ORIGINAL

Characteristics of storage and voiding symptoms in adult patients with type 2 diabetes with lower urinary tract symptoms

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Abstract : Aims : We aimed to assess the relationships between lower urinary tract symptoms (LUTS) and various parameters including diabetes complications in patients with type 2 diabetes. Methods : In this single-center cross-sectional study, we enrolled 404 patients hospitalized for diabetes. We ultimately analyzed data from 160 patients. To evaluate LUTS, the International Prostate Symptom Score and overactive bladder symptom score were used. The identified relationships were then analyzed considering parameters such as age, sex, body mass index (BMI), HbA1c, creatinine, and urinary albumin excretion. Results : The prevalences of overactive bladder (OAB), storage symptoms and voiding symptoms were 21.9%, 63.8%, and 39.4%, respectively. In multivariate logistic regression analysis, the coefficient of variation of the R-R interval, indicating autonomic neuropathy, correlated negatively with OAB, while BMI and duration of diabetes correlated positively with storage symptoms. A history of cerebrovascular disease correlated significantly with voiding symptoms in multivariate logistic analysis. Conclusions : Our analysis of diabetic patients with LUTS revealed differences in the characteristics of storage and voiding symptoms. These findings provide evidence that the features of LUTS associated with diabetes may have different pathogenic origins. J. Med. Invest. 71 : 237-245, August, 2024

Keywords **:** *Diabetes complications, lower urinary tract symptoms, type 2 diabetes*

INTRODUCTION

Diabetes mellitus (DM) is a chronic, systemic metabolic disorder that is becoming an increasingly serious health concern globally. DM can lead to severe damage to peripheral nerves, the retina, kidneys and various other organs. Urological complications associated with DM were recognized nearly nine decades ago (1). Previous studies have indicated that 25–90% of patients with DM exhibit urodynamic abnormalities (2). Urinary tract dysfunction has been shown to negatively impact quality of life, health perception, and depression, independently of other diabetes complications (3). Therefore, addressing urological complications can be one of the goals in managing diabetes. Lower urinary tract symptoms (LUTS) are defined by the International Continence Society as symptoms related to disorders involving storage, voiding, and post micturition symptoms (4). The mechanism of micturition involves a complex network between the nervous and urinary system. The micturition reflex comprises afferent pathways from the bladder to the brain and efferent pathways from the brain to the bladder, including sympathetic, parasympathetic, and somatic motor nerves. Three muscles, the bladder detrusor muscle, internal urethral sphincter, and external urethral sphincter play crucial roles in the micturition reflex. The bladder detrusor muscle and internal urethral sphincter are regulated by the sympathetic and parasympathetic nervous systems, while the external urethral sphincter is controlled by the somatic motor nervous system. During urine storage, sympathetic motor neurons relax the bladder detrusor muscle and contract the internal urethral sphincter. During urination, the brain signals the bladder detrusor muscle to contract and the internal urethral sphincter to relax through parasympathetic motor neurons. Concurrently, the pudendal nerve, a somatic motor neuron, is inhibited, leading to relaxation of the external sphincter. As the network involved in the micturition reflex is complex, LUTS manifests various symptoms, including storage, voiding, and post micturition symptoms.

Hyperglycemia resulting from DM induces LUTS through polyuria. Additionally, DM triggers systemic inflammation, leading to the development of microvascular complications such as neuropathy, retinopathy and nephropathy, as well as macrovascular complications due to atherosclerosis. Many of these complications can be linked to urological diseases. In diabetic neuropathy, damage occurs to the somatic motor, sympathetic, and parasympathetic nerves that control the micturition reflex. An association between LUTS and diabetic neuropathy was reported in patients with DM (5). As with neuropathy, albuminuria as a feature of diabetic nephropathy reportedly correlates with LUTS (6). Atherosclerosis plays a key role in the development of LUTS by inducing bladder ischemia, which then leads to functional and structural alteration of the detrusor muscle (7).

In the micturition reflex, the nervous and muscular systems that function during the storage and voiding phases differ. Therefore, background characteristics may differ between patients with storage and voiding symptoms. However, past reports on LUTS have not differentiated between these storage and voiding symptoms. It is potentially meaningful to separately assess the characteristics of patients with storage and voiding symptoms. This may be of value in formulating management strategies and revealing the mechanisms underlying LUTS.

In the present study, we assessed LUTS by categorizing it into storage and voiding symptoms. This study aimed to appraise the

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clinical characteristics and diabetes complications of patients with type 2 DM, by focusing on storage and voiding symptoms separately.

