Metabolic Syndrome Components Worsen Lower Urinary Tract Symptoms in Women with Type 2 Diabetes

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Context: Diabetic women are more susceptible to develop lower urinary tract symptoms (LUTS), especially overactive bladder (OAB). However, data regarding the effect of components of metabolic syndrome (MS) on this association are conflicting.

Objective: The objective of the study was to examine the potential role of MS in the development of LUTS in diabetic women.

Design: The study was a prevalence study conducted between 2005 and 2007.

Setting: The study was conducted in a university hospital.

Participants: A total of 518 women with type 2 diabetes aged 50–75 yr were included. They were subgrouped as MS (47.5%) and non-MS (52.5%) groups according to whether they fulfilled the criteria of MS.

Main Outcome Measure: We used American Urological Association Symptom Index (AUA-SI) to evaluate LUTS and Indevus Urgency Severity Scale to evaluate OAB, respectively.

Results: Women in the MS group had significantly higher storage and total AUA-SI scores as well as a higher prevalence of LUTS and OAB. Most intriguingly, the number of MS components was strongly associated with the LUTS severity because the AUA-SI scores increased in parallel to the number of components were present. Similar results were found between MS and OAB. Multivariate analysis revealed that peripheral neuropathy, but not MS, significantly predicted LUTS in diabetic women after age adjustment. However, MS remained significantly predictive for LUTS and OAB after additional adjustment for neuropathy.

Conclusions: Our results suggest that MS may especially influence LUTS and OAB in diabetic women, probably by compounding the effect of peripheral neuropathy. **(*J Clin Endocrinol Metab* 95: 1143–1150, 2010)**

Growing attention has been paid to metabolic syndrome (MS), which comprises several medical disorders including abdominal obesity, diabetes mellitus, dyslipidemia, and hypertension. MS is a highly prevalent problem of public health in the modern era and has been demonstrated to increase the risks for developing cardiovascular, kidney, and liver diseases (1–4). In the genitourinary tract, the impact of MS on erectile dysfunction has

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2009-1492 Received July 13, 2009. Accepted December 8, 2009.
First Published Online January 26, 2010

Abbreviations: ANCOVA, Analysis of covariance; AUA-SI, American Urological Association Symptom Index; CI, confidence interval; DC, diabetic cystopathy; FLUTS, female lower urinary tract symptoms; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; IUSS, Indevus Urgency Severity Scale; LUTS, lower urinary tract symptoms; MS, metabolic syndrome; OAB, overactive bladder; OR, odds ratio; PVR, postvoid residual; UTI, urinary tract infection.

been well documented (5, 6). Recent epidemiological surveys also demonstrated a significant association between MS and lower urinary tract symptoms (LUTS). In the Third National Health and Nutrition Examination Survey conducted on men older than 60 yr, the odds of having LUTS increased significantly in men with three or more components of MS when compared with their control counterparts [odds ratio (OR) 1.80; 95% confidence interval (CI) 1.11–2.94] (7). Patients with MS also had an increasing rate of prostate growth, which might account for the increasing prevalence of LUTS (8). In the secondary analysis of data from the Kaiser Permanente Continence Associated Risk Epidemiology Study, women with obesity and diabetes were significantly more likely to have pelvic floor disorders, such as stress urinary incontinence and overactive bladder (OAB) (9). Whereas the presence of LUTS is not generally life threatening, it impairs quality of life.

Until recently, data investigating the association between MS and LUTS in women are scant. Because women with diabetes are known to be associated with higher prevalence of bladder dysfunction, varied from impaired detrusor contractility to detrusor overactivity (10, 11) and given that MS is common among patients with diabetes (12), it is of interest to investigate whether MS plays a potential role in the development of LUTS in women with diabetes. To clarify this notion, we conducted a cross-sectional study on a cohort of women with type 2 diabetes treated regularly at diabetic clinics. We used the American Urological Association Symptom Index (AUA-SI) (13) to evaluate the severity of LUTS and correlated them with clinical profiles. In addition, because OAB has been reported to be common in patients with diabetes, we also used the Indevus Urgency Severity Scale (IUSS) (14) to investigate the possible association of MS with OAB.

