Asymptomatic Bacteriuria May Be Considered a Complication in Women With Diabetes

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OBJECTIVE — To study the prevalence of and risk factors for asymptomatic bacteriuria (ASB) in women with and without diabetes.

RESEARCH DESIGN AND METHODS — A total of 636 nonpregnant women with diabetes (type 1 and type 2) who were 18–75 years of age and had no abnormalities of the urinary tract, and 153 women without diabetes who were visiting the eye and trauma outpatient clinic (control subjects) were included. We defined ASB as the presence of at least 10^5 colony-forming units/ml of 1 or 2 bacterial species in a culture of clean-voided midstream urine from an individual without symptoms of a urinary tract infection (UTI).

RESULTS — The prevalence of ASB was 26% in the diabetic women and 6% in the control subjects ($P < 0.001$). The prevalence of ASB in women with type 1 diabetes was 21%. Risk factors for ASB in type 1 diabetic women included a longer duration of diabetes, peripheral neuropathy, and macroalbuminuria. The prevalence of ASB was 29% in women with type 2 diabetes. Risk factors for ASB in type 2 diabetic women included age, macroalbuminuria, a lower BMI, and a UTI during the previous year. No association was evident between current HbA_{1c} level and the presence of ASB.

CONCLUSIONS — The prevalence of ASB is increased in women with diabetes and might be added to the list of diabetic complications in these women.

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Patients with diabetes have an increased risk of infections (1,2), with the urinary tract being the most prevalent infection site (3,4). In fact, a 1940 autopsy study showed that 18% of the subjects with diabetes had a urinary tract infection (UTI) (5). Many UTIs are asymptomatic, and whether symptomatic UTIs are preceded by asymptomatic bacteriuria (ASB) is not known (6,7). In contrast with men, a higher prevalence of ASB has been found in women with diabetes than in women without the disease (4,6–9). Some investigators, however, have been unable to confirm this finding (10,11). Because more UTI complications (e.g., bacteremia, renal abscesses, renal papillary necrosis) are seen in patients with diabetes versus individuals without diabetes (12) and because renal involvement even without the presence of symptoms (e.g., subclinical pyelonephritis) is common (13,14), investigating the association between ASB and symptomatic UTI in women with diabetes is important.

Various risk factors for ASB in women with diabetes have been suggested, including sexual intercourse; age; and duration of, metabolic control of, and complications of diabetes (7–9,15–18). Most studies, however, included only a small number of patients from 1 hospital (or only tertiary care hospitals [18]), often without distinguishing between type 1 and 2 diabetes.

The aim of the present multicenter study, therefore, was to determine the prevalence of and the risk factors for ASB in a large number of women with either type 1 or type 2 diabetes.

RESEARCH DESIGN AND METHODS

Patient enrollment and evaluation

Women 18–75 years of age with either type 1 or type 2 diabetes were recruited between October 1996 and September 1997 from the diabetes outpatient clinics of University Hospital (Utrecht, the Netherlands) (a tertiary care hospital), 3 nonuniversity hospitals (Diakonessenhuis, Utrecht; Bosch Medicentrum's Hertogenbosch, den Bosch; and Catharina Hospital, Eindhoven), and the offices of 7 general practitioners in the Netherlands. Exclusion criteria were pregnancy, recent hospitalization or surgery (within the past 4 months), known urinary tract abnormalities (including cystopathy or recent urinary tract instrumentation), symptoms of a UTI (the presence of dysuria, frequency or urgency, stranguria, abdominal discomfort, or fever [4 patients]), or the use of antimicrobial drugs during the previous 14 days (which was the reason for exclusion in 20 patients). Approximately 75% (687) of

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Abbreviations: ASB, asymptomatic bacteriuria; cfu, colony-forming units; hpf, high-power field; OR, odds ratio; UTI, urinary tract infection.

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

the eligible women participated. No differences were evident regarding age or type and duration of diabetes between nonparticipating patients and the final study group (data not shown). At least 1 uncontaminated midstream urine sample was available from 648 women. The study had the approval of the ethics committees of all hospitals. All patients gave their written informed consent.

