry. Thus, it seems that ASB precedes symptomatic bacteriuria in these patients. Placebo-controlled antimicrobial therapy trials should prove whether treatment of ASB in women with type 2 diabetes should be advised.

We did not find that poor regulation of diabetes or the presence of diabetic cystopathy, neuropathy, macroalbuminuria, or macrovascular complications increased the risk of UTI development. The absence of correlation between the presence of bacteriuria and diabetes regulation, the presence of bladder residue, or macrovascular complications have been described before (4,5,17,18). We have shown that glucosuria enhances bacterial growth in vitro (19), but could not confirm this finding in vivo. In other words, glucosuria was not a risk factor for ASB (6) or the development of a symptomatic UTI. This might be the result

**Table 3—Risk factors for the development of a UTI in women with type 2 diabetes**

Risk factors	UTI-negative	UTI-positive	RR (95% CI)	P
n	348	267 (77)	81 (23)	
Age (years)	59.1 ± 11.8	60.5 ± 9.4	1.01* (0.99–1.03)	0.5
ASB	66 (25)	32 (42)	1.65 (1.02–2.67)	0.04
Macroalbuminuria	12 (6)	8 (11)	0.84 (0.41–1.70)	0.6
Macrovascular complications	76 (28)	25 (31)	1.59 (0.98–2.59)	0.06
Peripheral neuropathy	110 (41)	41 (51)	0.89 (0.57–1.38)	0.6
HbA <sub>1c</sub> (%) at inclusion	8.5 ± 1.7	8.6 ± 1.7	0.94† (0.82–1.09)	0.4
HbA <sub>1c</sub> (%) after 18 months	8.5 ± 4.2	8.1 ± 1.2	1.07† (0.85–1.39)	0.6

Data are n (%) or means ± SD, unless otherwise indicated. \*Units per year; †units per %.

of differences between the conditions in vitro (growth during 6 h) and in vivo (micturition every 4–6 h).

No consensus exists about treatment of ASB in diabetic patients (20). Many experts in the U.S. recommend treating ASB in diabetic patients because of the frequency and severity of upper UTI (1). On the other hand, European experts suggest that the benefit of treatment is doubtful (21), and therefore most diabetic women with ASB are not treated in Europe. This contradiction is the result of a lack of follow-up studies of diabetic women with untreated ASB. At this moment, it is not known whether diabetic patients with ASB should be treated, because it is unclear whether the treatment of ASB prevents either the development of symptomatic UTI or a decline in renal function. When a symptomatic UTI is present in diabetic patients, it has to be considered a complicated UTI. Consequently, it must be treated with agents that reach high tissue levels (e.g., amoxicillin-clavulanic acid, trimethoprim/sulfamethoxazole, or fluorquinolones) for a duration of 10–14 days (1,22). The eradication of microorganisms that cause UTI has been reported to be more difficult in diabetic patients than in nondiabetic patients because of an increased frequency of multidrug resistance (23,24).

The most important limitation of this study is that we did not culture the urine samples the moment the patient developed symptoms of a UTI. However, the Dutch Institute for Quality Assurance guidelines advise diagnosing UTIs with either sediment microscopy or a nitrite test (25), which was performed in 83% of the cases. Another restriction is that we only asked the women whether they had had sexual intercourse the week before study entry. We do not know if this is a good measurement for being sexually active during the follow-up period. However, we demonstrated that oral contraceptive use, which probably is associated with regular sexual intercourse, was also a risk factor for the development of a symptomatic UTI in women with type 1 diabetes. Furthermore, Scholes et al. (26) showed that any sexual intercourse during the patient's lifetime and sexual intercourse in the past year were strongly associated with the development of recurrent UTIs.

In conclusion, independent risk factors for the development of a UTI include sexual intercourse in women with type 1 diabetes and ASB at study entry in women with type 2 diabetes. Poor regulation of dia-

betes or the presence of neuropathy, bladder residue, macroalbuminuria, or macrovascular complications did not increase the risk of UTI development. Thus, the risk factors for UTI development in diabetic women are the same as those reported for women without diabetes.

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**APPENDIX** — The Diabetes Women Asymptomatic Bacteriuria Utrecht Study Group included the authors and the following physicians: E.W.M.T. ter Braak, M.C. Castro Cabezas, P.S. van Dam, T.W. van Haeften, P.C. Ligtenberg-Oldenburg, H.W. de Valk, H.E. Westerveld, and P.M.J. Zelissen, University Medical Center, Utrecht; B. Bravenboer, Catharina Hospital, Eindhoven; J.B.L. Hoekstra and W.M.N. Hustinx, Diakonessenhuis, Utrecht; K.P. Bouter, Bosch Medicentrum, 's-Hertogenbosch; the general practitioners C.L.M. Appelman, C.P. Bouter, W.H. Eizenga, Y.W.M. Gresnigt, W. van der Kraan, and M.E. Numans, Utrecht; and G. IJff, Amsterdam; the students M. Bellaar, M. Kuipers, and R. Jansen, who recruited the patients; and the medical microbiologists J. Verhoef, University Hospital, Utrecht; A.R. Jansz, St. Joseph Hospital, Veldhoven; P.M.N. Schneeberger, Bosch Medicentrum, 's-Hertogenbosch; and R.J.A. Diepersloot, Diakonessenhuis, Utrecht, at whose laboratories urinary cultures were performed.

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