MATERIALS AND METHODS

Study population

For this cross-sectional study, we enrolled 404 patients admitted to Kyorin University Hospital (Tokyo, Japan) for diabetes treatment between July 2016 and July 2018. We initially included all hospitalized patients with diabetes, assuming that it would be burdensome for those at outpatient clinics to devote the time required for measurement of the volume of urine remaining in the bladder after micturition by using ultrasonography for PVR as a study. To reduce the unknown influences of diabetes type, patients with forms of diabetes from other than type 2 were excluded. We also excluded patients undergoing treatment for LUTS or urological disorders potentially causing LUTS, such as benign prostatic hyperplasia. Patients taking sodium-glucose cotransporter 2 inhibitors, which can exacerbate LUTS, were also excluded. Other exclusion criteria included undergoing hemodialysis, non-agreement to participate, and incomplete data. Patients with inaccurate CVR-R due to arrhythmias such as extrasystole and atrial fibrillation, were regarded as having incomplete data. None of the patients was taking diuretic agents or diagnosed with lumbosacral spinal cord disease. We calculated the sample size for this study needed to achieve a statistical power of 80% and to detect a significant difference between the groups with storage symptoms versus voiding symptoms. This required more than 70 samples at a statistical power of 99.2%. The final analysis included a sample of 160 patients (Figure 1). This study adhered to Good Clinical Practice guidelines and the principles of the Declaration of Helsinki, receiving approval from the Kyorin University ethics committee (approval number 774). Written informed consent was obtained from all patients whose data were analyzed. To protect patient confidentiality, medical data was securely stored in a password protected database, and information allowing personal identification was removed from the database.

Measurements and Assessing the Complications and Characteristics of DM Patients

We collected information on age, sex, body mass index (BMI), HbA1c, creatinine, and urinary albumin excretion. In this study, the term "sex" was utilized instead of "gender" due to the classification being constrained by biological differences. BMI was calculated by dividing the patient's weight in kilograms by height in meters squared. HbA1c and creatinine levels were measured using venous blood samples taken upon admission. Urinary albumin excretion was measured through a 24-hour collection during hospitalization. The use of insulin and oral anti-hyperglycemic agents was confirmed by reviewing medical records. Patients injecting insulin at least once a day were categorized as receiving insulin treatment. Ankle reflexes were assessed with the subject in a kneeling position, and hypopallesthesia of the bilateral medial malleoli was considered to be present when the value was less than 10 seconds based on assessment using a C128 Hz tuning fork (8). The coefficient of variation of the R-R interval (CVR-R) was calculated using a 12-lead ECG performed at rest. Diabetic retinopathy (DR) was graded as follows : no- (NDR), simple- (SDR), pre-proliferative- (PPDR), or proliferative diabetic retinopathy (PDR). The glomerular filtration rate (GFR) was calculated using the Japanese Society of Nephrology equation : $eGFR = 194 \times Creatinine^{-1.094} \times age^{-0.287}$ (mL/min/1.73 m^2) (× 0.739 for women) (9). Hypertension was defined as being positive if systolic blood pressure was over 140 mmHg, diastolic blood pressure was over 90 mmHg, or both, or if the patient had been prescribed medication for hypertension. Dyslipidemia was considered positive if the serum low-density lipoprotein cholesterol concentration exceeded 140 mg/dL, the triglyceride concentration was over 150 mg/dL or the high-density lipoprotein cholesterol concentration was under 40 mg/dL, or if the patient had been treated with lipid-lowering agents. The duration of DM, coronary artery disease, cerebrovascular disease, and smoking habits were assessed based on self-administered questionnaires, medical records and/or admission data.

Assessment of LUTS

To assess LUTS based on the ICS symptom definitions (4), we employed the International Prostate Symptom Score (IPSS) (10),

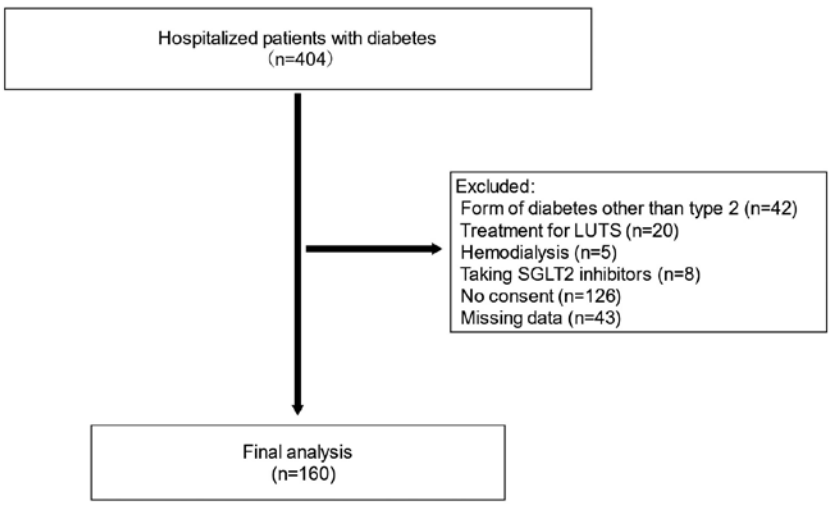

Figure 1. Flow diagram showing inclusion and exclusion criteria
LUTS, lower urinary tract symptoms ; SGLT2, sodium-glucose cotransporter 2.

