World J Urol
DOI 10.1007/s00345-013-1175-3

ORIGINAL ARTICLE

Overactive bladder in diabetes mellitus patients: a questionnaire-based observational investigation

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Received: 28 July 2012 / Accepted: 24 September 2013

Abstract
Purpose Bladder dysfunction, secondary to diabetes, is mainly characterized by poor bladder emptying and overflow incontinence. However, there is evidence in literature that storage symptoms, as those suggestive for overactive bladder (OAB), may also affect people with diabetes. The aim of this study was to evaluate the prevalence of overactive bladder, the complaint of urinary urgency with/without urge incontinence, usually with frequency and nocturia, in people with diabetes compared to healthy subjects (control group).
Methods Symptoms were assessed through the overactive bladder questionnaire (OAB-q), an investigative tool, specifically developed for OAB diagnosis.
Results OAB-q scores resulted higher in diabetic people than those of the control group. Age and disease duration resulted in measurements that showed a statistical correlation with the OAB-q scores.
Conclusions OAB symptoms are more prevalent in diabetic people than in non-diabetic people. This prompts further research to determine whether the onset of OAB symptoms can be considered as an indicator of diabetic neuropathy.

Keywords Overactive bladder · Diabetes mellitus · Lower urinary tract symptoms · Overactive bladder questionnaire

Abbreviations

BOO	Bladder outlet obstruction
DM	Diabetes mellitus
DO	Detrusor overactivity
LUTS	Lower urinary tract symptoms
MMSE	Mini-mental state examination
OAB	Overactive bladder
OAB-q	Overactive bladder questionnaire
UTI	Urinary tract infection

Introduction

Diabetic bladder dysfunction is mainly characterized by poor bladder emptying and overflow incontinence. However, recent evidence also indicates that storage symptoms, such as urinary urgency with/without urinary incontinence, which are usually associated with urinary frequency and nocturia, are significantly represented. The aim of this study was to assess the prevalence of these storage symptoms, more typical of overactive bladder (OAB) disorder [1], in diabetic people compared to non-diabetics. Correlation of the symptoms with the patient's sex, age, type of therapy, disease duration, and disease severity, as indicated by patient's HbA1c (glycated hemoglobin) levels, was also evaluated.

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Published online: 08 October 2013

Table 1 Baseline characteristics of enrolled patients and healthy subjects

	DM population	Controls
Males number (range age, mean and SD)	167 subjects (57–77 years, 62.4 ± 8.24)	166 subjects (59–74 years, 64.4 ± 7.77)
Females number (range age, mean and SD)	161 subjects (55–76 years, 60.4 ± 5.34)	167 subjects (57–76 years, 60.1 ± 6.37)
	DM under insulin regimen	DM under oral therapy
Males number (range age, mean and SD)	84 subjects (55–75 years, 60.4 ± 72.4)	83 subjects (57–75 years, 60.4 ± 8.14)
Females (range age, mean and SD)	80 subjects (56–73 years, 63.6 ± 3.3)	81 subjects (57–72 years, 62.1 ± 72.7)

Comment: demographic characteristics of DM and controls population

Data reported evidence that the cohorts do not present significant differences about sex and age distribution which could influence statistical analysis

Table 2 The short form of the overactive bladder questionnaire

During the past 4 weeks, how bothered were you by...	Not at all	A little bit	Some-what	Quite a bit	A great deal	A very great deal
1. An uncomfortable urge to urinate	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
2. A sudden urge to urinate with little or no warning	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
3. Accidental loss of small amounts of urine	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
4. Nighttime urination	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
5. Waking up at night because you had to urinate	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
6. Urine loss associated with a strong desire to urinate	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

This questionnaire is self-administered, easy to understand, and requires short compilation time

Patients and methods

A total of 400 Caucasian subjects (200 males and 200 females) with type 2 diabetes mellitus (DM) were recruited. Diagnosis of diabetes was considered the inclusion criteria and based on standard assessments [2]. All the patients signed an informed consent and were evaluated by physical examination, urinalysis, urine culture, free uroflowmetry with ultrasound evaluation of post-void residue (two tests), 24-h urine volume, and a Mini-Mental State Examination (MMSE). The exclusion criteria included urinary tract infection, post-voiding residue $\geq$100 mL and urinary flow indexes $\leq$15 mL/s (both suggestive for bladder outlet obstruction or detrusor underactivity), 24-h urine volume $\geq$3,000 mL (suggestive of polyuria), previous urological or gynecological surgery, previous or concomitant neoplastic conditions, cognitive impairment (MMSE $\leq$ 26/30), and significant neurological history. As a result, the initial cohort of patients considered for this study were 167 males and 161 females. Considering the same criteria, 333 healthy subjects without DM were also recruited (Table 1). OAB diagnoses and severity determinations were obtained using the short form of overactive bladder questionnaire (OAB-q) [3] (Table 2) and were supported by the recording of a 3-day voiding diary (in fact, OAB is consistent with at least 8 episodes of micturition per day or more, presence of urgency, and a strong and sudden desire to void) [4]. HbA1c level was also measured in all patients. Preliminary statistical considerations were undertaken to compare sex, age, and weight distributions within the study populations (χ^2 test and odds ratios for categorical variables, and Student's t test to evaluate differences of continuous measurements). A multiple linear regression model was used to evaluate the correlation between OAB-q scores and other study variables (age, disease duration, HbA1c).

