

Truncal Pruritus of Unknown Origin May Be a Symptom of Diabetic Polyneuropathy

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OBJECTIVE — Our goal was to ascertain the prevalence of pruritus in diabetic and nondiabetic subjects and the relevance of symptoms, signs, and nerve functions of diabetic polyneuropathy (DPN) of pruritus.

RESEARCH DESIGN AND METHODS — A large-scale survey of 2,656 diabetic outpatients and 499 nondiabetic subjects was performed. In diabetic subjects, the relationship between pruritus and age, sex, diabetic duration, A1C, Achilles tendon reflex (ATR), and abnormal sensation in legs was evaluated. In 105 diabetic subjects, nerve conduction studies, quantitative vibratory threshold (QVT), heart rate variability, and a fall of systolic blood pressure at a head-up tilt test (Δ BP) were performed, and the relationships between pruritus and nerve functions were evaluated.

RESULTS — Although the prevalence of truncal pruritus of unknown origin (TPUO) in diabetic subjects was significantly higher than that in age-matched nondiabetic subjects (11.3 vs. 2.9%, $P = 0.0001$), the prevalence of other pruritus was not different between the two groups. Multiple logistic regression analysis revealed that abnormal sensation and ATR areflexia were independent risk factors for TPUO in age, sex, duration of diabetes, and A1C. Δ BP in diabetic subjects with TPUO was significantly impaired compared with that in those without TPUO. Larger Δ BP was identified as a significant risk factor of TPUO independent of other nerve dysfunctions by multiple logistic regression analysis.

CONCLUSIONS — TPUO is significantly more frequent in diabetic than in nondiabetic individuals. TPUO is significantly associated with symptoms and signs of DPN, including impaired blood pressure response in a head-up tilt test. TPUO, therefore, might be a newly recognized symptom of DPN.

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We have an unproven idea that diabetic patients complain of pruritus more frequently than the general population does. A textbook of diabetology also describes this uncertainty as follows, “The frequency of generalized pruritus in diabetes is unknown; however, many believe that it is increased in diabetes” (1). As an itching sensation is thought to be transmitted by small unmyelinated sensory c-fibers (2), pruritus may reflect some abnormality of the peripheral nerve. In this study, we sought to clarify the prevalence of pruritus in diabetic and nondiabetic subjects and the relevance of

pruritus to the symptoms and signs of diabetic polyneuropathy (DPN) using a large-scale questionnaire survey. Furthermore, the relationships between pruritus and quantitatively assessed nerve functions were also examined.

RESEARCH DESIGN AND METHODS — The study comprised two investigations. The first investigation consisted of a questionnaire to assess the prevalence of pruritus and its relevance to neuropathic symptoms and signs. The second investigation was performed using quantitative neurological function

tests to determine what kind of nerve dysfunction is related to pruritus.

Prevalence of pruritus and its relevance to symptoms and signs of DPN

A large-scale survey of diabetic subjects was performed with the cooperation of the physicians of the Wakayama medical association. Between November 2006 and August 2007, questionnaires were sent to 48 medical practitioners and hospital physicians in Wakayama Prefecture, Japan. The questionnaires consisted of patient- and physician-completed portions, and both were returned to our department for analysis. A survey of nondiabetic subjects was performed with the cooperation of the health examination division of Wakayama Rosai Hospital. Between September 2006 and August 2007, the same questionnaires were used for nondiabetic subjects who had received annual medical examinations at their workplace. Participation was voluntary, and data that could identify individuals was not collected.

Items in questionnaire

Age (expressed as decade), sex, height, and body weight were obtained from all participants. Duration of diabetes, most recent A1C measurement, and Achilles tendon reflex (ATR) were provided by the physicians treating the diabetic participants. Subjective sensory symptoms were examined in diabetic and nondiabetic participants using four criteria: “numbness in toes and soles,” “dysesthesia in toes and soles,” “pain in feet,” and “painful leg cramp.” In this study, “numbness” was defined as an abnormal sensation with the absence of stimulation, and “dysesthesia” was defined as an abnormal sensation produced by ordinary stimuli. Final questions to diabetic and nondiabetic subjects concerned “pruritus” and its distribution in the body and the suspected cause of itching. Prevalence of pruritus and abnormal sensations were compared between diabetic and nondiabetic participants. The relations between pruritus and neurological symptoms, signs, and other clinical factors described above were also evaluated in diabetic participants.

