

Original Article

Aging and recurrent urinary tract infections are associated with bladder dysfunction in type 2 diabetes

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Accepted 3 August 2011

Abstract

Objective: The objective of this study was to demonstrate the diversity of urodynamic findings and temporal effects on bladder dysfunction in diabetes as well as to evaluate the predisposing factors that attenuate the storage and voiding function of diabetic women.

Material and Methods: In this prospective study, 181 women with type 2 diabetes mellitus (DM) and lower urinary tract dysfunction underwent complete urogynecological evaluations and urodynamic studies. The patients' histories of DM and the treatment agents used were documented from chart records and interviews. The urodynamic diagnoses were recategorized into two groups for comparison, namely overactive detrusor (detrusor overactivity and/or increased bladder sensation as well as mixed incontinence) and voiding dysfunction (detrusor hyperactivity with insufficient contractility and detrusor underactivity with poor voiding efficiency) in order to evaluate the temporal effect of DM on diabetic bladder dysfunction.

Results: The development of bladder dysfunction showed a trend involving time-dependent progression, beginning with storage problems (i.e. advancing from urodynamic stress incontinence to detrusor overactivity and/or increased bladder sensation) and eventually led to impaired voiding function. The duration of DM relative to the urodynamic diagnoses of these women was longer in women with voiding dysfunction (6.8 ± 2.8 years with urodynamic stress incontinence, 7.3 ± 6.5 years with detrusor overactivity and/or increased bladder sensation, and 10.4 ± 8.3 years with women with voiding dysfunction). Notwithstanding these findings, stepwise logistic regression analysis indicated that age and recurrent urinary tract infections were the two independent factors associated with developing voiding dysfunction.

Conclusion: The urodynamic study revealed a temporal effect on bladder function, and women with diabetic voiding dysfunction were found to have had a longer duration of DM than women with an overactive detrusor. However, aging and recurrent urinary tract infections are the two independent factors that contribute to impaired voiding function and diabetic bladder dysfunction.

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Keywords: age; diabetes mellitus; diabetic cystopathy; overactive detrusor; urinary tract infection; voiding dysfunction

Introduction

The prevalence of diabetes mellitus (DM) has increased steadily over the past decade in Taiwan. Chang et al [1]

reported that, from different investigations, 4.9–9.2% of the Taiwanese population have DM. Our previous survey of the community-based prevalence of lower urinary tract and pelvic floor dysfunction also revealed that 5.9% of women aged 20 years or older have DM [2].

DM has reached epidemic proportions worldwide, and bladder dysfunction is a frequent complication of diabetes, with a reported prevalence ranging from 25% to 87%, and also seeming to be related to the duration of DM [3]. In comparison

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with diabetic nephropathy, a life-threatening condition affecting around one-third of hemodialysis patients in Taiwan, which has drawn considerable attention in the past decades [4], DM-induced lower urinary tract dysfunction has received far less attention despite having a significant impact on quality of life and health risks [5].

The most common and bothersome lower urinary tract complication of DM is diabetic bladder dysfunction. Compared with controls, women with type 2 DM have a wider spectrum of lower urinary tract dysfunction, ranging from an increased risk for nocturia, a weaker urinary stream, smaller voided volumes, and a lower maximal flow rate through to diabetic bladder dysfunction with poor emptying and poor voiding efficiency [6,7]. The incidence of diabetic cystopathy or diabetic bladder dysfunction ranges from 27% to 85% in unselected diabetic patients who have undergone routine urodynamic studies [8].

Clinical features and urodynamic findings have shown that manifestations of diabetic bladder dysfunction involve not only a combination of storage and voiding bladder problems, but also time-dependent change [9]. Recent experimental evidence from studies of diabetic bladder dysfunction in small animal models has shown a temporal effect on diabetic bladder dysfunction [10]. In the early phase of bladder dysfunction, urodynamics reveals impairment or loss of sensation together with changes in the detrusor reflex. In the later phase, decompensation of bladder tissue and function results in the development of impaired detrusor contraction and attenuation of bladder emptying; these then lead to increasing postvoid residual urine or urinary retention [10–12].

Furthermore, impaired voiding function can result in recurrent urinary tract infections or asymptomatic bacteriuria [13]. Persistent episodes of infection and bacteriuria will diminish bladder sensation, which causes an increase in postvoid residual urine and decreased bladder contractility. In this study, we tried to demonstrate the diversities of urodynamic findings and evaluate the predisposing factors that attenuate storage and voiding function in diabetic women who present with lower urinary tract symptoms.

