Numbness and paresthesia in bilateral toes and soles, and disproportional sweating restricted to face and trunk are suitable symptoms useful for the diagnosis of diabetic symmetric polyneuropathy

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ABSTRACT

Aims/Introduction: In order to diagnose diabetic symmetric polyneuropathy (DSPN) more simply and accurately, we identified symptoms that correlated with neurological functions and existed more frequently in diabetic than non-diabetic subjects.

Materials and Methods: The relationships between 10 symptoms (numbness or paresthesia in toe and sole, numbness in hand, pain in foot or hand, coldness in legs, painful leg cramp, dizziness on standing, sweating restricted to face/trunk and frequent constipation/diarrhea) and clinical background, defined as DSPN and cardiovascular autonomic neuropathy (CAN) by the criteria proposed in the statement of the American Diabetes Association, and seven quantitative nerve function data were evaluated in 593 diabetic patients in Wakayama Medical University Hospital (WMUH). Furthermore, the prevalence of various symptoms was examined by three questionnaires: a WMUH survey (999 diabetic outpatients), a Nationwide survey (1524 male diabetic outpatients under a primary-care physician) and a Control survey (501 non-diabetic subjects).

Results: Bilateral 'numbness in toe and sole', 'paresthesia in toe and sole', 'pain in foot' and 'sweating restricted to face/trunk' were significantly associated with diabetes duration, retinopathy, probable and confirmed DSPN, possible and advanced CAN, and all or six nerve functions. Questionnaire surveys clarified that symptoms that are not rare (>15%) and more frequent in diabetic than non-diabetic subjects were bilateral 'numbness in toe and sole', 'paresthesia in toe and sole', 'coldness in legs', 'dizziness on standing' and 'sweating restricted to face/trunk'.

Conclusions: Therefore, bilateral 'numbness in toe and sole', 'paresthesia in toe and sole' and 'sweating restricted to face/trunk' are suitable symptoms useful for the diagnosis of DSPN. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2011.00124.x, 2011)

KEY WORDS: Diabetic symmetric polyneuropathy, Specific symptoms, Prevalence

INTRODUCTION

Diabetic symmetric polyneuropathy (DSPN) is the most common disorder of heterogeneous diabetic neuropathies[1]. Early and accurate diagnosis of DSPN is necessary to prevent its progression through appropriate management. Although recognizing symptoms is important for the initial diagnosis of DSPN, many symptoms in diabetic patients might be caused by something other than DSPN. In the latest statement of the American Diabetes Association (ADA), minimal criteria for DSPN were proposed and diagnostic criteria for cardiovascular autonomic neuropathy (CAN) were also described in the report[2]. Symptoms that are suitable and useful for diagnosis of DSPN should contain the following five features: (i) a close relationship with DSPN and CAN defined in the latest ADA statement[2]; (ii) a significant association with duration of diabetes or diabetic retinopathy; (iii) a close relationship with objective quantitative nerve functions; (iv) a higher prevalence in diabetic patients than in non-diabetic subjects; and (v) common or not rare symptoms. The aim of the present study was to identify the suitable symptoms for the diagnosis of DSPN that satisfied the aforementioned five conditions.

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MATERIALS AND METHODS

Investigation 1. Characteristic Symptoms of DSPN

Subjects and Their Symptoms

A total of 593 Japanese diabetic patients (372 male, 221 female) who received a medical interview, physical examination and multiple quantitative nerve function tests were studied. Of these,

249 were outpatients and 344 were inpatients of the Wakayama Medical University Hospital (WMUH) in Wakayama, Japan. Age, duration of diabetes and recent HbA_{1c} were 53.7 ± 11.2 years (mean ± SD), 12.4 ± 8.9 years and 8.92 ± 2.17%, respectively. The prevalence of simple and preproliferative/proliferative diabetic retinopathy were 15.9 and 39.6%, respectively. The value for HbA_{1c} (%) was estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula HbA_{1c} (%) = HbA_{1c} (Japanese Diabetes Society [JDS]) (%) + 0.4%[3].

