

Asymptomatic Bacteriuria in Diabetic Women

Urinary tract infection is an important clinical problem for people with diabetes (1). This observation is most apparent in the increased severity of infection that may occur in diabetic patients (2). Serious complications of urinary infection, such as emphysematous cystitis, pyelonephritis, or renal and perinephric abscess, occur virtually only in diabetic patients. On a population basis, diabetic women, depending on age, are 6–24 times more likely than nondiabetic women to be admitted for acute pyelonephritis, and diabetic men are 3.4–17 times more likely than their nondiabetic counterparts to be admitted for the same condition (3). Despite the frequency and importance of this problem, it has received relatively little attention, and many important scientific and clinical questions remain unanswered. Thus, the article in this issue by Geerlings et al. (4) is a welcome addition to our understanding of one aspect of this issue: asymptomatic bacteriuria in diabetic women.

Geerlings et al. (4) reported a prevalence of asymptomatic bacteriuria of 26 vs. 6% in diabetic women vs. a control group, respectively. This 4-fold increase in prevalence is remarkable, and it is not inconsistent with the estimated 3-fold difference between diabetic and nondiabetic women, as reported in a summary review of prevalence studies (5). Virtually all of these reports, however, are plagued by sampling biases, and such a limitation is also apparent in the study by Geerlings et al. The study population comprised a convenience sample of women who presented with asymptomatic bacteriuria at ambulatory clinics or physicians' offices. Thus, there is a possibility that these women represent a "more ill" population. In addition, it is not clear whether a sample of women attending ambulatory ophthalmology clinics represents an appropriate control group. What if the control group consisted of a group of women who were referred to ambulatory clinics because of neurologic or nephrologic problems? Whether the prevalence of asymptomatic bacteriuria is increased in diabetic versus nondiabetic women (and, if so, by how much) will not be determined until a population-based

study has been performed. Until then, we can only accept that, in populations of women sampled in ambulatory clinics, the prevalence of asymptomatic bacteriuria appears to be higher than that of nondiabetic women who presented with asymptomatic bacteriuria at other ambulatory clinics.

Geerlings et al. (4) defined asymptomatic bacteriuria as having 1 of 2 urine specimens with the appropriate quantitative count of any isolated organism. The standard criterion for asymptomatic bacteriuria is having 2 consecutive positive specimens (6); this is the criterion used in previously reported prevalence surveys. According to the standard diagnostic criterion, the prevalence of bacteriuria in the study population of Geerlings et al. would be 13 rather than 26%. This prevalence would still be greater than that of the control group (6%). It would also be more consistent with the findings of previous surveys that enrolled large numbers of women. In these reports, 7.9% of 1,072 (7), 9.5% of 400, and 9.1% of 341 diabetic women presented with asymptomatic bacteriuria (5).

If we accept the finding that there is an increased prevalence of asymptomatic bacteriuria in diabetic compared with nondiabetic women, to what can we attribute this finding? Reported studies, including the study of Geerlings et al., consistently found no association between the presence of asymptomatic bacteriuria and glucose control. Neither HbA_{1c} levels nor hyperglycemia and glycosuria are associated with asymptomatic bacteriuria (5,7). In populations of nondiabetic women, asymptomatic bacteriuria increases with frequency of sexual intercourse and with the use of spermicide, and, possibly, a diaphragm (8). Geerlings et al. (4) found no association between these factors and the presence of bacteriuria. This finding is somewhat surprising. Although the extent of the increase in the prevalence of asymptomatic bacteriuria in diabetic versus nondiabetic women remains controversial, reports on this subject have consistently identified no increase in the prevalence of asymptomatic bacteriuria in diabetic versus nondiabetic men (5). Thus, there must be some influences unique to the diabetic woman

that promote an increased prevalence of bacteriuria. The authors suggested that both the older mean age and the lower frequency of sexual intercourse in their study population may have compromised the sensitivity of their analyses of these factors (4). Clearly, further investigations must be conducted to determine the reasons for an increased prevalence of bacteriuria in diabetic women, but not in diabetic men, and whether this condition is driven by diabetes or is sex-specific.

In this study (4), the prevalence of pyuria among diabetic women with asymptomatic bacteriuria was relatively low. Only 33 and 68%, respectively, of type 1 and type 2 diabetic women with positive urine cultures had pyuria. Pyuria, however, was measured with a dip-slide method, which is not very sensitive and, consequently, could have underestimated the presence of pyuria. The inclusion of women with only 1 positive culture may have increased the inclusion of contaminated specimens and may have decreased the proportion of specimens with pyuria. In another large study, in which urinary leukocytes were measured by the more accurate hemocytometer method, only 25% of bacteriuric diabetic patients did not have pyuria, and pyuria was found to be less frequently associated with gram-positive infections (7). Geerlings et al. (4) speculated that the low leukocyte count is a marker for a dampened inflammatory response that promotes persistence of bacteriuria and contributes to the observed increased prevalence of bacteriuria in diabetic patients. However, the previous 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 (7). 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.

Which characteristics are associated with those diabetic women who are most likely to have asymptomatic bacteriuria? For women with type 1 diabetes, the duration of diabetes, the presence of peripheral

neuropathy, and the presence of macroalbuminuria were independently associated with asymptomatic bacteriuria; for women with type 2 diabetes, only age showed a significant association with asymptomatic bacteriuria in multivariate analyses. The observation that age is associated with asymptomatic bacteriuria is consistent for all ambulatory populations, regardless of whether or not they have diabetes (9). Other studies in diabetic women have reported variable observations. Generally, duration of diabetes (7) or the presence of diabetic complications, including retinopathy and nephropathy, are reported associations (5). Thus, asymptomatic bacteriuria in diabetic women is most strongly associated with long-term complications of diabetes. The most obvious questions concern the effect of diabetic neuropathy on bladder function and the effect of diabetic nephropathy on the occurrence and natural history of urinary infection.