Patients and Methods

Patient enrollment

Between October 2005 and June 2007, 850 women with type 2 diabetes receiving regular follow-up at the diabetes outpatient clinics at National Taiwan University Hospital and Taipei Jen Chi Hospital for more than 1 yr were asked to participate in our study. Among them, 610 patients consented to complete the questionnaires and uroflowmetry and were recruited to participate in this study (participation rate 71.7%). Diabetic women with concurrent neurological disorders (such as stroke, Parkinsonism, spinal cord injury, and multiple sclerosis, n = 27), active urinary tract infections (UTIs; n = 19), and previous major pelvic surgery (n = 35) as well as evidence of pelvic organ prolapse (n = 11) were excluded from the study. The remaining 518 eligible women were used for data analysis. The study protocol was approved by the Institutional Review Board of the National Taiwan University Hospital. All participants gave their written informed consent.

Clinical profiles

The parameters evaluated were age, duration of diabetes, type of diabetic therapy (diet, insulin, or hypoglycemic agents), secondary diabetic complications (retinopathy, nephropathy, and peripheral neuropathy), the number of UTIs during the past year, number of parity, and menopause status. Physical examination included blood pressure (millimeters of mercury), weight (kilograms), height (meters), waist and hip circumference (centimeters). Body mass index was calculated with body weight divided by the square of body height (kilograms per square meter). Waist hip ratio was calculated with waist circumference divided by hip circumference. The following laboratory data were obtained: fasting blood sugar, glycosylated hemoglobin (HbA1c), total and high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine, and urinalysis. Retinopathy was assessed by an ophthalmoscopy after pupil dilation with a mydriatic agent. Peripheral neuropathy was assessed by questioning patients about symptoms of paresthesia, dulled sensation, and pain in the legs and feet as well as measuring the sensory threshold (vibratory and thermal) on the feet. Patients were considered to have nephropathy if overt proteinuria (≥300 mg/dl), as determined using a dipstick or abnormal serum creatinine, was detected in more than half of the tests performed in the preceding year. Use of drugs potentially influencing lower urinary tract function, such as calcium antagonists, α- or β-adrenergic antagonists, antipsychotics, and diuretics was also recorded.

Definitions of MS

By following the most recent consensus report of National Cholesterol Education Program's Third Adult Treatment Panel (15), we defined a woman with MS as the simultaneous presence of three or more of these risk factors: central obesity (defined as waist circumference ≥80 cm based on a ethnicity-specific value for Chinese or South Asian population), raised blood pressure (defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mm Hg or treatment of previously diagnosed hypertension), raised fasting blood sugar (defined as fasting blood sugar ≥100 mg/dl or previously diagnosed type 2 diabetes), raised triglycerides (defined as serum triglyceride level ≥150 mg/dl or specific treatment for this lipid abnormality), and reduced HDL cholesterol (≤50 mg/dl or specific treatment for this lipid abnormality). According to this criteria, 246 patients (47.5%) had MS (study group), and the remaining 272 (52.5%) had no MS (control group).

Evaluation of LUTS and OAB

All patients were interviewed during the first visit of the study by trained assistants using a structured questionnaire containing the AUA-SI and the IUSS. The AUA-SI contains seven LUTS including three storage symptoms (frequency, urgency, and nocturia) and four voiding symptoms (incomplete emptying, weak stream, abdominal straining and intermittency). Each symptom is graded from 0 (not at all) to 5 (almost always) according to the frequency of symptom. Scores from these individual symptoms are aggregated to form total symptom score ranged from 0 to 35, which was further divided into storage symptom score (frequency + nocturia + urgency) and voiding symptom score (incomplete emptying + weak stream + intermittency + straining) (13).

The presence of OAB was defined according to the patient's complaint of urgency with or without urge incontinence as the core symptom, according to the International Continence Soci-

ety recommendations. The urgency degree was classified by the IUSS. All women were asked to rate their urgency severity before toilet voiding on the following scale: 0 (none), no urgency; 1 (mild), awareness of urgency but easily tolerated; 2 (moderate), enough urgency discomfort that interferes with or shortens usual activity or tasks; and 3 (severe), extreme urgency discomfort that abruptly stops all activity or tasks. Women with an IUSS score of 2 or greater were considered to have significant OAB (14).

