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Asymptomatic Bacteriuria in Women With Diabetes Mellitus

Effect on Renal Function After 6 Years of Follow-up

Ruby Meiland, MD, PhD; Suzanne E. Geerlings, MD, PhD; Ronald P. Stolk, MD, PhD; Patrick M. Netten, MD; Peter M. Schneeberger, MD, PhD; Andy I. M. Hoepelman, MD, PhD

Background: The long-term consequences of asymptomatic bacteriuria (ASB) on renal function in women with diabetes mellitus (DM) are unknown.

Methods: A prospective study was performed among women with type 1 or type 2 DM. Women with ASB (diagnosis based on findings from 1 urine culture specimen) were compared with women without ASB for differences in renal function development and incidence of hypertension.

Results: A total of 644 women were included in the study (296 with type 1 DM and 348 with type 2 DM; mean [SD] age, 51 [15] years) and followed up for a mean (SD) duration of 6.1 (1.9) years. The prevalence of ASB was 17%. In women with DM and ASB, the creatinine clearance decreased from 87 mL/min (1.45 mL/s) at baseline to 76 mL/min (1.27 mL/s) at study end point; in women with DM without ASB the creatinine clearance decreased from 97 to 88 mL/min (from 1.62 to 1.47 mL/s). In the multivariate analyses, adjusted for age, length of follow-up, duration of DM, and microalbuminuria at baseline, no association was found between ASB and the relative or absolute decrease in creatinine clearance; the same results were shown also when women with DM type 1 and women with DM type 2 were analyzed separately. Women with ASB developed hypertension more often than women without ASB (34% vs 37%; P = .045), but there was no significant association in the multivariate analysis (odds ratio, 1.5; 95% confidence interval, 0.7-3.6).

Conclusion: Women with DM (type 1 or type 2) with ASB do not have an increased risk for a faster decline in renal function or the development of hypertension after 6 years of follow-up.

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versity Medical Center Utrecht, 3 nonuniversity hospitals (Bosch Medicentrum, ’s Hertogenbosch, the Netherlands; Diakoneshuis, Utrecht, the Netherlands; and Catharina Hospital, Eindhoven, the Netherlands), or the offices of 5 general practitioners. Patients were asked to participate by their treating physician and enrolled by one of the investigators. Women aged 18 to 75 years were eligible to participate if they had either type 1 DM or type 2 DM (defined by the treating physician). Exclusion criteria were pregnancy, recent hospitalization or surgery (within the past 4 months), known urinary tract abnormalities, symptoms of a UTI, or the use of antimicrobial drugs within the previous 14 days. The study was approved by the medical ethics committee of all hospitals. All patients gave written informed consent.

DATA COLLECTION

All patients were interviewed at baseline using a standardized questionnaire including age, number of UTIs within the previous year, pregnancies, urinary tract surgery, recent sexual intercourse (within the past week), contraceptive use, menopausal status, and use of (local) estrogens, as published previously. Their medical records were reviewed at baseline and at study closure to collect additional information on type and duration of DM, secondary complications of DM, and medication. Blood pressure, weight, and height were recorded at baseline and study closure. Serum creatinine, hemoglobin A1c (HbA1c), and urinary albumin excretion were extracted from the electronic patient database. The mean (SD) time from the date of creatinine measurement until inclusion was 44 (163) days. In addition, the last creatinine measurement before the end of study (ie, January 1, 2005) was noted, and the date of blood withdrawal was taken at study end point for that individual. In case a patient died or needed kidney dialysis or kidney transplantation, the last ambulatory creatinine value was noted. The Cockcroft-Gault equation was used to estimate the glomerular filtration rate.

URINE SPECIMENS

All women were asked to provide 2 midstream urine specimens, 1 at baseline, and 1 in the following 4 months. For the second specimen, some of the women (<10%) used a urine dipslide (Orion Diagnostica, Espoo, Finland), which they sent to the laboratory in a return envelope. Finally, a part of the total study group was asked to provide additional urine samples at the study end point.