Materials and methods

In this prospective study from January 2003 to December 2006, we recruited 202 women with type 2 DM and lower urinary tract dysfunction who had been referred from either the medical or gynecology department to our urodynamic unit. All these women presented with symptoms of an overactive bladder with or without urinary incontinence, symptoms of voiding difficulty, or symptoms of stress urinary incontinence. All patients underwent a complete urogynecologic evaluation including a detailed history, a physical examination, urine analysis, a pad test to quantify urine leakage, and urodynamic study. The patients' history of DM and the treatment agents used were documented from chart records and interviews. Eight women without a detailed history or complete urodynamic data and 13 women with a history of anti-incontinence or a radical hysterectomy for cervical cancer were excluded

from this study. Finally, 181 women were recruited into this study. The study protocol was approved by the Institutional Review Board of Chung Shan Medical University Hospital, and informed consent was obtained from all patients.

Urodynamic examinations were performed using a Dantec Duet urodynamic unit (Medtronic, Copenhagen, Denmark) by a senior technician in an isolated room. Following uroflowmetry, the women were placed in the supine position. A 10 Fr catheter was used to drain urine from the bladder to check the postvoid residual urine volume. The above procedures were repeated if the summation of the void volume and residual urine was less than 200 mL. During filling cystometry, the bladder was filled with sterile water at room temperature at a filling rate of 30 mL/min.

Next the women changed to a sitting position and urinated while on a commode that was connected to a flowmeter (32K10 flow transducer; Medtronic, Copenhagen, Denmark). Volume at first desire to void (mL), volume at maximal bladder capacity (mL), maximal detrusor pressure while voiding (cmH₂O), maximal urinary flow rate (mL/s), opening pressure (cmH₂O), opening time (seconds), and electromyogram (EMG) activity (surface EMG) were measured. The abdominal pressure was recorded using a rectal balloon catheter. Detrusor pressure was calculated by subtracting abdominal pressure from intravesical pressure. A "rest and stress" (coughing repeatedly every 2–3 seconds) urethral pressure profile was performed using a dual sensor microtransducer (5 cm apart) with 200 mL of sterile water in the bladder. The transducer was withdrawn with the transducer facing the lateral wall (at the 3 o'clock position) and with a withdrawal speed of 2 mm/s by an electronic withdrawal device [(32H07) Puller Mechanism; Dantec].

The terminology for lower urinary tract function and the description of urodynamic diagnoses used in this study follow the criteria recommended by the International Continence Society Standardization Sub-Committee in 2002 [14], except where specific definitions have been used. Data including age, menopause, duration of menopause, body mass index, duration of DM, recurrent urinary tract infections (two episodes of urinary tract infections in 6 months), and anterior vaginal wall prolapse above stage II [15] were collected to determine the factors predisposing towards voiding dysfunction. Urinary tract infection was diagnosed if patients presented with urinary tract symptoms such as dysuria, urinary frequency, or fever, and urine analysis revealed pyuria (> 5 leukocytes per high-power field in centrifuged sediment) or a positive urine culture ($\geq 10^5$ colony-forming units/mL). Increased bladder sensation was defined as a bladder volume at first desire to void of less than 120 mL and/or a bladder capacity of less than 250 mL. Poor voiding efficiency was defined as a voided volume of less than 75% of bladder capacity (voided volume plus postvoid residual urine).

In order to evaluate the temporal effect of DM on diabetic bladder dysfunction, we reclassified the urodynamic diagnoses into the two groups for comparison, namely overactive detrusor and voiding dysfunction. Patients with urodynamic findings of detrusor hyperactivity with insufficient

contractility [16] together with an underactive detrusor with poor voiding efficiency (increased postvoid residual urine >50 mL or urinary retention) were classified as members of the voiding dysfunction (impaired voiding function) group. Patients with urodynamic findings and detrusor overactivity (and/or increased bladder sensation) and mixed incontinence were classified as members of the overactive detrusor group.

Data are presented as mean \pm standard deviation, median, or percentage depending on the variable. Patient characteristic variables in each subgroup were compared by one-way analysis of variance. The Student *t* test and Chi-square test were used for comparing differences between groups. Stepwise logistic regression was used to determine the contributing factors for voiding dysfunction. A value of $p < 0.05$ was considered to be statistically significant.

