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Urinary Tract Infections in Women With Type 1 Diabetes Mellitus: Survey of Female Participants in the Epidemiology of Diabetes Interventions and Complications Study Cohort

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Abstract

Purpose—We determined the prevalence of and risk factors for urinary tract infection in women with type 1 diabetes, and compared the prevalence of cystitis to that in nondiabetic women.

Materials and Methods—Women enrolled in the Epidemiology of Diabetes Interventions and Complications study were surveyed at year 10 as part of the Uro-EDIC study to assess the prevalence of cystitis and pyelonephritis in the preceding 12 months. Multivariate logistic regression models including measures of glycemic control and vascular complications of type 1 diabetes were used for risk factor analyses. The prevalence of cystitis in Uro-EDIC women was compared to that in a nondiabetic subset of women participants in the National Health and Nutrition Examination Survey III (NHANES III).

Results—A total of 550 women participated in the Uro-EDIC survey. The prevalence of cystitis and pyelonephritis in the preceding 12 months was 15% and 3%, respectively. Duration of diabetes, hemoglobin A1C, retinopathy, neuropathy, nephropathy, composite vascular complication score and intensive glycemic therapy during the Diabetes Control and Complications Trial, and Diabetes Control and Complications Trial cohort were not associated with cystitis or pyelonephritis. Sexual activity was associated with increased cystitis risk (adjusted OR 8.28; 95% CI 1.45, 158.32; p = 0.01). The adjusted prevalence of cystitis was 19.1% in Uro-EDIC women and 23.1% in NHANES III participants (adjusted OR 0.78; 95% CI 0.51, 1.22; p = 0.28).

Conclusions—In Uro-EDIC women sexual activity rather than measures of diabetes control and complications was the main risk factor for urinary tract infection. The prevalence of cystitis was similar to that in nondiabetic women participants in NHANES III.

Keywords

urinary tract infections; diabetes mellitus; type 1; prevalence; risk factors

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Study received institutional review board approval.

Urinary tract infections affect millions of women each year and incur billions of dollars in treatment costs.[1] Women with diabetes mellitus are thought to be at increased risk for UTI, presumably secondary to immunological, neurological or anatomical abnormalities.[2] Rare, severe complications of UTI have been associated with DM in case reports.[2] However, not until recently have prospective and controlled studies convincingly linked DM to an increased risk of symptomatic UTI.[3–6] Most prior studies of UTI and DM have focused on subjects with type 2 diabetes or on ASB.[3–10] Consequently little is known about the prevalence of and risk factors for symptomatic UTI in women with type 1 diabetes.

The purpose of this study was to evaluate the relationship of T1D and UTI among women in the DCCT/EDIC cohort. The DCCT demonstrated that intensive glycemic therapy for T1D reduced the development and progression of retinopathy, nephropathy and neuropathy.[11] Following the DCCT the majority of subjects enrolled in the EDIC long-term observational study where intensive glycemic therapy during DCCT was shown to have long lasting beneficial effects on the development of microvascular and macrovascular disease.[12] At EDIC year 10 subjects were surveyed regarding urological complications of T1D as part of the Uro-EDIC study. The objectives of the present analysis were to assess the prevalence of cystitis and pyelonephritis in Uro-EDIC women and the risk of these conditions associated with variables specific to T1D, including intensive vs conventional glycemic therapy during the DCCT. The prevalence of cystitis in Uro-EDIC women was compared to that in nondiabetic female participants in NHANES III.

Materials and Methods

Study Design

A single, self-administered survey of urological complications of T1D was completed by participating members of the EDIC cohort at year 10 of followup between September 1, 2002 and April 30, 2004. All EDIC subjects were invited to take the Uro-EDIC survey. Study procedures were approved by the institutional review boards of participating clinical centers.[13]

