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Authors

Appa, Ayesha A
Brown, Jeanette S
Creasman, Jennifer
[et al.](#)

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Clinical Predictors and Significance of Postvoid Residual Volume in Women with Diabetes

Ayesha A. Appa, BA¹, Jeanette S. Brown, MD¹, Jennifer Creasman, MSPH¹, Stephen K. Van Den Eeden, PhD², Leslie L. Subak, MD¹, David H. Thom, MD/PhD¹, Assiamira Ferrara, MD/PhD², and Alison J. Huang, MD/MAS¹

¹University of California, San Francisco

²Kaiser Permanente Division of Research

Abstract

Aims—To identify women with diabetes at risk of increased postvoid residual volume (PVR) and investigate the relationship of increased PVR to urinary symptoms in women with diabetes.

Methods—PVR was measured by bladder ultrasonography in a cross-sectional cohort of 427 middle-aged and older women with diabetes. Participants completed questionnaires assessing urgency incontinence, stress incontinence, daytime frequency, nocturia, obstructive voiding, and diabetes-related end-organ complications: heart disease, stroke, neuropathy. Serum HbA1c and creatinine were recorded.

Results—75% of participants had a PVR of 0–49, 13% had a PVR of 50–99, and 12% had a PVR \geq 100 mL. Approximately 59% of women with a PVR \geq 100 mL reported at least one lower urinary tract symptom. Women with diabetes and a PVR \geq 100 mL were more likely to report urgency incontinence (OR 2.18, CI 1.08–4.41) and obstructive voiding symptoms (OR 2.47, CI 1.18–5.17) than women with PVR <50 mL. In multivariable models, poorer glycemic control was associated with an increased likelihood of PVR \geq 100 mL (OR 1.30, CI 1.06–1.59 per 1.0-unit increase in HbA1c).

Conclusions—PVR volumes \geq 100 mL may indicate increased risk of urgency incontinence and obstructive voiding. Glycemic control may play a role in preventing increased PVR in women with diabetes.

Introduction

Women with diabetes are known to be at increased risk of developing lower urinary tract symptoms such as urgency, frequency, and incontinence. Although the exact mechanisms by which voiding dysfunction develops in women with diabetes are incompletely understood [1,2], one hypothesis is that diabetes leads to detrusor muscle insensitivity and impaired contractility, which in turn leads to urinary retention and voiding dysfunction [3]. As a result, the recommended clinical evaluation of lower urinary tract symptoms in women with

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Correspondence may be addressed to: Ayesha Appa, 301 Carl Street, #14, San Francisco, CA 94117, Phone: (310) 480-3548, Fax: (415) 353-9790, ayesha.appa@ucsf.edu.

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diabetes includes measurement of postvoid residual (PVR) volume to assess for difficulty with bladder emptying that may contribute to urinary symptoms or complicate their treatment [4,5]. Additionally, increased PVR has been examined as a mark of risk of other urologic complications such as urinary tract infection.

Nevertheless, very little is known about the clinical predictors and significance of PVR volumes in women with diabetes. While PVR volumes less than 50 mL are generally considered normal [6], there are very few data on the normal distribution of PVR in women with diabetes. Furthermore, few studies have investigated clinical parameters that predict increased PVR in women with diabetes or examined the relationship of increased PVR to specific urinary symptoms in this population [7,8,9].

To provide more insight into this issue, we measured PVR and collected detailed information about lower urinary tract symptoms in a multiethnic cohort of community-dwelling middle-aged and older women with diabetes. We examined whether PVR elevations are associated with increased risk of different lower urinary tract symptoms in women with diabetes, and sought to identify diabetes-related risk factors associated with an increased PVR. Our goal was to provide new insight into the clinical significance of increased PVR among women with diabetes that could help inform clinical evaluation and management of urinary symptoms in this population.

Subjects

This research was conducted within an observational study of risk factors for urinary tract dysfunction in middle-aged and older women with diabetes, the Diabetes Reproductive Risks of Incontinence Study at Kaiser (Diabetes RRISK). Between January 2003 and January 2008, women with diabetes were recruited from the Kaiser Permanente Northern California (KPNC), an integrated health care delivery system serving approximately 25% to 30% of the northern California population. Women were sampled from the KPNC Diabetes Registry, a system-wide database of patients that is updated annually through active surveillance of pharmacy, laboratory, and medical records, and has previously been shown to have a sensitivity of 96% and a false-positive rate of 2% [10]. Women enrolled in the KPNC medical system who were not listed in the diabetes registry but self-reported as having diabetes were also eligible if they met the following criteria normally used for registry inclusion: 1) use of a diabetes glycemic control medication, or 2) fasting blood sugar of 126 mg/dL or greater in the KPNC database.