All patients were interviewed during the first visit of the study and their medical history was obtained from the hospital files with a standardized questionnaire. This information included age, type and duration of diabetes, medication, secondary complications of the diabetes (retinopathy by funduscopy [background, nonproliferative, proliferative], macrovascular diseases [stroke, myocardial infarction, ischemia, intermittent claudication], peripheral neuropathy), pregnancies, or urinary tract surgery during the previous years, number of UTIs during the past year, recent pregnancy (<6 months ago), recent sexual intercourse (within 1 week), contraceptive method (oral contraceptives, condoms, intrauterine devices, cervical caps), menopausal status, and the use of (local) estrogens. Blood pressure, weight, and height (BMI) were also recorded. The following laboratory values were obtained: HbA_{1c}, serum creatinine, blood group, microalbuminuria, glucosuria, leukocyturia, and urinary pH. In addition, the bladder residue (≥5 ml) after micturition was measured in 106 randomly chosen patients with a bladder scan (19,20), and 3 standardized parasympathetic and 2 standardized sympathetic tests (previously described by Ewing and Clarke [21]) were performed in 40 (randomly chosen) patients to assess cardiovascular autonomic neuropathy (mild, moderate, and severe) as previously described (22).

Definitions

By following the 1985 WHO criteria, we defined diabetes as a fasting glucose concentration of ≥7.8 mmol/l, a 2-h glucose concentration of ≥11.1 mmol/l, or the use of glucose-lowering medications (oral agents or insulin) (23). Type 1 diabetes was defined as the absolute deficiency of insulin secretion (24) and, according to the data of the treating physician, was measured as the absence of C-peptide. Type 2 diabetes was defined as the combination of resistance to insulin action and an inadequate compensatory insulin secretory response (24). Peripheral neuropathy was defined as at least 1 positive test result from a standardized vibration, temperature, or monofilament test or (when these tests were not performed) the presence of at least 4 of the following symptoms: pain, burning, pricking, numbness, or tingling sensations in the feet; an absence of ankle jerks; disturbances in pinprick or light touch sense; or foot abnormalities (deformations, calluses, ulcers, fissures) (25). Hypertension was defined (in all age-groups) as a systolic blood pressure level >160 mmHg, a diastolic blood pressure level >95 mmHg, or the use of antihypertensive drugs (26). We measured albumin excretion with 24-h urine collection. We defined normoalbuminuria as albumin excretion <30 mg/24 h, we defined microalbuminuria as either the excretion of 30–300 mg albumin/24 h or the use of ACE inhibitors, and we defined macroalbuminuria as the excretion of at least 300 mg albumin/24 h.

ASB was defined as the presence of at least 10^5 colony-forming units (cfu)/ml of 1 or 2 bacterial species in clean-voided midstream urine sample from an individual without symptoms of a UTI (27). We defined contaminated urine as the presence of at least 3 different microorganisms in 1 urine specimen. These specimens were excluded.

Control group

To investigate the prevalence of ASB in women without diabetes for 8 weeks, all women visiting the eye and trauma outpatient clinic who did not have diabetes were asked to collect 2 consecutive midstream urine specimens. The response rate was 85%. The clinical characteristics of the patients who did not enter the study did not differ from the study group. Exclusion criteria were the same as for the women with diabetes. A total of 153 women were included (means ± SD age 47.8 ± 16.4 years).

Urine

Midstream clean voiding urine specimens were collected for the evaluation of bacteriuria with an interval of 2–4 months. All urine samples were immediately refrigerated and were cultured 2 h after collection. No correlation was found regarding the length of the interval between the 2 cultures and the presence of bacteriuria ($P > 0.2$). This means that the different time intervals (for example, 2 or 3 months) between the 2 cultures did not influence the results. Urine culture was performed according to standard procedures: urine was screened with either a uricult dipslide (Orion Diagnostica, Espoo, Finland) or a direct preparation. If $\geq 10^5$ cfu/ml were grown on the dipslide or if more than 5 leukocytes or 10 microorganisms were seen on the slide, then the urine was plated onto blood agar and MacConkey plates. All urine samples were plated using quantitative loops at Bosch Medicentrum and Diakonessenhuis. The results were read after 24 h. Microorganisms were identified with the Vitek automated identification system (bioMerieux, den Bosch, the Netherlands). If the urine was considered contaminated, then the patient was asked to submit another specimen.

