INTERNAL MEDICINE

Macrovascular Complications and Prevalence of Urgency Incontinence in Japanese Patients with Type 2 Diabetes Mellitus: The Dogo Study

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Abstract

Objective   Macrovascular diseases and urgency incontinence are common among Japanese patients with type 2 diabetes mellitus. However, little evidence exists regarding the association between stroke and urgency incontinence among patients with type 2 diabetes mellitus. We examined the associations between macrovascular complications and urgency incontinence among Japanese patients with type 2 diabetes mellitus.

Methods   The study subjects were 818 Japanese patients with type 2 diabetes mellitus. Urgency incontinence was defined as present when a subject answered "*once a week or more*" to the question: "*Within one week, how often do you leak urine because you cannot defer the sudden desire to urinate?*" We adjusted our analyses for sex, age, body mass index, duration of type 2 diabetes, current smoking, current drinking, hypertension, dyslipidemia, glycated hemoglobin, diabetic nephropathy, diabetic retinopathy, and diabetic peripheral neuropathy.

Results   The prevalence of urgency incontinence was 9.2%. Stroke was independently positively associated with urgency incontinence, with an adjusted odds ratio of 2.34 (95% confidence interval: 1.03-4.95). The associations between ischemic heart disease or peripheral artery disease and the prevalence of urgency incontinence were not significant.

Conclusion   In Japanese patients with type 2 diabetes mellitus, stroke, but not ischemic heart diseases or peripheral artery disease, was independently positively associated with urgency incontinence.

Key words: diabetes, incontinence, Japanese, stroke, macrovascular complications

Introduction

Subjects with urgency incontinence have worse scores on quality-of-life and depression scales, poorer quality of sleep, and lower work productivity than do matched controls (1, 2). The prevalence values of urgency incontinence among patients with type 2 diabetes mellitus were 1.9-

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26.4% in previous studies (3-11). In a Korean case-control study, urgency incontinence scores among cases with type 2 diabetes mellitus were higher than those among a control group (12). In an Italian case-control study, the prevalence of urgency incontinence among cases with type 2 diabetes mellitus were significantly higher than those of a healthy control (6). Diabetes was found to be significantly positively associated with urgency incontinence in a US study of 121,701 women (3), in a Norwegian study of 21,057 women (9), and in a US study of 2,763 postmenopausal women (12).

The prevalence of urgency incontinence among patients with stroke was 15.7-32.5% (13-15). Stroke was significantly positively associated with urgency incontinence in a US study of 3,809 elderly subjects (16). Prospective studies have demonstrated that diabetes mellitus was a risk factor for stroke (17, 18). However, little evidence exists regarding the association between stroke and urgency incontinence among patients with type 2 diabetes mellitus. In a US study of 2,994 women with type 2 diabetes mellitus, the prevalence of stroke among diabetic patients with weekly urinary incontinence was similar to that of patients with less than weekly urinary incontinence or no incontinence (19). In a Taiwanese study of 279 patients with type 2 diabetes mellitus, the association between stroke history and urgency incontinence among patients with type 2 diabetes mellitus was not significant (8).

In the present study, we examined the association between macrovascular complications and urgency incontinence among Japanese patients with type 2 diabetes mellitus.

Materials and Methods

Study population

The Dogo Study is a multicenter prospective cohort study that recruited 1,051 Japanese patients with previously diagnosed type 2 diabetes mellitus from September 2009 to September 2014 (median age at recruitment, 61.6 years; range, 19-88 years; 60.9% men). Collaborating physicians from 10 hospitals, who specialized in diabetes mellitus, were responsible for the diagnosis of type 2 diabetes mellitus as defined by the Japan Diabetes Society criteria. Excluded from our current analysis were 233 patients who had missing data on the variables under study. Thus, the final analysis sample consisted of 818 patients. The present study protocol received ethical approval from the institutional review board of the Ehime University Graduate School of Medicine. Written informed consent was obtained from all patients enrolled in the study.

Measurements

Each participant completed a self-administered questionnaire, which collected data on diabetes duration, current smoking habits, current drinking habits, use of antihypertensive medication, use of anti-hyperlipidemic medication, height, and weight. Each patient's body mass index (BMI) was calculated as their weight (kg) divided by the square of their height (m^2). Current smoking was defined as positive if a study subject reported smoking at least one cigarette per day. Current drinking was defined as present when subjects reported drinking habitually. Blood pressure was measured with a cuff in the sitting position, after a rest period of greater than 5 minutes. Hypertension was defined as positive if systolic blood pressure was >140 mmHg, diastolic blood pressure was >90 mmHg, or both, or if the patient had received anti-hypertensive medication. Dyslipidemia was defined as positive if the serum total cholesterol concentration was >220 mg/dL (5.69 mmol/L), triglyceride concentration was >150 mg/dL (1.69 mmol/L), high-density lipoprotein cholesterol concentration was <40 mg/dL (1.03 mmol/L), or if the patients were already being treated with lipid-lowering agents.

