

Asymptomatic Bacteriuria in Women with Type 2 Diabetes

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ABSTRACT

Asymptomatic bacteriuria (ASB) is a clinical problem that is little understood. The aim of the present study was to determine the prevalence and risk factors for ASB in women with type 2 diabetes. A total of 206 nonpregnant women with type 2 diabetes between the age of 30 to 83 years and had no abnormalities of the urinary tract were included. We defined ASB as the presence of more than 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). The prevalence of ASB was 19.4 percent in women with type 2 diabetes and 5 percent in the control subjects ($p < 0.001$). Age, a longer duration of diabetes, poor regulation of diabetes, sexual intercourse, glucosuria, a UTI during the previous year, peripheral neuropathy, macrovascular complications, microalbuminuria and macroalbuminuria were not significantly different between patients with and without bacteriuria. (*J Infect Dis Antimicrob Agents* 2003;20:89-95.)

INTRODUCTION

Urinary tract infection (UTI) is an important clinical problem for people with diabetes. On a population basis, women with diabetes are 6-24 times more likely than nondiabetic women to be admitted for acute pyelonephritis.¹ In fact, a 1940 autopsy study showed that 18 percent of the subjects with diabetes had a UTI.² Many UTIs are asymptomatic, and whether symptomatic UTIs are preceded by asymptomatic bacteriuria (ASB) is not known.^{3,4} A higher prevalence of ASB has been found in women with diabetes than in women without the disease.^{3,6} Some investigators, however, have been unable to

confirm this finding.^{7,8} More UTI complications e.g. bacteremia, renal abscesses and renal papillary necrosis, are seen in patients with diabetes comparing with individuals without diabetes.⁹ Renal involvement even without the presence of symptoms, e.g. subclinical pyelonephritis, is common.^{10,11} ASB has received relatively little attention, and many important scientific and clinical questions remain unanswered. Our effort is to understand one aspect of this issue concerning ASB in diabetic women.

Various risk factors for ASB in women with diabetes have been suggested, including sexual intercourse, age, and duration, metabolic control, and

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complications of diabetes.^{4-6,12-15}

The aim of the present study was to determine the prevalence of and the risk factors for ASB in women with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Patient enrollment and evaluation

Women aged 30 to 83 years with type 2 diabetes were recruited from October 2002 to March 2003 from the diabetes outpatient clinic of Bangkok Metropolitan Medical College and Vajira Hospital, a tertiary care hospital in Bangkok, Thailand. Exclusion criteria were pregnancy, recent hospitalization or surgery within the past 4 months, known urinary tract abnormalities including cystopathy or recent urinary tract instrumentation and symptoms of a UTI or the use of antimicrobial drugs during the previous 14 days. At least 1 uncontaminated midstream urine sample was available from the patients.

All patients were interviewed during the first visit of the study and their medical history was obtained from the hospital files and by using a standardized questionnaire. Data collected included age, type and duration of diabetes, medication, secondary complications of the diabetes i.e. retinopathy, stroke, myocardial infarction, myocardial ischemia, intermittent claudication and peripheral neuropathy, 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 i.e. oral contraceptives, condoms and intrauterine devices, menopausal status, and the use of local estrogens. Blood pressure, weight, and height were also recorded. The following laboratory values were obtained: HbA_{1c}, serum creatinine, microalbuminuria, glucosuria, leukocyturia, and urinary pH.

Definitions

By following the 1998 WHO criteria, we defined diabetes as a fasting plasma glucose concentration of

≥ 126 mg/dl and/or a 2-hour glucose concentration of ≥ 200 mg/dl.¹⁶ Type 2 diabetes was the diabetes that could be adequately controlled by diet, physical activity, treatment with oral antidiabetic agents or requiring insulin treatment after diagnosis of diabetes at least one year.¹⁷ Peripheral neuropathy was defined as a reduced vibration sense, temperature sense, joint position sense or 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).¹⁸ We measured albumin excretion with 24-hour urine collection. Normoalbuminuria was defined as the excretion of < 30 mg albumin/24 hour. Microalbuminuria was defined as the excretion of 30-300 mg albumin/24 hour. Macroalbuminuria was defined as the excretion of at least 300 mg albumin/24 hour.