Glucosuria, leukocyturia, and urinary pH values were determined using a dipslide method (Combur-Test; Boehringer Mannheim, Almere, the Netherlands).

Statistical analysis

Differences between patients with and without ASB were tested with the *t* test for continuous variables (age, duration of diabetes, BMI, HbA_{1c}, creatinine, postvoiding residual volume, and blood pressure) and the Mann-Whitney *U* test for dichotomous and ordinary variables (number of UTIs during the previous year, number of pregnancies, albuminuria, glucosuria, leukocyturia, and urinary pH). In addition, multiple logistical regression analysis was used for all other variables to calculate the odds ratios (ORs) for the presence of ASB. *P* values and ORs of all variables except duration of diabetes were adjusted for age. A 2-tailed *P* value of <0.05 was considered to be statistically significant. SPSS statistical software for Windows (Version 6.1; Chicago) was used.

RESULTS

Urine cultures

At least 1 uncontaminated midstream urine sample was available from 648 women. A total of 2 urine cultures were collected from 508 women. Of these, 417 had either 2 positive cultures with the same microorganism (n = 53, 13%) or 2 negative cultures (n = 364, 87%). A total of 91 women had 2 urine cultures with different culture results. Women with 2 cultures yielding 2 different microorganisms (regardless of the type of microorganism) in the consecutive cultures were excluded (n = 12, 1.9%) because their urine was considered to be contaminated. Therefore, 636 women were included in the study. A total of 36 women (5.7%) had a positive first culture and a negative second culture. These women had

Table 1—*Patient characteristics*

Patient characteristics	Type 1 diabetes	Type 2 diabetes
n	258	378
Age	40.9 ± 13.4	59.4 ± 11.4
University hospital	143 (55)	122 (32)
Nonuniversity hospital	115 (45)	232 (61)
General practitioner	0 (0)	24 (7)
Duration of diabetes (years)	18.8 ± 12.8	9.9 ± 7.8
Retinopathy (*n* = 620)	86 (34)	90 (25)
Macrovascular complications (*n* = 632)	31 (12)	112 (30)
Peripheral neuropathy (*n* = 585)	64 (26)	127 (37)
Cardiovascular neuropathy (*n* = 40)	13 (62)	16 (84)
UTI during the previous year	48 (19)	78 (21)
BMI (kg/m^2)	24.7 ± 4.3	29.4 ± 5.9
Systolic blood pressure (mmHg)	132 ± 18	144 ± 18
Diastolic blood pressure (mmHg)	75 ± 9	80 ± 10
HbA_{1c} (%)	8.6 ± 1.9	8.5 ± 1.7
Serum creatinine (μmol/l)	83 ± 60	80 ± 21
Normoalbuminuria	138 (70)	97 (42)
Microalbuminuria (*n* = 428)	44 (22)	113 (49)
Macroalbuminuria (*n* = 428)	15 (8)	21 (9)
Positive urine culture	53 (21)	110 (29)
E. coli in positive cultures	18 (35)	50 (46)

Data are *n*, means ± SD, or *n* (%). Number (*n*) of patients is given when the variable concerned is not measured in all patients.

not used antimicrobial drugs during the time between the 2 cultures. We hypothesized that that they spontaneously cleared the bacteria from their urine. A total of 43 women (6.8%) had a negative first culture and a positive second culture. These 2 groups (*n* = 79, 12% of the total number of patients) were classified as ASB$^+$. A total of 140 women collected only 1 urine specimen; 31 had a positive culture result, and 109 had a negative culture result. These women were defined as ASB$^+$ or ASB$^-$, respectively. We evaluated the clinical characteristics of women with 1 positive culture and women with 2 positive cultures and did not find any differences ($P > 0.2$). Therefore, we decided to analyze the risk factors in women with 1 and 2 positive cultures together and classified them as ASB$^+$.