Assessing macrovascular complications

Stroke and ischemic heart disease were defined based on the self-administered questionnaires, medical records, and/or admission data. Peripheral artery diseases were defined based on self-administered questionnaires, ankle brachial index (ABI) ≤0.9, medical records, and/or admission data. ABI values were measured using the Vasera VS-100 (Fukuda Denshi Co., LTD., Tokyo, Japan) and/or BP-203 RPEIII (Omron Co., LTD., Kyoto, Japan).

Assessing type 2 diabetes mellitus complications

Microvascular complications of type 2 diabetes mellitus included retinopathy, nephropathy, and neuropathy. Retinopathy was diagnosed based on the presence of hemorrhaging, microaneurysm, soft and hard exudates, areas of neovascularization, or laser coagulation scars in at least one eye. A diagnosis was conducted using florescence fundoscopy on dilated pupils within three months of recruitment. Several ophthalmology specialists were responsible for evaluating the fundus of all participants. The estimated glomerular filtration rate (eGFR) was calculated using serum creatinine (Cr): $194 \times$ serum $Cr^{-1.094} \times age^{-0.287}$ (if female $\times$ 0.739) (20). Diabetic nephropathy was defined as positive when the urine albumin-to-creatinine ratio was ≥30 mg/g creatinine and/or eGFR was <30 mL/min/1.73 m^2 (21). Diabetic peripheral neuropathy was diagnosed if the patients showed two or more of the following three characteristics: neuropathic symptoms (numbness, pain, paresthesia, or decreased sensation in the tips of the toes and bottoms of the feet), an absence of the Achilles reflex, or abnormal vibration perception threshold scores assessed with a 128-Hz tuning fork (22).

Assessing urgency incontinence

Study subjects were considered to have urgency incontinence if they answered "*once a week or more*" to the question: "*Within one week, how often do you leak urine because you cannot defer the sudden desire to urinate?*"

Table 1. Characteristics of the 818 Study Participants.

Variable	n (%)
Age, years, mean ± SD	61.9 ± 11.1
Male gender (%)	514 (62.8)
BMI, kg/m^2, mean ± SD	25.2 ± 4.8
HbA1c, %, mean ± SD	7.89 ± 1.85
Insulin therapy (%)	217 (26.5)
Duration of T2DM, years, mean ± SD	11.1 ± 10.2
Current drinking (%)	333 (40.7)
Current smoking (%)	148 (18.1)
Hypertension (%)	574 (70.2)
Hyperlipidemia (%)	618 (75.6)
Microvascular complications	
Diabetic peripheral neuropathy (%)	505 (61.7)
Diabetic retinopathy (%)	239 (29.2)
Diabetic nephropathy (%)	270 (33.0)
Macrovascular complications	
Stroke (%)	56 (6.9)
Ischemic heart disease (%)	89 (10.9)
Peripheral arterial disease (%)	59 (7.2)
Urgency incontinence (%)	75 (9.2)

BMI: body mass index, T2DM: type 2 diabetes mellitus

Statistical analysis

Estimations of crude odds ratios (ORs) and their 95% confidence intervals (CIs) were performed using logistical regression analyses for urgency incontinence in relation to macrovascular complications. Sex, age, body mass index, duration of type 2 diabetes, current smoking, current drinking, hypertension, dyslipidemia, glycated hemoglobin, diabetic nephropathy, diabetic retinopathy, and diabetic peripheral neuropathy were selected as potential confounding factors. Multiple regression logistic analyses were used to adjust for potential confounding factors. All statistical analyses were performed using the SAS software package version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Among the 818 patients with type 2 diabetes mellitus, the mean age of the study participants was 61.9 years, and the prevalence of urgency incontinence was 9.2%. The prevalence values of stroke, ischemic heart disease, and peripheral artery disease were 6.9%, 10.9%, and 7.2%, respectively (Table 1). Table 2 shows crude and adjusted ORs and 95% CIs for the prevalence of urgency incontinence in relation to macrovascular complications. The prevalence of urgency incontinence among diabetic patients with stroke was 17.9%, while the prevalence of urgency incontinence among those without stroke was 8.5%. In the crude analysis, stroke and peripheral arterial disease were positively associated with urgency incontinence. After adjustment for sex, age, BMI, duration of type 2 diabetes, current smoking, current drinking, hypertension, dyslipidemia, glycated hemoglobin, diabetic nephropathy, diabetic retinopathy, and diabetic peripheral

neuropathy, stroke was independently positively associated with urgency incontinence: the adjusted OR was 2.34 (95% CI: 1.03-4.95). The association between peripheral arterial disease and urgency incontinence disappeared. No evident relationships were found between ischemic heart disease or peripheral artery disease and urgency incontinence.