Quantitative urine culturing was performed as described in a previous report. Causative microorganisms were identified using the Vitek automated identification system (bioMerieux, Den Bosch, the Netherlands). When growth of 3 or more different microorganisms was seen, the urine specimen was considered to be contaminated. All patients and their physicians were blinded to the culture results.

The presence of leukocyturia was determined directly from an uncentrifuged midstream urine sample by microscopy (×400 magnification) or by a leukocyte esterase test (Combur-Test; Boehringer Mannheim, Almere, the Netherlands).

DEFINITIONS

We defined ASB as the presence of at least 105 colony-forming units/mL of 1 or 2 uropathogenic microorganisms in a single urine culture from a patient without symptoms of a UTI or fever. Albumin excretion was measured in a 24-hour urine sample, or the albumin-to-creatinine ratio in a single-void urine specimen was calculated. Normoalbuminuria was defined as an albumin excretion of less than 20 mg/L or an albumin-to-creatinine ratio less than 2.5 g/mmol, microalbuminuria as an albumin excretion of 20 to 200 mg/L or an albumin-to-creatinine ratio of 2.5 to 30 g/mmol, and macroalbuminuria as an albumin excretion of more than 200 mg/L or an albumin-to-creatinine ratio higher than 30 g/mmol.

The relative increase in creatinine and creatinine clearance was defined as the difference between the values at study end point and the baseline values, divided by the baseline values, and multiplied by 100. In addition, the absolute differences in creatinine level and creatinine clearance between baseline and end point were calculated.

Blood pressure was measured with a standard mercury sphygmomanometer after the subject had been seated for 5 minutes. Hypertension was defined as a systolic blood pressure higher than 140 mm Hg, and/or a diastolic blood pressure higher than 90 mm Hg, and/or the use of antihypertensive drugs.

STATISTICAL ANALYSIS

Absolute and relative values between baseline and follow-up of patients with and those without ASB were compared using the t test for continuous variables, the Mann-Whitney test for categorical variables, and the χ2 test for dichotomous variables. Because the Cockcroft-Gault formula for the estimation of the creatinine clearance includes age, adjusting for age in a multivariate model is not possible. Therefore, patients were stratified into 3 age strata (18-36 years, 37-55 years, and 56-75 years) to assess the impact of age on the association between ASB and the (relative increase in the) creatinine clearance. All analyses were performed on the entire study population and on women with type 1 DM and type 2 DM separately. Linear and logistic regressions were used to calculate the differences in blood pressure and the relative risk of hypertension, respectively, in the presence or absence of bacteriuria. Women with hypertension at baseline were excluded from the latter analyses. A P value of less than .05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS

A total of 716 women with DM were enrolled in this study, of whom 72 had to be excluded for the following reasons: they had no uncontaminated urine specimen (n=8), had no creatinine measurement at baseline or at study end point (n=27), had an anatomic kidney abnormality (n=8), or withdrew from the study within 12 months (n=29). The final study cohort consisted of 644 women: 296 women with type 1 DM and 348 women with type 2 DM. The mean (SD) duration of follow-up was 5.8 (2.1) years (median, 7.0 years) and 6.4 (1.8) years (median, 7.1 years) for women with type 1 DM and type 2 DM, respectively (range, 1.0-8.3 years).

Baseline characteristics of all women together, those with type 1 DM, and those with type 2 DM, are given in Table 1. Women with type 1 DM were younger but had a longer duration of DM than women with type 2 DM. At baseline, 201 women with type 2 DM (58%) were treated with insulin only; 97 (28%), with oral hypoglycemic medication only; 41 (12%), with a combination of both; and 5 (2%) were on a glucose-lowering diet only (data were incomplete for 4 women).
ASYMPTOMATIC BACTERIURIA

Two culture specimens were available from 516 of the 644 women. Of these women, 443 had either culture specimens that were positive for the same microorganism (n=47; 11%) or 2 culture specimens that were negative for microorganisms (n=396; 89%). A total of 73 women had 2 urine culture specimens with different results. There were no differences in clinical characteristics between the women with 2 culture specimens that were positive for microorganisms and the women whose first culture specimen was positive for microorganisms but who had a second culture specimen that was negative for microorganisms, not available, or positive for another uropathogen (for all comparisons, P>0.10). Therefore, we decided to base the presence of ASB on the results of the first collected culture specimen. In other words, when the findings for the first collected urine culture specimen were positive for microorganisms, the woman was considered to have ASB.

