

# Diabetes and the Risk of Acute Urinary Tract Infection Among Postmenopausal Women

EDWARD J. BOYKO, MD, MPH<sup>1,2</sup>  
STEPHAN D. FIHN, MD, MPH<sup>2,3</sup>  
DELIA SCHOLES, PHD<sup>4,5</sup>

CHI-LING CHEN, PHD<sup>4</sup>  
ESTHER H. NORMAND, RRT<sup>5</sup>  
PATRICIA YARBRO<sup>5</sup>

**OBJECTIVE** — To examine whether the presence of diabetes alters the risk of acute urinary tract infection (UTI) in postmenopausal women.

**RESEARCH DESIGN AND METHODS** — A case-control study of the Group Health Cooperative of Puget Sound (GHC), a staff-model nonprofit health maintenance organization in Washington State, was conducted. Subjects were women aged 55–75 years who had been members of GHC for at least 1 year and who had had an acute symptomatic UTI within the preceding month. Laboratory files were used to identify women with a urine culture that grew  $\geq 10^5$  colonies of a urinary pathogen. Medical records were reviewed to confirm the presence of acute, clinically symptomatic UTI. Control subjects were randomly selected from the GHC enrollment file, screened to remove women with recent UTI, and frequency matched to cases by age within 2 years. An interviewer ascertained self-reported clinician-diagnosed diabetes. Diagnosis of diabetes was confirmed by the GHC diabetes registry. A subsample of women underwent measurement of postvoid residual bladder volume ( $n = 748$ ) and culture of vaginal flora ( $n = 454$ ).

**RESULTS** — Of the 901 case and 913 control subjects, diabetes was reported in 13.1 and 6.8%, respectively. The health plan diabetes registry confirmed the diagnosis in 92% of women who self-reported the condition. The age-adjusted odds ratio (OR) for UTI in relation to self-reported clinician-diagnosed diabetes was 2.2 (95% CI 1.6–3.0). Adjustment for frequency of sexual intercourse and history of UTI had little effect on this estimate. Compared with nondiabetic women, higher UTI odds were seen in subjects who used oral hypoglycemic agents (OR 2.9 [95% CI 1.7–5.1]) and insulin (2.6 [1.5–4.6]) but not in subjects with untreated diabetes or diabetes treated by lifestyle changes (1.3 [0.7–2.3]). No significant difference was seen in the OR for UTI in diabetic women with disease of shorter duration ( $<10$  years, OR 1.9) or longer duration ( $\geq 10$  years, OR 2.6) or in relation to HbA<sub>1c</sub> level. Similar microbiologic pathogens were seen in diabetic and nondiabetic women. No significant differences were seen by diabetes status in mean postvoid residual bladder volume or vaginal flora.

**CONCLUSIONS** — Diabetes under pharmacologic treatment is associated with increased risk of clinically apparent UTI in postmenopausal women.

*Diabetes Care* 25:1778–1783, 2002

Urinary tract infection (UTI) accounts for considerable morbidity in adult women;  $>7$  million visits to physicians' offices for treatment of this condition occur annually in the U.S. (1). The belief that diabetes, a common metabolic disorder estimated to affect 16 million persons in the U.S., is associated with

a higher risk of UTI is widespread, as reflected by statements in textbooks (2) and review articles (3). Diabetes results in several abnormalities of the host defense system that might result in a higher risk of certain infections. These abnormalities include immunologic impairments, such as impaired migration, intracellular killing, phagocytosis, and chemotaxis in polymorphonuclear leukocytes from diabetic patients (4), and local complications related to neuropathy, such as impaired bladder emptying (5). Also, higher glucose concentration in urine may serve as a culture medium for pathogenic microorganisms.

Despite these abnormalities that would be expected to result in a higher risk of UTI, to our knowledge, there has been no direct demonstration of an association between diabetes and increased risk of clinically confirmed acute cystitis. Therefore, we conducted a case-control study of postmenopausal women enrolled in a prepaid health plan to determine whether the presence of this condition conferred a higher risk of urinary tract infection.

## RESEARCH DESIGN AND METHODS

### Study setting and participants

The study was conducted at Group Health Cooperative of Puget Sound (GHC), a staff-model nonprofit health maintenance organization with  $\sim 450,000$  members in western Washington State at the time of this investigation (1995–1996). Women aged 55–75 years were potentially eligible to participate if they resided in the Pierce, King, Thurston, or Snohomish counties of Washington State.

