Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9749-17
Intern Med 57: 2165-2168, 2018
http://internmed.jp

【 ORIGINAL ARTICLE 】

The Relationship between Bladder, Periarterial and Somatic Neuropathy in Diabetes

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Abstract:

Objective Diabetes commonly affects the bladder nerves. However, the relationship among bladder, periarterial and somatic neuropathy in diabetes is not well known. In the present study we investigated these relationships.

Methods A total of 110 diabetic subjects were enrolled in the study. All were referred for screening for diabetic neuropathy, irrespective of their symptoms. The patients included 61 men and 49 women; the mean age was 59.3 years (31-85 years); the mean disease duration was 14.0 years (5-30 years); and the mean HbA1c value was 10.1% (5.1-16.3%). We performed a nerve conduction study (NCS, A-alpha/beta and B fiber), ultrasound-based measurement of the post-void residual (PVR) volume (abnormal, >50 mL, mainly A-delta/C fiber) and postural blood pressure measurement (abnormal, >-20 mmHg, A-delta/C fiber). Fisher's exact probability test and Student's *t*-test were used to analyze the significance of differences.

Results NCS abnormality, an abnormal PVR volume, and postural hypotension were noted in 74, 19, and 36 of the subjects, respectively. There were clear relationships between NCS and an abnormal PVR volume ($p<0.05$), postural hypotension and an abnormal PVR volume ($p<0.05$), or NCS and postural hypotension ($p<0.01$). There were also subjects who had NCS abnormality alone, a high PVR volume alone or postural hypotension alone. An abnormal PVR volume was not associated with the HbA1c value, but was clearly related to the duration of diabetes ($p<0.05$).

Conclusion Bladder dysfunction was correlated with somatic and periarterial neuropathy. On the other hand, 16% of the cases of bladder dysfunction occurred in patients without somatic or periarterial neuropathy; thus, the regular measurement of the PVR volume is necessary.

Key words: diabetes, bladder, postural hypotension, diabetic neuropathy, small fiber neuropathy

(Intern Med 57: 2165-2168, 2018)
(DOI: 10.2169/internalmedicine.9749-17)

Introduction

Diabetes (1, 2) commonly affects the bladder nerves (3). Such patients often experience difficulty in emptying, a large post-void residual urine volume, reduced bladder sensation, and bladder over-activity (3). The associations between bladder and somatic neuropathy in patients with diabetes have been reported in various studies; the associated findings have included somatic pain sensation (somatic Aδ/C small fiber) (3), nerve conduction in the limbs (somatic large fiber) (4, 5), and sympathetic skin responses (sweating; autonomic Aδ/C small fiber) (6, 7). However, it is not well known whether bladder dysfunction occurs without somatic neuropathy, or whether bladder dysfunction is associated with postural hypotension. To answer this question, we performed three simple objective tests in diabetic patients.

Materials and Methods

A total of 110 subjects who fulfilled the diagnostic criteria for type 2 diabetes were enrolled in the study (1). All pa-

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Received: June 30, 2017; Accepted: November 21, 2017; Advance Publication by J-STAGE: February 9, 2018
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Table. The Three Objective Tests Performed in Screening for Diabetic Neuropathy.

	method	abnormality	relevant nerves
nerve conduction study	motor & sensory nerves in the four extremities (median, ulnar, tibial, superficial peroneal, sural)	distal symmetric sensorimotor polyneuropathy [Σ 2 nerve conduction deviates abnormal (peroneal motor nerve conduction velocity & sural amplitude)]	large diameter limb fiber: myelinated A (Aα-Aβ), B fibers (mean diameter 8-15 μm)
post-void residual urine measurement	transcutaneous bladder echography just after voiding	>50mL residual	small diameter bladder fiber: myelinated, unmyelinated Adelta-C fibers (mean diameter 1-3 μm)
postural blood pressure measurement	blood pressure measurement on lying and 5 min after active standing	>-20mmHg systolic pressure fall	small diameter perivascular fiber: myelinated, unmyelinated Adelta-C fibers (mean diameter 1-3 μm)