We also evaluated the urinary continence status among our cohort as well. Stress incontinence was considered to be loss of "control of your urine when you laugh, cough, or during physical activities," whereas urgent incontinence was defined as loss of "control of your urine because you feel urgent to urinate but cannot reach the bathroom in time."

Evaluation of uroflowmetry and postvoid residual (PVR)

Each subject was given 500 ml water and asked to void to completion over a standard rotating disc flowmeter (Dantec, Glostrup, Denmark) when a normal desire to void initiated. PVR was measured by suprapubic ultrasound immediately after voiding. The essential requirement for satisfactory urine flow rate was a minimum voided volume of 150 ml.

Statistical analysis

Data were expressed as mean with SD for continuous variables or as n with percentage for categorical variables by patients with/without MS (MS/non-MS groups). For comparison, a two-sample t test was performed to identify the dispersion of continuous variables between the MS and non-MS groups, whereas the Pearson χ^2 test was performed to the dispersion of categorical variables between MS and non-MS groups. Furthermore, an analysis of covariance (ANCOVA) analysis and multivariate logistic regression analysis were used to indicate the effect in LUTS, OAB, and the number of MS components after adjusting the age confounding effect. All statistical assessments were considered the significance level $\alpha = 0.05$. Statistical analyses were performed using SPSS 15.0 statistics software (SPSS Inc., Chicago, IL).

Results

Study population

Table 1 lists the general characteristics of the patients. The average age of the MS group was older than that of the control group (67.6 ± 8.6 *vs.* $63.1 \pm 9.863.9 \pm 9.9$ yr, $P < 0.001$). There was no difference between the two groups with respect to diabetic profile including duration of di-

TABLE 1. General characteristics of the diabetic women with/without MS

Variables	Non-MS group (n = 272)	MS group (n = 246)	*P* value
Mean age (yr)	63.1 ± 9.8	67.6 ± 8.6	<0.001
Diabetic profile			
Mean diabetic duration (yr)	11.6 ± 8.5	11.4 ± 8.6	0.56
Mean fasting blood sugar (mg/dl)	139.7 ± 42.5	133.9 ± 44.0	0.33
Mean HbA1c (%)	7.3 ± 1.2	7.2 ± 1.0	0.53
Diabetic complications, n (%)			
Retinopathy	110 (40.4)	104 (42.2)	0.63
Peripheral neuropathy	52 (19.1)	62 (25.2)	0.22
Nephropathy	66 (24.2)	42 (17.0)	0.16
Therapy, n (%)			0.17
Diabetic diet	4 (1.5)	8 (3.3)	
Oral hypoglycemic agents	234 (86.0)	190 (77.2)	
Insulin	16 (5.9)	14 (5.7)	
Combined	18 (6.6)	34 (13.8)	
Hypertension, n (%)	126 (46.3)	202 (82.1)	<0.001
Hyperlipidemia, n (%)	78 (28.6)	90 (36.5)	0.17
Mean total cholesterol (mg/dl)	195.3 ± 38.1	193.2 ± 37.2	0.66
Mean HDL cholesterol (mg/dl)	45.9 ± 6.7	42.2 ± 5.8	0.01
Mean triglycerides (mg/dl)	140.4 ± 69.8	171.4 ± 103.4	0.07
Mean BMI (kg/m^2)	22.8 ± 2.4	27.7 ± 3.8	<0.001
Mean WC (cm)	74.5 ± 4.7	90.0 ± 7.6	<0.001
Mean WHR	0.84 ± 0.05	0.87 ± 0.06	<0.001
UTIs in last year, n (%)	152 (55.8)	174 (70.1)	0.27
Menopause, n	217 (79.7)	296 (89.8)	0.001
Mean parity, n	3.4 ± 1.8	3.7 ± 1.8	0.21
Drugs			
Diuretics	22 (8.1)	24 (9.7)	0.64
Antihypertensive agents[a]	128 (47.5)	186 (75.6)	<0.001
Antipsychotics/tranquilizers	56 (20.6)	60 (24.4)	0.46
Urologic drugs[b]	10 (3.6)	24 (9.7)	0.05

BMI, Body mass index; WC, waist circumference; WHR, waist to hip ratio.

