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Risk factors associated with the progression of overactive bladder among patients with type 2 diabetes

Yiyi Zhu[1] | Zaisheng Zhu[2] | Jiajun Chen[2]

[1]Department of Endocrinology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China

[2]Department of Urology, Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, China

Correspondence
Zaisheng Zhu, Department of Urology, Jinhua Hospital, Zhejiang University School of Medicine, 365 East Renming Road, Jinhua, Zhejiang 321000, China.
Email: zaishengzhu@126.com

Abstract

Aim: To investigate the risk factors specific to diabetes mellitus that influence the progression of overactive bladder in Chinese population.

Methods: A total of 457 patients who were diagnosed with overactive bladder and diabetes mellitus at the Department of Endocrinology and Urinary Surgery Center of Zhejiang University Jinhua Hospital were enrolled from July 2015 to July 2018. Patients were assessed using a questionnaire and then divided into two groups according to the severity score: mild overactive bladder group and the moderate-severe overactive bladder group. Logistic analysis was performed to evaluate the risk factors associated with the progression of overactive bladder in diabetic patients.

Result: Among the 457 patients with diabetes mellitus and overactive bladder, there was a significant difference in the severity of overactive bladder, age, diabetes duration, symptomatic diabetic peripheral neuropathy as well as ankle reflex ($P < .05$) between the two groups. Moreover, multivariate analysis revealed that age (OR: 1.59, $P = .036$), duration of diabetes (OR: 1.41, $P = .049$) and symptomatic diabetic peripheral neuropathy (OR: 2.39, $P = .012$) were independent risk factors for the progression of overactive bladder.

Conclusion: In Chinese diabetic patients, overactive bladder progression is closely related with the severity of diabetes mellitus. Age, diabetic duration and symptomatic diabetic peripheral neuropathy are independent predictors of the severity of overactive bladder. Patients with symptomatic diabetic peripheral neuropathy are at risk of overactive bladder.

1 | INTRODUCTION

Diabetes mellitus (DM) is a disease characterised by severe complications such as retinopathy, nephropathy and neuropathy. Diabetic neuropathy is categorised into diabetic peripheral neuropathy (DPN) and autonomic neuropathy.[1] Diabetic bladder dysfunction is a type of automatic neuropathy which manifests as lower urinary tract involvement or as overactive bladder (OAB). According to 2010 IUGA/ICS joint report, OAB syndrome was defined as 'urinary urgency, usually accompanied by frequent nocturia, with or without urgency urinary incontinence (UUI), in the absence of urinary tract infection or other obvious pathological conditions'.[2]

DM and its associated complications have a significant impact on patients' quality of life. The magnitude of the effects of different DM complications on life quality are diverse. A 2017 cross-sectional study involving 1025 diabetic individuals showed that those with DM combined with overactive bladder (OAB) had the worst physical and mental quality of life compared with other DM complications.[3]

The causes of OAB development in diabetic patients include systemic inflammation, diabetic angiopathy and neuropathy, all of which lead to chronic ischaemia of the bladder[4] and central nervous system.[5] Therefore, early discovery of the risk factors for OAB progression in diabetic patients will boost the clinical management of these two diseases. However, majority of recent studies focused on the relationship between conditions such as urinary incontinence and diabetes bladder dysfunction.[6-11] To our knowledge, there are no reports on the risk factors associated with the severity of OAB in Chinese diabetic population.

To accurately evaluate the severity of OAB, a Chinese overactive bladder symptom score (OABSS) was adopted in this study.[12] This version was validated and found to be a reliable tool for assessing OAB in Chinese patients. The sum scores of OABSS range from 0 to 15, with higher numbers indicating high severity.[13] To determine the risk factors associated with OAB progression in patients with type 2 DM, we conducted a prospective investigation by recruiting 457 type 2 diabetic patients with OAB from July 2015 to July 2018, and analysed the severity of OAB in terms of age, gender and diabetic-related variables such as body mass index (BMI), DM duration, glycosylated haemoglobin A1c (HbA1c), DM treatment and DM-related complications.

What's known

- Some studies have reported that patients with type 2 diabetes mellitus (DM) are at risk of overactive bladder (OAB) compared with normal individuals. Most of previous research investigated the prevalence of OAB in diabetic patients and their quality of life.

What's new

- No study has assessed the risk factors of OAB progression in Chinese diabetic patients. This study was therefore designed to identify some parameters to evaluate the progression of OAB in diabetic patients. Our results provide a hint for assessing the development of OAB.