Results

The mean age and body mass index of our patients was 61.7 years (range 24–87 years) and 26.2 kg/m² (range 14.8–39.5 kg/m²). Median parity was four, and mean duration of DM was 8.5 years (range 1–30 years). There were 147 women who were menopausal, 68 women who were suffering from recurrent urinary tract infections, and 10 women with anterior vaginal wall prolapse above stage II. The urodynamic study revealed 20 (11.0%) women who had urodynamic stress incontinence, 76 (42.0%) women who had detrusor overactivity and/or increased bladder sensation, 21 (11.6%) women with mixed incontinence, 49 (27.1%) women who had detrusor hyperactivity and insufficient contractility, and 13 (7.2%) women with an underactive detrusor with poor voiding efficiency (Table 1). To control their DM, 2.7% of our patients used diet as a control, 84.2% were taking oral hypoglycemic agents, and 9.8% were on insulin.

Table 1
Basic characteristics of the women with diabetes mellitus (DM) ($n = 181$).

Variables	n (%)
Age (y), mean \pm SD (range)	61.7 \pm 11.8 (24–87)
Parity, median	4 (0–11)
Menopause	147 (79.9)
Body mass index (kg/m ²), mean \pm SD (range)	26.2 \pm 3.6 (14.8–39.5)
Years of DM, mean \pm SD (range)	8.5 \pm 7.1 (1–30)
Recurrent urinary tract infections	68 (37.0)
Cystocele (+) ^a	10 (5.4)
Urodynamic diagnosis	
Urodynamic stress incontinence	20 (11.0)
Detrusor overactivity and/or increased bladder sensation	76 (42.0)
Mixed incontinence	21 (11.6)
Detrusor hyperactivity and insufficient contractility	49 (27.1)
Underactive detrusor with poor voiding efficiency	13 (7.2)
Underactive detrusor with compensation by straining	2 (1.1)

^a Cystocele (+) = anterior vaginal wall prolapse above stage II.

During cystometry examination, it was found that, overall, 80.7% of these women with DM had detrusor overactivity and increased bladder sensation. These consisted of 47 (26.0%) women with detrusor overactivity, 21 (11.6%) women who had mixed incontinence, 22 (12.2%) women who had increased bladder sensation, seven (3.9%) women with both detrusor overactivity and increased bladder sensation, and 49 (27.1%) women who had detrusor hyperactivity and insufficient contractility.

The urodynamic study variables of the women with DM were significantly different for the various subgroups, these groups being urodynamic stress incontinence, detrusor overactivity and/or increased bladder sensation, detrusor hyperactivity and insufficient contractility, and underactive detrusor with poor voiding efficiency. Specifically, diabetic women with urodynamic stress incontinence were younger, had a lower body mass index, had had DM for a shorter duration, had more recently undergone menopause, and had had fewer recurrent UTIs (Table 2).

In this series, patients with detrusor overactivity and/or increased bladder sensation, or mixed incontinence, were clustered as having an overactive detrusor ($n = 97$). Women with impaired voiding function who had detrusor hyperactivity and insufficient contractility or an underactive detrusor with poor voiding efficiency were grouped as having voiding dysfunction ($n = 62$). The parameters of the urodynamic study for the voiding dysfunction group showed a lower mean flow rate (9.0 ± 5.8 vs. 18.9 ± 13.7 ; $p < 0.05$), a lower first desire to void (137.3 ± 48.8 vs. 173.1 ± 97.6 ; $p < 0.05$), and a prolonged opening time (16.4 ± 11.9 vs. 10.0 ± 8.6 ; $p < 0.05$). There was no significant difference between opening pressure, voiding detrusor pressure, maximal urethral pressure, maximal urethral closure pressure, and EMG activity before as well as during voiding between these two groups.

Variables such as age, a longer history of menopause, a longer history of DM, and recurrent urinary tract infections were significantly related to voiding dysfunction on univariate analysis (Table 3). However, stepwise logistic regression analysis indicated that recurrent urinary tract infection and age were the two independent factors for developing voiding dysfunction.

Discussion

Our urodynamic findings demonstrated that the development of bladder dysfunction showed a time-dependent progressive trend beginning with storage problems such as urodynamic stress incontinence and ranging onward to detrusor overactivity and/or increased bladder sensation, eventually leading to impaired voiding function. The duration of DM among these women with a urodynamic diagnosis was longer for women with voiding dysfunction (6.8 ± 2.8 years in urodynamic stress incontinence, 7.3 ± 6.5 years in detrusor overactivity and/or increased bladder sensation, and 10.4 ± 8.3 years in women with voiding dysfunction). Our findings are consistent with findings in animal models [10,12,17,18]. Furthermore, we also found that age and

Table 2
Variables of women with urodynamic stress incontinence (USI), detrusor overactivity and/or increased bladder sensation (DO/IBS), detrusor hyperactivity and insufficient contractility (DHIC), and detrusor underactivity (DU) with poor voiding efficiency.

