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Type 2 diabetes mellitus and risk of stress, urge, and mixed urinary incontinence

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Abstract

Purpose—To improve understanding of the etiologic relation between type 2 diabetes and urinary incontinence (UI), we examined associations between diabetes and UI type, among 71,650 women aged 37 to 79 years in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II).

Materials and Methods—From 1976 to 2000 in the NHS and 1989 to 2001 in NHS II, participants reported diagnoses of type 2 diabetes. Women with incident UI at least weekly were identified from 2000 to 2002 in NHS and 2001 to 2003 in NHS II. We pooled data from the two cohorts, and estimated odds ratios (ORs) and 95% confidence intervals (CIs) using multivariable logistic regression, adjusting for age, parity, body mass index, smoking, hysterectomy, functional limitations, menopausal status, postmenopausal hormone use, incontinence-promoting medications, and study cohort.

Results—The incidence of at least weekly UI was 5.3% (3,612/67,984) among women without type 2 diabetes and 8.7% (318/3,666) among women with diabetes. Overall, the multivariable-adjusted odds of incident UI were increased 20% (OR 1.2, 95% CI 1.0–1.3, p=0.01) among women with versus without type 2 diabetes. This increase appeared largely explained by significantly greater odds of urge UI (OR 1.4, 95% CI 1.0–1.9, p=0.03); there was no apparent association between diabetes and either stress (p=0.3) or mixed (p=0.6) UI, although confidence intervals were somewhat wide.

Conclusions—Our findings suggest that type 2 diabetes may especially influence urge UI. Further research is needed to confirm this finding and identify pathways linking these conditions.

Keywords

epidemiology; type 2 diabetes mellitus; urinary incontinence

INTRODUCTION

The prevalence of type 2 diabetes mellitus has increased in women of all ages in the United States over the past decade, with a 60% increase among women aged 65 to 74 years and about a 50% increase among women aged 45 to 64 years.[1]

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Urinary incontinence (UI) is also a common condition in women, with prevalence estimates ranging from 20–40% in women younger than age 60 years and from 30–50% in older women.[2] Several epidemiologic studies have observed increased risks of UI among women with type 2 diabetes,[3, 4] including a previous report in our Nurses' Health Study (NHS),[5] but a mechanism has not been established. Clues about a possible mechanism might be obtained by examining associations across specific UI types, which have different underlying causes, and diabetes. However, few prospective studies have examined associations between type 2 diabetes mellitus and UI type. At the time of our previous NHS analysis, we did not have data on UI type. Therefore, in the present study, we investigated the association of type 2 diabetes with incident stress, urge, and mixed urinary incontinence among women enrolled in the NHS, as well as our younger cohort of women in the NHS II.

MATERIALS AND METHODS

Study Population

The NHS was initiated in 1976 when 121,701 female nurses aged 30 to 55 years returned a mailed questionnaire about their health and lifestyle. Updated information has been collected using biennial questionnaires. Participants were asked about urinary incontinence on the 2000 and 2002 questionnaires. Among the women who provided information on UI in 2000 (n=83,423), 90% also provided information in 2002. Women who did and those who did not provide follow-up UI information were similar in mean age and body mass index (BMI), parity, and prevalence of UI, although the prevalence of diabetes was somewhat higher in non-responders (9 vs. 14%); however, since loss-to-follow-up was low and since UI prevalence did not vary by response group, any differences in diabetes prevalence would not meaningfully influence results.

The NHS II was initiated in 1989 when 116,671 female nurses aged 25 to 42 years completed and returned a questionnaire similar to that used in the NHS; subsequently, updated information has been collected using biennial questionnaires. The 2001 and 2003 NHS II questionnaires asked about UI symptoms. Of the women who responded to the UI questions in 2001 (n=85,640), 82% also responded to the UI questions in 2003. Responders and non-responders were similar in mean age, mean BMI, parity, and prevalence of diabetes and UI. Overall, 94,838 NHS participants responded to the 2000 questionnaire and 101,281 NHS II participants responded to the 2001 questionnaire. For these analyses of incident incontinence, we excluded NHS and NHS II participants missing data on UI at baseline (i.e., 2000 in NHS, 2001 in NHS II) or at the end of follow-up (i.e., 2002 in NHS, 2003 in NHS II) (n=38,403). These women were similar to all women responding to the 2000 and 2001 questionnaires in mean age, mean BMI, parity, and prevalence of diabetes. Because our analyses focused on incident UI, we also excluded women reporting any prevalent UI at baseline, defined as incontinence at least once per month or less than once per month of quantities at least enough to wet the underwear (n=84,819). In addition, to ensure that our reference group did not include women with any diabetes, we excluded women reporting a diagnosis of gestational diabetes (n=1,247). Thus, there were 38,945 NHS participants and 32,705 NHS II participants at risk for incident UI. The Institutional Review Board of Brigham and Women's Hospital approved these studies.