ASB was defined as the presence of more than 10⁵ 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.¹⁹ We defined contaminated urine as the presence of at least 3 different microorganisms in one urine specimen. These specimens were excluded.

Control group

The control group was 100 women with hypertension, dyslipidemia who were followed up in the same clinic. The clinical characteristics of the control group did not differ from the study group. Exclusion criteria were the same as for the women with diabetes.

Urine

Clean midstream urine specimens were collected for the evaluation of bacteriuria. All urine samples were immediately cultured within 2 hours of collection. All urine samples were plated on blood agar and Mac-Conkey plates using standard quantitative loops

(0.01 ml). The results were read within 24 hours. Microorganisms were identified using a standard biochemical media method.²⁰ To confirm the diagnosis, women with positive culture would be asked for the second urine specimen within 2 weeks after the first urine culture results. Women with 2 cultures yielding 2 different microorganisms in the consecutive cultures were excluded because their urine was considered to be contaminated. Women with two consecutive episodes of asymptomatic bacteriuria with the same species were classified as ASB+.

Glucosuria, leukocyturia, and urinary pH values were determined using a dipslide method (Combur-Test; Roche).

Statistical analysis

Differences between patients with and without ASB were tested with the student *t*-test for continuous variables (age, duration of diabetes, HbA_{1c}, creatinine) 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). A 2-tailed p-value of < 0.05 was considered to be statistically significant. Statistic Package for Social Science (SPSS) statistical software for Windows (Version 10.0) was used.

RESULTS

Of the total study group (n=206), 40 (19.4%) women were found to have ASB. In 42.5 percent of the positive cultures, >5 leukocytes/high-power field (hpf) were present in the urine. *Escherichia coli* was isolated in 30 out of 40 patients with ASB (75%). Isolated microorganisms included *Enterococcus* spp., *Streptococcus hemolyticus* group B, *Klebsiella pneumoniae* and *Lactobacillus*. Positive cultures for *Candida* spp. were not included because there is difficulty in differentiating *Candida* bacteriuria from vaginitis *Candida*.²¹

In the nondiabetic control group (100 patients), 5 patients (5%) had a positive urine culture result. *E. coli* was the causative microorganism in 4 out of 5 patients (80%). The prevalence of ASB was significantly higher in the patients with diabetes than in the control group (p < 0.001).

Mean age and the duration of diabetes were not statistically significant difference in both groups. There were not significant difference of the younger and the older (≥ 60 years) age, the longer (≥ 10 years) and the shorter duration of diabetes, the poor diabetes control (FPG ≥ 160 mg/dL, HbA_{1c} $\geq 8\%$) between the study and the control groups. No tendency to association was present between glucosuria and ASB

Table. Patient's characteristics, classified by presence or absence of ASB.

Patient characteristics	ASB-	ASB+	p-value
Number	166 (80.6)	40 (19.4)	
Age	60.4 \pm 0.8	60.3 \pm 1.6	0.667
Duration of diabetes (years)	9.5 \pm 0.6	9.1 \pm 0.9	0.099
Microalbuminuria	44 (26.5)	7 (17.5)	0.405
Macroalbuminuria	21 (12.7)	8 (20.0)	0.175
UTIs during the previous year	29 (17.5)	6 (15.0)	0.709
FPG (mg/dL)	173.9 \pm 4.6	179.2 \pm 10.5	0.617
HbA _{1c} (%)	8.44 \pm 0.16	8.62 \pm 0.33	0.615
Creatinine (mg/dL)	0.87 \pm 0.02	0.94 \pm 0.11	0.400
Peripheral neuropathy	56 (33.7)	8 (20.0)	0.092

Note: Data are n(%), means \pm SD, ASB=asymptomatic bacteriuria, ASB-=absence of ASB, ASB+=presence of ASB, UTI=urinary tract infection, FPG=fasting plasma glucose, Hb=hemoglobin

i.e. 59.0 percent of women without and 62.5 percent of women with ASB had glucosuria ($p = 0.688$). We could not demonstrate that any possible risk factors were different between ASB and non-ASB subjects (Table).