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See accompanying editorial, p. 210.

Nerve dysfunctions associated with pruritus

A total of 105 diabetic subjects (58 men and 47 women) aged <70 years who received medical interviews and quantitative nerve function tests were enrolled in this study. Forty-four patients were outpatients and 61 were inpatients of the Wakayama Medical University Hospital. Numbers of patients receiving insulin therapy with or without additional oral agents, oral hypoglycemic agents, and only diet/exercise therapy were 73, 29, and 3, respectively. Their mean \pm SD age, duration of diabetes, BMI, and recent A1C were 55.7 ± 9.6 years, 11.6 ± 8.8 years, 24.8 ± 4.3 kg/m², and $8.6 \pm 2.1\%$, respectively. Prevalence of proteinuria (intermittent and persistent proteinuria) and retinopathy (simple proliferative and proliferative retinopathy) was 29.1 and 45.9%, respectively. Subjects with systolic blood pressure >130 mmHg and/or diastolic blood pressure >85 mmHg or those receiving antihypertensive treatment were defined as hypertensive. Subjects with total cholesterol >5.69 mmol/l (220 mg/dl) and/or triglycerides >1.70 mmol/l (150 mg/dl) or those receiving antihyperlipidemia medication were defined as hyperlipidemic. The prevalence of hypertension and hyperlipidemia was 46.7 and 48.5%, respectively.

Nerve function tests

Four objective and quantitative tests (nerve conduction study, quantitative vibratory perception test, head-up tilt test, and heart rate variability test) were performed to evaluate the relationships between pruritus and various somatic and autonomic nerve functions. All examinations were conducted in a temperature-controlled room at 25°C. Methods for each examination are described only briefly in the following because they were described in our previous report (3).

Nerve conduction study. Motor nerve conduction velocity (MCV) between the wrist and elbow, compound muscle action potential (CMAP) of the ulnar nerve, sensory nerve conduction velocity (SCV) between the wrist and elbow, and sensory nerve action potential (SNAP) of the median nerve were measured using standard methods. Examinations were performed bilaterally, and an average value was used for analysis.

Quantitative vibratory perception threshold test. The quantitative vibratory perception threshold (QVT) at 125

Table 1—Comparison of the prevalence of neurological symptoms, pruritus, and subclassified pruritus between age-matched diabetic and nondiabetic subjects and the relevance of TPUO with the signs and symptoms of DPN

	Influence of diabetes		Influence of TPUO	
	Nondiabetic	Diabetic	TPUO(−)	TPUO(+)
n	391	391	2,172	316
Sex (male/female)	239/144	229/162	1,186/943	160/151
Age (years)	NE	NC	60.2 \pm 12.0	63.1 \pm 12.3*
Duration (years)	NE	8.4 \pm 7.1	10.9 \pm 8.5	13.5 \pm 9.5*
BMI (kg/m ²)	22.5 \pm 3.3	25.1 \pm 4.8†	24.0 \pm 4.3	24.0 \pm 5.0
A1C (%)	NE	7.3 \pm 1.5	7.0 \pm 1.4	7.1 \pm 1.2
Numbness in toes and soles (%)	8.0	27.5†	27.6	41.3*
Dysesthesia in toes and soles (%)	4.4	16.6†	17.9	28.6*
Pain in feet (%)	4.4	9.6‡	8.7	16.6*
Painful leg cramp (%)	36.1	31.8	34.0	47.4*
Bilateral areflexia in ATR (%)	NE	16.7	18.1	34.3*
Pruritus (%)	14.6	26.3†	14.9	100*
TPUO (%)	2.9	11.3†	0	100*
Head and neck pruritus of unknown origin (%)	0.8	0	NC	NC
Leg pruritus of unknown origin (%)	1.1	1.6	NC	NC
Pruritus due to dermatitis (%)	4.1	4.1	NC	NC
Pruritus due to athlete's foot (%)	1.5	3.8‡	NC	NC

Data are means \pm SD or %. Statistical analyses were made by unpaired *t* test and χ^2 test. **P* < 0.001 vs. TPUO(−). †*P* < 0.001 vs. nondiabetic subjects. ‡*P* < 0.05 vs. nondiabetic subjects. NC, not calculated; NE, not examined.

Hz was semiquantitatively assessed at the tips of big toes using a vibratory sensation meter (AU02A; RION, Tokyo, Japan).