### Selection of case subjects

Case subjects were women aged 55–75 years who had been members of GHC for at least 1 year and who had had an acute symptomatic UTI within the preceding month. Each month, we reviewed the computerized central laboratory files to

From the <sup>1</sup>Epidemiologic Research and Information Center (ERIC), VA Puget Sound, Seattle, Washington; the <sup>2</sup>Department of Medicine, University of Washington, Seattle, Washington; the <sup>3</sup>Northwest Health Services Research and Development Program, VA Puget Sound, Seattle, Washington; the <sup>4</sup>Department of Epidemiology, University of Washington, Seattle, Washington; and the <sup>5</sup>Center for Health Studies, Group Health Cooperative of Puget Sound, Seattle, Washington.

Address correspondence and reprint requests to Edward J. Boyko, MD, MPH, Seattle ERIC, VA Puget Sound 152E, 1660 South Columbian Way, Seattle, WA 98108. E-mail: eboyko@u.washington.edu.

Received for publication 17 September 2001 and accepted in revised form 2 July 2002.

**Abbreviations:** GHC, Group Health Cooperative of Puget Sound; 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.

identify all women who had a urine culture during the preceding month that grew  $\geq 10^5$  colonies of a urinary pathogen. We excluded women whose urine samples were obtained during treatment for a previously diagnosed UTI or who had asymptomatic bacteriuria. This review yielded more case subjects than could be interviewed in a given month, so subjects were selected from the last date of the month backward to minimize recall bias.

We reviewed the medical records of potential case subjects for documentation of an acute, symptomatic UTI, defined as the presence of dysuria, frequency, or urgency for  $\leq 2$  weeks. Absence of symptoms led to exclusion. The remaining women were screened further by telephone interview to determine eligibility for the study.

### Selection of control subjects

Each month, we randomly selected age frequency-matched (within 2 years) women from the GHC enrollment file to serve as control subjects. These subjects must have been enrollees of GHC for at least 1 year at the time of selection. Also, computerized hospital discharge and laboratory files were screened to eliminate women with evidence of a UTI within the preceding month. Records of either a clinical diagnosis of UTI or a urine culture with  $\geq 10^5$  uropathogenic organisms per milliliter within the preceding month were grounds for exclusion as control subjects.

### Final selection of case and control subjects

After securing permission from their primary care physicians, potential case and control subjects were sent a recruitment letter describing the study; the letter advised the individuals that we would contact them by telephone to schedule an interview and explained how to decline participation. We made up to 10 attempts to reach each woman by telephone. When a potential study subject was contacted, we confirmed that she was still an active member of GHC and a resident of the predetermined geographic catchment area. Remaining women were questioned further regarding the presence of the following health conditions and were excluded from the study if any were present: neurologic problems that might interfere with voiding, severe disability, dementia, se-

vere psychiatric disorder, use of a urinary drainage appliance (including straight or indwelling catheter), residence in a nursing home, end-stage renal disease, or active cancer. We then described the study procedures to the remaining eligible subjects, requested verbal consent, and scheduled an interview with those who consented. All procedures used in the study were approved by the human subjects committees of the University of Washington and Group Health Cooperative.

### Data collection

We conducted all interviews by telephone over a 24-month period from 1994–1996 with the aid of computer-assisted telephone interviewing software (CiIII; Sawtooth Software, Ketchum, ID). This software can be programmed to incorporate complex branching logic and can perform automatic range checks and examine internal consistency. The interview was extensively tested and revised before deployment in the field. During the first and last months of the study, 10% of interviews were monitored by a second interviewer, who simultaneously recorded responses to assess reliability. Inter-rater reliability was  $>90\%$  for all items.

Presence of diabetes was determined by the response given to the following question “Have you ever been told by a doctor or nurse that you have diabetes?” The following diabetes characteristics were also assessed by interview: age of diagnosis, current treatment, history of diabetic coma or ketoacidosis, and continuous use of insulin since diagnosis. Subjects with onset of diabetes before 30 years of age, continuous use of insulin, and history of coma/ketoacidosis were defined as having type 1 diabetes.