The important clinical concerns are, of course, the contribution of asymptomatic bacteriuria in diabetic women to morbidity, either the short-term risk of developing a symptomatic urinary infection and its more serious complications or the longer-term risks of developing serious diabetic complications (e.g. nephropathy). Earlier studies have reported no increase in symptomatic urinary infection, hypertension, or renal impairment in women with asymptomatic bacteriuria (10,11). However, preliminary data from current ongoing studies suggest that women with asymptomatic bacteriuria may have an increased risk of symptomatic urinary infection (12,13). If these reports are confirmed, the question remains whether diabetes or asymptomatic bacteriuria is, in fact, the issue. In nondiabetic populations, women with an increased prevalence of asymptomatic bacteriuria also have an increased frequency of symptomatic infection, which likely reflects an underlying biologic propensity to urinary infection rather than a direct risk due to the presence of asymptomatic bacteriuria. It does not necessarily follow that treatment of asymptomatic bacteriuria will decrease the frequency of symptomatic urinary infection. In fact, in other populations, such as young girls (14), treatment of asymptomatic bacteriuria is

associated with an increased frequency of symptomatic urinary tract infection. Long-term prospective intervention studies are needed to clarify the risks and benefits of different management strategies for asymptomatic bacteriuria. Currently, there is not sufficient evidence to allow specific recommendations to recommend for or against screening or treatment of asymptomatic bacteriuria in diabetic women.

As Geerlings et al. (4) note, current approaches to management differ between U.S. and European physicians. In the U.S., treatment of bacteriuria is recommended, even though specific screening recommendations do not exist; in Europe, bacteriuria is not treated. Even if diabetic women with asymptomatic bacteriuria are at risk for symptomatic urinary infection, the overall cost benefit of screening and treating large numbers of asymptomatic diabetic women at frequent intervals (relative to the impact of symptomatic infection) needs to be evaluated. The questions are complex and wide-ranging. We need to build on our current clinical observations and prevalence surveys to create a foundation of knowledge that is sufficient for developing a rational and appropriate approach for caring for the diabetic patient who has a urinary infection.

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References

- Joshi N, Caputo GM, Weitekamp MR, Karkmen AW: Infections in patients with diabetes mellitus. *N Engl J Med* 341:1906-1912, 1999
- Patterson JE, Andriole VT: Bacterial urinary tract infections in diabetes. *Infect Dis Clin North Am* 11:735-750, 1997
- Nicolle LE, Friesen D, Harding GKM, Roos LL: Hospitalization for acute pyelonephritis in Manitoba Canada, during the period from 1989 to 1992: impact of diabetes, pregnancy, and aboriginal origin. *Clin Infect Dis* 22:1051-1056, 1996
- Geerlings SE, Stolk RP, Camps MJL, Netten PM, Hoekstra JBL, Bouter KP, Bravenboer B, Collet JT, Jansz AR, Hoepelman AIM: Asymptomatic bacteriuria might be considered a diabetic complication in women with diabetes. *Diabetes Care* 23:744-749, 2000
- Zhanell GG, Harding GKM, Nicolle LE: Asymptomatic bacteriuria in patients with diabetes mellitus. *Rev Infect Dis* 13:150-154, 1991
- Rubin RH, Sharpiro ED, Andriole VT, Davis RJ, Stamm DE: Evaluation of new anti-infective drugs for the treatment of urinary tract infection. *Clin Infect Dis* 15 (Suppl. 1): S216-S227, 1992
- Zhanell GG, Nicolle LE, Harding GKM, and the Manitoba Diabetic Urinary Infection Study Group: Prevalence of asymptomatic bacteriuria and associated host factors in women with diabetes mellitus. *Clin Infect Dis* 21:316-322, 1995
- Nicolle LE: Uncomplicated urinary tract infection in women. In *Infections of the Kidney and Urinary Tract*. Cattell WR, Ed. New York, Oxford University Press, 1996, p. 115-128
- Kunin CM: *Urinary Tract Infections: Detection, Prevention, and Management*. 5th ed. Baltimore, MD, Williams and Wilkins, 1997
- Batalla MA, Bakodimos MC, Bradley RF: Bacteriuria in diabetes mellitus. *Diabetologia* 7:297-301, 1971
- Forland M, Thomas VL: The treatment of urinary tract infections in women with diabetes mellitus. *Diabetes Care* 8:499-506, 1985
- Geerlings SE, Stolk RP, Camps MJL, Netten PM, Collet TJ, Hoepelman IM: Asymptomatic bacteriuria in diabetic females precedes symptomatic urinary tract infection (Abstract). In *Proceedings of the 39th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy*. San Francisco, CA, American Society of Microbiology, 1999, p. 113
- Zhanell GG, Nicolle LE, Harding GKM: Untreated asymptomatic bacteriuria in women with diabetes mellitus is associated with high rates of pyelonephritis (Abstract). In *Proceedings of the 39th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy*, San Francisco, CA, American Society of Microbiology, 1999, p. 664
- Hansson S, Jodal U, Lincoln K, Svanborg-Eden C: Untreated asymptomatic bacteriuria in girls. II. Effect of phenoxymethylpenicillin and erythromycin given for intercurrent infections. *BMJ* 298:856-859, 1989