Other eligibility criteria included age between 40 and 80 years, enrollment in KPNC since age 24, and at least half of any childbirths at a KPNC facility (to allow ancillary evaluation of the contribution of obstetric history to voiding dysfunction). However, women were not required to have any urinary symptoms or history of urinary tract dysfunction to participate. To ensure a racially/ethnically-diverse sample, women in minority groups were purposefully sampled to achieve a target race/ethnicity composition of 20% African-American, 20% Latina, 20% Asian, and 40% white [11].

The final study population consisted of 427 women with diabetes. Although autoantibody data were not collected systematically to provide a definitive determination of Type 1 versus Type 2 diabetes mellitus, only 7 participants (less than 2% of all women with diabetes) reported that they were diagnosed with diabetes before the age of 30 and started on insulin at the time of diagnosis, suggesting that the vast majority of participants had Type 2 Diabetes Mellitus.

Materials and Methods

Postvoid residual volume measurements were obtained in 427 women using a portable ultrasound device, the BladderScan BVI 3000 [12], at their RRISK study visit. Participants presenting for their study visit were asked to empty their bladders completely, after which a PVR reading was obtained by a trained, experienced urogynecology nurse practitioner. According to standard operating procedure [12], the nurse practitioner uncovered the area between each participant's umbilicus and pubic hairline, prepped and placed the scanhead at approximately 3 cm superior to the symphysis pubis so that it pointed toward the expected bladder location, and checked that the head of the icon on the scan head was pointed toward the participant's head. After confirming that the participant's bladder was centered in the crosshairs of the aiming display, the nurse practitioner obtained a single PVR measurement. Ultrasound devices were set to the "FEMALE" setting unless participants indicated that they had undergone hysterectomy.

Structured-item questionnaire measures that were previously validated against a 7-day voiding diary were used to assess urgency- and stress-type urinary incontinence as well as other lower urinary tract symptoms such as diurnal frequency, nocturnal frequency, and obstructive voiding at the same study visit [13]. Weekly urgency incontinence was defined as any weekly urine leakage occurring when participants felt the urge to urinate but could not reach a bathroom in time. Weekly stress incontinence was defined as any weekly urine leakage occurring when participants laughed or coughed, or during physical activities. Women were considered to have diurnal frequency if they reported having to urinate 8 times or more while awake during an average day, and to have nocturia if they awakened to urinate 2 times or more during the night. Obstructive voiding symptoms were assessed by the American Urological Association (AUA) Symptom Index [14]: participants who reported incomplete emptying, intermittent stream, weak stream, or abdominal straining at least half of the time in the past month (items a, c, e, and f on the AUA Index respectively) were considered to have obstructive voiding symptoms. Symptom outcome definitions were not mutually exclusive, in that participants could report more than one of the above symptoms at the same time.

Structured-item questionnaires were also used to collect data on participants' demographic background; medical, urogynecologic and surgical history; menopausal status; and medication use (including glycemic control, anticholinergic, and diuretic medications) at this visit. Participants also underwent brief physical examination including measurement of weight and height for calculation of body mass index (kg/m^2), and contributed blood samples for measurement of serum creatinine and HbA1c.

Four main types of diabetes-related end-organ complications were assessed using questionnaire, physical examination, and/or laboratory data: heart disease, stroke, peripheral neuropathy, and renal dysfunction. Heart disease and stroke were assessed by asking participants whether a doctor or other health care provider had ever told them that they had "heart attack, angina, or other heart disease" or "stroke," respectively. Peripheral neuropathy was assessed using the Michigan Neuropathy Screening Instrument, a validated measure that incorporates data from both self-reported symptom history and physical examination of the lower extremities (foot inspection, vibration sensation, reflex testing, and monofilament testing); scores of 2 or greater are indicative of neuropathy [15]. Renal dysfunction was assessed by estimating glomerular filtration rate (GFR) from serum creatinine levels and participant age and weight using the Cockcroft-Gault equation; participants with a GFR <90 were considered to have at least stage 1 renal dysfunction. Additionally, self-reported history of urinary tract infection treated by antibiotics in the past year was assessed as another potential complication of diabetes.