Subjective symptoms were assessed using 10 question items: (i) Do you feel 'asleep numbness' in your toe and sole? 'Numbness in toe and sole'; (ii) Do you feel abnormal sensation or dullness in your toe and sole; for example, as a sense of skin adhered with paper? 'Paresthesia in toe and sole'; (iii) Do you feel numbness in your hand? 'Numbness in hand'; (iv) Do you feel pain in your leg and/or foot, particularly below the knee? 'Pain in foot'; (v) Do you feel pain in your hand? 'Pain in hand'; (vi) Do you feel coldness in your both legs? 'Coldness in legs'; (vii) Do you get painful muscle cramps in your leg at least once a month? 'Painful leg cramp'; (viii) Do you feel dizziness on standing? 'Dizziness on standing'; (ix) Do you have increased sweating on your face and/or chest accompanied by decreased sweating on the lower body? 'Sweating restricted to face/trunk'; and (x) Do you have constipation or diarrhea frequently, or alternating? 'Frequent constipation/diarrhea.' All questions were asked to obtain adequate responses. Response options to the initial five questions were 'bilaterally yes', 'right side yes', 'left side yes' and 'no', responses to other questions were 'yes' or 'no'. In the present study, pain includes various painful sensations, such as pricking, stabbing, burning or aching pain, because most Japanese people do not express detailed pain sensations separately in their daily life. Thus, previous Japanese reports on the effect of therapeutic drugs on DSPN have used only 'numbness', 'paresthesia' and 'pain' as sensory symptoms[4,5].

Objective Nerve Functions and Defined DSPN and CAN

Objective nerve functions were evaluated by the Achilles tendon reflex (ATR) in the knee-standing position and quantitative nerve function tests. Quantitative nerve function tests consist of seven tests: motor nerve and F-wave conduction velocity (MCV, FCV) in the ulnar nerve, sensory nerve conduction velocity and action potential (SCV, SNAP) in the median nerve, coefficient of variation of R-R intervals in electrocardiogram during deep breathing (CVdb), a fall in systolic blood pressure during head-up tilt (ΔBP) and 125 Hz quantitative vibratory perception threshold at the big toe (VPT125). Methods of neurological examination were described previously[6].

We judged the nerve function data impaired as follows: MCV, FCV, SCV, SNAP, logarithmic CVdb and VPT125 were distributed normally, values exceeding the range of means ± 2 SD of the age-matched healthy subjects in our institution were judged as impaired. Abnormal ΔBP was defined by the American Autonomic Society criteria[7]. Namely, a fall in systolic blood pressure of more than 20 mmHg and/or a fall in diastolic blood pressure of more than 10 mmHg were judged to be abnormal values.

We then diagnosed DSPN and CAN according to the modified criteria of the latest ADA statement[2]. Subjective symptoms were excluded from the criteria, because the aim of the present study was to examine the reliability of symptoms. Probable DSPN was defined by abnormalities in both the ATR and VPT125. Confirmed DSPN was defined by one or two abnormalities in ATR and VPT125, and nerve conduction abnormalities, which were diagnosed by more than one impaired value in both the ulnar and median nerve. Possible CAN was defined by one or more impairment in CVdb and ΔBP. Advanced CAN was defined by impairment in both the CVdb and ΔBP.

Association of Symptoms With Clinical Background, Defined Types of DSPN and CAN and Objective Nerve Functions

Relationships between the prevalence of symptoms and background data, such as age, duration, HbA_{1c} and retinopathy; and types of DSPN and CAN, including probable DAPN, confirmed DSPN, possible CAN and advanced CAN, were evaluated among the groups divided by these parameters. Actual data of seven nerve function tests were also compared between symptomatic and asymptomatic patients to clarify the relationship between subjective symptoms and objective nerve functions.

Data are expressed as percentage and means ± SD. Statistical analyses were carried out by chi squred-test for a 2 × 2 or 2 × 3 contingency table and ANOVA followed by Scheffé's method as a *post-hoc* test using statistical software (Statview-J5.0; Hulinks, Tokyo, Japan).

Investigation 2. Prevalence of Symptoms in Diabetic and Non-Diabetic Subjects

Research Design and Subjects

In order to clarify the prevalence of symptoms characteristic to DSPN, three self-administered questionnaires were carried out. The first survey was carried out on 999 outpatients (508 male, 467 female, 23 unknown) of the special diabetes clinic in WMUH (WMUH survey). The second survey was carried out as part of a nationwide survey that was mainly aimed at assessing the prevalence of erectile dysfunction[8]; the sample analyzed for the present study was 1524 male diabetic outpatients under primary-care physicians (Nationwide survey). The third survey was taken by 501 non-diabetic individuals (311 male, 168 female, 22 unknown) who underwent corporate health screening examinations (Control survey). Male subjects in the Control survey were analyzed separately (Male Control survey).