and the overactive bladder symptom score (OABSS) (11). The IPSS questionnaire consists of seven questions : incomplete emptying, daytime frequency, intermittency, urgency, weak stream, straining, and nocturia. Each question is rated on a scale from 0 (never) to 5 (almost always). The IPSS questions are categorized into storage, voiding, and post micturition symptoms. Storage symptoms include the combination of daytime frequency, urgency, and nocturia, while voiding symptoms comprise the combination of intermittency, weak stream, and straining. Post micturition symptoms involve incomplete emptying. We defined storage symptoms as being positive if the patient's storage symptoms score (daytime frequency, urgency, and nocturia) exceeded 2 points, and voiding symptoms as being positive if the patient's voiding symptoms score (intermittency, weak stream, and straining) exceeded 2 points, based on the IPSS score. The OABSS is a symptom assessment questionnaire designed to quantify OAB symptoms. It comprises 4 questions related to OAB symptoms : daytime frequency, night-time frequency, urgency, and urgency incontinence. The maximal scores assigned are 2, 3, 5, and 5 for daytime frequency, night-time frequency, urgency, and urgency incontinence, respectively. OAB was considered to be present if the score for question 3 in the urgency section of the OABSS exceeded 2 points, and the total OABSS score was over 3, in accordance with the Japanese guidelines (12). Post-void residual urine (PVR) was defined as the volume of urine remaining in the bladder after micturition, measured by using ultrasonography. A residual urine volume exceeding 50 mL was considered to be positive for PVR, adopting the cut-off specified in the Japanese OAB guidelines (12). To investigate undiagnosed benign prostatic hyperplasia, urinary flow measurement with uroflowmetry and PVR measurement with ultrasound were conducted. None of the patients in our study exhibited pelvic organ prolapse, symptomatic urinary tract infection, or gross hematuria suggestive of carcinoma in situ of the bladder. Uroflowmetry and PVR measurement were performed as bladder function tests for OAB,.

Statistical Analysis

Categorical variables were compared using the chi-squared test or Fisher's exact test. Continuous variables were assessed using the Mann–Whitney U test. Comparisons among the four groups were conducted with the Kruskal-Wallis test, and Tukey's post hoc tests were employed for each pair of groups. The presence or absence of OAB was analyzed using multivariate logistic regression analysis, adjusting for age and sex as covariates. The presence or absence of storage symptoms was evaluated using multivariate logistic regression analysis, adjusting for age, sex, BMI, and duration of DM as covariates. The presence or absence of voiding symptoms was assessed using multivariate logistic regression analysis, adjusting for age, sex, and cerebrovascular disease as covariates. Data are presented as median (interquartile range). Statistical analyses were carried out using R version 3.1.3.25, or Excel version 16.35. The significance level was set at a p-value <0.05.

RESULTS

We analyzed data from 160 patients with type 2 DM (91 men, 69 women). The characteristics of these patients are presented in Table 1. Among the 160 patients, 35 (21.9%) were diagnosed with OAB. Univariate analysis revealed that the duration of DM was

Table 1. Patient characteristics

	All patients (n = 160)	Men (n = 91)	Women (n = 69)
Age, years	61.5 (50.0 - 70.0)	58.0 (47.5 - 68.5)	66.0 (54.0 - 73.0)
BMI, kg/m^2	26.6 (23.9 - 29.8)	26.4 (23.2 - 28.4)	26.6 (24.4 - 30.6)
Duration, months	90.0 (4.0 - 168.3)	96.0 (2.5 - 168.0)	840 (8.0 - 180.0)
HbA1c, %	9.4 (8.0 - 10.8)	9.5 (8.0 - 11.2)	9.3 (8.0 - 10.5)
Treatment (insulin)	132 (82.5)	77 (84.6)	55 (79.7)
ATR (-)	98 (61.3)	56 (61.5)	42 (60.9)
Hypopallesthesia	93 (58.1)	49 (53.8)	44 (63.8)
CVR-R, %	2.0 (1.4 - 2.7)	2.0 (1.4 - 2.7)	2.1 (1.5 - 2.7)
NDR	94 (58.8)	94 (58.8)	94 (58.8)
SDR	35 (21.9)	35 (21.9)	35 (21.9)
PPDR	6 (3.8)	6 (3.8)	6 (3.8)
PDR	25 (15.6)	25 (15.6)	25 (15.6)
eGFR, mL/min/1.73m^2	84.0 (62.0 - 104.0)	84.0 (62.0 - 104.0)	84.0 (62.0 - 104.0)
UAE, mg/day	10.7 (4.0 - 76.0)	10.7 (4.0 - 76.0)	10.7 (4.0 - 76.0)
Hypertension	99 (61.9)	99 (61.9)	99 (61.9)
Dyslipidemia	114 (71.2)	114 (71.2)	114 (71.2)
CAD	21 (13.1)	21 (13.1)	21 (13.1)
CVD	9 (5.6)	9 (5.6)	9 (5.6)
Smoking never	75 (46.9)	75 (46.9)	75 (46.9)
past	49 (30.6)	49 (30.6)	49 (30.6)
current	46 (22.5)	46 (22.5)	46 (22.5)