We collected additional information on covariates during the interview, including ethnicity, level of education, history of UTI, and frequency of sexual intercourse. Because 1:1 matching was not used, the history of time-limited exposures that occurred near the time of UTI onset was assessed using an alternate strategy. This was accomplished by setting one “reference date” for each monthly sample of case and control subjects. For each monthly sample, the 15th day of that month was programmed into the interviewing software to serve as the temporal point of reference for all questions relat-

ing to time-limited exposures during the month before the UTI. For example, “In the month before July 15th, did you have sexual intercourse?” The mean and median times from the reference date to the time of the interview were 62 and 60 days, respectively.

We used the GHC diabetes registry to confirm diabetes status as determined by interview. This registry captures information from several GHC databases, including laboratory, pharmacy, and hospital discharge summary, at monthly intervals to continuously update the diabetes status of enrollees. Subjects are entered into this registry for specified time periods (indicated in parentheses) if they meet the following criteria: 1) hospital discharge diagnosis of diabetes at any time (indefinite); 2) random plasma glucose level  $\geq 200$  mg/dl (12 months); 3) fasting plasma glucose level  $\geq 140$  mg/dl (12 months); 4)  $HbA_{1c} \geq 7.0\%$  (12 months); and 5) receipt of a prescription for insulin or oral hypoglycemic agent (3 years). The time-limited membership of the registry was designed to exclude individuals in whom transient hyperglycemia developed due to secondary conditions, such as use of corticosteroids or occurrence of stressful illnesses. The nature of this time-limited membership probably leads to underascertainment of diabetic subjects who remain well controlled with lifestyle modification only and those who have not been previously diagnosed. Of the 178 diabetic subjects identified in this study by interview, 163 were included in the GHC diabetes registry (92%). This analysis confirmed the validity of self-reported diabetes diagnosis in this study.

$HbA_{1c}$  measurements were extracted from the GHC laboratory database for study subjects with diabetes. Of the 178 individuals with diabetes, one or more  $HbA_{1c}$  measurements were found for 159 (89%). The most recent  $HbA_{1c}$  measurement before the reference date was used in this analysis. These were collected between September 1993 and September 1996, and three different assays were used for this measurement over this time period: total glycohemoglobin by column affinity chromatography,  $HbA_{1c}$  by immunoassay, and  $HbA_{1c}$  by high-performance liquid chromatography. For 50% of the diabetic subjects, this measurement was obtained within 84 days of the reference date, and for 75% of diabetic subjects, the measurement was obtained

Table 1—Characteristics of study subjects by case and control status

| Characteristic                   | Case subjects<br>(n = 901) | Control subjects<br>(n = 913) | P value |
|----------------------------------|----------------------------|-------------------------------|---------|
| Mean age (years $\pm$ SD)        | 66.1 $\pm$ 6.2             | 66.2 $\pm$ 6.3                | 0.835   |
| Married or living as married     | 588 (65.4%)                | 576 (63.2%)                   | 0.333   |
| Ethnicity                        |                            |                               | 0.106   |
| Caucasian                        | 838 (93.2%)                | 841 (92.3%)                   |         |
| African-American                 | 19 (2.1%)                  | 23 (2.6%)                     |         |
| Asian-American                   | 21 (2.4%)                  | 36 (4.0%)                     |         |
| Other                            | 19 (2.1%)                  | 10 (0.6%)                     |         |
| Educational level                |                            |                               | 0.091   |
| $\leq 12$ years                  | 373 (41.6%)                | 368 (40.6%)                   |         |
| $>12$ years to completed college | 392 (43.4%)                | 416 (45.6%)                   |         |
| More than college                | 133 (15.0%)                | 127 (14.0%)                   |         |
| Annual income                    |                            |                               | 0.865   |
| $< \$25,000$                     | 293 (37.4%)                | 293 (36.9%)                   |         |
| $\$25,000$ – $50,000$            | 361 (46.1%)                | 376 (47.3%)                   |         |
| $> \$50,000$                     | 130 (16.6%)                | 126 (15.6%)                   |         |

Data are n (%).

within 172 days of the reference date. Remaining HbA<sub>1c</sub> measurements were taken 172–508 days before the reference date.