Measurement of incident urinary incontinence

Identical questions about UI were asked at baseline and at the end of follow-up in both cohorts. Participants were asked, "During the last 12 months, how often have you leaked or lost control of your urine?" Response options were never, less than once per month, 2-3 times per month, about once per week, and almost every day. Women who reported UI were then asked, "When you lose your urine, how much usually leaks?" Response options were a few drops, enough to wet your underwear, enough to wet your outer clothing, and enough to wet the floor. A

reliability study among 200 participants in the NHS demonstrated high reproducibility of responses to these UI questions.[5] In addition to women who reported no UI at baseline, we considered those who reported leaking a few drops less than once per month at baseline at risk for incident UI because we did not consider this to be clinically significant incontinence.[6, 7] Incident cases were defined as those reporting UI at least once per week at the end of follow-up. Non-cases were women reporting no UI or leaking a few drops less than once per month again at the end of follow-up.

In the NHS, due to the large number of incident UI cases, a supplementary questionnaire containing validated questions to assess UI type[8] was mailed to a random sample of approximately 80% of the cases (n=2,183) and completed by 84%. The same supplementary questionnaire was mailed to approximately 98% of incident cases in NHS II (n=1,169) and completed by 79%. Women were asked about the frequency in which they leaked urine (never, rarely, sometimes, or often) during various circumstances. These circumstances included coughing or sneezing, lifting things, laughing, and exercise (stress UI symptoms) as well as having an urge to urinate when a toilet was not available or experiencing a sudden feeling of bladder fullness (urge UI symptoms). UI type was classified as stress UI if women reported experiencing stress UI symptoms more often than urge UI symptoms, and as urge UI if urge UI symptoms were reported more often then stress UI symptoms. Women were classified as having mixed UI when stress and urge UI symptoms were equally common.

Measurement of type 2 diabetes mellitus

On each biennial questionnaire, study participants were asked to report a diagnosis of diabetes. In a validation study of 62 NHS participants with self-reported diabetes, 98% of the reports of diabetes were confirmed by medical record reviews, according to standard diagnostic criteria.[9] Another sub-study found a very low prevalence of undiagnosed diabetes among women who did not self-report a diabetes diagnosis (0.5%).[10]

Statistical analysis

Women who did not meet our definition of either case or non-case (i.e., those with new leaking less than once per month of more than a few drops) were excluded from these analyses because their continence status was not clear (n=12,564). Multivariable logistic regression was used to calculate odds ratios (ORs) and their 95% confidence intervals (CIs) for each case definition (i.e., all, stress, urge, mixed UI) separately in each cohort, adjusting for potential UI risk factors identified from the literature, including age, parity, BMI, cigarette smoking, hysterectomy, functional limitations, menopausal status and postmenopausal hormone use, and use of medications that may affect continence (diuretics, calcium channel blockers, and angiotensin-converting enzyme inhibitors). In general, all covariates reflected participant status at baseline (i.e., 2000 in NHS, 2001 in NHS II). Functional limitations were defined as a self-report of being substantially limited in climbing 1 flight of stairs, walking 1 block, or bathing or dressing oneself.

Because results of the cohort-specific analyses were similar to each other, we pooled the data after confirming that there also was no statistical evidence of heterogeneity. Interaction terms for type 2 diabetes by cohort were not statistically significant in any model (interaction term p-values were 0.36 for any UI, 0.63 for stress UI, 0.12 for urge UI, 0.60 for mixed UI). We adjusted for covariates from the cohort-specific analyses, as well as study cohort, in the pooled analyses. Two-tailed p-values <0.05 were considered statistically significant. All data were analyzed using SAS 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

In 2000, NHS participants were aged 54–79 years and, in 2001, NHS II participants were aged 37–54 years. In each cohort, women with type 2 diabetes were slightly older than those without type 2 diabetes (mean age 67.8 vs. 66.0 in NHS, 47.2 vs. 46.0 years in NHS II; Table 1). Obesity, previous hysterectomy, and use of medications that may affect continence (i.e., diuretics, calcium channel blockers or angiotensin-converting enzyme inhibitors) were more common among women with type 2 diabetes.

Among NHS and NHS II participants at risk for incident UI at baseline, 3,612 of 67,984 women without type 2 diabetes (5.3%) and 318 of 3,666 women with type 2 diabetes (8.7%) reported developing UI at least once per week at the end of the 2-year follow-up period.