2 | SUBJECTS, MATERIALS AND METHODS

2.1 | Patient enrolment

This investigation was a cross-sectional study in which a total of 457 patients with type 2 DM and OAB were enrolled. The diagnosis of type 2 diabetes mellitus was based on WHO guidelines and was confirmed by a physician in the endocrinology department of our centre. Patients with fasting plasma glucose ≥7 mmol/L or 2-hour postprandial glucose ≥11.1 mmol/L were diagnosed as diabetic.[14] The diagnosis of OAB was confirmed by OABSS scoring system using the following diagnostic criteria: patients with urgency scores of OABSS ≥2 and an overall score ≥3 (Table S1). Patients with the following diseases were excluded from this study: pelvic organ prolapse, spinal cord injury (eg, spinal cord injury, lumbar rigidity, spinal bifida, etc), neuropathy (eg, Parkinson's disease, multiple sclerosis, etc), previous bladder and urethral lesions, history of urinary tract tuberculosis, A history of major pelvic or bladder surgery, urinary tract infections, and gestational diabetes.

This investigation was approved by the Ethics Committee of Jinhua Hospital Zhejiang University, and all patients provided a written informed consent.

2.2 | Demographic and health status information

All 437 patients completed a self-administered questionnaire under the guidance of medical staff, which comprised of demographic data as well as items relevant to DM and OAB. The demographic items of the questionnaire included age, gender, height, weight, HbA1c, DM duration, DM treatment, history of hypertension, heart disease, hyperlipaemia and cerebrovascular disease. Based on the WHO classification, BMI was defined as the weight in kilograms divided by the square of the height in metres (kg/m^2).[15]

2.3 | Assessment of symptomatic DPN

All the patients underwent careful clinical examination based on pinprick, temperature, vibration perception (using a 128-Hz tuning fork), 10-g monofilament pressure sensation at the distal halluces and ankle reflexes. If the examination results were positive, DPN was highly suspected. Patients with positive results in more than one clinical tests and typical symptomatology were diagnosed as symptomatic DPN.[16] The typical symptoms included the numbness, paraesthesia, burning pain, dysesthesia and muscle cramps.

2.4 | Assessment of the severity of OAB

The Chinese version of OABSS is a clinician-administered questionnaire containing four items related to OAB symptoms: day-time frequency, night-time frequency, urgency and urgency incontinence. The total scores range from 0 to 15, with higher scores indicating higher symptom severity. Participants were categorised according to their symptom severity as follows: mild (OABSS 3-5), moderate (OABSS 6-11) and severe (OABSS 12-15).[12,13] Participants in this study were classified into two groups, ie, mild group (OABSS 3-5) and moderate-severe group (OABSS 6-15).

2.5 | Statistics analysis

Statistics analysis was performed using data such as general factors (age, gender, height, weight, BMI), factors related to diabetes (HbA1c, DM treatment and DM duration), factors of DPN (ankle reflex and vibratory sensibility) and items in OAB (OABSS). All data are presented as mean ± SE for continuous variables, or as numbers and percentages for categorical variables. The independent sample *t* test was used to identify differences between continuous variables,

while the Pearson χ^2 analysis was performed for categorical variables. Multiple logistic regression analysis was applied to assess the contribution of the risk factors to mild OAB and moderate-severe OAB groups. The SPSS ver. 16 (SPSS Inc, Chicago) was used for statistical analysis. $P < .05$ were considered to indicate statistical significance.

3 | RESULTS

The demographic and biochemical data of all diabetic patients are listed in Table 1. A total of 437 patients were enrolled according to the study criteria. The participants were 40-49 years old with a median age of 62.1 years. They had different durations of DM ranging from 6 to 36 years (mean 11.3 years). The body mass index (BMI) of the patients ranged from 17.1 to 36.6 kg/m^2 (mean; 24.3 kg/m^2). The biochemical tests for haemoglobin A1C (HbA1c) ranged from 4% to 12% with an average of 6.7%. Among the subjects, 88 patients were given oral hypoglycaemia drugs and 301 were put on insulin treatment, while 68 patients were given a combination of both treatments. Regarding the disease history and complications, cerebrovascular disease was found in 109 patients, heart disease in 165 patients, stroke, hypertension and hyperlipaemia were identified in 32, 288 and 284 patients, respectively. Most importantly, 55.58% patients had diabetic DPN, including 44.20% patients with obvious nervous symptoms and 11.38% patients without symptoms.