Autonomic nerve function tests (head-up tilt test and heart rate variability test). Sympathetic vasomotor function was evaluated by a head-up tilt test. Orthostasis-induced decreases in brachial systolic blood pressure after passive standing in a 70° head-up position (Δ BP) were examined. Parasympathetic cardiovascular function was evaluated by the heart rate variability test. Coefficients of variation of RR intervals on the electrocardiogram during deep breathing (CV-DB) were determined.

Comparisons between pruritus and neurological functions

Actual data from neurological examinations and the prevalence of impaired values were compared between patients with and without pruritus. Because nerve conduction data (MCV, SCV, CMAP, and SNAP) and vibratory thresholds (QVT) were distributed normally, values exceeding the range of means \pm 2 SD of the healthy subjects in our institute (4) were judged as impaired. CV-DB results that were converted into logarithms were dis-

tributed normally, and data that were more than the means $-$ 2 SD of logarithms of healthy subjects (5) was considered impaired. Because Δ BP values in the head-up tilt test were not distributed normally, decisions regarding impairment were judged according to the criteria of the American Autonomic Society (6): a decrease in upright systolic blood pressure of at least 20 mmHg.

Statistical analysis

Data are expressed as means \pm SD. Statistical analyses were performed by χ^2 test, unpaired *t* test, and multiple logistic regression analysis using statistical software (Statview-J5.0TM; Hulinks, Tokyo, Japan). *P* < 0.05 was considered significant.

RESULTS

Prevalence of pruritus and its relevance to symptoms and signs of DPN

Questionnaires were collected from a total of 3,042 diabetic patients, with an average of 64 per clinic or hospital. The data for 386 diabetic subjects who did not reply to the questions concerning pruritus were excluded from analysis, and the data