Table 3 Overactive bladder questionnaire scores

DM patients	Healthy subjects	*P* value*
18.69 ± 8.9	11.37 ± 5.1	$P < 0.0001$
DM males	DM females	
14.4 ± 1.5	14.2 ± 2.3	NS
DM oral therapy	DM insulin therapy	
12.87 ± 1.21	13.39 ± 1.47	NS

Mean OAB-q scores were significantly higher in DM subjects compared to the control group. In patients with diabetes, there were no significant differences in OAB-q scores between males and females, and between people under oral therapy compared to those treated by injectable insulin

* *P* value was considered statistically significant when < 0.005

Table 4 Bladder diary variables, mean (±SD)

	Healthy subjects	Patients with diabetes	*P* values
Total fluid intake per 24 h (mL)	1,280 (±67.9)	1,309 (±68.4)	N.S.
Total micturitions per 24 h	6.6 (±1.7)	9.6 (±1.2)	<0.001
Urgency episodes per 24 h	0.4 (±1.9)	3.5 (±1.1)	<0.001
UUI episodes per 24 h	0	1.2 (±0.7)[a]	<0.001
Nocturnal micturitions per 24 h	1.1 (±1.3)	2.3 (±1.2)	<0.001

N.S. not significant, *UUI* urge urinary incontinence

[a] UUI episodes per 24 h are referred to 41 patients (12.5 %) of people with diabetes

Results

Sex (χ^2, $P = 0.1$), mean age, and weight distributions (*t* test, $P = 0.3$) were similar for all subjects with/without diabetes. The majority of participants fell in the normal body mass index (BMI) ranges in both populations (69.9 % in DM individuals and 84 % in healthy subjects). None of the patient presented BMI ≥ 29. Most represented comorbidities were blood hypertension and hypercholesterolemia, and they were equally distributed in the different populations examined. None of the patient was on treatment with antimuscarinics or other drugs with anticholinergic activity. Among the diabetic patients, the mean disease duration was slightly longer for subjects who were treated with injectable insulin (8.4 ± 5.8 years, range ± SD) compared to those who received only oral therapy (6.9 ± 4.9 years, range ± SD). The OAB-q and voiding diaries indicated that 35.7 % of the DM group and 4.8 % of the healthy subjects were diagnosed with OAB, which is a statistically significant difference. OAB prevalence was slightly higher in females (36.1 %) than in males (34.9 %). Mean OAB-q scores were significantly higher in the diabetic patients compared to the healthy subjects, without significant difference depending on sex and type of therapy (Table 3). The voiding diaries supported the outcome of the OAB questionnaire (Table 4). No statistical difference regarding daily fluid intake was observed between DM patients and healthy subjects. Mean urinary episodes per 24 h resulted 9.6 ± 1.2 in DM cohort and 6.6 ± 1.7 in healthy subjects. Mean urinary urgency episodes per 24 h resulted 3.4 in diabetic subjects under oral therapy and 3.7 in those under insulin regimen. No statistical significant difference was found between males and females. Urinary urgency incontinence episodes were reported by 41 of DM individuals (12.5 % of population), 28 women and 13 men.

A multiple linear regression analysis showed that in diabetic patients, the resulting OAB-q scores were significantly influenced by age and disease duration ($R^2 = 0.136$; age, $P = 0.002$; disease duration, $P = 0.005$). No significant difference was observed between the two therapeutic groups of people with diabetes with respect to their mean HbA1c values (people treated with injectable insulin: 6.47 ± 1.21 g/dL vs. people under oral therapy 6.91 ± 2.01 g/dL, *t* test $P = 0.51$). However, Pearson's analysis showed no statistical correlation between the OAB-q scores and HbA1c measurements in people with diabetes treated with injectable insulin (Pearson's coefficient $P = 0.24$; $r = 0.68$; $\chi^2 = 0.2$) and in subjects under oral therapeutic regimen (Pearson's coefficient $P = 0.24$; $r = 0.68$; $\chi^2 = 0.2$).