At baseline, the prevalence of ASB was 17% for the total study group. The prevalence was lower in women with type 1 DM compared with women with type 2 DM, but multivariate analysis revealed that this was due to the difference in age.

Escherichia coli was the causative uropathogen in 74 (67%) of the 110 women with ASB. Other isolated microorganisms included enterococci (9%), group B streptococci (8%), Klebsiella pneumoniae (6%), Staphylococcus aureus (3%), Proteus mirabilis (2%), Enterobacter species (2%), and, sporadically, Proteus vulgaris, gram-positive cocci, Citrobacter freundii, and Serratia rubidaea (together, <4%). The prevalence of leukocyturia (5 or more leukocytes per high-power field) was 15% in women with ASB and 3% in women without ASB. Women with ASB had a significantly shorter length of follow-up than women without ASB; therefore, all further analyses were corrected for the length of follow-up.

Urine samples were collected from 139 women at study end point or at least 3 years after the first urine culture, after a mean (SD) follow-up period of 5.3 (1.4) years. Women with ASB at baseline had an almost 8-fold increased risk of having ASB at this point compared with women without ASB at baseline (6 [43%] of 14 women with ASB vs 11 [9%] of 125 women without ASB at baseline; odds ratio, 7.7; 95% confidence interval, 1.9-31.0; P=.004, after adjusting for age and length of follow-up). In 5 of 6 women who had ASB on both occasions, E coli grew from both urine samples.

RENAL FUNCTION AND HYPERTENSION

The creatinine clearance decreased from 87 mL/min at baseline to 76 mL/min (from 1.45 to 1.27 mL/s) at study end point in women with DM with ASB, and from 97 to 88 mL/min (from 1.62 to 1.47 mL/s) in those without ASB (Figure). In the univariate analysis, ASB was associated with a higher mean (SD) relative decrease in creatinine clearance.

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>All Women (n = 644)</th>
<th>Women With Type 1 DM (n = 296)</th>
<th>Women With Type 2 DM (n = 348)</th>
<th>Patients for Whom Data Were Available, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic bacteriuria</td>
<td>110 (17)</td>
<td>36 (12)</td>
<td>74 (21)</td>
<td>644</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>51.1 (15.2)</td>
<td>41.1 (13.1)</td>
<td>59.6 (11.2)</td>
<td>644</td>
</tr>
<tr>
<td>Duration of DM, mean (SD), y</td>
<td>14.6 (11.5)</td>
<td>20.3 (12.7)</td>
<td>9.9 (7.6)</td>
<td>640</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.4 (5.5)</td>
<td>24.7 (3.8)</td>
<td>29.6 (5.7)</td>
<td>644</td>
</tr>
<tr>
<td>Hypertension</td>
<td>320 (50)</td>
<td>81 (28)</td>
<td>239 (69)</td>
<td>642</td>
</tr>
<tr>
<td>Hemoglobin A(<em>1)</em> level, mean (SD)</td>
<td>8.5 (1.6)</td>
<td>8.4 (1.4)</td>
<td>8.5 (1.7)</td>
<td>643</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min, mean (SD)</td>
<td>95 (34)</td>
<td>99 (29)</td>
<td>92 (37)</td>
<td>644</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>189 (32)</td>
<td>69 (26)</td>
<td>120 (38)</td>
<td>587</td>
</tr>
<tr>
<td>Macrovascular complications</td>
<td>138 (21)</td>
<td>34 (12)</td>
<td>104 (30)</td>
<td>643</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>193 (31)</td>
<td>110 (38)</td>
<td>83 (23)</td>
<td>631</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>98 (16)</td>
<td>32 (11)</td>
<td>66 (21)</td>
<td>606</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>31 (5)</td>
<td>12 (4)</td>
<td>19 (6)</td>
<td>606</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DM, diabetes mellitus; UTI, urinary tract infection.