Women were invited to attend the study clinic after the interview, during which time postvoid residual volume was measured using ultrasonography (BladderScan BVI 2500+; Diagnostic Ultrasound Corporation, Redmond, WA). Three measurements were made, and the average of these three values was used in the analysis. We also obtained a swab sample of the vaginal introitus for culture. Standard laboratory methods using blood and MacConkey agar plates were used to identify *Enterobacteriaceae* and gram-positive cocci. We also cultured specimens for lactobacilli and yeast. The results of vaginal swab cultures were reported semiquantitatively on a scale of 0–4+.

The mean and median times from the reference date to the study clinic visit were 107 and 99 days, respectively. A total of 748 women presented for measurement of postvoid residual bladder volume, and of these, 454 provided a vaginal swab sample for microbiologic culture.

### Statistical methods

Comparison of categorical variables was performed using an exact test for contingency tables, whereas mean values were compared using the unpaired Student's *t* test (6). Conditional logistic regression analysis was used to estimate odds ratios

(ORs) for UTI associated with exposures of interest while adjusting for covariates; strata were defined by the “reference date” (as described above) for case subjects and corresponding control subjects (7). ORs and 95% CIs were constructed using standard methods (7). Stata software (version 6; Stata, College Station, TX) was used for all statistical analyses. Postestimation test commands within Stata were used to statistically compare ORs between and within categories of a covariate using the Wald test.

**RESULTS** — A total of 1,092 case and 1,271 control subjects met the eligibility criteria for the study, but 13% of the former and 22% of the latter declined participation. In addition, we did not succeed in contacting a number of eligible subjects (4% of case subjects and 6% of control subjects). The final participation rate among eligible subjects was 83% of case subjects and 72% of control subjects. Characteristics of study subjects by case and control status are shown in Table 1. Case and control subjects were similar with regard to mean age, marital status, ethnicity, highest educational level attained, and annual income category.

Age-adjusted ORs for potential risk factors of interest and proportion exposed are shown in Table 2. The age-adjusted relative OR of UTI was significantly greater than one for presence of diabetes. The elevation in risk of UTI among diabetic women was mainly present in those

under pharmacologic treatment to reduce plasma glucose levels. No increase in odds of UTI was seen in diabetic women treated by lifestyle changes or not treated for diabetes. ORs for UTI of a similar magnitude were seen for insulin and oral hypoglycemic agent treatments. A direct comparison of the ORs for insulin and oral hypoglycemic treatments showed no statistically significant difference ( $P = 0.869$ ). No significant linear trend was seen between duration of diabetes and odds of UTI among diabetic women (data not shown). When duration of diabetes was dichotomized at the median value, a higher OR for UTI was seen in women with diabetes for  $>10$  years as compared with those having diabetes for  $\leq 10$  years, but these ORs did not differ significantly ( $P = 0.269$ ). Although type 2 diabetes was associated with a higher OR for UTI than type 1 diabetes, no significant difference was seen in the relative odds of UTI by diabetes type ( $P = 0.441$ ).

Mean HbA<sub>1c</sub> level ( $\pm$ SD) did not differ by case or control status among the 159 diabetic women for whom this measurement was available (case subjects  $10.3 \pm 0.3\%$ , control subjects  $10.0 \pm 0.4\%$ ;  $P = 0.567$ ) or when we restricted this comparison to measurements taken within 6 months (case subjects  $10.2 \pm 0.3\%$ , control subjects  $10.5 \pm 0.5\%$ ;  $P = 0.549$ ) or 3 months (case subjects  $10.0 \pm 0.3\%$ , control subjects  $10.1 \pm 0.4\%$ ;  $P = 0.808$ ) before the time of the UTI. Only HbA<sub>1c</sub> measurements taken within 180 days of the UTI were used in remaining analyses. Similar ORs for UTI were seen in women with HbA<sub>1c</sub> levels  $>8.0$  or  $\leq 8.0$  (Table 2). No significant linear trend was seen between HbA<sub>1c</sub> level and odds of UTI among diabetic women in analyses adjusted for age alone as well as age, frequency of sexual intercourse over the past year, and history of UTI (data not shown). Adjustment for the type of HbA<sub>1c</sub> assay method did not substantially alter the results of these analyses (data not shown).