Discussion

Diabetes may contribute to urinary disorders due to bladder dysfunction. However, specific data are lacking regarding the prevalence of OAB disorder in people with diabetes. In fact, few authors report OAB symptoms among the lower urinary tract symptoms (LUTS) associated with diabetes [5, 6]. Bladder dysfunction, secondary to diabetes, is widely believed to be characterized by voiding disorders secondary to impaired bladder contractility. Despite this traditional consideration, there is evidence that storage symptoms, such as urinary urgency and urgency incontinence, and alterations in the bladder filling phase are also well represented [7]. Recent results from studies involving animal models show a temporal effect of diabetes on the bladder: the early stage of the disease seems to be associated with compensated bladder function, whereas the later phase is associated with decompensated detrusor function and both storage and emptying disorders [7]. These data were supported by a prospective study based on urodynamic and bladder sensory function assessments, which showed that 13 % of women suffering from early-stage diabetes

presented OAB symptoms, secondary to detrusor overactivity (DO) [8]. Furthermore, this study, based on electrophysiological investigations, demonstrated that diabetes can affect the bladder, presumably via a peripheral pathogenetic mechanism that induces DO. Other studies, based on urodynamic tests, supported the finding that increased bladder sensitivity and DO and consequent overactive bladder symptoms are well represented in people with type 2 diabetes [9, 10]. Various mechanisms have been hypothesized for altered bladder function in diabetes, involving autonomic neuropathy associated with the modification of bladder nerve growth factor expression, nerve cell apoptosis, and modification of muscarinic receptor gene expression [11]. Recent findings support the belief that bladder apoptosis is involved in diabetic cystopathy via the activation of the mitochondrial pathway and that increased bladder response to stimulation reproduces the cooling reflex shown in experimental models (streptozotocin-induced diabetes in rats) [12]. These last evidences could particularly explain the development of overactive bladder symptoms in people with diabetes, as the consequence of an altered bladder function with possible neurogenic origin. In addition, some clinical data support the neurogenic origin of OAB symptoms in people with diabetes. For example, Fayyad et al. [13] showed that these symptoms were most bothersome in women and that neuropathy and HbA1c were risk factors for voiding dysfunctions. Yamaguchi et al. [14] also reported results of a retrospective analysis of 2,300 diabetic individuals and suggested that OAB symptoms commonly involved both the central and peripheral neurogenic pathways for DO, with a high rate of multiple cerebral infarctions and peripheral nerve irritation leading to increased bladder sensation. Based on these evidences, further research should be directed toward determining whether the onset of OAB symptoms in people with diabetes might be an indicator of diabetic neuropathy. The present study shows that OAB symptoms are common in diabetics. The results also confirm that in diabetic patients, the age and the disease duration represent risk factors for developing OAB symptoms, as already demonstrated for general population and in other pathological conditions such as Parkinson's disease [15]. These results agree with other investigations that describe diabetes as a risk factor for developing LUTS, including OAB symptoms [16]. In the present study, people with diabetes and OAB did not suffer from polyuria (which represented an exclusion criteria), indicating that storage and emptying symptoms, bothersome in people with diabetes, are not simply the consequence of increased urine production, as previously reported [17]. Nevertheless, mean glycated hemoglobin of the enrolled population had a value above the normal range, and the study did not show association between this parameter and OAB-q scores. However, basing on the evidence of this investigation, it might be postulated that people with poorly controlled diabetes can develop complications including urinary symptoms as already reported in literature [5]. As a further consideration, there is clear evidence that diabetes and OAB have a negative impact on quality of life. Data obtained from this investigation are particularly remarkable considering that more than 142 million people worldwide are estimated to suffer from diabetes and that a significant proportion of them could be vulnerable to OAB symptoms during the course of their disease. These epidemiological data, supported by evidence from the present study, reflect the possible socio-economic burden of this association, especially when combined with the aging of the global population and the established relationships between age, diabetes, and OAB symptoms. A potential limit of this study could be represented by the fact that only patients with type II DM were evaluated. However, we selected this population especially considering the increase in data provided by literature regarding the association between LUTS and type II DM [18–21]. Among these manuscripts, there are no investigations specifically dedicated to OAB symptoms. For this reason, even if the conclusion of our research is not something completely unknown, we designed a study which could provide a scientifically determined information on the higher incidence of OAB symptoms in diabetic patients.

Conclusion

This study showed that OAB symptoms are more prevalent in people with diabetes than in healthy people. Age and disease duration measurements showed a statistical correlation with the OAB-q scores. Various experimental and clinical findings supported a possible neurogenic origin of OAB symptoms in people with diabetes, suggesting that further research is required to determine whether the OAB symptoms represent markers of diabetic neuropathy.

Conflict of interest The authors declare that they have no conflict of interest.

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