[a] Antihypertensive agents included calcium antagonists, α- or β-adrenergic agonists, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers.

[b] Urologic drugs included α-adrenergic antagonists (not for hypertension), antimuscarinics and desmopressin.

TABLE 2. LUTS in diabetic women with/without MS

Variables	Non-MS group (n = 272)	MS group (n = 246)	*P* value[a]
Storage symptom score	3.8 ± 3.4	5.4 ± 3.7	<0.001[b]
Frequency	1.1 ± 1.7	1.2 ± 1.7	0.58
Urgency	1.1 ± 1.7	2.1 ± 1.8	<0.001[b]
Nocturia	1.6 ± 1.3	2.2 ± 1.3	0.002[b]
Voiding symptom score	2.6 ± 4.3	3.8 ± 5.1	0.06
Incomplete emptying	0.8 ± 1.5	1.2 ± 1.7	0.05
Weak urinary stream	0.6 ± 1.5	1.0 ± 1.8	0.08
Intermittency	0.6 ± 1.5	1.2 ± 1.8	0.003[b]
Hesitancy	0.5 ± 1.3	0.4 ± 1.1	0.11
Total symptom score	6.5 ± 6.5	9.2 ± 7.6	0.001[b]
LUTS score (%)			0.001[b]
Less than 8	186 (69.4)	138 (56.1)	
8–19	62 (23.1)	80 (32.5)	
20 or greater	20 (7.5)	28 (11.4)	
Quality-of-life score	1.6 ± 2.1	3.3 ± 2.4	<0.001[b]
IUSS score	0.8 ± 1.2	1.6 ± 1.2	<0.001[b]
OAB, n (%)	74 (27.2)	128 (52.0)	<0.001[b]
Urinary incontinence, n (%)			
Stress incontinence	30 (11.0)	22 (8.9)	0.22
Urge incontinence	49 (18.0)	54 (21.9)	0.58
Uroflowmetry[c]			
Voided volume (ml)	199.5 ± 85.2	190.3 ± 79.4	0.35
Peak flow rate (Qmax, ml/sec)	13.9 ± 7.2	13.0 ± 7.3	0.54
PVR (ml)	74.3 ± 30.5	76.0 ± 27.3	0.92
PVR ≥100 ml, n (%)	16 (7.7)	26 (12.3)	0.33

Qmax, Maximum flow rate.

[a] *P* value was observed to compare the dispersion of variables between MS and non-MS groups by adjusting the age effect.

[b] $P < 0.05$, which indicated the dispersion of variables was significantly different between MS and non-MS groups, adjusting the age effect.

[c] Uroflowmetry data were available for 208 non-MS (76.5%) and 212 MS (86.2%) participants.

abetes, fasting blood sugar level, HbA1c level, prevalence of diabetic complications, and diabetic therapy. As expected, other metabolic profiles such as serum level of HDL cholesterol, waist circumference, *etc.*, were significantly greater in the MS group. Of note, more patients in the MS group were under treatment for LUTS conditions (9.7 *vs.* 3.6%, $P = 0.049$).

The comparison of LUTS between the MS and non-MS groups is shown in Table 2. Compared with the non-MS group, the MS group reported significantly higher storage (5.4 ± 3.7 *vs.* 3.8 ± 3.4, $P < 0.001$) and total symptom scores (9.2 ± 7.6 *vs.* 6.5 ± 6.5, $P = 0.001$) and a borderline increase in voiding symptom score (3.8 ± 5.1 *vs.* 2.6 ± 4.3, $P = 0.06$). When individual symptoms were compared, the average score of urgency ($P < 0.001$), nocturia ($P = 0.001$), and intermittency ($P = 0.003$) was significantly higher in the MS group. The prevalence of OAB, as defined by an IUSS score of 2 or greater, was 52.0% in the MS group and 27.2% in the non-MS group, respectively ($P < 0.001$). The overall prevalence of stress urinary incontinence and urge urinary incontinence in diabetic women was 10.0 and 19.9%, respectively. There was no significant difference between the non-MS and MS groups with respect to the prevalence of incontinence. Uroflometry including average voided volume, maximum flow rate, and PVR were comparable between the two groups. However, more patients in MS group were associated with greater PVR (PVR ≥100 ml), but the association did not achieve statistical significance ($P = 0.33$). All data were present after adjusting the age confounding effect.