Discussion

To our knowledge, this is the first study to show that stroke was found to be independently positively associated with urgency incontinence among Japanese patients with type 2 diabetes mellitus.

In an Italian study of 80 patients with ischemic cerebrovascular disease, the prevalence of urgency incontinence was 32.5% (13). In a Japanese study of 500 patients with chronic-phase stroke, the prevalence of urgency incontinence was 28.2% (14). In a Norwegian study of 315 patients with acute stroke, the cumulative incidence of urgency incontinence was 13.9% within three months from the onset of stroke (15). In the present study, the prevalence of urgency incontinence among diabetic subjects with stroke was 15.7%.

Among patients with type 2 diabetes mellitus, the association between macrovascular complications and urgency incontinence is still unclear. In a Taiwanese study of 279 patients with type 2 diabetes mellitus, the association between stroke history and urgency incontinence was not significant (OR 2.55, p=0.082) (8). In a US study of 2,994 women with type 2 diabetes mellitus, the prevalence of stroke among diabetic patients with weekly urinary incontinence was similar to that of patients with less than weekly urinary incontinence or no incontinence (19). These findings are inconsistent with the present results. The discrepancies among studies may be explained, at least in part, by differences in the sample size; characteristics such as age, sex, race, BMI, and prevalence of stroke; and the confounding factors considered. Stroke may directly injure neuro-micturition pathways (23). Dysfunction of the prefrontal cortex or limbic system may cause urgency incontinence: the limbic system prevents urgency incontinence via suppression of unwanted emotional reactions, and activation of the prefrontal cortex is important for maintaining voluntary control of voiding (24). Several pieces of evidence exist regarding the association between imaging findings in the brain and urgency incontinence. In a US study of 99 elderly adults, the volume of white matter change in the brain was positively associated with urgency incontinence (25). In the previously cited Japanese study of 500 patients with chronic-phase stroke, the grading of deep white matter hyperintensity was positively associated with urgency incontinence (14). In a US study of 97 elderly subjects, the presence of white matter change in the right frontal and right inferior frontal regions predicted incontinence severity (26). In a Japanese study of 63 elderly subjects, the association between white matter lesions on magnetic resonance imaging and severe urgency inconti-

Table 2. **Crude and Adjusted Odds Ratios and 95% Confidence Intervals for Urgency Incontinence in Relation to Macrovascular Complications.**

Variable	Prevalence (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Stroke			
No	65/762 (8.5)	1.00	1.00
Yes	10/56 (17.9)	2.33 (1.07–4.66)	2.34 (1.03–4.95)
Ischemic heart disease			
No	68/729 (9.3)	1.00	1.00
Yes	7/89 (7.9)	0.83 (0.34–1.75)	0.65 (0.26–1.42)
Peripheral arterial disease			
No	65/759 (8.6)	1.00	1.00
Yes	10/59 (17.0)	2.18 (1.001–4.34)	1.78 (0.78–3.74)

Odds ratios were adjusted for sex, age, body mass index, duration of type 2 diabetes, current smoking, current drinking, hypertension, dyslipidemia, glycated hemoglobin, diabetic retinopathy, diabetic nephropathy, and diabetic peripheral neuropathy. OR: odds ratio, CI: confidence interval

nence was significant (27). The association between ischemic heart disease and urgency incontinence is still unclear.

Our results are consistent with those of a Taiwanese study of 279 patients with type 2 diabetes mellitus (8) and of a US study of 2,994 women with type 2 diabetes mellitus showing no association between ischemic heart disease and urgency incontinence (19). To our knowledge, no evidence exists regarding the association between peripheral artery disease and urgency incontinence.

Several limitations associated with the present study warrant mention. First, this was a cross-sectional study; therefore, we cannot conclude that there is a causal relationship between stroke and urgency incontinence. Second, we were unable to diagnose benign prostate hyperplasia because we were unable to measure the size of the prostate and post-void residual volume. Third, data on brain imaging in the present study were not available. Fourth, data on history of hysterectomy or prostatectomy were not available in the present study. Fifth, the definition of stroke was based on the self-administered questionnaires, medical records, and/or admission data. We could not separate the type of stroke. Similarly, the definition of ischemic heart diseases was based on the self-administered questionnaires, medical records, and/or admission. We might have underestimated the prevalence of ischemic heart disease. As the prevalence values of asymptomatic myocardial ischemia were 34-42% among patients with diabetes (28). The misclassification regarding stroke and ischemic heart disease might affect the association between macrovascular complications and urgency incontinence. Sixth, we did not assess the autonomic nervous function. As diabetic autonomic neuropathy may cause urgency incontinence. Finally, all data on urgency incontinence were self-reported. However, previous studies have established the reliability and validity of self-reported urinary incontinence (3).

In conclusion, stroke, but not ischemic heart diseases or peripheral artery disease, was found to be significantly positively associated with urgency incontinence in Japanese patients with type 2 diabetes mellitus.

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