SI conversion factor: To convert creatinine clearance to milliliters per second, multiply by 0.01667.

*Unless indicated otherwise, values are given as number (percentage) of patients.
At baseline, 50% of the total study group were diagnosed as having hypertension. After excluding these women and the women with missing values for hypertension at end point (n=4), the remaining cohort consisted of 318 women. A total of 39 women (12%) of these 318 women had ASB. Women with ASB developed hypertension more often than women without ASB (54% vs 37%; \( P = .045 \)). For women with type 1 DM and type 2 separately, the difference was not statistically significant (\( P > .10 \)). In the multivariate analysis, including age, duration of DM, and length of follow-up, the association between ASB and hypertension disappeared (\( P > .20 \)); a higher age was the strongest predictor for hypertension.

After 6 years of follow-up, we found no association between ASB and a decline in renal function or the development of hypertension in women with type 1 DM or type 2 DM. As shown, women with ASB at baseline had a lower creatinine clearance at study end point, a faster relative decrease in creatinine clearance, and hypertension more often when compared univariately with women without ASB. However, the differences were mainly explained by differences in age and duration of DM, and all differences disappeared in the multivariate analyses.

To our knowledge, no large cohorts of women with DM have been followed long enough to prospectively study the consequences of ASB on renal function. We have previously described the consequences of ASB during a follow-up period of 18 months in a cohort partly overlapping the cohort described herein. Women with type 1 DM and ASB showed a tendency toward a faster decline in renal function than women without ASB (relative increases in serum creatinine level after 18 months were 4.6% and 1.5%, respectively). Of the total study population, 20% developed a UTI. No association was present between symptomatic UTIs and any variation in renal decline after 18 months.11 In a small Polish study13 (25 patients with DM, including both men and women), too, no differences in the incidence of hypertension and creatinine levels were found between patients with ASB and those without ASB after 14 years. As we de-

### Table 2. Risk Factors for Creatinine Clearance Below 60 mL/min After 6 Years of Follow-up Among a Cohort of Women With DM

<table>
<thead>
<tr>
<th>Risk Factor at Baseline (Patients, No.)</th>
<th>Age, 18-36 y</th>
<th>Age, 37-55 y</th>
<th>Age, 56-75 y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Creatinine Clearance, mL/min, Per Age Category</strong></td>
<td>( \geq 60 (n = 136) )</td>
<td>( &lt; 60 (n = 4) )</td>
<td>OR</td>
</tr>
<tr>
<td>Asymptomatic bacteriuria</td>
<td>14 (10)</td>
<td>1 (25)</td>
<td>2.9</td>
</tr>
<tr>
<td>DM</td>
<td>21 (15)</td>
<td>1 (25)</td>
<td>1.2</td>
</tr>
<tr>
<td>Type 1</td>
<td>122 (90)</td>
<td>4 (100)</td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td>14 (10)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Duration of DM, mean (SD), y (640)</td>
<td>12 (8)</td>
<td>2 (8)</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>121 (30)</td>
<td>59 (31)( \dagger )</td>
<td></td>
</tr>
<tr>
<td>HbA1c (643)</td>
<td>8.1 (1.3)</td>
<td>9.7 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Hypertension (642)</td>
<td>24 (28)</td>
<td>2 (50)</td>
<td>4.6</td>
</tr>
<tr>
<td>Microalbuminuria (606)</td>
<td>20 (15)</td>
<td>2 (67)( \dagger )</td>
<td></td>
</tr>
<tr>
<td>Macroalbuminuria (606)</td>
<td>3 (2)</td>
<td>1 (33)( \dagger )</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DM, diabetes mellitus; HbA1c, hemoglobin A1c; UTI, urinary tract infection.

*SI conversion factor: To convert creatinine clearance to milliliters per second, multiply by 0.01667.