Study Population

Detailed descriptions of the methods of the DCCT and EDIC studies have been published previously.[11–13] Between 1983 and 1989, 1,441 women and men 13 to 39 years old with T1D and no history of severe diabetic complications were enrolled in the DCCT. The primary prevention cohort consisted of 726 subjects with no retinopathy, a urinary AER less than 40 mg/24 hours and diabetes duration of 1 to 5 years. The secondary intervention cohort consisted of 715 subjects who had mild to moderate non-proliferative retinopathy, urinary AER 200 mg or less per 24 hours and diabetes duration of 1 to 15 years. There were 711 subjects randomized to intensive glycemic therapy consisting of 3 or more insulin injections daily or subcutaneous infusion of insulin with an external pump guided by frequent blood glucose self-monitoring. The target preprandial blood glucose level was between 70 and 121 mg/dl, the target glycated hemoglobin value was less than 6.05% and a goal of therapy was to improve glycemic control without causing associated severe hypoglyemia. A total of 730 subjects were assigned to conventional therapy consisting of 1 to 2 insulin injections daily. There were no target blood glucose levels and the therapeutic goal was freedom from symptoms of hyperglycemia and from frequent or severe hypoglycemia. After an average of 6.5 years of followup the DCCT was discontinued and subjects from both treatment groups were advised to practice intensive glycemic therapy under the supervision of their own health care provider. Of the surviving DCCT participants 1,375 (96%) enrolled in EDIC and underwent standardized annual history, physical examination and laboratory testing as previously described.[13] In the EDIC study 550 (84%) women at year 10 volunteered to participate in the Uro-EDIC survey. While 591 (83%)

men also participated in Uro-EDIC, the prevalence of UTI was too low (4% reporting cystitis and 0% reporting pyelonephritis in the preceding 12 months) for meaningful risk factor evaluation and so the following analyses were restricted to women.

Data Sources and Variables of Interest

An episode of cystitis or pyelonephritis was defined as an answer of 1 or more in response to the questions from the Uro-EDIC questionnaire: "How many times in the last 12 months were you diagnosed with a bladder infection" and, separately, "a kidney infection?" Questionnaire data regarding sexual activity and urinary incontinence were included in risk factor analyses, as were history, physical examination and laboratory measurements collected during EDIC year 10.[13] Primary risk factors of interest included DCCT treatment group, DCCT cohort, duration of diabetes, current hemoglobin A1C, and measures of microvascular and macrovascular complications of T1D.

The 1-year prevalence of cystitis in Uro-EDIC women was compared to that in a sample of nondiabetic women enrolled in NHANES III.[14] NHANES III was conducted between 1988 and 1994, and included a survey question regarding the prevalence of bladder infection within the preceding 12 months. In the present analysis the NHANES III sample was restricted to white, nonpregnant women 20 to 59 years old without DM who provided information about cystitis.

Statistical Methods

For the risk factor analyses the statistical significances of univariate associations between the cystitis and pyelonephritis outcomes with 49 candidate variables were assessed using the Pearson chi-square and Fisher exact tests for categorical variables, and the Wilcoxon rank sum test for continuous variables. Candidate variables included measurements from EDIC year 10 as well as from the Uro-EDIC questionnaire. As recommended by Hosmer and Lemeshow those variables that were nominally significant at the $p \leq 0.15$ level were included in a multivariable logistic regression model along with DCCT treatment group, DCCT cohort, age, premenopausal/postmenopausal status, sexual activity in the last 12 months (yes or no), and a composite vascular complication score of 0 to 4 based on a history of proliferative retinopathy, nephropathy, neuropathy or cardiovascular/cerebrovascular event.[13,15] Confidence intervals were estimated from a Wald chi-square test and p values were estimated from a likelihood ratio test. If the Wald chi-square test gave different results from the likelihood ratio test the confidence intervals were estimated from the likelihood ratio test. A p value ≤ 0.01 was considered statistically significant.

In the analysis of the combined Uro-EDIC and NHANES III samples the survey function in SAS was used to accommodate features of the complex NHANES III survey design including stratified cluster sampling. Using a survey logistic model adjusting for age, body mass index, parity, hysterectomy, postmenopausal status, hormone replacement therapy, sexual partner in the preceding 12 months and current smoking status, the adjusted prevalence of cystitis in the Uro-EDIC cohort that would be expected if covariate patterns were the same as in the NHANES III sample using the weighted NHANES III prevalence, and the adjusted odds ratio for the contrast between Uro-EDIC and NHANES III were estimated, and $p \leq 0.01$ was considered statistically significant. SAS® Version 9.0 was used to perform the analyses.

Results

A total of 550 (84%) women participated in the Uro-EDIC survey, of whom 528 and 507 provided information regarding the occurrence of cystitis and pyelonephritis in the preceding

12 months, respectively. Characteristics of the women included in the cystitis analysis are listed in table 1. Characteristics of the women included in the pyelonephritis analysis were similar.