Multivariate conditional logistic regression models were estimated to determine whether the association between diabetes and diabetes characteristics was due to confounding by frequency of sexual intercourse or history of UTI. Results of these models are shown in Table 2. Results are very similar to those shown in the age-adjusted models in Table 2 for presence of diabetes, diabetes treatment, dia-

Table 2—ORs for UTI by exposures of interest adjusted for age and in multivariate models

| Exposure                                     | Case subjects | Control subjects | Age-adjusted OR (95% CI) | Multivariate OR* (95% CI) |
|--|---------------|------------------|--------------------------|---------------------------|
| Diabetes                                     |               |                  |                          |                           |
| Absent                                       | 781 (86.9%)   | 849 (93.2%)      | 1.0 (referent)           | 1.0 (referent)            |
| Present                                      | 118 (13.1%)   | 62 (6.8%)        | 2.2 (1.6–3.0)            | 2.2 (1.5–3.1)             |
| Diabetes treatment                           |               |                  |                          |                           |
| Diabetes absent                              | 781 (86.9%)   | 849 (93.3%)      | 1.0 (referent)           | 1.0 (referent)            |
| None/lifestyle changes                       | 27 (3.0%)     | 23 (2.5%)        | 1.3 (0.7–2.3)            | 1.4 (0.8–2.5)             |
| Oral medication                              | 50 (5.6%)     | 19 (2.1%)        | 2.9 (1.7–5.1)            | 2.8 (1.6–5.1)             |
| Insulin                                      | 41 (4.6%)     | 10 (2.1%)        | 2.6 (1.5–4.6)            | 2.7 (1.4–4.9)             |
| Duration of diabetes                         |               |                  |                          |                           |
| Diabetes absent                              | 781 (87.1%)   | 849 (93.3%)      | 1.0 (referent)           | 1.0 (referent)            |
| <10 years                                    | 56 (6.2%)     | 35 (3.9%)        | 1.9 (1.2–2.9)            | 2.0 (1.2–3.2)             |
| ≥10 years                                    | 60 (6.7%)     | 26 (2.9%)        | 2.6 (1.6–4.3)            | 2.4 (1.5–4.0)             |
| Diabetes type                                |               |                  |                          |                           |
| Diabetes absent                              | 783 (87.0%)   | 850 (93.2%)      | 1.0 (referent)           | 1.0 (referent)            |
| Type 1 diabetes                              | 4 (0.4%)      | 4 (0.4%)         | 1.3 (0.3–5.2)            | 1.1 (0.3–4.6)             |
| Type 2 diabetes                              | 113 (12.6%)   | 58 (6.4%)        | 2.2 (1.6–3.1)            | 2.2 (1.6–3.2)             |
| HbA <sub>1c</sub> within 180 days of the UTI |               |                  |                          |                           |
| Diabetes absent                              | 781 (90.3%)   | 849 (95.8%)      | 1.0 (referent)           | 1.0 (referent)            |
| Diabetes present HbA <sub>1c</sub> ≤8.0%     | 40 (4.6%)     | 17 (1.9%)        | 2.5 (1.4–4.5)            | 2.4 (1.3–4.5)             |
| Diabetes present HbA <sub>1c</sub> >8.0%     | 44 (5.1%)     | 20 (2.3%)        | 2.7 (1.6–4.7)            | 2.7 (1.5–4.9)             |

Data are n (%). \*Adjusted for age, history of UTI, and average frequency of sexual intercourse over the past year.

betes type, and duration of disease. Similar results were obtained in models that adjusted for age and frequency of sexual intercourse only (data not shown). Similar results were also obtained whether sexual intercourse was entered as a frequency-over-the-past-year variable, with coding as shown in Table 2, or a frequency-over-the-past-month variable, with coding of none, 1, 2, 3, 4, and >4 times (data not shown).

The frequency of urinary pathogens identified at the time of the UTI, in  $\geq 10^5$  colony-forming units per milliliter, by diabetes status was compared within the 901 cases; the diabetic proportion is given first for each of the following organisms: *Escherichia coli* 0.75, 0.83; *Enterococcus* 0.05, 0.02; *Proteus* species 0.04, 0.04; group B streptococcus 0.04, 0.02; *Klebsiella* species 0.07, 0.05; and all others 0.05, 0.04. These frequencies did not significantly differ in exact contingency table analysis ( $P = 0.172$ ).