After adjusting for potential confounding factors, there were significantly increased odds of incident UI among NHS participants with type 2 diabetes compared to those without diabetes (OR 1.2, 95% CI 1.0–1.4). The odds ratio for UI was identical in NHS II participants (OR 1.2, 95% CI 0.9–1.7). (Data not shown in table)

In the combined analyses, women with type 2 diabetes had significantly increased odds of developing UI compared to women without diabetes (OR 1.2, 95% CI 1.0–1.3, p=0.01, Table 2). This increase in overall UI odds appeared to be explained mostly by a significant increase in the odds of developing urge UI (OR 1.4, 95% CI 1.0–1.9, p=0.03). Associations between type 2 diabetes and both stress (OR 1.1, 95% CI 0.9–1.4, p=0.3) and mixed (OR 0.9, 95% CI 0.7–1.3, p=0.6) UI were not statistically significant. However, the confidence interval for the stress UI odds ratio substantially overlapped with the confidence interval for the urge UI odds ratio, and thus apparent differences in risk of urge and stress UI among women with diabetes should be interpreted with caution. Adjustment for BMI as a continuous variable, rather than a categorical variable, did not alter the results.

DISCUSSION

Overall, in this analysis of two large prospective studies, we observed significant, increased odds of developing UI among women with type 2 diabetes. Diabetes appeared to be more strongly associated with the odds of incident urge UI, although further data are needed.

Among the few epidemiologic studies which have examined diabetes and UI type, the majority have been cross-sectional. Nevertheless, these limited data generally support a specific relation between diabetes and urge UI. For example, in a cross-sectional study of over 21,000 women aged 20 years and older, the prevalence of urge UI, but not stress UI, was elevated among those with diabetes (urge UI OR 1.49, 95% CI 1.03–2.16; stress UI OR 0.87, 95% CI 0.66–1.14).[11] Likewise, among 2,763 postmenopausal women, the prevalence of urge UI was higher in women with diabetes compared with those without diabetes (OR 1.49, 95% CI 1.11–2.00), but there was no significant difference in the prevalence of stress UI between the two groups (OR 0.82, 95% CI 0.58–1.14).[12]

Similarly, in sparse prospective data, diabetes was associated with incident overactive bladder (OR 2.2, 95% CI 1.3–3.6), defined as urgency with or without UI, but not with incident stress UI, in a prospective study of women aged 40 years and older.[13] However, a 5-year study of 3,000 women aged 42–52 years found an elevated risk of mixed UI among women with diabetes (OR 3.02, 95% CI 1.12–8.10), but observed no association between diabetes and either stress or urge UI.[6] However, this study used a broader UI definition than ours (i.e., UI at least monthly) and, due to a small number of cases with diabetes, likely had limited power to detect modest relative risks, particularly for urge UI.

Several hypothesized mechanisms linking type 2 diabetes and UI may be particularly relevant to urge UI, and could help begin to explain how diabetes may lead to an increase in UI development. For example, a cross-sectional study of 246 women with diabetes found an elevated prevalence of at least weekly UI in women with versus those without neuropathic pain (OR 2.37, 95% CI 1.27–4.42) and in those with versus those without macroalbuminuria (OR 3.82, 95% CI 0.95–15.33).[14] These results suggest that type 2 diabetes-related microvascular damage could potentially affect the pelvic floor and lead to dysfunction of the bladder or sphincter muscles. Diuresis caused by hyperglycemia may lead to urinary frequency, further contributing to the risk of urge UI. In addition, structural changes consistent with detrusor overactivity, such as widening gaps between myocytes, degenerated nerve fibers,[15] and an increased density of muscarinic receptors,[16] have been observed in the bladders of diabetic rats.

Some limitations of our study should be considered. All information on urinary incontinence was self-reported. However, previous studies have established the reliability and validity of self-reported UI data.[5, 17] In addition, previous findings indicate that self-reported UI type is highly specific,[18] which is most important to achieve valid results in prospective studies.[19]

Diabetes data were also self-reported. However, a previous validation study in NHS participants demonstrated very high validity of self-reported diabetes diagnoses.[9] In addition, in a random sample of NHS participants who did not report a diabetes diagnosis, we found evidence of undiagnosed type 2 diabetes in less than 1% of women,[10] suggesting that misclassification of type 2 diabetes status is unlikely to have substantially impacted our effect estimates. Moreover, the presence of participants with undiagnosed diabetes among the non-cases in our study would tend to attenuate the observed associations.

Due to the limited number of incident UI cases with diabetes, we did not have adequate power to examine the relation of urge UI with indicators of diabetes severity, such as diabetes complications, duration, and glycemic control. However, we will be able to conduct a more detailed investigation of diabetes severity and urinary incontinence incidence with further follow-up. Also, although limited data suggest that pre-diabetes may increase UI risk[14], we did not collect data on pre-diabetes and other studies are needed to address this issue.