Study population

The patient characteristics of the study population are given in Table 1. Both the patients and their physicians were blinded for the culture results. Women with type 2 diabetes more often had peripheral and cardiovascular neuropathy than women with type 1 diabetes. This is probably the result of the higher age of women with type 2 diabetes. A total of 29 women with type 1 diabetes and 98 women with type 2 diabetes used ACE inhibitors at study entry. They all had hypertension and were classified as having microalbuminuria. Severe autonomic cardiovascular neuropathy was present in 3 of the 20 tested women with type 1 diabetes and in 2 of the 20 tested women with type 2 diabetes. Postvoiding bladder residue was measured in 106 patients; none of them had a residue of >50 ml. Only 5 women with type 1 diabetes and 14 women with type 2 diabetes had a postvoiding residue between 25 and 50 ml. No differences in the risk of having ASB were evident for patients from university versus nonuniversity hospitals.

Of the total study group (*n* = 636) (type 1 and type 2 diabetes grouped together), 163 (26%) women were ASB$^+$. In 58% of the positive cultures, >5 leukocytes/high-power field (hpf) were present in the urine. *Escherichia coli* was isolated in 68 patients (42%). Other isolated microorganisms included *Enterococcus species, Proteus vulgaris, Proteus mirabilis, Streptococcus hemolyticus* group B and group G, *Klebsiella pneumoniae, Klebsiella oxytoca, Enterobacter cloacae, Staphylococcus aureus*, and coagulase-negative *Staphylococci*. We did not consider cultures positive for *Candida* species to be a positive result because we studied the prevalence of bacteriuria and because differentiating *Candida* bacteriuria from *Candida* vaginitis is difficult.

In the nondiabetic control group (153 patients), 9 patients (6%) had a positive urine culture result. *E. coli* was the causative microorganism in 7 of those patients (78%). After adjusting for age, the prevalence of ASB was significantly higher in the patients with diabetes than in the control group ($P < 0.001$).

Risk factors for ASB

A total of 53 women with type 1 diabetes (entire group *n* = 258) were ASB$^+$ (prevalence 21%), with *E. coli* being the causative microorganism in 18 women (35%) (Table 1). More than 5 leukocytes/hpf were present in 33% of the positive cultures. Risk factors for the presence of ASB in type 1 diabetic patients are shown in Table 2. Only the presence of peripheral neuropathy and macroalbuminuria remained significant risk factors when multivariate logistical regression analysis (for diabetes duration, peripheral neuropathy, and macroalbuminuria) was used. No differences in these analyses were evident between the peripheral neuropathy group tested with the standardized vibration, temperature, or monofilament test (already investigated by the patients' physicians) and the peripheral neuropathy group tested by the investigators.

Table 2—*Risk factors for women with type 1 diabetes*

Risk factors	ASB$^-$	ASB$^+$	OR	*P*
n	205 (79)	53 (21)		
Age	40.3 ± 13.5	43.1 ± 13.1		0.2
Duration of diabetes (years)	17.9 ± 12.9	22.4 ± 12.1		0.02
Peripheral neuropathy (*n* = 245)	44 (23)	20 (40)	2.2	0.03
Microalbuminuria (*n* = 197)	30 (20)	14 (30)	1.8	0.1
Macroalbuminuria (*n* = 197)	8 (5)	7 (16)	3.6	0.02
HbA_{1c} (%)	8.5 ± 1.5	8.8 ± 2.9		0.3

Data are *n* (%), means ± SD, or ORs. Risk factors for asymptomatic bacteriuria (ASB) in women with DM type 1. Number (*n*) of patients is given when the variable concerned is not measured in all patients.

Table 3—*Risk factors for women with type 2 diabetes*

Risk factors	ASB$^-$	ASB$^+$	OR	*P*
n	268 (71)	110 (29)		
Age	58.0 ± 11.7	63.0 ± 10.0		<0.001
Duration of diabetes (years)	9.3 ± 7.1	11.3 ± 9.1		0.05
Microalbuminuria (*n* = 231)	78 (46)	35 (52)	1.1	0.5
Macroalbuminuria (*n* = 231)	10 (6)	11 (15)	2.9	0.03
UTIs during the previous year	48 (18)	30 (27)	1.9	0.02
BMI (kg/m^2)	29.9 ± 6.2	28.3 ± 4.8	0.96	0.04
HbA_{1c} (%)	8.6 ± 1.7	8.5 ± 1.6		0.7

Data are *n* (%), means ± SD, or ORs. Risk factors for asymptomatic bacteriuria (ASB) in women with type 2 diabetes.

