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SHORT COMMUNICATION

H. Karunajeewa · D. McGechie · G. Stuccio · N. Stingemore · W. A. Davis · T. M. E. Davis

Asymptomatic bacteriuria as a predictor of subsequent hospitalisation with urinary tract infection in diabetic adults: The Fremantle Diabetes Study

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Abstract *Aims/hypothesis:* We examined the prognosis of well-characterised community-based diabetic patients with asymptomatic bacteriuria (ASB). *Methods:* We studied 496 adults with type 1 or 2 diabetes participating in a prospective observational study. In addition to detailed clinical and laboratory data, a single mid-stream urine sample was taken for aerobic culture and antibiotic-sensitivity testing. ASB was defined as $\geq 10^5$ colony-forming units/ml of one or two organisms without symptoms of urinary infection. Patients were followed for 2.9±0.6 years for hospital admission for/with urosepsis or death. *Results:* Thirty-six patients (7.3%) had ASB, comprising 33 females (14.4% of all females) and three males (1.1% of all males). Only female sex predicted ASB amongst a range of variables including indices of metabolic control. Twenty-nine patients (5.8%) were subsequently hospitalised with urosepsis. Of these, urosepsis was the principal diagnosis in 12 (41%). In a Cox proportional hazards model, ASB was associated with an increased risk of hospitalisation for urosepsis as principal diagnosis (hazard ratio [95% CI] 4.4 [1.2–16.5]; p=0.004). ASB did not predict the combined endpoint of hospitalisation with urosepsis as principal or secondary diagnosis (2.3 [0.8–6.7]; p=0.12), or of non-urinary sepsis as principal (n=12) or principal/secondary (n=28) diagnosis (p>0.3). *Conclusions/interpretation:* ASB identifies diabetic patients who are at significantly increased risk of subsequent urosepsis requiring hospitalisation. Further large-scale studies are needed to establish the cost-effectiveness of screening for, and pre-emptive treatment of ASB, especially in females.

H. Karunajeewa · G. Stuccio · W. A. Davis · T. M. E. Davis (✉)
School of Medicine and Pharmacology, Fremantle Hospital, University of Western Australia,
P.O. Box 480 Fremantle, WA, 6959, Australia
e-mail: tdavis@cyllene.uwa.edu.au
Tel.: +61-8-94313229
Fax: +61-8-94312977

D. McGechie · N. Stingemore
Department of Microbiology, Fremantle Hospital, Fremantle, WA, Australia

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Abbreviations ACR: urinary albumin:creatinine ratio · ASB: asymptomatic bacteriuria · FDS: Fremantle Diabetes Study · ICD: International Classification of Diseases · MSU: mid-stream urine · UTI: urinary tract infection · WA: Western Australia

Introduction

Although asymptomatic bacteriuria (ASB) is more common in diabetic than non-diabetic women [1], there are limited data relating to its management and consequences in diabetes. Type 2 diabetic women with ASB have a greater risk of developing a symptomatic urinary tract infection (UTI) than those without [2], but antimicrobial treatment does not reduce the incidence of UTI or its complications [3]. Available data have, however, been derived from clinic-based samples with little information relating to possible confounding variables such as glycaemia [1–3]. Because there is a need for prospective, population-based studies in well-characterised diabetic patients, we examined the prevalence and predictors of ASB in a representative Australian cohort and assessed the relationship between ASB and subsequent hospitalisation for urosepsis.

Subjects and methods

Patients We studied 496 participants in The Fremantle Diabetes Study (FDS), a prospective observational study in a community of 120097 people in Western Australia (WA). The FDS protocol was approved by the Human Research Ethics Committee, Fremantle Hospital and all patients gave informed consent to participation. Details of study procedures, and of recruited and non-recruited patients, have been published elsewhere [4]. We identified

2258 eligible subjects between 1993 and 1996, and recruited 1426 (63%) to annual assessments. The present sample comprised the 94.1% of 527 non-pregnant adults attending between November 1999 and November 2000 who were willing and able to provide mid-stream urine (MSU).

Clinical and laboratory methods At each FDS visit, detailed clinical data were recorded and fasting biochemical tests performed [4]. In the present sub-study, a single MSU was taken for aerobic culture and antibiotic-sensitivity testing. ASB was defined as $\geq 10^5$ colony-forming units/ml of one or two organisms without symptoms of UTI such as dysuria and frequency [5]. Each patient's primary-care physician was informed of the result and left to manage the patient at his/her discretion.