There were 79 (15%) women who reported 1 or more diagnoses of cystitis in the preceding 12 months and 17 women had 3 or more cystitis episodes. On univariate analysis comparing women reporting 1 or more episodes of cystitis to those reporting no cystitis, DCCT treatment group, DCCT cohort, duration of diabetes, current hemoglobin A1C, history of diabetic retinopathy, nephropathy or peripheral neuropathy, and the composite vascular complication score were not associated with cystitis. Report of any sexual activity in the last 12 months (97% vs 90%, $p = 0.03$), having a sexual partner during the last 12 months (100% vs 88%, $p < 0.01$), more frequent sexual activity in the last 12 months ($p = 0.07$), nonwhite race (8% vs 3%, $p = 0.05$), mild to moderate (but not heavy) exercise ($p = 0.08$), abstinence from alcohol (71% vs 62%, $p = 0.12$), lower total cholesterol (mean 180 mg/dl vs 188 mg/dl, $p = 0.04$) and lower triglyceride level (mean 71 mg/dl vs 81 mg/dl, $p = 0.02$) were associated with cystitis at $p \leq 0.15$, and were added along with prespecified covariates to the multivariate model. Only report of any sexual activity in the last 12 months was associated with a significant increase in cystitis risk (aOR 8.28; 95% CI 1.45, 158.32; $p = 0.01$) on multivariate analysis (table 2). Report of a sexual partner in the last 12 months was not included in the multivariate model as all subjects with cystitis reported a sexual partner.

There were 16 (3%) women who reported 1 or more diagnoses of pyelonephritis in the preceding 12 months and 2 of these reported more than 1 episode. On univariate analysis comparing women reporting 1 or more episodes of pyelonephritis to those reporting no pyelonephritis, DCCT treatment group, DCCT cohort, duration of diabetes, hemoglobin A1C, history of diabetic retinopathy, nephropathy or peripheral neuropathy, composite vascular complication score and measures of sexual activity were not associated with pyelonephritis. History of diabetic ketoacidosis (33% vs 15%, $p = 0.06$), smoking (47% vs 27%, $p = 0.14$) and current oral contraceptive use (31% vs 15%, $p = 0.13$) were associated with pyelonephritis at $p \leq 0.15$, and were added along with prespecified covariates to the multivariate model. None of the covariates included in the multivariate analysis was significant at $p \leq 0.01$ (table 2).

Characteristics of the Uro-EDIC and NHANES III cohorts are compared in table 3. There were significant differences in age, parity, postmenopausal status, and use of hormone replacement therapy. Most women in each cohort had a sexual partner in the preceding 12 months. The adjusted prevalence of cystitis in the preceding 12 months was 19.1% for Uro-EDIC women and 23.1% for women in the NHANES III cohort. The adjusted odds ratio for cystitis in the Uro-EDIC cohort compared to the NHANES III cohort was 0.78 (95% CI 0.51, 1.22; $p = 0.28$).

Discussion

In women with T1D in the Uro-EDIC cohort the prevalence of cystitis in the preceding 12 months was 15% and that of pyelonephritis was 3%. Duration of DM, glycemic control as measured by hemoglobin A1C and vascular complications of DM were not associated with an increased risk of cystitis or pyelonephritis. The prevalence of cystitis in Uro-EDIC women was similar to that in a subset of nondiabetic women from the NHANES III cohort. These findings are particularly important in that there are few published studies that assess the prevalence of and risk factors for symptomatic UTI in women with T1D.

The finding of a 15% prevalence of cystitis in the preceding 12 months translates into an incidence similar to previously reported rates of cystitis in the United States of 13,000/100,000 women per year.[1] A 3% prevalence of pyelonephritis in the preceding 12 months in Uro-EDIC would suggest a higher incidence than the reported rates of pyelonephritis in the United States of 11 to 28/10,000 women.[6,16,17]

The relationship of traditional measures of diabetes severity to risk of UTI is not clear from prior studies. Hemoglobin A1C and microvascular complications of DM, including nephropathy and neuropathy, have not been associated with symptomatic UTI in women with T1D or T2D,[7] while the duration of DM and insulin use have been variably associated.[3–4] Peripheral neuropathy and macroalbuminuria have been described as risk factors for ASB in women with T1D.[8] However, ASB has not been found to be a risk factor for symptomatic UTI in T1D as it is in T2D.[7,9,10] It is possible that women with T1D may be at increased risk for ASB, in part due to increased adherence of type 1 fimbriated E. coli to uroepithelial cells most notable in poorly controlled DM, but due to impaired cytokine secretion ASB does not progress to symptomatic UTI.[8,18,19] Given the absence of an association between glycemic control or complications of T1D and UTI among Uro-EDIC women, it is not surprising that there was also no association between UTI and DCCT treatment group or DCCT cohort. Of note, there was no association between treatment group assignment and UTI during the DCCT.[20]

Sexual intercourse is a clear risk factor for cystitis in women with T1D[7] as it is in nondiabetic women.[21] In Uro-EDIC women there was an increased risk of cystitis (aOR 8.28; 95% CI 1.45, 158.32; $p = 0.01$) associated with any sexual activity in the last 12 months. It is probable that the measure of degree of sexual activity was not sensitive enough to discern an association with pyelonephritis in this study.