DISCUSSION

In this study, we found that the prevalence of ASB is higher in women with diabetes than in women without diabetes (19.4 vs 5%). As in uncomplicated UTIs, *E. coli* causes the majority of infections. We found no difference in the percentage of *E. coli* in women with diabetes *versus* women without the disease (75% vs 80%), and this differs from the results of previous studies^{21,22} which show 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.

Vejlsgaard et al¹⁴ and Keane et al⁶ 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. Some studies also showed that a longer duration of the diabetes^{5,15} and the presence of longstanding complications (peripheral neuropathy)⁵ increased the risk of developing ASB. As the present study, these findings could not be confirmed by other studies.^{4,7,12}

Age is a well-known risk factor for bacteriuria in women without diabetes.²³ Age was also the most important risk factor for ASB in type 2 diabetic patients in the study by Geerlings et al in the year 2000.²¹ Earlier studies did not find an increased incidence of ASB in elderly women with diabetes.^{3,5,12,15,24} We also could not demonstrate that older age increased risk of developing ASB. Other possible risk factors for ASB in type 2 diabetic patients were macroalbuminuria and a UTI during the previous year. These risk factors have been previously reported in type 2 diabetic patients.^{7,12,14} 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.²¹

In an earlier study,¹³ 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. However, this lack of association between the presence of diabetic cystopathy and bacteriuria has been shown before.²⁵ However, we did not study about autonomic neuropathy or postvoiding bladder residue. We were also unable to show a correlation between the presence of peripheral neuropathy and ASB.

Studies have demonstrated in women with and without diabetes that recent sexual intercourse, the use of a diaphragm, or the use of spermicide-coated condoms increases the risk of developing bacteriuria.^{12,26-29} 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 our patients, 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.³⁰⁻³² 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.³² Thus, diabetic complications and bacteriuria may partly have the same pathogenesis. Geerlings et al²¹ reported that the prevalence of pyuria among diabetes women with ASB was relatively low. Only 42.5 percent of our patients with ASB had leukocyturia. Geerlings et al found that diabetic women with ASB have lower urinary cytokine concentrations and therefore decreased urinary leukocyte numbers compared with nondiabetic women

with ASB.³³ They have also shown that no differences in granulocyte functions are present among bacteriuric diabetic, nonbacteriuric diabetic, and non diabetic control subjects.³⁴ 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. However, in another large study, only 25 percent of bacteriuric diabetes patients did not have pyuria. This study found that diabetic women with lower urinary leukocyte counts were significantly more likely to clear bacteriuria spontaneously, an observation at variance with the proposed hypothesis.¹⁵ Thus, both the implications of the presence and degree of pyuria and our understanding of the local urinary inflammatory response are also issues for further study.

No consensus exists regarding the treatment of ASB in diabetic patients.³⁵ Many experts in the US recommend treating ASB in diabetic patients because of the frequency and severity of upper UTIs.⁹ On the other hand, European experts believe that the benefit of treatment is doubtful³⁶, 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. Until recently, Harding et al³⁷ reported a prospective, randomized trial comparing antimicrobial therapy with no antimicrobial therapy in women with diabetes and ASB, which showed that antimicrobial therapy cleared bacteriuria in the short term, but did not decrease the numbers of symptomatic episodes and hospitalizations during long-term follow-up. Treatment also did not alter the time to the first symptomatic episode of UTI.

In conclusion, we have shown in this study of type 2 diabetic women that the prevalence of ASB is higher in women with diabetes than in women without diabetes. We could not confirm that age, a longer duration of diabetes, poor regulation of diabetes, glucosuria, sexual intercourse, a UTI during the previous year, peripheral neuropathy, macrovascular complications, microalbuminuria and macroalbuminuria

were different between bacteriuria and nonbacteriuria subjects.

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