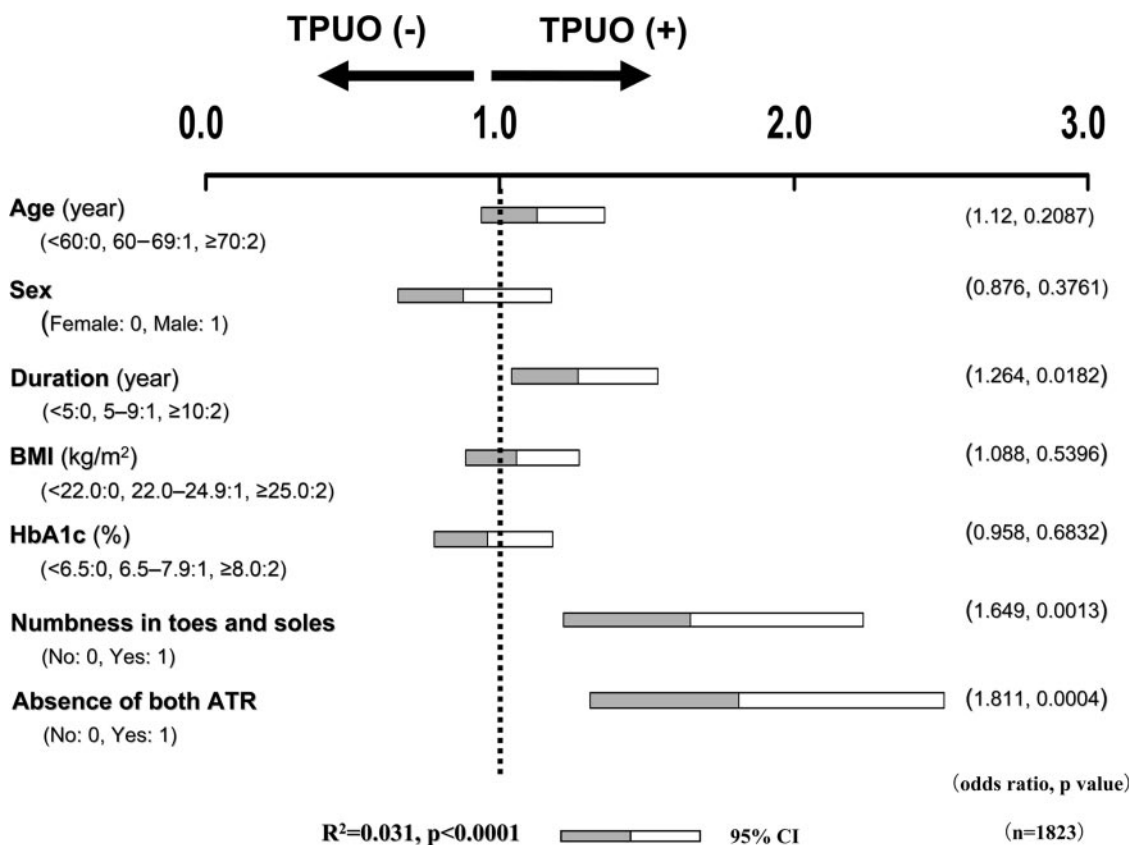


Figure 1—Multiple logistic regression analysis with TPUO as an independent variable revealed that dysesthesia, ATR areflexia, and duration were significant risk factors for TPUO with odds ratios of 1.649, 1.811, and 1.264, respectively. Horizontal columns show the 95% CIs of each independent factor.

of the remaining 2,656 diabetic subjects (1,440 men, 1,161 women, and 55 not specified) were included. Their ages were distributed from 20 to 80 years. Half of the subjects included were aged 60 or 70 years. Average \pm SD duration of diabetes was 11.4 ± 8.8 years, and A1C was $7.05 \pm 1.34\%$. Questionnaires were collected from 499 nondiabetic subjects (307 men, 170 women, and 22 not specified). Although their age distribution was also from 20 to 80 years, half of those included were aged 40 and 50 years and were significantly younger than the diabetic subjects.

Prevalence of pruritus and symptoms and signs of DPN

Because of the significant difference in the age distribution between diabetic and nondiabetic subjects, the prevalence of pruritus, abnormal sensations, and painful leg cramp was calculated in age-matched diabetic and nondiabetic samples and compared between the two groups. The same numbers of diabetic and nondiabetic subjects for the analysis were randomly selected for each decade

of age using a stratified sampling method. Therefore, the data from 391 participants from each group (aged 20–29 years, $n = 9$; 30–39 years, $n = 62$; 40–49 years, $n = 121$; 50–59 years, $n = 122$; 60–69 years, $n = 57$; 70–79 years, $n = 16$; and ≥ 80 years, $n = 4$) were evaluated. Pruritus was subclassified by itching site and cause into five categories: truncal pruritus of unknown origin (TPUO), head and neck pruritus of unknown origin, pruritus caused by dermatitis, and pruritus due to athlete’s foot. Frequency was also examined.

The prevalence of numbness in toes and soles, dysesthesia in toes and soles, pain in feet, and pruritus in diabetic subjects was significantly higher than that in nondiabetic subjects. The prevalence of painful leg cramps was not different between the two groups. The prevalence of total pruritus in diabetic subjects was significantly higher than that in nondiabetic subjects (26.3 vs. 14.6%, $P < 0.001$). In subclassified pruritus, TPUO occurred more frequently in diabetic than in nondiabetic subjects (11.3 vs. 2.9%, $P < 0.001$), and the prevalence of pruritus

due to athlete’s foot was higher than that in nondiabetic subjects ($P = 0.047$). However, the prevalence of pruritus in other sites and that due to dermatitis was not different between the two groups. Therefore, the characteristic pruritus in diabetic subjects seemed to be TPUO. TPUO was seen in 12.7% (316 of 2,488) of the total diabetes group. In the patients with DPN judged by bilateral ATR areflexia, the prevalence of TPUO was 20.5% (84 of 410). In the asymptomatic patients with DPN who complained of no abnormal sensation, TPUO was observed in 15.2% (31 of 204). There was no significant sex difference in the prevalence of TPOU in diabetic and nondiabetic subjects.

Relevance of pruritus to signs and symptoms of DPN

The age of patients with TPUO and duration of DPN were significantly higher than those of patients without TPUO. The prevalence of all symptoms of DPN (numbness in toes and soles, dysesthesia in toes and soles, pain in feet, and painful leg cramps) and bilateral areflexia of ATR

in the patients with TPUO was significantly higher than those in the patients without TPUO (Table 1). Thus, multiple logistic regression analysis was performed to confirm the risk factors for TPUO. Seven clinical factors were correlated into scores (age: <60 years, 0, 60–69 years, 1, and ≥ 70 years, 2; sex: female, 0 and male, 1; duration of diabetes: <5 years, 0, 5–9 years, 1, and ≥ 10 years, 2; BMI: <22.0 kg/m², 0, 22.0–24.9 kg/m², 1, and ≥ 25.0 kg/m², 2; A1C: <6.5%, 0, 6.5–7.9%, 1, and $\geq 8.0\%$, 2; dysesthesia: no, 0 and yes, 1; and absence of both ATR: no, 0 and yes, 1) and adopted as independent variables. As a result, numbness in toes and soles, ATR areflexia, and longer duration of diabetes were identified as the independent risk factors of TPUO (Fig. 1).