Association between the number of metabolic components and LUTS/OAB

We stratified patients in the MS group into three groups based on the number of metabolic components they had (three, four, and five). Subgroup comparison of LUTS score to the non-MS group was made. As shown in Table 3, the average total, storage, and voiding symptom score were all significantly higher in patients having four and five metabolic components but not in those having three metabolic components. Likewise, subgroup comparisons also showed that the increase in the prevalence of OAB was observed only in patients having four (OR 3.1, 95% CI 1.9–5.1) or five (OR 4.9, 95% CI 2.5–9.4) metabolic components.

Risk factors for OAB in women with type 2 diabetes

Age-adjusted ORs for LUTS, as well as for OAB, were also examined in multivariate logistic regression models

TABLE 3. The association between LUTS and OAB and the number of components of MS in diabetic women with/without metabolic syndrome

	Non-MS group (n = 272)	MS group (n = 246)		
	No. of risk factors <3	No. risk factors = 3	No. risk factors = 4	No. risk factors = 5
Patients, n (%)	272 (52.5)	102 (19.7)	96 (18.5)	48 (9.3)
Storage symptom score	3.8 ± 3.4	3.8 ± 2.5	5.7 ± 3.2[a]	8.1 ± 5.0[a]
Voiding symptom score	2.6 ± 4.3	2.4 ± 4.0	3.3 ± 4.1	7.7 ± 6.9[a]
Total symptom score	6.4 ± 6.4	6.3 ± 5.3	9.0 ± 5.4[a]	15.8 ± 10.8[a]
OR (95% CI) for LUTS	1.0	0.7 (0.4–1.2)	2.1 (1.3–3.4)[b]	3.3 (1.7–6.3)[b]
Patients with OAB, n (%)	74 (27.2)	42 (41.2)	54 (56.3)	32 (66.7)
OR (95% CI) for OAB	1.0	1.7 (1.1–2.8)[b]	3.1 (1.9–5.1)[b]	4.9 (2.5–9.4)[b]

No. risk factors, Number of components of MS.

[a] $P < 0.05$ indicated the dispersion in storage symptom score, voiding symptom score, and total symptom score was significantly higher compared with the patients who were without MS, and had the number of risk factors less than 3 through ANCOVA-adjusting age effect.

[b] $P < 0.05$ indicated the risk of patients who were with MS, and the no. of risk factors three or greater were significantly higher compared with the patients who were without MS and had the number of risk factors less than three through logistic regression model-adjusting age effect.

(Table 4). Diabetic women with peripheral neuropathy were more than twice as likely to experience LUTS and 98% more likely to have OAB. A presence of MS showed only a marginal association with LUTS; however, it was a significant factor for OAB (OR 2.6, 95% CI 1.6–4.1). When the MS was substituted by its components in the regression analysis, we found hypertension, raised triglycerides, and reduced HDL cholesterol were independently associated with LUTS and OAB.

Discussion

In the present study, 36.7% of women with type 2 diabetes were considered to have moderate to severe LUTS (total AUA-SI score >7) on careful questioning at the diabetic clinics. However, only 6.6% had been treated, which is consistent with a previous study showing that diabetic cystopathy (DC) is common in women with type 2 diabetes regularly treated in the outpatient clinics but is frequently not recognized by patients and physicians due to its insidious development (16). It has received far less attention despite having a significant impact on quality of life and with significant individual health risks. Usually by the time urologists are consulted, DC has reached an advanced (decompensated) stage.