We adjusted for a number of potential confounding factors in our statistical analyses. Nonetheless, in an observational study, confounding cannot be ruled out as a potential explanation for the observed results. Finally, findings from these cohorts of nurses may not be generalizable to broader populations of women. In particular, because our study participants are predominantly white, our findings may not be generalizable to non-white women. While the prevalence of self-reported diabetes in the NHS (7%) and NHS II (2%) is slightly lower than estimates of diabetes prevalence in the general population (approximately 11% and 5%, respectively, in women of similar age[1]), we reported incidence rates for UI that were similar to those reported in other studies of Caucasian populations.[20] Thus, our findings are likely applicable to Caucasian women.

CONCLUSIONS

In summary, across these middle-aged and older women, we observed a consistent, modest elevation in the odds of urinary incontinence in those with type 2 diabetes compared with those without type 2 diabetes. Our results suggest that type 2 diabetes may particularly influence risk of urge UI; further research is needed to better investigate this relation and to identify mechanisms through which type 2 diabetes could affect development of urge UI. If these findings are confirmed, research also will be needed to explore ways to prevent urge UI among women with diabetes.

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Table 1

Characteristics of study participants at baseline[a]

	NHS		NHS II	
	No Type 2Diabetes (n=29,210)	**Type 2 Diabetes (n=2,349)**	**No Type 2 Diabetes (n=26,918)**	**Type 2 Diabetes (n=609)**
Age ± SD (mean in years)	66.0 ± 7.0	67.8 ± 6.8	46.0 ± 4.7	47.2 ± 4.5
Race/Ethnicity (%)				
White	90.7	85.7	92.9	88.0
Non-White / Missing	9.3	14.3	7.1	12.0
Postmenopausal (%)	98.8	99.5	31.7	46.3
Postmenopausal hormone therapy (%, among postmenopausal women)				
Former user	28.6	30.9	4.5	8.7
Current user	39.0	27.4	13.9	18.2
Parity (%)				
None	7.3	7.7	22.1	32.0
1–2 births	36.1	32.7	50.4	49.8
≥3 births	55.4	58.8	25.4	16.1
Hysterectomy (%)	31.9	38.9	15.1	24.8
BMI (kg/m^2, %)				
<22	21.4	8.6	27.0	9.0
22 to 24	28.4	15.2	27.5	13.1
25 to 29	32.6	35.4	23.5	18.1
≥ 30	15.5	38.4	14.4	52.7
Cigarette Smoking (%)				
Never	44.5	44.4	67.0	64.0
Former	45.5	47.9	24.8	27.3
Current	9.8	7.5	8.1	8.7
Medication Use (%)[b]	25.3	48.0	7.4	35.8

[a] Baseline is 2000 for NHS and 2001 for NHS II. Some percentages may not sum to 100 due to missing values. Women who reported incident incontinence less than once per month of more than a few drops of urine were excluded from analyses since their continence status was unclear (n=12,564).

[b] Medications included are those that may affect continence: diuretics, calcium channel blockers, and angiotensin-converting enzyme inhibitors

Table 2

Type 2 diabetes and odds of urinary incontinence[a]

	Type 2 diabetes		P value
	No	Yes	
Non-cases	52,516	2,640	
Any incontinence			
Cases	3,612	318	
OR (95% CI)[b]	1.0 (referent)	1.2 (1.0–1.3)[c]	0.01
Stress incontinence			
Cases	1,362	94	
OR (95% CI)[b]	1.0 (referent)	1.1 (0.9–1.4)	0.3
Urge incontinence			
Cases	480	53	
OR (95% CI)[b]	1.0 (referent)	1.4 (1.0–1.9)[c]	0.03
Mixed incontinence			
Cases	660	51	
OR (95% CI)[b]	1.0 (referent)	0.9 (0.7–1.3)	0.6

[a] Urinary incontinence was defined as urine leakage at least once per week. Results are from combined analyses of the NHS and NHS II cohorts. Women who reported incident incontinence less than once per month of more than a few drops of urine were excluded from analyses since their continence status was unclear (n=12,564).

[b] OR, odds ratio. Adjusted for age (5-year categories), parity (0, 1–2, ≥ 3 births), BMI (<22, 22–24, 25–29, ≥ 30 kg/m^2), cigarette smoking (never, former, current), hysterectomy (yes/no), functional limitations (yes/no), menopausal status/postmenopausal hormone use (premenopausal, missing menopausal status, postmenopausal/never used hormone therapy, formerly used hormone therapy, currently use hormone therapy), use of medications that may affect continence (diuretics, calcium channel blockers, and angiotensin-converting enzyme inhibitors; yes/no), cohort (NHS, NHS II).

[c] Values were rounded to 1 significant digit; however, lower limit of confidence interval is >1.0 and odds ratio is statistically significant.