Nerve dysfunctions associated with pruritus

The prevalence of total pruritus and TPUO in 105 diabetic patients was 32 and 19%, respectively. There was no significant difference in all clinical background data between TPUO(+) and TPUO(–) groups (Table 2). In the comparison of actual neurological data, only Δ BP in the TPUO(+) group was significantly higher than that in the TPUO(–) group. In the comparison of prevalence of impaired nerve functions, impaired Δ BP and CV-DB occurred in a significantly higher frequency in the TPUO(+) group than in the TPUO(–) group (Table 2). Multiple logistic regression analysis was also performed to examine neurological function, which is closely related to TPUO. Seven clinical and neurological factors were converted into scores (age: <50 years, 0, 50–59 years, 1, and ≥ 60 years, 2; sex: female, 0 and male, 1; duration of diabetes, <5 years, 0; 5–9 years, 1, and ≥ 10 years, 2; impaired SCV: no, 0 and yes, 1; impaired CV-DB: no, 0 and yes, 1; impaired Δ BP: no, 0 and yes, 1; and impaired QVT: no, 0 and yes, 1), and they were adopted as independent variables, respectively. As a result, impaired Δ BP was identified as a significant risk factor of TPUO (Fig. 2).

CONCLUSIONS— The first investigation (a large-scale survey) revealed the following three findings: 1) the prevalence of pruritus, especially TPUO, in diabetic patients was significantly higher than that in age-matched nondiabetic subjects; 2) $\sim 12\%$ of diabetic outpatients of general physicians complained of TPUO, and this prevalence was four times

Table 2—Clinical characteristics and neurological data of diabetic patients divided into two groups based on TPUO

	TPUO(+)	TPUO(–)	P
n (%)	20 (19.0)	85 (81.0)	
Age (year)	58.0 \pm 11.3 (20)	55.2 \pm 9.1 (85)	0.238
Sex (male/female)	11/94	7/38	0.981
BMI (kg/m ²)	24.2 \pm 4.5 (19)	24.9 \pm 4.3 (83)	0.487
A1C (%)	8.5 \pm 1.8 (18)	8.7 \pm 2.1 (83)	0.774
Duration of diabetes (years)	12.8 \pm 8.2 (20)	11.4 \pm 8.9 (85)	0.534
Proteinuria (more than intermittent proteinuria) (%)	8/20 (40.0)	22/83 (26.5)	0.233
Retinopathy (more than SDR) (%)	12/20 (60.0)	32/76 (42.1)	0.153
Dyslipidemia (%)	10/20 (50.0)	41/85 (48.2)	0.887
Hypertension (%)	11/20 (55.0)	38/85 (44.7)	0.406
MCV (m/s)	49.9 \pm 5.2 (20)	50.9 \pm 5.1 (84)	0.396
Prevalence of impaired MCV (%)	8/20 (40.0)	28/84 (33.3)	0.573
CMAP (mV)	5.92 \pm 1.2 (19)	6.35 \pm 2.1 (84)	0.384
Prevalence of impaired CMAP (%)	5/20 (25.0)	16/83 (19.3)	0.569
SCV (m/s)	55.4 \pm 5.5 (19)	56.6 \pm 4.9 (78)	0.355
Prevalence of impaired SCV (%)	11/19 (55.0)	32/81 (39.5)	0.210
SNAP (μ V)	24.8 \pm 16.4 (20)	25.3 \pm 18.7 (79)	0.909
Prevalence of impaired SNAP (%)	4/20 (20.0)	16/80 (20.0)	0.999
QVT (dB)	21.2 \pm 9.5 (20)	19.4 \pm 9.4 (85)	0.376
Prevalence of impaired QVT (%)	9/20 (45.0)	25/85 (29.4)	0.180
Δ BP (mmHg)	19.2 \pm 15.8 (20)	10.4 \pm 15.2 (84)	0.014
Prevalence of impaired Δ BP (%)	13/20 (65.0)	17/84 (20.2)	<0.001
CV-DB (%)	4.29 \pm 3.56 (19)	4.91 \pm 3.99 (83)	0.538
Prevalence of impaired CV-DB (%)	10/20 (50.0)	23/85 (27.1)	0.047