TABLE 1 Demographic and biochemical data of diabetic patients with OAB (n = 457)

Parameter	Value
Age (y)	62.1 ± 11.8
Sex	
Male	173 (37.86%)
Female	284 (62.14%)
Body mass index (kg/m^2)	24.3 ± 4.4
Diabetes duration (y)	11.3 ± 6.6
HbA1c	6.7 ± 1.3
HbA1c (%)	
<7%	369 (80.74%)
≥7%	88 (19.26%)
Treatment	
Oral drug	88 (19.26%)
Insulin	301 (65.86%)
Oral drug + insulin	68 (14.88%)
DPN	254 (55.58%)
With symptoms	52 (11.38%)
Without symptoms	202 (44.20%)
History of stroke	32 (7.00%)
History of cerebrovascular disease	109 (23.85%)
History of hypertension	288 (63.02%)
History of hyperlipaemia	284 (62.14%)
History of heart disease	165 (34.14%)
OABSS	
Mild OAB	326 (71.33%)
Moderate OAB	110 (24.07%)
Severe OAB	21 (4.60%)

Note: Value represents mean ± standard error or numbers (%).
Abbreviations: DPN, diabetic peripheral neuropathy; HbA1c, glycosylated haemoglobin A1c; OAB, overactive bladder; OABSS, overactive bladder symptom score.

According to OABSS, 71.33% (326/457) patients displayed mild OAB, those with moderate OAB accounted for 24.07% (110/457) and the rest accounted for 4.6% (21/457), designated as the severe group. There were significant differences in the severity of OAB in term of age (<60/≥60 year), duration of diabetes (<10/≥10 years), bilateral ankle reflex (presence or absence) and symptomatic DPN (presence or absence) between the groups (Table 2).

In the multivariate analysis, the duration of diabetes (<10/≥10 years), symptomatic DPN (presence or absence) and age (<60/≥60 years old) were identified as independent risk factors associated with the progression of OAB. Among them, symptomatic DPN (presence or absence) was of the most important factor (odds ratio 2.39; 95% confidence interval [CI] 1.63-3.54) (Table 3).

4 | DISCUSSION

By 2010, it was estimated that the overall prevalence of diabetes mellitus in Chinese adult population had reached 11.6%.[17] The most common and bothersome chronic complication of lower urinary tract in DM is diabetic bladder dysfunction (DBD), which affects 43.0%-87.0% of diabetic patients.[18] However, DBD has not been sufficiently studied. In general, the function of the bladder is based on urodynamic evaluation. Yet, to complete the examination, a double-lumen cystometry catheter and balloon rectal catheter are required, which is not convenient, especially for diabetic patients with mild symptom OAB. This method is applied in diabetic patients with difficulties in urinating or patients with uroschesis indicated for surgery. Given that this examination is invasive, it is not suitable for OAB patients as it may aggravate OAB. For instance, it may cause irreversible changes to the bladder function, and if the diagnosis is delayed, it may lead to difficulties in OAB treatment. Therefore, it is important to explore the risk factors associated with OAB to facilitate early detection of OAB and boost the treatment of this condition.

In this study, age, duration of DM, symptomatic DPN and ankle reflexes were significantly different between the mild OAB group and moderate-severe OAB group. In the multivariate analysis, age, the duration of diabetes and symptomatic DPN were found to be independent risk factors for the progression of OAB. A previous report showed that the development and severity of DPN was closely associated with DM duration and age.[19] Taken together, we can infer that as the DM duration and age increases, the likelihood of DPN developing increases, and the OAB symptoms

TABLE 2 Univariate analysis of variance of mild OAB and moderate-severe OAB in diabetic patients

Variable	Mild OAB	Moderate-Severe OAB	OR (95% CI)	*P* value
Sex				
Male	128 (73.99)	45 (26.01)		
Female	198 (69.72)	86 (30.28)	0.89 (0.59-1.27)	.390
Age (y)				
<60	129 (74.57)	44 (25.43)		
≥60	197 (69.37)	87 (30.63)	2.11 (1.36-2.93)	.011*
BMI (kg/m^2)				
<25	215 (68.25)	100 (31.75)		
25	111 (78.17)	31 (21.83)	0.79 (0.57-1.12)	.213
Diabetic duration (y)				
<10	133 (76.88)	40 (23.12)		
≥10	193 (67.96)	91 (32.04)	1.49 (1.02-2.17)	.029*
HbA1c (%)				
<7	265 (71.82)	104 (28.18)		
≥7	61 (69.32)	27 (30.68)	1.09 (0.71-1.24)	.566
Treatment				
Oral drug	62 (70.45)	26 (29.55)		
Insulin	217 (72.09)	84(27.91)	0.83 (0.47-1.28)	.863
Oral drug + insulin	47 (69.12)	21 (30.88)	1.01 (0.52-1.77)	.802
Ankle reflexes				
Present	143 (76.06)	45 (23.94)		
Absent	183 (68.03)	86 (31.97)	1.29 (1.02-2.01)	.049*
Vibration perception				
Present	168 (69.71)	73 (30.29)		
Absent	158 (73.15)	58 (26.85)	0.84 (0.60-1.15)	.998
Symptomatic DPN				
Present	123 (60.89%)	79 (39.11%)		
Absent	203 (79.61%)	52 (20.39%)	2.47 (1.71-3.53)	.009**
Stoke history				
With	19 (59.38%)	13 (40.62%)		
Without	307 (72.24%)	118 (27.76%)	1.66 (0.99-3.17)	.074
Cerebrovascular history				
With	52 (47.71%)	57 (52.29%)		
Without	274 (78.74%)	74 (21.26%)	0.33 (0.12-0.95)	.952
Hypertension history				
With	219 (76.04%)	69 (23.96%)		
Without	107 (63.31%)	62 (36.69%)	0.66 (0.30-1.01)	.763
Hyperlipaemia history				
With	215 (75.70%)	69 (24.30%)		
Without	111 (64.16%)	62 (35.84%)	0.54 (0.28-0.94)	.911
Heart disease history				
With	121 (77.56%)	35 (22.44%)		
Without	205 (68.11%)	96 (31.89%)	0.81 (0.62-1.25)	.332