The median and interquartile range are given for continuous data, while number and percentage of the total are given for nominal data. BMI, body mass index ; HbA1c, hemoglobin A1c ; ATR, Achilles tendon reflex ; CVR-R, coefficient of variation of R-R interval ; NDR, no diabetic retinopathy ; SDR, simple diabetic retinopathy ; PPDR, pre-proliferative diabetic retinopathy ; PDR, proliferative diabetic retinopathy ; eGFR, estimated glomerular filtration rate ; UAE, urine albumin excretion ; CAD, coronary artery disease ; CVD, cerebrovascular disease.

significantly longer in patients with OAB than in those without OAB (144.0 [78.0-234.0] months with OAB vs 72.0 [3.0-156.0] months without OAB, p=0.009). CVR-R was significantly lower in patients with than in those without OAB (1.5 [1.1-2.2] with OAB vs 2.2 [1.6-2.8] without OAB, p=0.001). In the multivariate logistic regression analysis, after adjusting for age and sex, CVR-R and dyslipidemia demonstrated independent negative correlations with OAB (odds ratio [OR] 0.56, 95% confidence interval [CI] 0.35-0.88, p=0.01, and OR 0.41, 95% CI 0.18-0.92, p=0.03, respectively) (Table 2).

Of the 160 patients, 102 (63.8%) experienced storage symptoms. Univariate analysis revealed the duration of DM to be significantly longer in patients with than in those without storage symptoms (120.0 [39.0-210.0] months with storage symptoms vs 60.0 [1.3-156.0] months without storage symptoms, p=0.003). BMI and duration of DM showed positive correlations with storage symptoms in multivariate logistic regression analysis after adjusting for age, sex, BMI, and duration of DM (OR 1.09, 95% CI 1.01-1.18, p=0.03, and OR 1.00, 95% CI 1.00-1.01, p=0.02, respectively) (Table 3).

Of the 160 patients, 63 (39.4%) experienced voiding symptoms. Univariate analysis indicated a significant correlation between a history of cerebrovascular disease and voiding symptoms (12.7% with voiding symptoms vs 1.0% without voiding symptoms, p=0.003). In the multivariate logistic regression analysis, a history of cerebrovascular disease was associated with voiding symptoms after adjusting for age, sex, and cerebrovascular disease (OR 11.7, 95% CI 1.40-97.5, p=0.023) (Table 4).

As demonstrated in Table 5, patients with voiding symptoms exhibited a significantly higher prevalence of storage symptoms (p<0.001). Additionally, the duration of DM was significantly longer in patients with storage symptoms or with both voiding and storage symptoms than in those with neither (144.0 [67.5-174.0] months with storage symptoms, 120.0 [36.0-216.0] months with both voiding and storage symptoms, and 48.0 [1.0-144.0] months with neither, p=0.01) (Table 5).

PVR volume was not available for 28 patients. Among the remaining 132 patients, 16 (12.1%) had a PVR volume exceeding 50 mL. In the univariate analysis, the duration of DM was significantly longer in patients with PVR than in those without

Table 2. Comparison of demographic characteristics and diabetes complications in patients with and without OAB

	OAB (-) (n = 125)	OAB (+) (n = 35)	*p*-value
Age, years	61.0 (49.0 – 70.0)	64.0 (54.0 - 71.0)	0.31
Sex (men)	71 (59.2)	19 (54.3)	0.70
BMI, kg/m^2	26.7 (23.9 - 29.9)	25.7 (23.6 - 27.9)	**0.23**
Duration, months	72.0 (3.0 - 156.0)	144.0 (78.0 - 234.0)	0.009
HbA1c, %	9.4 (8.1 - 10.8)	9.1 (7.8 - 10.5)	0.49
Treatment (insulin)	105 (84.0)	27 (77.1)	0.33
ATR (-)	72 (57.6)	26 (74.3)	0.08
Hypopallesthesia	74 (59.2)	19 (54.3)	0.70
CVR-R, %	2.2 (1.6 - 2.8)	1.5 (1.1 - 2.2)	**0.001**
NDR	76 (60.8)	18 (51.4)	0.29
SDR	24 (19.2)	11 (31.4)	
PPDR	6 (4.8)	0 (0.0)	
PDR	19 (15.2)	6 (17.1)	
eGFR, mL/min/1.73m^2	84.0 (62.0 - 104.0)	83.0 (62.0 - 103.0)	0.98
UAE, mg/day	10.0 (3.9 - 73)	12.3 (4.8 - 93.0)	0.56
Hypertension	75 (60.0)	24 (68.6)	0.43
Dyslipidemia	94 (75.2)	20 (57.1)	0.06
CAD	14 (11.2)	7 (20.0)	0.25
CVD	7 (5.6)	2 (5.7)	1.00
Smoking never	58 (46.4)	17 (48.6)	0.97
past	39 (31.2)	10 (28.6)	
current	28 (16.0)	8 (22.9)	

Results of multivariate logistic regression analysis

	OR	95%CI	*p*-value
Duration	1.00	1.00 – 1.01	0.05
CVR-R	0.56	0.35 – 0.88	**0.01**
Dyslipidemia	0.41	0.18 – 0.92	**0.03**

Adjusted for age and sex

The median and interquartile range are given for continuous data, while number and percentage of the total are given for nominal data. OAB, overactive bladder ; OR, odds ratio ; CI, confidence interval.