Mean bladder residual volume ( $\pm$ SD) did not differ by diabetes status in the subsample of 682 nondiabetic and 66 diabetic women who underwent this measurement (diabetes absent  $19.5 \pm 28.2$  ml, diabetes present  $18.3 \pm 24.5$  ml;  $P = 0.780$ ) or by case/control status (case subjects,  $n = 397$ ,  $18.6 \pm 29.1$  ml; control

subjects,  $n = 352$ ,  $20.3 \pm 26.4$  ml;  $P = 0.818$ ). Diabetic women reported a significantly higher prevalence of any urinary incontinence than nondiabetic women (62.8 vs. 50.2%, respectively;  $P = 0.006$ ). In the subsample of women who underwent vaginal culture for assessment of microbiologic colonization, no statistically significant differences by diabetes status were seen in vaginal colonization with *E. coli*, *Lactobacillus acidophilus*, gram-negative rods other than *E. coli*, or yeast organisms, but when examined by case/control status, women with prior UTI had a significantly higher prevalence of *E. coli* colonization (Table 3).

**CONCLUSIONS**— This study confirms that diabetes is associated with a higher risk of acute symptomatic UTI in postmenopausal women. Women undergoing pharmacologic treatment for diabetes were mainly at higher risk, suggesting an association between severity of diabetes and risk of UTI. The risk of UTI was similar, regardless of whether diabetes was present for  $\leq 10$  or  $>10$  years. One would expect a higher risk of UTI with longer duration of diabetes, as is the case with some diabetes complications, such as retinopathy or neuropathy (8). Failure to detect an association with duration of

diabetes may be due to the frequent occult onset of type 2 diabetes (9). This analysis found no significant association between degree of glycemic control as assessed by HbA<sub>1c</sub> level and odds of UTI, although it is possible that the small sample size of diabetic women with this measurement may have resulted in insufficient power to detect a clinically meaningful difference. Furthermore, the association between diabetes or diabetes characteristics and UTI risk could not be explained by confounding due to frequency of sexual intercourse, a major risk factor for UTI (10), or even history of UTI. The small number of subjects with type 1 diabetes ( $n = 8$ ) precluded making definitive conclusions about whether UTI risk varies by diabetes type. There was no marked difference in the type of microorganism causing the UTI in the diabetic and nondiabetic women. *E. coli* was the predominant pathogen in both groups.

Several potential mechanisms for a higher occurrence of UTI in diabetic women were explored in this study. Assuming that bladder residual volume and vaginal flora were similar when measured in our study clinic after the occurrence of UTI, it did not seem that diabetic women differed from nondiabetic women with regard to either postvoid residual mean



Table 3—Presence of diabetes and case/control status in relation to vaginal flora assessed after occurrence of UTI in a subsample of women (n = 454)

| Characteristic  | Diabetes absent<br>(n = 417) | Diabetes present<br>(n = 37)  | P value |
|---|------------------------------|-------------------------------|---------|
| Number with vaginal <i>E. coli</i> present                              | 164 (39.3%)                  | 17 (46.0%)                    | 0.431   |
| Number with vaginal <i>L. acidophilus</i> present                       | 260 (62.7%)                  | 26 (70.3%)                    | 0.357   |
| Number with vaginal gram-negative rod other than <i>E. coli</i> present | 26 (6.2%)                    | 4 (10.8%)                     | 0.292   |
| Number with vaginal yeast present                                       | 48 (11.5%)                   | 7 (18.9%)                     | 0.186   |
|   | Case subjects<br>(n = 262)   | Control subjects<br>(n = 192) |         |
| Number with vaginal <i>E. coli</i> present                              | 119 (45.4%)                  | 62 (32.3%)                    | 0.005   |
| Number with vaginal <i>L. acidophilus</i> present                       | 167 (63.4%)                  | 119 (62.3%)                   | 0.714   |
| Number with vaginal gram-negative rod other than <i>E. coli</i> present | 18 (6.9%)                    | 12 (6.3%)                     | 0.793   |
| Number with vaginal yeast present                                       | 32 (12.2%)                   | 23 (12.0%)                    | 0.940   |

Data are n (%).

urine volume or vaginal microbial environment. Measurement of these characteristics before occurrence of UTI is needed to confirm these results. The higher prevalence of self-reported urinary incontinence among diabetic women suggests altered voiding physiology that may be linked to higher risk of UTI in a manner to be determined.