Data are means \pm SD (n) unless indicated otherwise. n = 105. Statistical analyses were made by unpaired t test and χ^2 test.

that of nondiabetic subjects; and 3) bilateral sensory symptoms in the feet and ATR areflexia occurred in a significantly higher frequency in diabetic subjects with TPUO than in diabetic subjects without TPUO, and numbness in toes and soles and ATR areflexia were identified as significant risk factors of TPUO by multivariate analysis. From these findings, TPUO was suspected of being a complication of diabetes, and DPN was suspected of being a possible origin of TPUO.

The second investigation, using several quantitative nerve function tests, revealed the following two findings: 1) impaired blood pressure response to a head-up tilt test and impaired heart rate variability during deep breathing occurred in a significantly higher frequency in TPUO(+) diabetic subjects than in TPUO(–) diabetic subjects; and 2) only impaired blood pressure responses to head-up tilt were identified as significant risk factors of TPUO by multivariate analysis. These findings suggested that autonomic nerve dysfunction, especially sympathetic nerve dysfunction, might be the most plausible candidate for the origin of TPUO.

Many clinicians may have an impression that pruritus is more frequent in diabetic patients than in nondiabetic individuals. Although pruritus in the feet due to tinea pedis and pudendal pruritus due to candidiasis have been reported to be highly prevalent in diabetic patients (7,8), there is little epidemiological evidence of pruritus with diabetes. In this study, we clearly demonstrated the higher prevalence of TPUO in diabetic than in nondiabetic subjects, and TPUO was observed in $\sim 12\%$ of general diabetic outpatients in a frequency similar to that of the symptom of “pain in feet.” On the other hand, the prevalence of pruritus in the head and neck or legs and pruritus caused by dermatitis were not different between diabetic and nondiabetic subjects.

The etiology of TPUO has not been elucidated. Our survey showed that TPUO was significantly associated with sensory disturbance in the legs and areflexia of ATR. These findings were thought to be characteristic for DPN (9). Moreover, detailed neurological evaluation indicated that an impaired blood pressure response to a head-up tilt test