PVR (174.0 [84.0-279.0] months with PVR vs 72.0 [4.0-156.0] months without PVR, p=0.005). CVR-R was significantly lower in patients with than in those without PVR (1.6 [1.1-1.8] with PVR vs 2.1 [1.5-2.8] without PVR, p=0.03) (Table 6).

DISCUSSION

In the general population, the prevalence of OAB is reportedly 12.4% in individuals over 40 years of age in Japan (13), and 16.9% after age-adjusted analysis based on a questionnaire survey conducted in Taiwan (14). Previously, we examined the prevalence of LUTS in medical check-up recipients over 40 years of age, 7.6% of whom had diabetes, using the same diagnostic criteria as in this study. The prevalence was 14.3% for OAB, 39.9% for storage symptoms, and 18.7% for voiding symptoms (15). In the present study, the prevalences of OAB, storage symptoms, and voiding symptoms were 21.9%, 63.8%, and 39.4%, respectively. This study demonstrated a higher prevalence of LUTS in patients with type 2 DM than in the general population. Previous investigators reported the prevalence of OAB in patients with diabetes to be 24.2% in Japan (16) and 22.5% in Taiwan (5), results which aligned closely with the findings in this study.

The detrimental effects of hyperglycemia can be categorized into microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) and macrovascular complications involving arteriosclerosis (coronary artery disease, peripheral arterial disease, and cerebrovascular disease). Microvascular complications are associated with the duration of DM and glycemic control, while macrovascular complications are linked to cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, and smoking. Diabetic neuropathy is classified into peripheral neuropathy and autonomic neuropathy. Diagnostic criteria for peripheral neuropathy include sensory symptoms, decreased ankle reflexes, and diminished vibratory sensation (8). Heart rate variability is commonly used to assess autonomic neuropathy. CVR-R is a widely utilized and simple approach employed in Japan as a time-domain analysis method for R-R interval fluctuations, with its reduction reflecting cardiac autonomic neuropathy. The micturition reflex involves sympathetic

Table 3. Comparison of demographic characteristics and diabetes complications in patients with and without storage symptoms

	Storage symptoms (-) (n = 58)	Storage symptoms (+) (n = 102)	*p*-value
Age, years	61.0 (49.3 - 69.0)	63.0 (50.0 - 71.8)	0.37
Sex (men)	30 (56.9)	60 (58.8)	0.87
BMI, kg/m^2	26.1 (23.6 - 27.5)	27.1 (24.3 - 30.2)	0.06
Duration, months	60.0 (1.3 - 156.0)	120.0 (39.0 - 210.0)	**0.003**
HbA1c, %	9.5 (7.9 - 11.0)	9.3 (8.0 - 10.8)	0.80
Treatment (insulin)	47 (81.0)	85 (83.3)	0.83
ATR (-)	32 (55.2)	66 (64.7)	0.24
Hypopallesthesia	33 (56.9)	60 (58.8)	0.89
CVR-R, %	2.1 (1.5 - 3.1)	2.0 (1.4 - 2.6)	0.19
NDR	34 (58.6)	60 (58.8)	0.68
SDR	12 (20.7)	23 (22.5)	
PPDR	1 (1.7)	5 (4.9)	
PDR	11 (19.0)	14 (13.7)	
eGFR, mL/min/1.73m^2	84.0 (62.0 - 105.5)	83.5 (62.3 - 102.8)	0.82
UAE, mg/day	10.0 (5.1 - 76.0)	12.2 (4.0 - 72.8)	0.96
Hypertension	31 (53.4)	68 (66.7)	0.13
Dyslipidemia	44 (75.9)	70 (68.6)	0.37
CAD	8 (13.8)	13 (12.7)	1.00
CVD	1 (1.7)	8 (7.8)	0.16
Smoking never	28 (48.3)	47 (46.1)	0.15
past	13 (22.4)	36 (35.3)	
current	17 (29.3)	19 (17.6)	

Results of multivariate logistic regression analysis

	OR	95%CI	*p*-value
Age	1.01	0.98 – 1.17	0.57
Sex	1.63	0.80 – 3.32	0.18
BMI	1.09	1.01 – 1.18	**0.03**
Duration	1.00	1.00 – 1.01	**0.02**

The median and interquartile range are given for continuous data, while number and percentage of the total are given for nominal data.

nerves, parasympathetic nerves, and somatic motor nerves, with different nervous systems functioning during the storage and voiding phases. Given that both peripheral and autonomic neuropathy can contribute to LUTS, it is potentially meaningful to differentiate between those two forms of neuropathy for a comprehensive evaluation of neuropathic disorders. Furthermore, considering that different nervous systems function during the storage and voiding phases, distinguishing between storage and voiding symptoms allows for a more nuanced assessment of LUTS. Additionally, atherosclerosis induced by diabetes can lead to LUTS through chronic bladder ischemia (7). Furthermore, damage to the central nervous system resulting from cerebrovascular disease, one of the typical arteriosclerotic diseases, causes bladder dysfunction (17). Therefore, it is essential to consider macrovascular complications when evaluating LUTS.