Compared to nondiabetic women from NHANES III Uro-EDIC women with T1D did not have an increased prevalence of cystitis. In contrast, several recent studies have documented an increased risk of symptomatic UTI associated with DM, although the majority of subjects represented likely had T2D.[3–6] A possible explanation for the difference in UTI risk associated with DM between Uro-EDIC and other studies may be that T1D and T2D affect UTI risk disproportionately. Alternatively increased rates of pyelonephritis in diabetic patients may have driven the increased risk of UTI in other studies as a strong association between DM and pyelonephritis has previously been shown.[6] However, given the relatively low incidence of pyelonephritis, this seems unlikely to be the only explanation. The risk of pyelonephritis associated with T1D was not evaluated in this study as there was no measure of pyelonephritis prevalence in NHANES III.

Finally, differences in study populations and methodologies clearly contributed to variations in findings. Uro-EDIC participants represent a fairly homogeneous population of women with relatively well controlled T1D and close followup. While NHANES participants have served as a comparison group in epidemiological studies, they represent a less highly selected population based sample. To make an informative comparison between these 2 populations the NHANES III comparison group was restricted to nondiabetic white women 20 to 59 years old and adjustments were made for population characteristics listed in table 3. Of note, of the characteristics considered in the comparison of Uro-EDIC and NHANES III participants, sexual activity is the most likely potential confounder and it occurred with similar frequency in both groups. As a more detailed measure of sexual activity than the report of a sexual partner among the NHANES III participants was unavailable, it is possible that varying degrees of sexual activity between the comparison groups may have confounded the results. Therefore, reproduction of these findings in other study populations may be needed before one can conclude that women with T1D are not at increased risk for cystitis compared to nondiabetic women.

The major strength of this study is the detailed characterization of control and complications of DM in women in the Uro-EDIC cohort. The use of the NHANES III comparison group is another element that distinguishes this study from others. A relative weakness to be acknowledged is the use of a survey design, and the inherent biases associated with subject selection and recording UTI diagnoses based on recall. However, the annual followup of the

Uro-EDIC women likely improved the accuracy of their survey responses. Finally, in addition to the noted differences in study populations between Uro-EDIC and NHANES III, NHANES III took place several years earlier than the Uro-EDIC survey. More recent versions of NHANES did not include an appropriate measure of cystitis.

Conclusions

Sexual activity rather than glycemic control and vascular complications of DM was associated with an increased risk of UTI in women with T1D. Intensive glycemic therapy during the DCCT did not reduce the risk of UTI 9 to 10 years later in EDIC. Further studies are warranted to explore whether women with T1D are at increased risk for pyelonephritis and more complicated UTI compared to nondiabetic women, and to confirm that women with well controlled T1D may not be at increased risk for cystitis.

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Abbreviations and Acronyms

AER
albumin excretion rate

aOR
adjusted odds ratio

ASB
asymptomatic bacteriuria

DCCT
Diabetes Control and Complications Trial

DM
diabetes mellitus

EDIC
Epidemiology of Diabetes Interventions and Complications

NHANES III
National Health and Nutrition Examination Survey III

T1D
type 1 diabetes

T2D
type 2 diabetes

Uro-EDIC
Urological Complications of Epidemiology of Diabetes Interventions and Complications

UTI
urinary tract infection

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Table 1

Characteristics of 528 Uro-EDIC women included in cystitis analysis

No. DCCT treatment group (%):		
Conventional	257	(49)
Intensive	271	(51)
No. DCCT cohort (%):		
Primary prevention	268	(51)
Secondary intervention	260	(49)
Mean age (SD)	43	(7.1)
No. nonwhite race (%)	19	(4)
No. married (%)*	376	(73)
No. postmenopausal (%)*	117	(23)
Mean yrs T1D (SD)	23	(5.0)
Mean current A1C (SD)*	7.9	(1.3)
No. retinopathy ever (%)	510	(97)
No. nephropathy (%):		
AER less than 40 mg/24 hrs	404	(77)
AER 40–300 mg/24 hrs	101	(19)
AER greater than 300 mg/24 hrs	23	(4)
No. peripheral neuropathy (%)*	159	(32)
No. composite vascular complication score (%):†		
0	376	(71)
1	114	(22)
2	29	(5)
3	7	(1)
4	2	(less than 1)
No. sexual activity in last 12 mos (%)*	468	(91)
Median lifetime cystitis episodes (range)*	1.0	(0.0–6.0)
Mean age at first cystitis (SD)*	23	(9.0)
Median lifetime pyelonephritis episodes (range)*	0.0	(0.0–3.0)
Mean age at first pyelonephritis (SD)*	23	(11.7)
No. ever hospitalized for cystitis or pyelonephritis (%)*	45	(9.8)