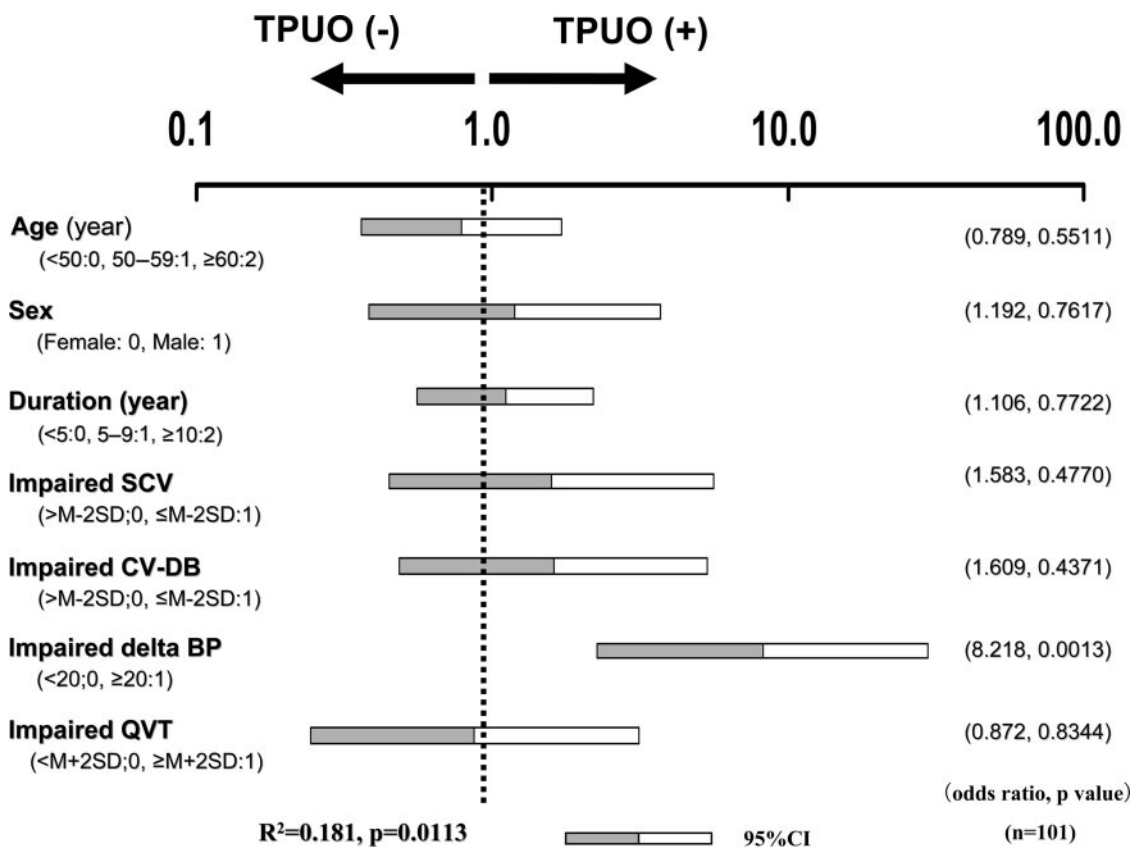


Figure 2—Multiple logistic regression analysis clarified that the only significant risk factor for TPUO was the impairment of blood pressure response to a head-up tilt test, and the odds ratio was 8.218. Horizontal columns show the 95% CIs.

was most closely associated with TPUO. This impairment reflected the deterioration of sympathetic nerve function (10). We therefore think that TPUO is a symptom of DPN, especially in sympathetic nerve dysfunction. Two possible mechanisms are proposed as an etiological theory of TPUO. First, because sympathetic nerve function includes the sudomotor function (11), sympathetic dysfunction caused hypohydrosis and resulted in dry skin. It is well known that pruritus occurs frequently with dry skin. In dry skin the barrier function of the skin is decreased, and the threshold for itching is lowered; therefore, TPOU is elicited. In fact, increased numbers of mast cells and histamine content have been reported in experimental dry skin in mice (12). A second possibility is that the damage to sensory c-fibers by DPN causes pruritus directly. Superficial skin pain is considered to be caused by abnormal firing of the pain nerve fiber in patients with DPN (13). Similarly, abnormal firing of the nerve fiber in pruritus may induce TPOU. In fact, hyperplasia of the c-fibers in the epidermis has been reported in dermatitis with strong pruritus (14). The unmyeli-

nated c-fiber that transmits pruritus is a fiber similar to the sympathetic nerve ending in the skin. Thus, a significant association between TPUO and orthostatic intolerance seems to be reasonable. Both of the two etiological factors, the dry skin due to sudomotor hypofunction and direct nerve fiber damage by DPN, may be involved in TPUO. To determine the etiology of TPOU accurately, a skin biopsy and nerve fiber staining with antiprotein gene product 9.5 antibody in patients with TPUO will be necessary (15). Although discussion of treatment of diabetic truncal pruritus is beyond the scope of this study, two kinds of drugs might be useful. One is an antihistaminic agent that may be effective for mild pruritus due to dry skin and the other is a neurotropic agent such as gabapentin that may be effective for severe TPOU such as uremic pruritus (16).

From the viewpoint of clinical practice, TPOU seems to be useful for not misdiagnosing DPN. Some investigators have reported that ~50% of patients with DPN did not complain of sensory disturbance in their legs, which is a symptom typical of DPN (17). It is therefore necessary to

do a neurological examination such as vibratory perception threshold and ATR for the diagnosis of DPN. However, it is not feasible to examine ATR and vibratory perception threshold in all diabetic outpatients because of the remarkable increase in the diabetic population. Consequently, it is important to be familiar with the symptoms of DPN other than the sensory disturbance of the legs. By recognizing TPOU as a subjective symptom of DPN, it may be possible to reduce the misdiagnosis of DPN. Indeed, 15% of asymptomatic patients with DPN, who showed bilateral ATR areflexia and no abnormal sensations, complained of TPOU in our questionnaire survey.

In summary, the prevalence of TPOU in diabetic patients is significantly higher than that in nondiabetic individuals, and TPOU is significantly associated with symptoms and signs of DPN, one of which is orthostatic hypotension. TPOU, therefore, may be a newly recognized symptom of DPN.

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