tients were referred for screening for diabetic neuropathy, irrespective of their symptoms. The study population included 61 men and 49 women [mean age, 59.3 years (31-85 years); mean disease duration, 14.0 years (5-30 years); mean HbA1C, 10.1% (5.1-16.3%)]. With the exception of 12 patients who were treated with oral sulphonylurea, thiazolidine derivatives or dipeptidyl peptidase-4 inhibitors, most were untreated patients with HbA1c values that ranged from 5.1 to 7.2%. None had comorbid diseases that might cause postural hypotension or urinary dysfunction (i.e., multiple system atrophy or Parkinson's disease). None were taking drugs that might interfere with postural hypotension or urinary dysfunction. All patients were able to walk independently, and no patients had numbness in the extremities or dizziness on standing. All patients completed a urinary questionnaire (international prostate symptom score, IPSS, which is used in neurological diseases). We chose three objective tests to screen for diabetic neuropathy. 1) Somatic neuropathy: motor and sensory nerve conduction study [NCS, bilateral median, ulnar, tibial, superficial peroneal and sural nerves; A-alpha and B large fiber; typical distal symmetric sensorimotor polyneuropathy (DSPN) is a symmetrical length dependent sensorimotor polyneuropathy attributable to chronic hyperglycemia, metabolic derangement, and microvessel alteration. An abnormality of NCS that may be subclinical appears to be the first objective and quantitative indication of DSPN. We used Dyck's criteria 5 (abnormal Σ 2 nerve conduction deviation (peroneal motor nerve conduction velocity and sural amplitude)) (2). The normal limit of NCS in our institute was described previously (8)]. 2) Bladder neuropathy: ultrasound-based measurement of the post-void residual (PVR) volume (measured just after voluntary voiding, abnormality >50 mL (9), A-delta/C small fiber). 3) Periarterial neuropathy: postural blood pressure measurement (Schellong test), between lying to active standing (9) (abnormality, >-20 mmHg (10): A-delta/C small fiber) (Table). We also examined the relationship between the PVR volume and the HbA1c value and duration of diabetes. Fisher's exact probability test, Spearman's rank correlation coefficient, and Student's *t*-test were used to analyze the statistical significance of differences. All patients gave their informed consent before participating in the study.

Results

IPSS revealed moderate symptoms (IPSS >8/35) in 9 men and 4 women. The PVR volume was not related to the HbA1c value, while it was clearly related to the duration of diabetes ($p<0.05$) (Fig. 1). NCS abnormality, an abnormal PVR volume and postural hypotension were noted in 74 (67%), 19 (17%, almost the same volume in men and women) and 36 (33%) of the subjects, respectively. In particular, most patients were unaware of post-voiding urinary retention. There were clear relationships between NCS and an abnormal PVR volume ($p<0.05$), postural hypotension and an abnormal PVR volume ($p<0.05$), and NCS and postural hypotension ($p<0.01$) (Fig. 2). There were also subjects who had NCS abnormality alone (40/110, 36% in total; 40/74, 54% of patients with NCS abnormality), an abnormal PVR alone (3/110, 3% in total; 3/19, 16% with an abnormal PVR volume) and postural hypotension alone (5/110, 4.5% in total; 5/36, 14% of the patients with postural hypotension).

Discussion

Previously, it was not well known whether bladder dysfunction occurs without somatic neuropathy, or whether bladder dysfunction is related to postural hypotension in patients with diabetes (11). To answer these questions, we chose three objective tests, which are not painful, easy to perform in elderly individuals, and applicable to all subjects.