DC can occur in a number of ways, from impaired detrusor contractility to detrusor overactivity. It has been attributed primarily to peripheral neuropathy, involving autonomic and somatic nerves (17). Recent evidence also suggests that diabetes alters the function of detrusor muscle and urothelium as well (18). An interesting question is whether DC is secondary to diabetic chronic complications alone or compounded by coexisting comorbidities. Until recently, limited studies investigated the risk factors for DC. Based on a study showing that the prevalence of MS is very high among people with diabetes (12), it is of interest to investigate the role of MS in the development of DC. In the present study, after adjusting the age effect,

TABLE 4. Adjusted odds ratios for LUTS and OAB in women with type 2 diabetes

	Adjusted OR for LUTS			Adjusted OR for OAB		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Duration (yr)	0.98	(0.95–1.10)	0.17	0.96	(0.93–0.99)	0.01
Mean HbA1c level (%)	1.03	(0.83–1.27)	0.82	0.93	(0.74–1.17)	0.53
Diabetic complications						
Neuropathy	2.78	(1.60–4.84)	<0.001	1.98	(1.13–3.47)	0.02
Nephropathy	0.56	(0.33–0.96)	0.04	0.46	(0.26–0.82)	0.01
Retinopathy	1.18	(0.74–1.87)	0.48	0.99	(0.63–1.55)	0.95
MS[a]	1.52	(0.96–2.40)	0.07	2.58	(1.64–4.06)	<0.001
Hypertension (n)[b]	1.70	(1.11–2.62)	0.02	1.65	(1.28–2.87)	0.02
Triglycerides ≥150 mg/dl[b]	1.86	(1.24–2.80)	0.003	1.92	(1.04–2.24)	0.002
HDL cholesterol ≤50 mg/dl[b]	2.02	(1.33–3.01)	0.001	2.12	(1.41–3.21)	<0.001
WC ≥80 cm[b]	0.94	(0.61–1.44)	0.77	1.52	(0.99–2.32)	0.05

All models are adjusted for age. WC, Waist circumference.

[a] The MS is analyzed with diabetic duration, mean HbA1c level, and diabetic complications in the regression model.

[b] The MS is substituted by its components in the regression analysis.

we found that MS affected the storage and, to a lesser extent, the voiding symptoms in women with type 2 diabetes. The most significant LUTS complained were urgency, nocturia, and intermittency. The uroflowmetry showed voiding parameters including peak flow rate and PVR were similar between the two groups. It seemed that MS did not impair the detrusor contractility nor increase the bladder outlet resistance because the urinary flow rate is a composite measure of the interaction between pressure generated by the detrusor and resistance offered by the urethra. Based on the aforementioned information, we assume MS has more impact on the storage function rather than the voiding function.

A number of recent surveys revealed the presence of OAB symptom, describing it as urgency, with or without incontinence, usually with urinary frequency and nocturia, in a significant number of diabetic patients, affecting 39–61% of subjects (19, 20). OAB in diabetic patients may be secondary to multiple cerebral infarction due to diabetic cerebral vasculopathy (central mechanism) or peripheral nerve irritation for detrusor overactivity and increased bladder sensation (peripheral mechanism) (13). Decreased functional capacity is another important causative factor for OAB (21, 22). Clinically, OAB symptom (urgency, frequency and nocturia) can be measured with storage symptom part of the AUA-SI questionnaire. However, because the core symptom of OAB is urgency, and it is also the most bothersome clinical presentation. Herein we incorporated another validated instrument, IUSS, into the questionnaire to highlight the significance of urgency. In the present study, OAB symptom defined by IUSS was more prevalent in diabetic women with MS. The OR related to OAB also increased as the number of components of MS increased (OR 3.1–4.9).