Questionnaires

All participants who consented to the questionnaires did so voluntarily. All surveys were filled out at the distribution site of questionnaire forms and the completed forms were returned to researchers. The question items of the WMUH and Control surveys were the same as the aforementioned items in

Table 1 | Prevalence of subjective symptoms and diminished Achilles tendon reflex in 593 diabetic patients by sex, age, duration, diabetic retinopathy and HbA_{1c}

	Sex		Age (years)			Duration (years)			Diabetic retinopathy			HbA_{1c}		
	Female *n* = 221 (%)	Male *n* = 372 (%)	20–49 *n* = 166 (%)	50–59 *n* = 218 (%)	60– *n* = 209 (%)	0–5 *n* = 128 (%)	6–14 *n* = 164 (%)	15– *n* = 172 (%)	No *n* = 205 (%)	Simple *n* = 73 (%)	Prepro-proliferative *n* = 182 (%)	<6.9 *n* = 42 (%)	6.9–8.3 *n* = 120 (%)	8.4– *n* = 285 (%)
Subjective symptoms														
Numbness in toe and sole														
No symptom	163 (73.8)	239 (64.2)	114 (68.7)	150 (68.8)	138 (66.0)	96 (75.0)	118 (72.0)	105 (61.0)	151 (73.7)	50 (68.5)	112 (61.5)	31 (73.8)	79 (65.8)	201 (70.5)
Unilateral	6 (2.7)	20 (5.4)	8 (4.8)	7 (3.2)	11 (5.3)	2 (1.6)	10 (6.1)	10 (5.8)	8 (3.9)	4 (5.5)	7 (3.8)	0 (0)	6 (5.0)	14 (4.9)
Bilateral	52 (23.5)	114 (30.4)	44 (26.5)	61 (28.0)	60 (28.7)	30 (23.4)	36 (21.9)	57 (33.2)*	46 (22.4)	19 (26.0)	63 (34.6)*	11 (26.2)	35 (29.2)	70 (24.6)
Paresthesia in toe and sole														
No symptom	188 (85.1)	292 (78.5)	141 (84.9)	169 (77.5)	170 (81.3)	114 (89.0)	132 (80.5)	124 (72.1)	181 (88.3)	56 (76.7)	130 (71.4)	34 (81.0)	84/(70.0)	236 (82.8)
Unilateral	7 (3.20)	6 (1.6)	2 (1.2)	9 (4.1)	2 (1.0)	2 (1.6)	7 (4.3)	4 (2.3)	3 (1.5)	2 (2.7)	5 (2.7)	1 (2.4)	6 (5.0)	6 (2.1)
Bilateral	26 (11.8)	74 (19.9)#	23 (13.9)	40 (18.4)	37 (17.7)	12 (9.4)	25 (15.2)	44 (25.6)***	21 (10.2)	15 (20.6)	47 (25.8)***	7 (16.6)	30 (25.0)	43 (15.1)
Numbness in hand														
No symptom	182 (82.4)	312 (83.9)	149 (88.0)	178 (81.5)	170 (81.3)	110 (85.9)	137 (83.5)	136 (79.0)	169 (82.4)	61 (83.6)	151 (83.0)	38 (90.5)	92 (76.7)	239 (83.9)
Unilateral	10 (4.5)	19 (5.1)	4 (2.4)	13 (6.0)	12 (5.7)	6 (4.7)	9 (5.5)	12 (7.0)	12 (5.9)	4 (5.5)	9 (4.9)	0 (0)	12 (10.0)	12 (4.2)*
Bilateral	29 (13.1)	41 (11.0)	16 (9.6)	27 (12.4)	27 (12.9)	12 (9.4)	18 (11.0)	24 (14.0)	24 (11.7)	8 (11.0)	22 (12.1)	4 (9.5)	16 (13.3)	34/(11.9)
Pain in foot														
No symptom	134 (87.8)	331 (83.6)	147 (88.5)	181 (83.0)	177 (84.7)	113 (88.3)	142 (86.6)	136 (79.1)	172 (83.9)	67 (91.8)	147 (80.8)	35 (83.3)	102 (85.0)	244 (85.6)
Unilateral	4 (1.8)	9 (2.4)	4 (2.4)	4 (1.8)	5 (2.4)	3 (2.3)	5 (3.0)	3 (1.7)	6 (2.9)	2 (2.7)	3 (1.6)	1 (2.4)	2 (1.7)	7 (2.5)
Bilateral	23 (10.4)	52 (14.0)	15 (9.0)	33 (15.1)	27 (12.9)	12 (9.4)	17 (10.4)	33 (19.2)*	27 (13.2)	4 (5.5)	32 (17.6)*	6 (14.3)	16 (13.3)	34 (11.9)
Pain in hand														
No symptom	216 (97.8)	355 (65.4)	164 (98.8)	206 (94.5)	201 (96.2)	124 (96.9)	159 (87.0)	163 (94.8)	197 (96.1)	68 (93.2)	177/182 (97.3)	41 (97.6)	111 (92.5)	279 (97.9)
Unilateral	3 (1.4)	4 (1.1)	0 (0)	4 (1.8)	3 (1.4)	1 (0.8)	2 (1.2)	3 (3.5)	4 (2.0)	2 (2.7)	0/182 (0)	0 (0)	4 (3.3)	1 (0.4)*