Descriptive statistics were first used to examine the distribution of lower urinary tract symptoms (i.e., urgency incontinence, stress incontinence, diurnal frequency, nocturnal frequency, and obstructive voiding) and of PVR (i.e., PVR of <50 mL, 50 to 99 mL, and 100 mL) in all women with diabetes. Chi-square tests were performed to assess for differences in the unadjusted prevalence of each type of symptom among women with PVR of 50 to 99 mL and PVR ≥ 100 mL versus PVR <50 mL. Multivariable logistic regression models were then developed to examine the strength of associations between PVR and lower urinary tract symptoms, independent of other demographic and clinical characteristics. In these models, women with PVR volumes of 50 to 99 mL and 100 mL or greater were compared to a reference group of women with PVR volumes of <50 mL. Separate analyses were developed for each urinary symptom modeled as an independent outcome, adjusted for age, race/ethnicity, body mass index, menopausal status, symptomatic pelvic organ prolapse, prior pelvic surgery, anticholinergic medication use, and diuretic medication use (as variables with the potential to influence both lower urinary tract symptoms and PVR in this population).

Next, additional multivariable logistic regression models were developed to examine relationships between diabetes-specific characteristics (i.e., use of insulin or oral anti-glycemic agents; end-organ complications such as stroke, heart disease, peripheral neuropathy, or renal dysfunction; duration of diabetes; and HA1C level as a measure of glycemic control) and increased PVR. Due to the low prevalence of some of these factors (e.g., stroke) in our study population, we focused these analyses on the outcome of PVR of 100 mL or greater, to maximize statistical power. Models were again adjusted for age, race/ethnicity, menopausal status, body mass index, symptomatic pelvic organ prolapse, any pelvic surgery, anticholinergic medication, and antidiuretic medication. All analyses were performed using SAS statistical software Version 9.2 (SAS Institute, NC). All study procedures were approved the institutional review boards of both the University of California San Francisco and the Kaiser Foundation Research Institute.

Results

Demographic and clinical characteristics of the 427 participants are summarized in Table 1. Mean (SD) age was 55.7 (8.8) years, and less than half of women were white. One third of women were insulin-treated, approximately 13% had a history of heart disease, less than 10% had a history of stroke, approximately 40% had evidence of renal dysfunction, and nearly two thirds had evidence of peripheral neuropathy. Mean HbA1c was 7.4% (57 mmol/mol) with SD of 1.6%, and the mean (SD) duration of diabetes among this cohort was 9.8 (8.8) years. The most commonly reported urinary symptom was stress incontinence, followed by urgency incontinence, obstructive voiding symptoms, diurnal frequency, and nocturia. Overall, the prevalence of urinary symptoms was higher among RRISK participants with diabetes compared to RRISK participants without diabetes of similar age (i.e., 56% of women with diabetes vs. 49% of women without diabetes reported at least one urinary tract symptom, $P < 0.01$).

PVR volumes in this study ranged from 0 to 824 mL with a mean (SD) of 42.0 (77.5) mL. Figure 1 illustrates the distribution of PVR volumes among women with diabetes; 318 women of 427 (74.5%) had PVR volumes under 50mL, 57 women of 427 (13.3%) had PVR volumes between 50mL and 99mL, and 52 women of 427 (12.2%) had PVR volumes of 100mL or greater. Over half of women in each PVR category met definitions for having at least one of the following urinary symptoms: stress incontinence, urgency incontinence, diurnal frequency, nocturia, and obstructive voiding (Table 2).

In multivariable analyses adjusting for age, race/ethnicity, body mass index, menopausal status, symptomatic pelvic organ prolapse, any prior pelvic/abdominal surgery, anticholinergic medication use, and diuretic medication use, women with diabetes with PVR ≥ 100 mL had an over two-fold increased odds of experiencing urgency incontinence and a 2.5-fold increased odds of experiencing obstructive voiding symptoms, compared to women without diabetes with PVR < 50 mL (Table 3). Relative to a < 50 mL PVR, no association was found for any measure of urinary symptoms and a PVR of 50–99. We did observe elevated odds of a PVR ≥ 100 mL compared to < 50 mL for any weekly urgency and obstructive voiding. No significant associations were observed for the other urinary symptoms.

Table 4 summarizes the results of the multivariable analyses examining associations between diabetes-related clinical characteristics and PVR elevation, adjusted for all of the same demographic and clinical co-variables listed above, as well as all diabetes-related clinical characteristics in the model. Higher HbA1c was associated with increased odds of having a PVR ≥ 100 mL (i.e., more than 30% increased odds for each 1.0-unit increase in HbA1c level). No other potential clinical markers of severity (insulin use, heart disease, stroke, peripheral neuropathy, renal dysfunction, recent urinary tract infection history, or duration of diabetes) were independently associated with PVR ≥ 100 mL in these analyses.