How do the MS components affect the lower urinary tract of diabetic women? Recent evidence suggests that MS may be involved in the pathogenesis of both microvascular and macrovascular complications in patients with type 2 diabetes (23, 24). In the present study, there was no difference between the MS and non-MS groups regarding the hyperglycemia control and the prevalence of diabetic microvascular complications. Thus, the difference is less likely to be microvascular origin. On the other hand, because MS predicts atherosclerosis and cardiovascular risk (25–27) and atherosclerosis-induced chronic bladder ischemia may produce significant changes in bladder structure and function, leading to noncompliance and overactivity (28, 29), the link between MS and DC may be secondary to diabetic macrovascular morbidities. However, in a recent survey in Vienna, a significant association was not found between MS and LUTS in either men or women, which suggested that vascular risk factors do not play a role in the development of LUTS (30). What are the reasons for this discrepancy? A possible explanation for this difference is that most participants were nondiabetic subjects in their study cohort, and we assume MS without a presence of diabetes or hyperglycemia has limited effect on lower urinary tract. Therefore, bladder dysfunction observed in women with type 2 diabetes is attributable mostly to complications of diabetes, probably the diabetic neuropathy, and further compounded by MS components, resulting in worsened LUTS. The effect is multifactorial and the relative risk of each MS component is multiplied to a cumulative risk.

According to our hypothesis, the logistic regression analysis demonstrated that peripheral neuropathy, but not MS, significantly predicted LUTS in women with type 2 diabetes after age adjustment. However, there was a trend of the association between MS and LUTS ($P = 0.07$). Interestingly, after additional adjustment for diabetic neuropathy, MS remained significantly predictive for LUTS and OAB in our cohort, with an adjusted OR of 1.71 (95% CI 1.19–2.47, $P = 0.004$) for LUTS and 2.80 (95% CI 1.94–4.05, $P < 0.001$) for OAB, respectively. This result suggests that neuropathy alone does not explain the full amount of future LUTS and OAB risks that are conferred by the MS; the MS, as defined by National Cholesterol Education Program's Third Adult Treatment Panel criteria, exerts additional risk beyond diabetic neuropathy. Furthermore, if the MS was replaced by its individual components, we found hypertension, raised triglycerides, and reduced HDL cholesterol were independent risk factors for LUTS and OAB in our cohort. In summary, the present study suggests that MS and its components are risk factors for LUTS, especially OAB, in women with type 2 diabetes. Given that subjects with MS are at increased risk for subclinical atherosclerosis and subsequent cardiovascular events, it is intriguing to investigate the relationship between LUTS and clinical cardiovascular events. A longitudinal study is needed to observe whether worsened LUTS, as erectile dysfunction in some men, is a harbinger of cardiovascular events in women with type 2 diabetes (31).

Several aspects of our analysis merit further discussion. First, because this is a population that has been followed up for diabetes at a clinic and presumably their diabetes is relatively well-controlled, it seems possible that associations between MS risk factors and LUTS may be underestimated. Another study, based on a representative group of diabetic women, should be conducted to evaluate the impact of MS on lower urinary tracts. Second, AUA-SI has been validated for female lower urinary tract symptoms (FLUTS) and has now evolved from an instrument specifically designed for benign prostatic hyperplasia to one ap-

plied to LUTS in general in men and even in women. AUA-SI is also correlated highly with the degree of bother due to FLUTS, and higher AUA-SI scores are associated with a negative impact on quality of life in women as well (32). Furthermore, Okamura *et al.* (33) performed the psychometric analysis of AUA-SI for FLUTS and concluded the reliability and validity of the AUA-SI for women were as great as those for men. Another critical issue of this study is the definition of LUTS. It is difficult to compare the results from different investigations due to a lack of standardized, validated nomenclature of LUTS in the literature. Rohrmann *et al.* (7) used four of the seven symptoms of AUA-SI questionnaire (nocturia, incomplete emptying, hesitancy, and weak stream) to characterize LUTS and considered men as having LUTS if they reported three of four of the symptoms. In our study, we also used the AUA-SI questionnaire to evaluate LUTS among diabetic women but arbitrarily defined LUTS as subjects having AUA-SI score greater than 7 (moderate to severe symptom).

Conclusion

In the present study, we propose diabetes-related complication, such as peripheral neuropathy, is the main predictor of cystopathy in women with type 2 diabetes, but the risk of DC is modified by the presence of MS components. We suggest that diabetic women with more MS components complaining of LUTS warrant more extensive evaluations and more aggressive treatments. Further work is needed to determine whether improved control of some modifiable factors, such as glucose, cholesterol, waist circumference, body weight, and blood pressure, would eliminate or reduce the extent of LUTS and OAB in this population.

Acknowledgments

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Disclosure Summary: The authors have nothing to disclose.

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