We utilized the OABSS questionnaire to assess storage symptoms. This meant that storage symptoms were evaluated using two indices : one based on the OAB criteria and the other based on the IPSS criteria, as outlined in the Methods section. Our criteria, based on IPSS, diagnosed relatively mild storage symptoms as compared to the criteria based on OABSS. The multivariate logistic regression analysis identified decreased CVR-R, an indicator of autonomic neuropathy, as a factor contributing to an increased risk of OAB (Table 2). Conversely, indicators of peripheral neuropathy, such as diminished or absent Achilles tendon reflex and impaired vibration sense, were not significantly associated with OAB. This was consistent with the widely accepted understanding that autonomic nerves play a more significant role than somatic nerves in the micturition reflex. The duration of DM was linked to a higher prevalence of OAB in univariate analysis and storage symptoms in multivariate logistic regression analysis (Table 2, 3). This result was consistent with our expectations, given that the onset of diabetic autonomic and peripheral neuropathy is closely related to the duration of DM. In contrast, the lack of a significant relationship between storage symptoms and autonomic or peripheral neuropathy indicators themselves might be attributable to the inclusion of cases with relatively mild neuropathy as compared to those with OAB. A higher BMI was associated with storage symptoms diagnosed based on our criteria in multivariate

Table 4. Comparison of demographic characteristics and diabetes complications in patients with and without voiding symptoms

	Voiding symptoms (-) (n = 97)	Voiding symptoms (+) (n = 63)	*p*-value
Age, years	58.0 (48.0 - 69.0)	65.0 (56.0 - 72.0)	0.03
Sex (men)	54 (55.7)	31 (58.7)	0.75
BMI, kg/m^2	26.6 (24.1 - 28.7)	26.6 (23.7 - 30.5)	0.95
Duration, months	84.0 (3.0 - 156.0)	120.0 (36.0 - 222.0)	0.26
HbA1c, %	9.5 (8.1 - 11.3)	9.3 (7.9 - 10.5)	0.18
Treatment (insulin)	83 (85.6)	49 (77.8)	0.21
ATR (-)	60 (61.9)	38 (60.3)	0.87
Hypopallesthesia	57 (58.8)	36 (57.1)	0.87
CVR-R, %	2.1 (1.5 - 2.8)	1.9 (1.4 - 2.5)	0.13
NDR	53 (54.6)	41 (65.1)	0.31
SDR	22 (22.7)	13 (20.6)	
PPDR	3 (3.1)	3 (4.8)	
PDR	19 (19.6)	6 (9.5)	
eGFR, mL/min/1.73m^2	85.0 (65.0 - 104.0)	77.0 (61.0 - 104.0)	0.39
UAE, mg/day	14.0 (3.9 - 102.0)	9.0 (4.8 - 34.1)	0.48
Hypertension	56 (57.7)	43 (68.3)	0.19
Dyslipidemia	72 (74.2)	42 (66.7)	0.37
CAD	11 (11.3)	10 (15.9)	0.48
CVD	1 (1.0)	8 (12.7)	**0.003**
Smoking never	44 (45.4)	31 (49.2)	0.47
past	28 (28.9)	21 (33.3)	
current	25 (25.8)	11 (17.5)	

Results of multivariate logistic regression analysis

	OR	95%CI	*p*-value
Age	1.02	1.00 – 1.04	0.069
Sex	1.29	0.65 – 2.56	0.461
CVD	11.7	1.40 – 97.5	0.023

The median and interquartile range are given for continuous data, while number and percentage of the total are given for nominal data.

logistic regression analysis (Table 3). Liu *et al*. demonstrated a significant association between age, duration of DM, and the presence of neuropathy with OAB (5). Furthermore, obesity has been linked to both OAB and urinary incontinence (18). Excess body weight increases abdominal pressure, thereby causing or exacerbating detrusor instability (19). The findings reported in these previous studies were consistent with our results. The association between OAB and autonomic neuropathy has been established in non-DM patients (20). In our study, we demonstrated an association between autonomic neuropathy, a major and early microvascular complication, and storage symptoms based on the OAB criteria. Additionally, a link was observed between the duration of DM and storage symptoms, based on both the OAB criteria and our IPSS criteria. Given that autonomic neuropathy is one of the microvascular complications and the duration of DM is closely associated with microvascular complications, our findings raise the possibility of an link between storage symptoms and microvascular complications.

We evaluated voiding symptoms based on the criteria of the IPSS outlined in the Methods section. Voiding symptoms were found to be associated only with cerebrovascular disease (Table 4), suggesting a potential association with atherosclerosis. Type 2 DM is known to induce atherosclerosis, leading to chronic bladder ischemia. It is also recognized as a risk factor for cerebrovascular disease. Conversely, cerebrovascular disease itself may contribute to bladder dysfunction, thereby contributing to LUTS (17).