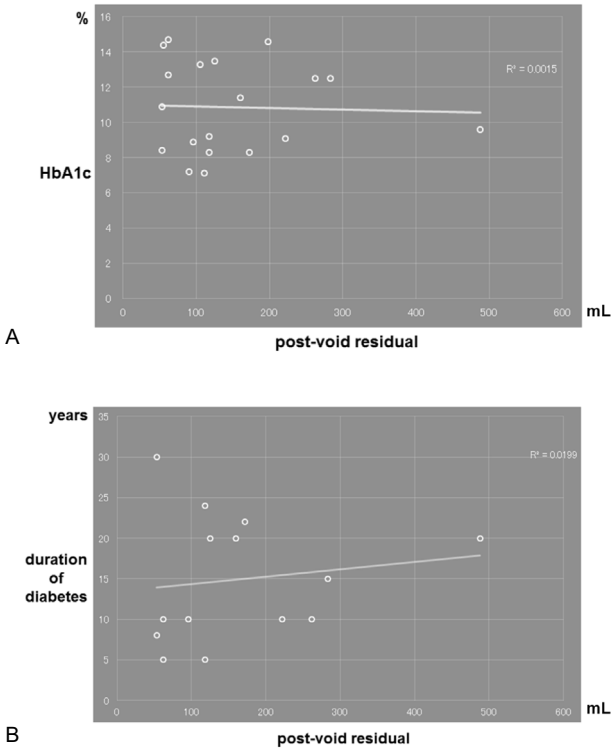

Figure 1. The relationship between the post-void residual volume and the HbA1c value (A), and the duration of diabetes (B). The post-void residual volume was not related to HbA1C value, while it was clearly related to the duration of diabetes (p<0.05).

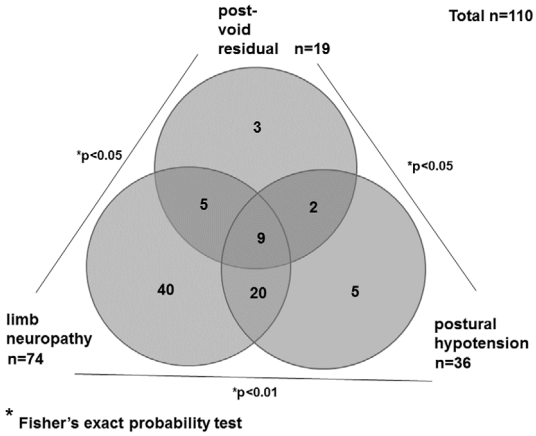

Figure 2. The abnormalities in the three objective tests and their relationships.

The results of the present study showed that 17% of the diabetic subjects had an abnormal PVR volume. Notably, most patients were unaware of their urinary retention; this is in accordance with the findings of previous reports (12). The PVR volume was associated with the duration of diabetes ($p<0.05$), which is also in accordance with the findings of previous reports (4). However, the correlation coefficient was rather low (R2=0.0199); this might have also been affected by a case involving a patient with an extremely high PVR volume (500 mL).

To the best of our knowledge, we showed-for the first time-that bladder neuropathy was correlated with somatic and peri-arterial neuropathies ($p<0.05$). These findings indicate that bladder, somatic and peri-arterial neuropathies might share the same pathological process, which could include hyperglycemia-induced molecular changes (i.e., the intra-neuronal polyol cascade) or ischemia of the vasa nervosum (13, 14).

The results of the present study also showed that a proportion of subjects had an abnormal PVR volume alone (16% of the subjects with an abnormal PVR volume), without somatic or peri-arterial neuropathy. We do not know the exact reason for this discrepancy. However, bladder-specific pathophysiology might include over-distension injury (due to polyuria) and changes in the urothelium (15, 16). In addition, there are different nerve receptors in the bladder and vessels (muscarinic M3 receptors and alpha-1A/D receptors are abundant in the lower urinary tract, while alpha-1B receptors are abundant in the arterial wall) (17). This finding is clinically relevant and the regular measurement of the PVR volume seems necessary in diabetes as bladder neuropathy might occur insidiously in such patients.

The present study is associated with some limitations. We only measured the PVR volume and did not investigate the urodynamics or perform a prostate ultrasound examination to investigate bladder neuropathy. Thus, prostatic hyperplasia in men and storage dysfunction in both sexes might have been missed. Further studies that include a bladder diary and a urodynamics study are warranted.

In conclusion, bladder dysfunction was correlated with somatic and periarterial neuropathy. On the other hand, in 17% of the patients with bladder dysfunction, bladder dysfunction occurred without somatic or periarterial neuropathy; thus, the regular measurement of the PVR volume seems necessary.

The authors state that they have no Conflict of Interest (COI).

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