\( \dagger \)Univariate analyses. Unless indicated otherwise, values are given as number (percentage) of patients. The total number of patients is 644 unless otherwise stated in parentheses.

\( P < .05 \).
scribed in a previous report, women with DM with ASB are characterized by a longer duration of DM with the presence of secondary complications such as microalbuminuria or macroalbuminuria. In the present study, women with DM and ASB already had a lower creatinine clearance at baseline (Figure).

Because we found no evidence that ASB in itself can lead to a decline in renal function, either in women with type 1 DM or in women with type 2 DM, it is not likely that treatment of ASB will lead to a decrease in the incidence of diabetic nephropathy. This is in accordance with a recent study of women with DM with ASB in which a comparison was made between women who received antibiotic therapy and women who received placebo. In that study, no difference was seen in serum creatinine levels after a mean follow-up of 2 years.

In the study described herein, the prevalence of leukocyturia in women with DM with ASB was only 15%. This might be due to the lower urinary cytokine excretion that is correlated with a lower urinary leukocyte number and is lower in patients with DM compared with those without DM but with ASB, as we have demonstrated before. The lower prevalence of leukocyturia could not be explained by our definition of ASB based on a single culture specimen because in our patient group the prevalence of pyuria in women with 2 consecutive positive cultures was not higher than in women with a first positive and a second negative culture.

In individuals without DM, a correlation between ASB and hypertension has been shown by some authors but not by others, as reviewed previously. We found a high prevalence of hypertension in our cohort. Hypertension was defined as a blood pressure higher than 140/90 mm Hg or the use of antihypertensive medication. An overestimation of prevalence of hypertension is possible; for instance, some individuals might have been treated with angiotensin-converting enzyme inhibitors to treat microalbuminuria. But it is unlikely that this will affect the associations between ASB and hypertension.

The results of our study are strengthened by the prospective design, the large sample size, and the long follow-up.

Our study has several limitations. A potential limitation is our reliance on 1 culture sample to diagnose ASB. We made the assumption that however bacteriuria might be transient in a percentage of the study subjects with ASB, bacteriuria at 1 point reflects a higher susceptibility to recurrent and persistent bacteriuria in general, even after antimicrobial therapy. Our findings on the follow-up cultures as described in the “Asymptomatic Bacteriuria” subsection, as well as previous findings of others, are supportive of this assumption. In this study, bacteriuria with E. coli especially seemed to persist. It has been described previously that type 1–fimbriated E. coli can invade the superficial epithelial cells that line the luminal bladder surface and subsequently replicate, establishing a persistent bacterial reservoir within the bladder mucosa.

A second limitation is that the clinical evaluations during follow-up were not fully standardized. This was not possible because the study describes the clinical practices of different outpatient clinics. However, all participating physicians were following the international or national guidelines for care of patients with DM, and therefore the variability was limited.

We do not have complete information about the antimicrobial treatment for UTIs during the total follow-up period. But as previously reported, no association was found between antimicrobial use and renal function decline after 18 months of follow-up.

Finally, we conclude that our hypothesis that ASB will lead to renal function deterioration in women with DM can be rejected because we found no difference in renal function development, in either women with type 1 DM or those with type 2 DM, after a mean follow-up of 6 years. Also, the incidence of hypertension was not increased when comparing women with ASB vs women without ASB. Therefore, in our opinion, at this time, screening and subsequent treatment for ASB are not indicated in patients with DM.

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Author Contributions: Study concept and design: Meland, Geerlings, Stolk, and Hoepelman. Acquisition of data: Meland, Geerlings, and Netten. Analysis and interpretation of data: Meland, Geerlings, and Stolk. Drafting of the manuscript: Meland and Geerlings. Critical revision of the manuscript for important intellectual content: Netten, Schneeberger, and Hoepelman. Statistical analysis: Meland and Stolk. Obtained funding: Geerlings and Hoepelman. Administrative, technical, and material support: Meland and Schneeberger. Study supervision: Hoepelman.

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