To our knowledge, no controlled study has previously demonstrated an association between diabetes and confirmed, clinically apparent UTI in a generally healthy community-dwelling population. The National Health and Nutrition Examination Survey II (NHANES II) included a nationally representative sample of the U.S. population during the years 1976–1980 and provides information to address this question. This study established the presence of diabetes by interview or oral glucose tolerance test in several thousand women, who were also questioned regarding whether they had had a UTI during the past 12 months. Similar self-reported prevalence of UTI was seen in women aged 45–74 years with previously diagnosed diabetes (11.8%), previously undiagnosed diabetes (10.1%), and normal glucose tolerance (10.4%) (11). Although a major problem with these data is the lack of confirmation of UTI diagnosis, they suggest a similar prevalence of recent UTI regardless of diabetes status in this age group of women.

Much of the pertinent literature on this question has examined the prevalence of asymptomatic bacteriuria, de-

fined as  $\geq 10^5$  microorganism colonies per milliliter of urine, in relation to diabetes. Asymptomatic bacteriuria is believed to lead to a higher risk of UTI (12), and this has recently been shown in women with type 2 diabetes in particular (13). A number of controlled, cross-sectional studies of the association between bacteriuria and diabetes have been published, as recently summarized (11). Of the 12 reviewed studies, 75% reported higher prevalence of bacteriuria in diabetic subjects, ranging from two- to fourfold times the frequency in control subjects (14–25). Two of these studies demonstrated higher prevalence of bacteriuria with increasing duration of diabetes but no association with HbA<sub>1c</sub> level (15,23). With regard to nosocomial bacteriuria, one prospective study demonstrated 2.3-fold higher odds of this outcome in relation to diabetes in hospital inpatients with an indwelling Foley catheter (26).

Numerous precautions were taken to minimize potential bias in this population-based study. To prevent misclassification of UTI, we used a case definition (acute urinary symptoms plus a culture yielding  $\geq 10^5$  microorganisms per milliliter) that is more than 95% specific for this diagnosis (27) and confirmed this diagnosis using data from medical records, laboratory files, and patient interviews. To avoid the biases associated with selection of control subjects from clinical or other “convenience” settings, we randomly selected these women from the entire GHC enrollment population in the four counties targeted. We attempted to

minimize recall bias by interviewing cases as soon as possible after the occurrence of UTI (28). Reliability among interviewers was high, and the computer-assisted interview was designed to minimize interviewer errors with built-in branching logic and range checks. Subject participation frequency among the total eligible population was high for a study of this type, therefore reducing the potential for selection bias. Given that the population was mainly Caucasian, the results may not be generalizable to other ethnic groups. A major advantage of this study is that it reflects the influence of diabetes and other risk factors on risk of UTI in a population-based sample of generally healthy, community-dwelling women. In “convenience” or referral populations, selection bias may be present and generalizability of findings may be limited.

The diagnosis of diabetes was confirmed for most cases using the GHC diabetes registry. It is likely that diabetes was also present in women not reporting this condition, given that many cases of this disease remain undiagnosed (8). Such misclassification is likely to have been nondifferential and, therefore, would have resulted in a bias in any association found toward the null value. One might speculate that history of UTI would lead to higher diagnostic suspicion and possibly more frequent detection of diabetes in women with this history. If history of UTI is a marker for enhanced diagnostic surveillance for diabetes, then adjustment for this history would have been expected to lead to a diminution in the association be-

tween diabetes and UTI risk, which was not observed.

In conclusion, diabetes was related to a substantial increase in risk of UTI in older women enrollees of this health plan.