	USI (n = 20)	DO/IBS (n = 97)	DHIC (n = 49)	DU (n = 13)
Age (years)	57.0 ± 10.9	60.1 ± 11.4	66.3 ± 10.4	65.2 ± 16.4*
Body mass index (kg/m ²)	24.2 ± 2.1	26.2 ± 3.8	26.9 ± 3.3	24.7 ± 4.1
Years of diabetes mellitus	6.8 ± 2.8	7.3 ± 6.5	10.4 ± 8.3	11.2 ± 6.6*
Years of menopause	7.0 ± 4.2	11.6 ± 9.3	16.8 ± 9.7	20.3 ± 10.9
Menopause, n (%)	12 (60.0)	74 (76.3)	45(91.8)	12 (92.3)
Recurrent urinary tract infection, n (%)	5 (25.0)	24 (24.7)	36 (53.1)	10 (76.9)*

The variables of the patients' characteristics in each subgroup were compared by one-way analysis of variance (ANOVA).

* Age, years of diabetes mellitus, and recurrent urinary tract infection showed significant differences among the four subgroups $p < 0.05$.

recurrent urinary tract infections were predisposing factors toward the progressive development of voiding dysfunction. These findings are consistent with previous clinical speculation related to urodynamic findings among diabetic women [8,11,12,19].

Lifford et al [20] reported that prevalent incontinence and incident incontinence (relative risk 1.28 and 1.21, respectively) were significantly greater in women with DM than in women without it. Women with DM have a 2.5-fold increased risk of urinary incontinence compared with non-diabetic women (41% vs. 22.1%) [21]. Kebapci et al [19] revealed that 12.5% of diabetic women with lower urinary tract symptoms had urodynamic stress incontinence. In the current study, urodynamic stress incontinence was found in 11.0% of women with type 2 DM who had lower urinary tract symptoms. Women with urodynamic stress incontinence were found in this study to be younger and to have had fewer recurrent episodes of urinary tract infection than women with other types of bladder dysfunction, especially women with voiding dysfunction (Table 2). However, the increased risk of stress incontinence in women with DM could not be determined in our study due to the lack of a control group, and a control group was not included in our study because of ethical considerations.

A retrospective study by Yamaguchi et al [22] using a digitized database of 2300 case records found that 42% of patients had detrusor overactivity and 14% had increased bladder sensation. The frequency of detrusor overactivity in patients with increased bladder sensation was 58%. They discovered that overactive bladder symptoms, which commonly occur with diabetic cystopathy and detrusor

overactivity, increased with age, but not with the duration of diabetes. The prevalence of overactive bladder-related urodynamic findings was higher in our study than in that of Yamaguchi et al (80.7% vs. 55%) [22]. Our findings show that a higher percentage of overactive bladder-related findings might result from a greater motor or sensory neuropathy of the bladder in diabetic women. The duration of DM in women with detrusor overactivity and/or increased bladder sensation was less than that of women with detrusor hyperactivity and insufficient contractility (7.3 ± 6.5 years vs. 10.4 ± 8.3 years). Our results are consistent with the proposed natural history of progression of DM bladder dysfunction described for the streptozotocin-induced rat model of DM. Daneshgari et al [10] hypothesized that storage problems such as detrusor overactivity or increased bladder sensation occur at an early phase of bladder dysfunction and voiding problems, and that a hypocontractile detrusor or impaired detrusor contraction occurs during the later phase due to decompensated function.

Our previous community survey demonstrated an increased presence of lower urinary tract dysfunction as age increased [2]. Haylen et al [23] found that the prevalence of voiding difficulty was 39% for women who were referred for an initial urogynecologic assessment including urodynamics. In this study, 34.3% of diabetic patients had impaired voiding function, their mean age being 66.2 ± 11.8 years. We found that patients with impaired voiding function were older (66.2 ± 11.8 vs. 60.1 ± 11.4 years; $p < 0.05$) and had a longer history of DM (7.3 ± 16.5 years vs. 10.5 ± 7.9 years; $p < 0.05$).

However, the question remains of whether age is a predisposing factor for voiding difficulty in women with DM. Therefore, we recategorized our patients into an overactive detrusor group and a voiding dysfunction group. After step-wise logistic analysis, we found that age and recurrent urinary tract infections were independent factors for developing impaired voiding function. However, one of the limitations of this study is that we did not assess the degree of control of DM and the occurrence of other systemic diseases in these study participants, which could theoretically have impacted on the severity of lower urinary tract symptoms.