A total of 110 women with type 2 diabetes (entire group *n* = 378) were ASB$^+$ (prevalence 29%), with *E. coli* being the causative microorganism in 50 women (46%). More than 5 leukocytes/hpf were present in 68% of the positive cultures. Risk factors for ASB in type 2 diabetic patients are shown in Table 3. Only age remained a significant risk factor when a multivariate logistical regression analysis (for age, macroalbuminuria, BMI, and UTIs during the previous year) was performed.

The HbA_{1c} levels in both type 1 and type 2 diabetic patients did not influence the risk of ASB. No tendency to association was present between glucosuria and ASB: 42% of the women without and 38% of the women with ASB had glucosuria (P = 0.4). Postmenopausal women had an increased risk of ASB (P = 0.01); however, because older women are postmenopausal, this risk factor disappeared after adjusting for age. Moreover, in both type 1 and type 2 diabetic patients, the presence of cardiovascular autonomic dysfunction, a postvoiding bladder residue, sexual intercourse during the week before study entry, various methods of contraception (condoms, diaphragms), or (local) estrogen treatment did not increase the odds of developing ASB. We also could not find a correlation between cardiovascular autonomic disturbances or the presence of peripheral neuropathy and a bladder residue after micturition.

CONCLUSIONS — In this study, we found that the prevalence of ASB is higher in women with diabetes than in women without diabetes (26 vs. 6%). We also noted a lower percentage of *E. coli* in women with diabetes versus women without the disease (42 vs. 78%), which confirms the results of a study by Lye et al. (28) that showed that *E. coli* is the predominant microorganism in UTIs in diabetic patients, but that *E. coli* occurs in significantly lower numbers than in control subjects.

We found that the risk factors for ASB in women with type 1 diabetes are a longer duration of diabetes and the presence of macroalbuminuria and peripheral neuropathy. Therefore, a longer duration of diabetes with the presence of complications seemingly increases the risk of ASB in type 1 diabetic women. Macroalbuminuria, as an expression of severe structural damage in the kidney, may increase the vulnerability to bacterial attacks, thus resulting in an increased risk of developing ASB. No comparable studies of only women with type 1 diabetes are available. Therefore, we must compare our results with those of studies with women with type 2 diabetes or with combined analyses of women with type 1 and type 2 diabetes. Vejlsgaard (17) and Keane et al. (9) found a correlation among duration of the diabetes, the presence of microvascular diseases, and the presence of ASB in type 1 and 2 diabetic patients. When women with type 2 diabetes were studied separately, some studies showed that a longer duration of the diabetes (8,18) and the presence of long-standing complications (peripheral neuropathy, peripheral vascular disease) (8) increased the risk of developing ASB. These findings could not be confirmed by other studies (7,10,15). All of these studies, however, were conducted in single hospitals or with smaller numbers of patients than in the present study.

Age is a well-known risk factor for bacteriuria in women without diabetes (29). Age was also the most important risk factor for ASB in type 2 diabetic patients in the present study. Earlier studies, however, have reported contradictory results (30), with most not showing an increased incidence of ASB in elderly women with diabetes (6,8,15,18). Other risk factors for ASB in type 2 diabetic patients in this study were macroalbuminuria, a lower BMI, and a UTI during the previous year. Except for the lower BMI, these risk factors have been reported previously in type 2 diabetic patients (10,15,17). Previous UTI as a risk factor for ASB indicates that bacteriuria can be present with or without symptoms in the same patient. The significant positive correlation of a lower (but still very high) BMI with ASB in women with type 2 diabetes is difficult to explain. The correlation is probably a coincidence because BMI disappeared as a risk factor in the multivariate analysis and had an OR of nearly 1.

In an earlier study (16), women with diabetes (type 1 and 2) with ASB had significantly more cardiovascular autonomic function disturbances than nonbacteriuric women. Furthermore, those disturbances did not correlate with the presence of a postvoiding bladder residue. Because this risk factor disappeared in the present study after adjusting for age, we could not demonstrate that the presence of cardiovascular autonomic dysfunction or a postvoiding bladder residue increased the odds of developing ASB. This lack of association between the presence of diabetic cystopathy and bacteriuria has been shown before (31). We were also unable to show a correlation among the presence of peripheral neuropathy, bladder residue, and ASB.