**Acknowledgments**—This work was supported by National Institutes of Health Grant RO1-DK-43134.

## References

1. Patton JP, Nash DB, Abrutyn E: Urinary tract infection: economic considerations. *Med Clin North Am* 75:495–513, 1991
2. Viberti GC, Walker JD, Pinto J: Diabetic nephropathy. In *International Textbook of Diabetes Mellitus*. Vol. 2. Alberti KGMM, DeFronzo RA, Keen H, Zimmet P, Eds. New York, John Wiley & Sons, 1992, p. 1301–1302
3. Patterson JE, Andriole VT: Bacterial urinary tract infections in diabetes. *Infect Dis Clin North Am* 11:735–750, 1997
4. Valerius NH, Eff C, Hansen NE, Karle H, Nerup J, Soeberg B, Sorenson SF: Neutrophil and lymphocyte function in patients with diabetes mellitus. *Acta Med Scand* 211:463–467, 1982
5. Hosking DJ, Bennett T, Hampton JR: Diabetic autonomic neuropathy. *Diabetes Care* 27:1043–1054, 1978
6. Pagano M, Halvorsen K: An algorithm for finding the exact significance levels of rxc tables. *J Am Stat Assoc* 76:931–934, 1981
7. Kleinbaum D, Kupper L, Morgenstern H: *Epidemiologic Research: Principles and Quantitative Methods*. Belmont, CA, Wadsworth, 1982
8. Harris M: Summary. In *Diabetes in America*. 2nd ed. Harris M, Cowie C, Stern M, Boyko E, Reiber G, Bennett P, Eds. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995, p. 1–13 (NIH publ. no. 95–1468)
9. Harris MI, Klein R, Welborn TA, Knuiman MW: Onset of NIDDM occurs at least 4–7 years before clinical diagnosis. *Diabetes Care* 15:815–819, 1992
10. Strom BL, Collins M, West SL, Kreisberg J, Weller S: Sexual activity, contraceptive use, and other risk factors for symptomatic and asymptomatic bacteriuria: a case-control study. *Ann Intern Med* 107:816–823, 1987
11. Boyko E, Lipsky B: Diabetes and infection. In *Diabetes in America*. 2nd ed. Harris M, Cowie C, Stern M, Boyko E, Reiber G, Bennett P, Eds. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995, p. 485–499 (NIH publ. no. 95–1468)
12. Kunin CM: *Detection, Prevention, and Management of Urinary Tract Infection*. Philadelphia, Lea & Febiger, 1987
13. Geerlings SE, Stolk RP, Camps MJL, Netten PM, Collet TJ, Hoepelman AIM: Risk factors for symptomatic urinary tract infection in women with diabetes. *Diabetes Care* 23:1737–1741, 2000
14. Kass EH: Asymptomatic infections of the urinary tract. *Trans Assoc Am Phys* 69:56–64, 1956
15. Keane EM, Boyko EJ, Reller LB, Hamman RF: Prevalence of asymptomatic bacteriuria in subjects with NIDDM in San Luis Valley of Colorado. *Diabetes Care* 11:708–712, 1988
16. Abu-Bakare A, Oyaide SM: Asymptomatic bacteriuria in Nigerian diabetics. *J Trop Med Hyg* 89:29–32, 1986
17. Bahl AL, Chugh RN, Sharma KB: Asymptomatic bacteriuria in diabetics attending a diabetic clinic. *Indian J Med Sci* 24:1–6, 1970
18. Hansen RO: Bacteriuria in diabetic and non-diabetic outpatients. *Acta Med Scand* 176:721–730, 1964
19. Jaspan JB, Mangera C, Krut LH: Bacteriuria in Black diabetics. *S Afr Med J* 51:374–376, 1977
20. Joffe BI, Seftel HC, Distiller LA: Asymptomatic bacteriuria in diabetes mellitus. *S Afr Med J* 48:1306–1308, 1974
21. Ooi BS, Chen BT, Yu M: Prevalence and site of bacteriuria in diabetes mellitus. *Postgrad Med J* 50:497–499, 1974
22. O'Sullivan DJ, Fitzgerald MG, Meynell MJ: Urinary tract infection: comparative study in the diabetic and normal population. *Br Med J* 1:786–788, 1961
23. Schmitt JK, Fawcett CJ, Gullickson G: Asymptomatic bacteriuria and hemoglobin A1. *Diabetes Care* 9:518–520, 1986
24. Vejlsgaard R: Studies on urinary infection in diabetics. I. Bacteriuria in patients with diabetes mellitus and in control subjects. *Acta Med Scand* 179:173–182, 1966
25. Vigg B, Rai V: Asymptomatic bacteriuria in diabetics. *J Assoc Physicians India* 25:57–61, 1977
26. Platt R, Polk BF, Murdock B, Rosner B: Risk factors for nosocomial urinary tract infection. *Am J Epidemiol* 124:977–985, 1986
27. Stamm WE, Counts GW, Running KR, Fihn SD, Turck M, Holmes KK: Diagnosis of coliform infection in acutely dysuric women. *N Engl J Med* 307:463–468, 1982
28. Coughlin SS: Recall bias in epidemiologic studies. *J Clin Epidemiol* 43:87–91, 1990