Characteristics of the 507 women in the pyelonephritis analysis were similar.

*Sample is less than 528 women for some characteristics due to incomplete survey response, including married 517, postmenopausal 509, current A1C 516, peripheral neuropathy 498, sexual activity in last 12 months 515, lifetime cystitis episodes 423, age at first cystitis 178, lifetime pyelonephritis episodes 464, age at first pyelonephritis 74 and ever hospitalized for cystitis or pyelonephritis 460 women.

†Composite vascular complication score of 0 to 4 based on a history of proliferative retinopathy, nephropathy, neuropathy or cardiovascular/cerebrovascular event (13).

Table 2

Multivariate analysis of risk factors for cystitis and pyelonephritis

	Cystitis*			Pyelonephritis†		
	aOR	**95% CI**	**p Value**	**aOR**	**95% CI**	**p Value**
Conventional vs intensive treatment (DCCT)	0.70	0.40, 1.22	0.21	0.19	0.04, 0.85	0.02
Primary vs secondary DCCT cohort	1.60	0.92, 2.79	0.09	0.71	0.19, 2.76	0.62
Age (per 1-yr increase)	0.98	0.94, 1.03	0.47	0.95	0.85, 1.07	0.38
After vs before menopause	1.41	0.66, 3.00	0.38	1.02	0.15, 6.87	0.98
Composite vascular complication score:‡			0.07			0.04
0	1	—		1	—	
1	2.09	1.12, 3.91		—	—	
2–4	0.96	0.26, 3.52		—	—	
1–4	—	—		4.48	1.08, 18.54	
Sexual activity last 12 mos	8.28	1.45, 158.32§	0.01§	0.90	0.10, 7.76	0.92

*Additional covariates in the cystitis multivariate model were not statistically significant at p ≤0.01: race (p = 0.05), frequency of sexual intercourse in the last 12 months (p = 0.43), exercise (p = 0.20), alcohol use (p = 0.13), total cholesterol (p = 0.11), triglycerides (p = 0.22).

†Additional covariates in the pyelonephritis multivariate model were not statistically significant at p ≤0.01, including smoking (p = 0.06), oral contraceptive use (p = 0.04), diabetic ketoacidosis ever (p = 0.39).

‡Composite vascular complication score of 0 to 4 based on a history of proliferative retinopathy, nephropathy, neuropathy or cardiovascular/cerebrovascular event (13).

§Likelihood ratio test.

Table 3

Characteristics of Uro-EDIC and NHANES III comparison samples

	No. Uro-EDIC (%)	No. NHANES III (%)	p Value
Total participants	550	598	
Age:			<0.01
20–29	8 (1.5)	162 (27)	
30–39	169 (31)	202 (34)	
40–49	248 (45)	146 (24)	
50 +	125 (23)	89 (15)	
Live births:			<0.01
0	165 (30)	31 (6.3)*	
1	112 (20)	108 (22)*	
2 or More	273 (50)	347 (72)*	
Postmenopausal	130 (24)*	91 (15)	<0.01
Hormone replacement therapy	65 (15)*	62 (10)	0.05
Hysterectomy	66 (12)	91 (15)*	0.16
Body mass index (kg/m^2):			<0.01
Less than 25	183 (34)*	364 (61)	
25–30	222 (42)*	129 (22)	
30 or Greater	130 (24)*	105 (18)	
Smoker	74 (14)*	196 (33)	<0.01
Sexual partner in last 12 mos	473 (90)*	550 (92)*	0.11

Column percentages may not equal 100% due to rounding.

*Sample is smaller for some characteristics due to incomplete survey response, including live births NHANES III 485, postmenopausal Uro-EDIC 534, hormone replacement therapy Uro-EDIC 440, hysterectomy NHANES III 595, body mass index Uro-EDIC 535, smoker Uro-EDIC 540, sexual partner last 12 months Uro-EDIC 527, NHANES III 595.