Discussion

This study provides new insight into the clinical significance of PVR among community-dwelling women with diabetes. We found that lower urinary tract symptoms were common among women with diabetes in all PVR categories. However, women with diabetes with PVR volumes of 100 mL or greater were significantly more likely to report symptoms of urgency incontinence and obstructive voiding compared to those with PVR less than 50 mL in adjusted analyses. Our findings are in line with past research indicating that PVR is not the sole mediator of urinary tract dysfunction in women with diabetes [16], but our results do suggest that PVR may be an important marker of risk for specific types of urinary tract symptoms in this population.

Our study also detected significant associations between HbA1c level and increased PVR in women with diabetes. Specifically, we found that each 1.0 unit increase in HbA1c above 6.0 (42 mmol/mol) was associated with a 35% increased odds of having a PVR of 100 mL or greater. This suggests the possibility that glycemic control may play a role in preventing women with diabetes from developing problems with bladder emptying and associated urinary tract symptoms.

While our research suggests that poorly controlled diabetes may be associated with elevations in PVR consistent with detrusor muscle insufficiency, it must be acknowledged that there are multiple possible etiologies for increased PVR among women with diabetes. Bladder outlet obstruction, including urethral stricture or external sphincter hyperactivity, with or without concurrent detrusor muscle inadequacy, could be responsible for some elevation in PVR among women regardless of diabetes [17].

A few previous studies relying on smaller referral populations have also pointed to associations between increased PVR and urinary tract symptoms or have explored factors associated with increased PVR in women with diabetes. Lee, et al [7] found that PVR elevations of 100 mL or greater were associated with increased risk of urgency incontinence as well as obstructive voiding symptoms. Yu et al [18] reported that voiding difficulty as indicated by multiple uroflow measurements, including PVR, was associated with intermittency and hesitancy in women with diabetes. In contrast, Jackson et al [16] did not find that increased PVR was independently associated with having severe incontinence in

women with diabetes; however, only 14 participants with diabetes had a PVR >100 mL, limiting power to investigate associations. Kepbaci, et al [9] also reported that increased PVR among women with diabetes was associated with poorer glycemic control. In contrast, an earlier investigation published by the Lee group in 2004 [8] suggested that peripheral neuropathy, rather than glycemic control, was the main independent predictor of PVR elevation in women with diabetes. However, only about a third of participants were classified as having peripheral neuropathy in that study, which relied upon retrospective chart review for collection of clinical data.

This study benefits from an ethnically diverse, population-based sample of women with diabetes, measurement of multiple markers of diabetes disease severity, and structured assessment of multiple different types of urinary tract symptoms. However, several limitations of this research should be noted. First, this was a cross-sectional study, in which changes in PVR and in urinary symptoms were not assessed prospectively over time. Second, PVR was measured at a single visit using portable bladder ultrasonography, without confirmation from invasive methods such as urinary catheterization. Third, the prevalence of some diabetes-related complications in this sample was relatively low (e.g., stroke), which may have limited the statistical power of our analyses of the relationship of diabetes-related complications to PVR volumes. Furthermore, the observational design of this study did not permit us to evaluate the clinical effects of using PVR measurements to guide treatment or determine whether intensification of diabetes therapy can bring about reductions in PVR. A follow-up prospective clinical trial may be indicated to address these questions.

In summary, this study provides evidence that PVR volumes of 100 mL or greater are associated with increased risk of both urgency incontinence and obstructive voiding in women with diabetes, and that women with diabetes with worse glycemic control are more likely to have increased PVR. Future research should assess whether interventions that improve glycemic control and prevent diabetes-related complications may result in improved PVR and decreased urinary symptoms in women with diabetes.