Bilateral	2 (0.9)	13 (3.5)	2 (1.2)	8 (3.7)	5 (2.4)	3 (2.3)	3 (1.8)	6 (3.5)	4 (2.0)	3 (4.1)	5/182 (2.8)	1 (2.4)	5 (4.2)	5 (1.8)
Coldness in legs														
No symptom	51/81 (63.0)	68/95 (71.6)	29/46 (63.0)	45/62 (72.6)	45/68 (66.2)	33/42 (78.6)	27/42 (64.3)	29/49 (59.2)	47/63 (74.6)	14/23 (60.9)	26/43 (60.5)	7/7 (100.0)	16/24 (66.7)	63/95 (66.3)
Symptomatic	30/81 (37.0)	27/95 (28.4)	17/46 (37.0)	17/62 (27.4)	23/68 (33.8)	9/42 (21.4)	15/42 (35.7)	20/49 (40.8)	16/63 (25.4)	9/23 (39.1)	17/43 (39.5)	0/7 (0)	8/24 (33.3)	32/95 (33.3)
Painful leg cramp														
No symptom	147/207 (71.0)	256/347 (73.8)	122/157 (77.7)	151/204 (74.0)	130/193 (67.4)	88/125 (70.4)	117/147 (79.6)	98/154 (63.6)	138/194 (71.1)	45/64 (70.3)	121/164 (73.8)	27/36 (75.0)	76/108 (70.4)	189/265 (71.1)
Symptomatic	60/207 (29.0)	91/347 (26.2)	35/157 (22.3)	53/204 (26.0)	63/193 (32.6)	37/125 (29.6)	30/147 (20.4)	66/154 (36.4)**	56/194 (28.9)	19/64 (29.7)	43/164 (26.2)	9/36 (25.0)	32/108 (29.6)	76/265 (28.9)
Dizziness on standing														
No symptom	166 (75.1)	281/366 (76.8)	122 (73.5)	166/216 (76.9)	159/205 (77.6)	100/127 (78.7)	129/162 (79.6)	126/170 (74.1)	159/205 (77.6)	58/71 (81.7)	135/179 (75.4)	30/41 (73.2)	94/119 (79.0)	214/282 (75.9)
Symptomatic	55 (24.9)	85/366 (23.2)	44 (26.5)	50/216 (23.1)	46/205 (22.4)	27/127 (21.3)	33/162 (20.4)	44/170 (25.9)	46/205 (22.4)	13/71 (18.3)	44/179 (24.6)	11/41 (26.8)	25/119 (21.0)	68/282 (24.1)
Sweating restricted to face/trunk														
No symptom	175/220 (79.5)	289/366 (79.0)	134 (80.7)	166/215 (77.2)	164/205 (80.0)	108 (84.4)	136/162 (83.0)	123/168 (73.2)	173/204 (84.8)	58/71 (81.7)	134/179 (74.9)	35 (83.3)	90/118 (76.3)	230/281 (81.9)
Symptomatic	45/220 (20.5)	77/366 (21.0)	30 (19.3)	49/215 (22.8)	41/205 (20.0)	20 (15.6)	26/162 (16.6)	45/168 (26.8)*	31/204 (15.2)	13/71 (18.3)	45/179 (25.1)*	7 (16.7)	28/118 (23.7)	51/281 (18.1)
Frequent constipation/diarrhea														
No symptom	199/220 (90.5)	319/366 (87.2)	140 (84.3)	196/215 (91.2)	182/205 (88.8)	120 (93.8)	145/162 (89.5)	144/168 (85.7)	188/204 (92.2)	65/71 (91.5)	153/179 (85.5)	37 (88.1)	105/118 (89.0)	253/281 (90.0)
Symptomatic	21/220 (3.6)	47/366 (12.8)	26 (15.7)	19/215 (8.8)	23/205 (11.2)	8 (6.3)	17/162 (10.5)	25/168 (14.3)	16/204 (7.8)	6/71 (8.5)	26/179 (14.5)	5 (11.9)	13/118 (11.0)	28/281 (10.0)
Objective nerve function test														
Achilles tendon reflex														
Normal	67/210 (31.9)	108/355 (30.4)	70/161 (43.5)	60/208 (28.8)	45/196 (23.0)	67/124 (54.0)	40/157 (25.5)	27/165 (16.4)	95/197 (48.2)	23/71 (32.4)	21/176 (11.9)	15/39 (38.5)	29/118 (24.6)	84/272 (30.9)
Unilaterally decreased	2/210 (1.0)	5/355 (1.4)	1/161 (0.6)	2/208 (1.0)	4/196 (2.0)	2/124 (1.6)	1/157 (0.6)	2/165 (1.2)	3/197 (1.5)	1/71 (1.4)	1/176 (0.6)	0/39 (0)	0/118 (0)	5/272 (1.8)
Bilaterally decreased	141/210 (67.1)	242/355 (68.2)	90/161 (55.9)	146/208 (70.2)	147/196 (75.0)***	55/124 (44.4)	116/157 (73.9)	136/165 (82.4)***	99/197 (50.3)	47/71 (66.2)	154/176 (87.5)***	24/39 (61.5)	88/118 (75.4)	183/272 (67.3)