Details of hospitalisations between MSU screening and the end of June 2003 were obtained from the WA Data Linkage System [6], which includes details of all WA hospital separations and deaths. Hospitalisations with urosepsis were identified from the International Classification of Diseases (ICD) 9th revision (ICD-9-CM) or 10th revision (ICD-10-AM) codes for UTI, cystitis, pyelonephritis, orchitis, epididymitis and prostatitis, as either principal diagnosis (that immediately responsible for admission) or secondary diagnosis (contributing to, but not the major cause of, hospitalisation). We also used ICD codes to identify hospitalisations for non-urinary sepsis including sepsis, septicaemia and/or abscess.

Statistical methods Statistical analysis was by SPSS for Windows (Version 11.5; SPSS, Chicago, IL, USA). Data are presented as proportions, means±SD, geometric mean (SD range) or median [interquartile range] as appropriate. Student's *t*-test or the Mann–Witney *U*-test was used for two-sample comparisons and Fisher's exact test for two proportions. To determine whether ASB was an independent predictor of hospitalisation, variables with $p<0.20$ in univariate analysis were included in a forward conditional Cox proportional hazards model with variable entry at $p<0.05$ and removal at $p>0.10$.

Results

Patient characteristics Compared with the 930 FDS patients who were not included, the present patients were younger (60.4±11.0 vs 63.0±14.3 years), more likely to be male (53.8% vs 47.4%) and had shorter diabetes duration (3.0 [0.6–7.3] vs 5.0 [1.4–11.0] years; $p<0.03$ in each case), but similar percentages had type 2 diabetes (90.4% vs 91.3%; $p=0.56$). Of those not included, 38.2% had died by the end of June 2003 compared with 6.0% of the present cohort ($p<0.001$). Thirty-six of the present patients had ASB (see Table 1). Of the organisms cultured, 74% were *Escherichia coli*. In univariate analyses, the ASB-positive and ASB-negative groups differed only by sex.

Hospitalisations during follow-up During 2.9±0.6 years of follow-up, 29 patients (5.8%; 16 females, 13 males) were hospitalised with urosepsis. This group included 5 of 36 (13.9%) with, and 24 of 460 (5.2%) without prior ASB ($p=0.05$). Urosepsis was the principal diagnosis in 12 (41%). Of these, six were female and six male, while three (two females and one male) had a prior history of ASB and nine (four females and five males) did not.

The results for each infection category are summarised in Table 2. For urosepsis (principal diagnosis), ASB predicted future hospitalisation after adjusting for ln(urinary albumin: creatinine ratio [ACR]) and, for urosepsis (principal/secondary diagnosis), infection status was associated with a non-significant two-fold increase in hospitalisation risk after adjusting for age and ln(ACR). For non-urinary sepsis, whether as principal or principal/secondary diagnosis, ASB status was not associated with risk of hospitalisation.

Table 1 Characteristics of the present patients at the time of screening according to asymptomatic bacteriuria (ASB) status

	No ASB	ASB	*p* value
Number (%)	460 (92.7)	36 (7.3)	–
Age (years)	66.1±11.0	67.7±10.5	0.40
Sex (% male)	56.4	8.3	<0.001[a]
Type of diabetes (%)			
1	8.5	5.6	–
2	91.1	94.4	0.76
Secondary	0.4	0	–
Diabetes duration (years)	9.2 [6.6–13.2]	10.3 [6.8–15.7]	0.29
BMI (kg/m^2)	28.7±5.0	30.7±6.5	0.08
Serum creatinine (mmol/l)	92±41	79±19	0.08
Serum urea (mmol/l)	6.7 (4.6–9.9)	6.8 (4.5–10.2)	0.96
Urinary albumin: creatinine (mg/mmol)	2.4 (0.4–12.8)	3.3 (1.0–10.6)	0.14
Fasting plasma glucose (mmol/l)	8.6 [6.9–10.6]	9.4 [7.4–11.4]	0.33
HbA$_1$c (%)	7.4 [6.7–8.3]	7.4 [6.7–8.4]	0.75
Peripheral neuropathy (%)[b]	55.8	60.0	0.73
Orthostatic hypotension (%)[c]	23.3	28.6	0.54
Deceased by 30 June 2003 (%)	6.5	0	0.15