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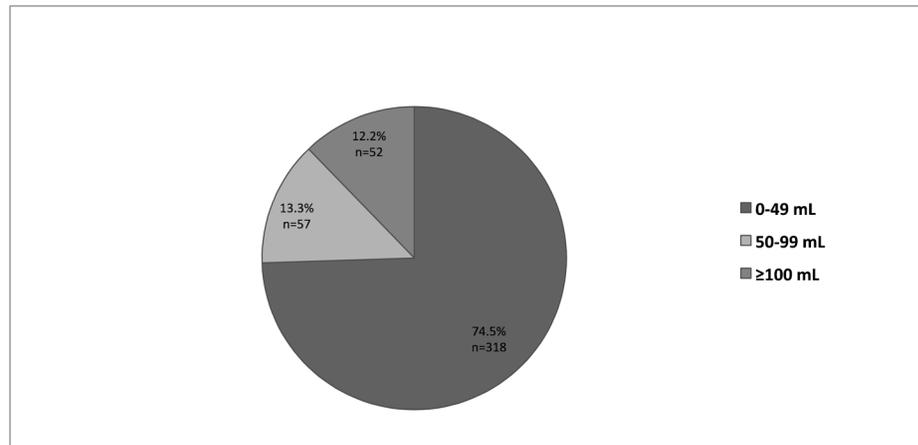


Figure 1. Distribution of Postvoid Residual Volumes Among Women with Diabetes (n=427)

Table 1

Demographic & Clinical Characteristics of Participants

Characteristic	Participants (N = 427)
<i>Demographic</i>	
Age (years)	55.7 ± 8.8
Race/Ethnicity	
White	173 (40.6%)
African American	85 (20.0%)
Latina	95 (22.3%)
Asian	73 (17.1%)
Other	95 (22.3%)
Married or living as married	268 (62.9%)
<i>General</i>	
Mean (sd) body mass index (kg/m ²)	33.9 ± 7.9
Postmenopausal (without menses > 1 year.)	315 (73.8%)
Excellent/very good self-reported health	76 (17.8%)
<i>Clinical</i>	
Urinary tract infection in the past year	75 (17.7%)
Pelvic organ prolapse on exam *	321 (80.7%)
Prior hysterectomy	70 (16.4%)
Bilateral oophorectomy	41 (9.6%)
Prior surgery for incontinence	11 (2.6%)
Prior surgery for prolapse	8 (1.9%)
Other pelvic or abdominal surgery	122 (28.6%)
<i>Clinical, Diabetes-specific</i>	
Mean HbA1c (mmol/mol)	7.4% ± 1.6% (57 ± 18)
History of heart disease **	57 (13.3%)
History of stroke [¶]	26 (6.1%)
Peripheral neuropathy [¶]	272 (64.6%)
Stage 1+ renal dysfunction ^δ	166 (39.2%)
Mean (sd) duration of diabetes (years)	9.8 (8.8)
<i>Diabetes medication</i>	
Oral glycemic agents	241 (56.4%)
Insulin	130 (30.4%)
<i>Clinical, Urinary-specific</i>	
Any weekly stress incontinence ^Δ	125 (29.2%)
Any weekly urgency incontinence ^Φ	116 (27.2%)
Diurnal frequency ^λ	86 (20.1%)

Characteristic	Participants (N = 427)
Nocturia ^Ω	76 (17.8%)
Obstructive voiding ^ς	90 (21.1%)
Any of the above urinary symptoms	252 (59.0%)
<i>Medications</i>	
Estrogens (systemic + vaginal)	40 (9.4%)
Anticholinergics (antimuscarinics or tricyclic antidepressants)	44 (10.3%)
Diuretics	170 (39.8%)

Data are presented as mean ± SD or number (percentage)

* Pelvic Organ Prolapse Quantitation score ² assessed by provider on gynecologic exam

** Self-reported history of clinician-diagnosed “heart attack, angina, or heart disease”

^Π Self-reported history of clinician-diagnosed stroke

^Ψ Michigan Neuropathy Screening Instrument score ²

^δ Glomerular filtration rate <90 estimated by the Cockcroft-Gault equation

^Δ At least weekly urine leakage occurring when participants laughed or coughed, or during physical activities.

^Φ At least weekly urine leakage occurring when participants felt the urge to urinate but could not reach a bathroom in time.

^λ Having to urinate 8 times or more while awake during an average day.

^Ω Awakening to urinate 2 times or more during the night.

^ς Defined as reporting any obstructive symptoms about half the time or more from the modified American Urological Association BPH Score Index (item a: incomplete emptying, item c: intermittent stream, item e: weak stream, item f: abdominal straining).