Studies have demonstrated in women with (15) and without (32,33) diabetes that recent sexual intercourse, the use of a diaphragm (32,33), or the use of spermicide-coated condoms (34,35) increases the risk of developing bacteriuria. We could not, however, demonstrate that recent sexual intercourse was a risk factor in our patient group. Furthermore, we found no differences between the different contraceptive methods. Higher age and the lower frequency of sexual intercourse of the patients in our study (compared with the studies mentioned above) were probably the reasons for the absence of an association between sexual intercourse and bacteriuria.

Our results may indicate that ASB is a complication of diabetes in women. Endothelial dysfunction, oxidative stress, and the increased formation of advanced glycosylation end products may play a role in the development of diabetic complications (36–38). Interestingly, these factors may also contribute to the development of infections because these factors can lead to

disturbances in monocyte migration and cytokine and chemoattractant production (38). Thus, diabetic complications and bacteriuria may partly have the same pathogenesis. Only 33% of women with type 1 diabetes and ASB had leukocyturia. We have now found that diabetic women with ASB have lower urinary cytokine concentrations and therefore decreased urinary leukocyte numbers compared with nondiabetic women with ASB (39). We previously have shown that no differences in granulocyte functions are present among bacteriuric diabetic, nonbacteriuric diabetic, and nondiabetic control subjects (40). The increased prevalence of ASB in diabetic patients is probably partly the result of a lower leukocyte number and not the result of a dysfunction of granulocytes in diabetic patients compared with control subjects.

No consensus exists regarding the treatment of ASB in diabetic patients (41). Many experts in the U.S. recommend treating ASB in diabetic patients because of the frequency and severity of upper UTIs (12). On the other hand, European experts believe that the benefit of treatment is doubtful (42), and therefore most diabetic women with ASB are not treated in Europe. This contrast is the result of a lack of follow-up studies of diabetic women with untreated ASB. At this time, whether diabetic patients with ASB should be treated is not known because whether treatment of ASB prevents the development of symptomatic UTI or a decline in renal function is not clear. Long-term follow-up studies (like the ongoing study with our patient group) will show whether ASB becomes symptomatic and affects renal function in diabetic patients and whether treatment of ASB is warranted.

In conclusion, we have shown in this multicenter study of type 1 and type 2 diabetic women that the prevalence of ASB is higher in women with diabetes than in women without diabetes. Risk factors in women with type 1 diabetes include a longer duration of diabetes, peripheral neuropathy, and macroalbuminuria. In women with type 2 diabetes, older age is the strongest risk factor. Other risk factors for these women include macroalbuminuria, a lower BMI, and a UTI during the previous year. Therefore, we conclude that ASB may be considered a complication of diabetes in women.

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APPENDIX

Members of the Diabetes Mellitus Women Asymptomatic Bacteria Utrecht Study Group

Besides the authors of this article, the Diabetes Mellitus Women Asymptomatic Bacteriuria Utrecht (DWABU) Study Group also includes the following: physicians Edith W.M.T. ter Braak, Manuel C. Castro Cabezas, Timon W. van Haeften, Christina Ligtenberg-Oldenburg, Harold W. de Valk, Tineke Westerveld, and Pierre M.J. Zelissen, University Hospital, and W.M.N. Hustinx, Diakonessenhuis, Utrecht; recruiting students Maryke Bellaar, Monique Kuipers, and Rosemaryn Jansen (University Hospital, Utrecht); general practitioners Cees L.M. Appelman, Kees Bouter, Wim H. Eizenga, Y. Wim M. Gresnigt, Wim van der Kraan, and Manon E. Numans, Utrecht, and Gerard Ijff, Amsterdam; and medical microbiologists Jan Verhoef (University Hospital, Utrecht), Peter M.N. Schneeberger (Bosch Medicentrum, den Bosch), and Rob J.A. Diepersloot (Diakonessenhuis, Utrecht) at whose laboratories the urinary cultures were performed.

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