Data are percent, means±SD, geometric mean (SD range) or median [interquartile range]
[a]Statistically significant *p* values
[b]A score of >2/8 using the Michigan Neuropathy Screening Instrument clinical portion [6]
[c]A fall of ≥20 mmHg systolic or ≥10 mmHg diastolic on standing

Table 2 Cox proportional hazards models of time to complicated urinary sepsis and non-urinary sepsis as principal diagnosis and as principal or secondary diagnosis

Variable	Hazard ratio (95% CI)	*p* value
For complicated urinary sepsis as a principal diagnosis		
Ln(ACR)[a]	1.5 (1.1–1.9)	0.004[b]
ASB		
No	1	–
Yes	4.4 (1.2–16.5)	0.029[b]
For complicated urinary sepsis as a principal or secondary diagnosis		
Age (10-year increase)	1.8 (1.1–2.8)	0.014[b]
Ln(ACR)[a]	1.3 (1.1–1.6)	0.005[b]
ASB		
No	1	–
Yes	2.4 (0.9–6.3)	0.08
For non-urinary sepsis as a principal diagnosis		
Ln(ACR)[a]	1.4 (1.1–1.9)	0.009[b]
ASB		
No	1	–
Yes	1.0 (0.13–8.0)	0.98
For non-urinary sepsis as a principal or secondary diagnosis		
Ln(serum urea)[a]	4.6 (2.3–9.4)	<0.001[b]
ASB		
No	1	–
Yes	0.4 (0.1–2.6)	0.31

Hazard ratios and 95% CIs are shown for variables significant in the models

ACR urinary albumin: creatinine ratio, *ASB* asymptomatic bacteriuria

[a]A 2.72-fold increase in ACR or serum urea corresponds to an increase of 1 in ln(ACR) or ln(serum urea)

[b]Statistically significant *p* values

Discussion

The present data demonstrate that ASB detected by culture of a single screening MSU was independently associated with a greater than a four-fold risk of future hospitalisation for urosepsis as a principal diagnosis in community-dwelling diabetic patients. Previous studies of both non-diabetic and diabetic women have found an association between ASB and subsequent symptomatic UTI [7], but we focused on morbidity severe enough to justify hospitalisation. The association between ASB and urosepsis is strengthened by the observation that our patients with and without ASB had a similar risk of future hospitalisation for non-urinary sepsis, suggesting that ASB is more than a non-specific marker of host susceptibility to bacterial infection.

The overall prevalence of ASB among our females (14.4%) was within the range reported in other studies of diabetic women (8–26%) [1–3]. Because our sample was population—rather than clinic—based and represented a 'survivor' subset of FDS participants, it may have comprised healthier diabetic patients than in other studies. However, variables reflecting diabetes severity, including glycaemic control and microangiopathy, were not associated with ASB in our cohort. We diagnosed ASB using a single urine culture as the most practicable, cost-effective way to screen patients routinely. Although the definition of ASB has conventionally required two urine cultures taken >24 h apart, this practice does not improve specificity compared with a single specimen collection [5]. These considerations suggest that our point prevalence of ASB was valid.

A variety of potential ASB risk factors have been assessed in previous, mostly small-scale studies with inconsistent results. For diabetes-specific variables, most [1–3] but not all [8] studies have found no relationship between glycaemic control and ASB. Chronic complications such as nephropathy and neuropathy have been associated with ASB in type 1 but not type 2 diabetic patients [1, 7], a pattern that also holds for longer diabetes duration [7]. In some of these studies, a small sample size and restricted number of variables limit the conclusions that could be drawn. In the present population-based study, female sex was the sole variable predicting ASB.

Early studies found no increase in the subsequent risk of UTI in diabetic patients with ASB [9]. However, in a recent 18-month prospective study of 636 diabetic women [2], the 378 type 2 subjects with ASB had almost double the risk of symptomatic UTI, consistent with the present data for urosepsis requiring hospitalisation. Our ASB-positive patients were similar to those without ASB for variables that could influence the decision to hospitalise a diabetic patient with urosepsis, e.g. glycaemic control and renal function. In addition, hospitalisation rates for non-urinary sepsis were similar in the two groups. Therefore, the increased rate of urosepsis-related hospitalisation was strongly related to the presence of ASB.