We further examined the prevalence of storage symptoms and voiding symptoms and revealed that patients with voiding symptoms had a significantly higher rate of storage symptoms (Table 5). This finding indicated an elevated risk of storage symptoms in patients with voiding symptoms. Additionally, we compared the characteristics of patients categorized into four groups : neither voiding nor storage symptoms, storage symptoms only, voiding symptoms only, and both storage and voiding symptoms. An association between the duration of DM and storage symptoms was suggested (Table 5).

Regarding PVR, the duration of DM and CVR-R were associated with a higher prevalence of PVR (Table 6). These results tended to be consistent with those of storage rather than voiding

Table 5. Prevalences of storage and voiding symptoms

	Storage symptoms (-)	Storage symptoms (+)	Total	*p*-value
Voiding symptoms (-)	49 (30.6%)	48 (30.0%)	97 (60.6%)	
Voiding symptoms (+)	9 (5.6%)	54 (33.8%)	63 (39.4%)	**< 0.001**
Total	58 (36.2%)	102 (63.8%)	160 (100%)	

	Neither storage nor voiding symptoms (n = 49)	Storage symptoms (n = 48)	Voiding symptoms (n = 9)	Storage and voiding symptoms (n = 54)	*p*-value
Age, years	59.0 (47.0 - 68.0)	57.5 (48.8 - 70.3)	68.0 (62.0 - 69.0)	65.0 (55.3 - 73.5)	0.16
Sex (men)	23 (46.9)	31 (64.6)	7 (77.8)	30 (55.6)	0.19
BMI, kg/m^2	26.0 (23.1 - 27.6)	27.1 (24.9 - 29.7)	26.4 (23.8 - 27.0)	26.9 (23.4 - 31.4)	0.25
Duration, months	48.0 (1.0 - 144.0)	144.0 (67.5 -174.0)*	96.0 (36.0 - 228.0)	120.0 (36.0 - 216.0)**	**0.01**
HbA1c, %	9.6 (8.3 - 11.3)	8.7 (8.1 - 11.3)	8.4 (7.4 - 9.3)	9.5 (8.0 - 10.6)	0.17
Treatment (insulin)	39 (79.6)	44 (91.7)	8 (88.9)	41 (75.9)	0.18
ATR (-)	27 (55.1)	33 (68.8)	5 (55.6)	33 (61.1)	0.56
Hypopallesthesia	28 (57.1)	29 (60.4)	5 (55.6)	31 (57.4)	0.98
CVR-R, %	2.5 (1.5 - 3.2)	2.0 (1.5 - 2.6)	2.0 (1.4 - 2.0)	1.9 (1.4 - 2.6)	0.17
NDR	30 (61.2)	23 (47.9)	4 (44.4)	37 (68.5)	
SDR	9 (18.4)	13 (27.1)	3 (33.3)	10 (18.5)	
PPDR	0 (0.0)	3 (6.2)	1 (11.1)	2 (3.7)	
PDR	10 (20.4)	9 (18.8)	1 (11.1)	5 (9.3)	
eGFR, mL/min/1.73m^2	91.0 (69.4 - 107.0)	83.5 (61.8 - 98.9)	65.0 (55.0 - 70.0)	82.5 (63.5 - 107.8)	0.06
UAE, mg/day	10.0 (4.0 - 76.0)	17.5 (3.8 - 142.0)	9.0 (8.2 - 73.0)	9.1 (4.3 - 28.0)	0.62
Hypertension	25 (51.0)	31 (64.6)	6 (66.7)	37 (68.5)	0.30
Dyslipidemia	37 (75.5)	35 (72.9)	7 (77.8)	35 (64.8)	0.62
CAD	7 (14.3)	4 (8.3)	1 (11.1)	9 (16.7)	0.65
CVD	0 (0.0)	1 (2.1)	1 (11.1)***	7 (13.0)	**0.02**
Smoking never	26 (53.1)	18 (37.5)	2 (22.2)	29 (53.7)	
past	8 (16.3)	20 (41.7)	5 (55.6)	16 (29.6)	
current	15 (30.6)	10 (20.8)	2 (22.2)	9 (16.7)	

The chi-squared test was used to compare the prevalences of storage and voiding symptoms. The Kruskal-Wallis test was performed for continuous variables, Fisher's exact test for comparison of categorical variables among the four groups. The median and interquartile range are given for continuous data, while number and percentage of the total are given for nominal data.
*p < 0.05 vs Neither storage nor voiding symptoms
**p < 0.05 vs Neither storage nor voiding symptoms
***p < 0.05 vs Neither storage nor voiding symptom

symptoms. This observation may suggest a potential relationship between PVR and storage symptoms.