Table 2
Prevalence of Urinary Symptoms Among Women with Diabetes, by Postvoid Residual Volume (PVR) Category

	PVR=0–49 mL (N=318)	PVR=50–99 mL (N=57)	PVR 100 mL (N=52)	P*	P**
Any weekly stress incontinence ^Δ	93 (29.2%)	15 (26.3%)	17 (32.7%)	0.65	0.61
Any weekly urgency incontinence ^Φ	85 (26.7%)	12 (21.1%)	19 (36.5%)	0.34	0.15
Diurnal frequency ^λ	65 (20.4%)	13 (22.8%)	8 (15.4%)	0.69	0.40
Nocturia ^Q	55 (17.3%)	10 (17.5%)	11 (21.2%)	0.96	0.50
Obstructive voiding ⁵	60 (19.0%)	14 (24.6%)	16 (30.8%)	0.32	0.05
Any of the above urinary symptoms	188 (59.1%)	31 (54.4%)	33 (63.5%)	0.58	0.51

* P-value for comparison between women with PVR=50–99 versus PVR=0–49 mL.

** P-value for comparison between women with PVR 100 versus PVR=0–49 mL.

^Δ At least weekly urine leakage occurring when participants laughed or coughed, or during physical activities.

^Φ At least weekly urine leakage occurring when participants felt the urge to urinate but could not reach a bathroom in time.

^λ Having to urinate 8 times or more while awake during an average day.

^Q Awakening to urinate 2 times or more during the night.

⁵ Defined as reporting any obstructive symptoms about half the time or more from the modified American Urological Association BPH Score Index (item a: incomplete emptying, item c: intermittent stream, item e: weak stream, item f: abdominal straining).

Table 3

Adjusted Associations between Urinary Symptoms and Postvoid Residual Volumes (PVR) *

	PVR 50–99 vs. PVR < 50 OR (95% CI)	PVR 100 vs. PVR < 50 OR (95% CI)
Any weekly stress incontinence ^Δ	0.8 (0.4 – 1.6)	1.4 (0.7 – 2.8)
Any weekly urgency incontinence ^Φ	0.8 (0.4 – 1.9)	2.2 (1.1 – 4.4)
Diurnal frequency ^λ	1.3 (0.6 – 2.7)	0.6 (0.2 – 1.5)
Nocturia ^Ω	1.2 (0.5 – 2.9)	1.5 (0.7 – 3.4)
Obstructive voiding ^ζ	1.2 (0.6 – 2.7)	2.5 (1.2 – 5.2)

* Odds ratios and confidence intervals obtained through multivariable logistic regression models, adjusted for age, race/ethnicity, body mass index, menopausal status, symptomatic pelvic organ prolapse, any pelvic surgery, anticholinergic medication use, and antidiuretic medication use.

^Δ At least weekly urine leakage occurring when participants laughed or coughed, or during physical activities.

^Φ At least weekly urine leakage occurring when participants felt the urge to urinate but could not reach a bathroom in time.

^λ Having to urinate 8 times or more while awake during an average day.

^Ω Awakening to urinate 2 times or more during the night.

^ζ Defined as reporting any obstructive symptoms about half the time or more from the modified American Urological Association BPH Score Index (item a: incomplete emptying, item c: intermittent stream, item e: weak stream, item f: abdominal straining).

Table 4

Adjusted Associations between Diabetes-Related Characteristics and Postvoid Residual Volume 100*

Characteristics	OR (95% CI)
Current insulin use	0.65 (0.21 – 2.04)
Oral glyemic agent use	0.51 (0.19 – 1.37)
History of heart disease**	1.17 (0.47 – 2.92)
History of stroke ^{II}	2.53 (0.80 – 7.95)
Peripheral neuropathy ^Ψ	1.03 (0.51 – 2.09)
Stage 1+ renal dysfunction ^δ	0.90 (0.35 – 2.30)
HbA1c, per 1.0 unit increase above 6.0	1.35 (1.11 – 1.63)
History of urinary tract infection in the past year ^κ	1.01 (0.51 – 1.97)
Duration of diabetes, per 5 years ^Σ	1.08 (0.89 – 1.32)

* Odds ratios and confidence intervals obtained through multivariable logistic regression models, adjusted for age, race/ethnicity, body mass index, menopausal status, symptomatic pelvic organ prolapse, any pelvic/abdominal surgery, anticholinergic medication, antidiuretic medication, and all other variables in this table.

** Self-reported history of clinician-diagnosed “heart attack, angina, or other heart disease”

^{II} Self-reported history of clinician-diagnosed stroke

^Ψ Michigan Neuropathy Screening Instrument score ≥ 2

^δ Glomerular filtration rate <90 via Cockcroft-Gault equation

^κ Self-reported history of urinary tract infection requiring antibiotic treatment.

^Σ Self-reported duration of diabetes mellitus.