Because of the FDS design, we did not document management of ASB or UTI during follow-up. However, in one placebo-controlled study [3], antibiotic treatment of ASB in diabetic women did not reduce the incidence of subsequent symptomatic UTI. This suggests that prompt treatment of our ASB-positive patients would not have influenced the primary outcome, namely urosepsis as principal diagnosis. However, in the same study [3], the rates of pyelonephritis and hospitalisation for UTI were 50% lower in the antibiotic-treated group. Although not statistically significant, the study was inadequately powered to detect such differences. These data suggest that, since it is likely that a proportion of our patients were treated for ASB, the rate of hospitalisation for urosepsis in our ASB-positive group was conservative. In addition, the effect of prompt treatment should wane with time. The adjusted Cox survival curves showed no such time-dependency.

The mechanisms underlying the predisposition to urosepsis in diabetic patients with ASB are unclear. It is possible that undetected renal tract abnormalities such as nephrolithiasis contributed to both ASB and urosepsis. We found no association between neuropathy and urosepsis, but neuropathic bladder dysfunction, together with leucocyte dysfunction, and enhanced bacterial replication and uroepithelial adhesion, may also have played a role [1]. ACR was an independent predictor of urosepsis in our patients and the presence of nephropathy may have in-

creased the risk of clinically silent renal parenchymal infection that led to urosepsis [10]. Nevertheless, non-urinary sepsis as a principal diagnosis was also associated with ACR, suggesting that patients with microangiopathy are at increased risk of severe infections in general.

Diabetes confers an increased risk of morbidity from UTIs, including rare but serious conditions such as emphysematous cystitis and xanthogranulomatous pyelonephritis [1]. Further adequately powered multicentre intervention studies are, therefore, needed to determine whether active screening for, and prompt antibiotic treatment of, ASB in diabetes is cost-effective. Since regular screening for microalbuminuria is recommended for all diabetic patients, such studies could be easily incorporated into routine care.

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References

1. Stapleton A (2002) Urinary tract infections in patients with diabetes. Am J Med 113(Suppl 1A):80S–84S
2. Geerlings SE, Stolk RP, Camps MJ et al (2001) Consequences of asymptomatic bacteriuria in women with diabetes mellitus. Arch Intern Med 161:1421–1427
3. Harding GK, Zhanel GG, Nicolle LE, Cheang M, Manitoba Diabetes Urinary Tract Infection Study Group (2002) Antimicrobial treatment in diabetic women with asymptomatic bacteriuria. N Engl J Med 347:1576–1583
4. Davis TME, Zimmet P, Davis WA, Bruce DG, Fida S, Mackay IR (2000) Auto-antibodies to glutamic acid decarboxylase in diabetic patients from a multiethnic Australian community: the Fremantle Diabetes Study. Diabetic Med 17:667–674
5. Geerlings SE, Brouwer EC, Gaastra W, Hoepelman AI (2000) Is a second urine specimen necessary for the diagnosis of asymptomatic bacteriuria? Clin Infect Dis 31:e3–e4
6. Gillett M, Davis WA, Jackson D, Bruce DG, Davis TME (2003) Prospective evaluation of carotid bruit as a predictor of first stroke in type 2 diabetes: The Fremantle Diabetes Study. Stroke 34:2145–2151
7. Geerlings S, Stolk R, Camps M et al (2000) Asymptomatic bacteriuria may be considered a complication in women with diabetes. Diabetes Mellitus Women Asymptomatic Bacteriuria Utrecht Study Group. Diabetes Care 23:744–749
8. Bonadio M, Boldrini E, Forotti G et al (2004) Asymptomatic bacteriuria in women with diabetes: influence of metabolic control. Clin Infect Dis 38:e41–e45
9. Forland M, Thomas VL (1985) The treatment of urinary tract infections in women with diabetes mellitus. Diabetes Care 8: 499–506
10. Forland M, Thomas V, Shelokov A (1977) Urinary tract infections in patients with diabetes mellitus. Studies on antibody coating of bacteria. JAMA 238:1924–1926