Geerlings et al [24] demonstrated that the urothelium in patients with DM is susceptible to infection, particularly with *Escherichia coli*. They found that type I fibrillated *Escherichia coli* adhered twice as well to diabetic bladders as to

Table 3
Comparison of the variables in patients with overactive detrusor and voiding dysfunction.

	Overactive detrusor (n = 97)	Voiding dysfunction (n = 62)	p
Age (y)	60.1 ± 11.4	66.2 ± 11.8	0.002
Years of diabetes mellitus	7.3 ± 6.5	10.5 ± 7.9	0.009
Years of menopause	11.6 ± 9.3	17.5 ± 10.0	0.000
Menopausal	74 (76.3)	57(91.9)	0.01
Recurrent urinary tract infection, n (%)	24 (24.7)	36 (58.1)	0.000

Table 4
Comparison of urodynamic variables in patients with an overactive detrusor and voiding dysfunction.

	Overactive detrusor (n = 97)	Voiding dysfunction (n = 62)	p
Voiding time (s)	40.9 ± 25.7	51.2 ± 39.3	0.072
Mean flow rate (mL/s)	18.9 ± 13.7	9.0 ± 5.8	0.000
First desire to void (mL)	137.3 ± 48.8	173.1 ± 97.6	0.009
Vesical pressure (cmH ₂ O)	62.4 ± 24.6	66.3 ± 27.5	0.354
Detrusor pressure	27.0 ± 13.9	26.3 ± 14.7	0.763
Urethral resistance	0.6 ± 0.1	3.5 ± 0.5	0.000
Resting maximal urethral pressure	97.5 ± 34.5	105.6 ± 53.0	0.287
Resting maximal urethral closure pressure	97.5 ± 35.6	105.6 ± 53.0	0.173
Opening pressure	26.4 ± 12.6	29.9 ± 15.3	0.201
Opening time	10.0 ± 8.6	16.4 ± 11.9	0.001
EMG activity	0.6 ± 0.7	0.5 ± 0.7	0.441
EMG activity during opening time	1.2 ± 1.2	0.9 ± 1.1	0.172

In women with diabetes, overactive detrusor was defined as detrusor overactivity and/or increased bladder sensation, or mixed incontinence.

Voiding dysfunction was defined as detrusor hyperactivity and insufficient contractility or underactive detrusor with poor voiding efficiency; these were grouped into the category of voiding dysfunction.

EMG = electromyogram.

control bladders. Evidence from an epidemiologic study also suggests that asymptomatic bacterial infections and symptomatic urinary tract infections occur more commonly in women with DM than nondiabetic controls [25]. Boyko et al [13] conducted a prospective study and found that diabetic women had a higher relative risk of urinary tract infection and asymptomatic bacteriuria (relative risk 1.8 and 2.3, respectively) compared with nondiabetic women. In our study, 37% of the women with DM had recurrent urinary tract infections, and 58.1% of the patients with voiding impairment had experienced recurrent urinary tract infections. Based on our results, we hypothesize that recurrent urinary tract infections might cause the progressive development of diabetic bladder dysfunction, which then progresses from compensated storage problems to decompensate voiding function.

In this study, we found a significantly lower mean flow rate and prolonged opening time in the voiding dysfunction group, but there was no increase in voiding detrusor pressure at maximal flow and EMG activity before as well as during voiding (Table 4). A rat model of DM has revealed that there is less relaxation of the urethral smooth muscle during voiding in rats with DM than in healthy rats [26]. Deindl et al [27] reported that there are two different pathogenic mechanisms for urethral obstruction and that both external urethral sphincter and pelvic floor dysfunction may contribute to dysfunctional voiding in women. In the current study, our eligible data limit the further interpretation of whether impaired voiding function can be attributed to urethral dysfunction in these diabetic women. Further studies, including a well-designed clinical study or, probably more usefully, a longitudinal study, need to be conducted to clarify this issue.

In conclusion, the progression of bladder dysfunction has a time-dependent trend beginning with storage problems and

eventually leading to impaired voiding function. Women with voiding dysfunction have a longer duration of DM. However, aging and recurrent urinary tract infections are the two independent factors that contribute to impaired voiding function among patients with diabetic bladder dysfunction.

Acknowledgments

The funding for this study was provided by NSC 92-2314-B-040-025 and NSC 93-2314-B-040-014 from the National Science Council (NSC) of Taiwan.

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