*P < .05,
**P < .01 represent statistical difference.

TABLE 3 Multivariate analysis of variance of mild OAB and moderate-severe OAB in diabetic patients

Variable	Mild OAB	Moderate-Severe OAB	OR (95% CI)	*P* value
Age (y)				
<60	129 (74.57)	44 (25.43)		
≥60	197 (69.37)	87 (30.63)	1.59 (1.01-2.44)	.036*
Diabetic duration (y)				
<10	133 (76.88)	40 (23.12)		
≥10	193 (67.96)	91 (32.04)	1.41 (1.01-2.06)	.049*
Ankle reflexes				
Present	143 (76.06)	45 (23.94)		
Absent	183 (68.03)	86 (31.97)	0.97 (0.39-1.41)	.322
Symptomatic DPN				
Present	123 (60.89%)	79 (39.11%)		
Absent	203 (79.61%)	52 (20.39%)	2.39 (1.63-3.54)	.012*

*$P < .05$,
**$P < .01$ represent statistical difference.

deteriorates. Moreover, experiments have shown that the pathogenesis of DPN is associated with hyperglycaemia, glucotoxicity, impaired insulin signalling combined with other risk factors that promote nervous structural changes.[20] DPN is mainly characterised by demyelinization, axonal degeneration and fibre loss.[21] The causes of diabetic bladder dysfunction are primary peripheral and autonomic neuropathy. The neuropathy affects sensory afferent pathways, causing the insidious onset of impaired bladder sensation, and ultimately decreasing the detrusor contractility and bladder dysfunction. This may explain the association between DPN and OAB. However, further investigations are required to explore other potential causes.

Interestingly, even ankle reflex showed a positive association with OAB progression, but it was not found to be an independent risk factor. In fact, ankle reflex was previously regarded as a strong indicator of diabetic neuropathy in asymptomatic patients.[22] Although it has a high sensitivity and specificity of 91.5% and 67.4%, respectively,[23] it was not suitable for evaluating the severity of neuropathy. However, for patients presenting with symptomatic DPN, it may serve as the cut-off point to recognise the severity of OAB. A detailed diagnosis of symptomatic DPN should include the signs and symptoms as well as quantitative peripheral sensory tests. The typical symptoms, such as numbness, paraesthesia, burning pain, dysesthesia and muscle cramps, should be observed during diagnosis. It is conceivable that patients whose neuropathic condition has increased beyond the threshold of developing symptoms are more likely to suffer from serious neuropathy compared with presymptomatic patients.[16] The presence of neuropathic symptoms reflects severe DM. Therefore, this parameter can be used to reflex the progression of OAB.

There are several limitations in this study. First, it is a single centre research, therefore, the results might not represent all diabetic patients and cannot be generalised. Second, the participants were elderly patients who might suffer from neurogenic bladder because of multiple etiologic factors such as benign prostatic hyperplasia, uracratia, urinary tract infection and other conditions. These conditions were not found or evaluated, but transrectal ultrasounds and urine flow rate examination were performed to reduce the research error. In addition, recall bias may affect the accuracy of the result as patients might not fully remember their disease history, and hence may provide inaccurate information. Hence, our results should be interpreted with caution.

In conclusion, in type 2 diabetes with OAB, the severity of OAB is associated with symptomatic diabetic peripheral neuropathy, duration of diabetes and age. Importantly, symptomatic diabetic peripheral neuropathy aggravates OAB. Hence, these three parameters should be monitored in clinical practice when evaluating diabetic patients with OAB.

ORCID

Yiyi Zhu https://orcid.org/0000-0003-1184-8333

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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