Associations between LUTS and peripheral neuropathy have been reported in patients with type 1 DM (6) and type 2DM (5, 21). Additionally, the association between LUTS and autonomic neuropathy has been noted in men with type 1 DM (6). However, these studies did not distinguish between storage and voiding symptoms of LUTS. In the present study, we evaluated storage and voiding symptoms separately, and revealed characteristics distinguishing the two. Storage symptoms alone, but not voiding symptoms, were linked to autonomic neuropathy, a major microvascular complication of DM, and the duration of DM, which is closely associated with microvascular complications. In contrast, voiding symptoms were associated with cerebrovascular disease, a significant macrovascular complication. The pathogenesis differs between microvascular and macrovascular complications, necessitating distinct management strategies for these disorders. Glucose lowering treatment is recommended to mitigate the impact of microvascular complications, whereas modifications of cardiovascular risk factors, such as hypertension, dyslipidemia, and smoking, diminish the impacts of macrovascular complications. Based on the LUTS results obtained in this study, it appeared that the pathogenetic factor might differ between storage and voiding symptoms. This supports our assumption that different management strategies might be needed for these disorders. In other words, glucose lowering treatment might be recommended to prevent storage symptoms, while modifications of cardiovascular risk factors would presumably be advisable when the aim is to prevent voiding symptoms.

This study has several limitations. As this was a pilot study, and the patient population was relatively small, derived from hospitalized patients at a single facility. Consequently, the results need to be validated through large-scale, multicenter investigations. While our study indicated an association between voiding symptoms and cerebrovascular disease in multivariate logistic regression analysis, the relatively wide 95% confidence interval suggests the need for confirmation with a larger sample size. In this study, HbA1c did not exhibit a significant correlation with LUTS, although the association between LUTS and glycemic control was reported previously (6). The variation in the duration of DM among our patients might have contributed to HbA1c inaccurately reflecting long-term glycemic control. Obstructive sleep apnea syndrome (OSAS) may worsen LUTS, and the relationship between LUTS and OSAS has been demonstrated in patients with diabetes (22, 23). While none of our study participants was receiving continuous positive airway pressure treatment for OSAS, patients with mild or undiagnosed OSAS may have been enrolled. Regarding cerebrovascular disease, it is challenging to establish a pure relationship with LUTS as cerebrovascular disease itself can cause LUTS. Additionally, urinary symptoms are closely linked to prostate hyperplasia and chronic prostatitis in men, as well as urinary tract infections and pelvic organ prolapse in women. Although our study excluded patients receiving treatment for LUTS due to these urological disorders, undiagnosed disorders were not taken into account. Being a pilot cross-sectional study, both men and women had to be included in order to reach the patient number for statistical analysis. The results need to be validated through large-scale

Table 6. Comparison of demographic characteristics and diabetes complications in patients with and without PVR

	PVR (-) (n = 116)	PVR (+) (n = 16)	*p*-value
Age, years	61.0 (50.0 - 70.0)	64.5 (48.3 - 70.5)	0.90
Sex (male)	65 (56.0)	13 (81.2)	0.06
BMI, kg/m^2	26.6 (23.9 - 29.9)	26.4 (24.9 - 29.7)	0.98
Duration, months	72.0 (4.0 - 156.0)	174.0 (84.0 - 279.0)	**0.005**
HbA1c, %	9.5 (8.1 - 10.7)	9.0 (7.7 - 11.3)	0.76
Treatment (insulin)	98 (84.5)	12 (75.0)	0.31
ATR (-)	70 (60.3)	12 (75.0)	0.29
Hypopallesthesia	65 (56.0)	7 (43.8)	0.43
CVR-R, %	2.1 (1.5 - 2.8)	1.6 (1.1 - 1.8)	**0.03**
NDR	74 (63.8)	7 (43.8)	0.30
SDR	23 (19.8)	5 (31.2)	
PPDR	4 (3.4)	0 (0.0)	
PDR	15 (12.9)	4 (25.0)	
eGFR, mL/min/1.73m^2	84.0 (61.0 - 104.3)	83.5 (67.3 - 99.8)	0.78
UAE, mg/day	12.1 (4.5 - 81.8)	11.2 (4.7 - 46.7)	0.90
Hypertension	73 (62.9)	11 (68.8)	0.79
Dyslipidemia	86 (74.1)	9 (56.2)	0.15
CAD	13 (11.2)	3 (18.8)	0.41
CVD	9 (7.8)	0 (0.0)	0.60
Smoking never	52 (44.8)	8 (50.0)	0.24
past	36 (31.0)	7 (43.8)	
current	28 (24.1)	1 (6.2)	

The median and interquartile range are given for continuous data, while number and percentage of total are given for nominal data.
PVR, post-void residual urine volume

investigations conducted separately for men and women.

CONCLUSIONS

We showed the prevalence of LUTS to be higher in patients with type 2 DM than in the general population. The findings indicated decreased CVR-R, high BMI, and a long duration of DM to be associated with a greater prevalence of storage symptoms. Cerebrovascular disease was identified as being associated with voiding symptoms. This distinction raises the possibility that storage and voiding symptoms have a different pathogenesis, emphasizing the need for management strategies tailored to each specific disorder.

CONFLICT OF INTERESTS / COMPETING INTERESTS

None of the authors has any conflicts of interest to declare.

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