Relationships between symptoms or Achilles tendon reflex and background data were evaluated. Unilateral and bilateral symptoms were separately analyzed. #$P < 0.05$ analyzed by chi-squared test for 2 × 2 contingency table. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ analyzed by chi-squared test for 2 × 3 contingency table. The value for HbA_{1c} (%) was estimated as a NGSP equivalent value (%) calculated by the formula HbA_{1c} (%) = HbA_{1c} (JDS) (%) + 0.4%.

Table 2 | Prevalence of subjective symptoms and diminished Achilles tendon reflex in 593 diabetic patients by defined diabetic symmetric polyneuropathy and cardiovascular autonomic neuropathy

	Probable DSPN		Confirmed DSPN		Possible CAN		Advanced CAN	
	No *n* = 367 (%)	Yes *n* = 214 (%)	No *n* = 377 (%)	Yes *n* = 162 (%)	No *n* = 270 (%)	Yes *n* = 297 (%)	No *n* = 499 (%)	Yes *n* = 75 (%)
Subjective symptoms								
Numbness in toe and sole								
No symptom	289 (78.8)	108 (50.5)	287 (76.1)	76 (46.9)	209 (77.4)	174 (58.6)	351 (70.4)	36 (48.0)
Unilateral	13 (3.5)	11 (5.1)	20 (5.3)	4 (2.5)	16 (5.9)	10 (3.4)	26 (5.2)	0 (0)*
Bilateral	65 (17.7)	95 (44.4)***	70 (18.6)	82 (50.6)***	45 (16.7)	113 (38.0)***	122 (24.4)	39 (52.0)***
Paresthesia in toe and sole								
No symptom	324 (88.2)	146 (68.2)	331 (87.8)	105 (64.8)	239 (88.5)	221 (74.4)	415 (83.2)	50 (66.7)
Unilateral	9 (2.5)	4 (1.9)	11 (2.9)	1 (0.6)	7 (2.6)	6 (2.0)	12 (2.4)	1 (1.3)
Bilateral	34 (9.3)	64 (29.9)***	35 (9.3)	56 (34.6)***	24 (8.9)	70 (23.6)***	72 (14.4)	24 (32.0)***
Numbness in hand								
No symptom	317 (86.3)	167 (78.0)	319 (84.6)	130 (80.3)	227 (84.1)	243 (81.8)	420 (84.2)	57 (76.0)
Unilateral	19 (5.2)	10 (4.7)	20 (5.3)	7 (4.3)	13 (4.8)	15 (5.1)	25 (5.0)	2 (2.7)
Bilateral	31 (8.5)	37 (17.3)**	38 (10.1)	25 (15.4)	30 (11.1)	39 (13.1)	54 (10.8)	16 (21.3)**
Pain in foot								
No symptom	332 (90.5)	162 (75.7)	337 (89.3)	117 (72.2)	242 (89.6)	241(81.1)	430 (86.2)	59 (78.7)
Unilateral	7 (1.9)	5 (2.3)	7 (1.9)	5 (3.1)	4 (1.5)	8 (2.7)	11 (2.2)	1 (1.3)
Bilateral	28 (7.6)	47 (22.0)***	33 (8.8)	40 (24.7)***	24 (8.9)	48 (16.2)**	58 (11.6)	15 (20.0)*
Pain in hand								
No symptom	357 (97.3)	202 (94.4)	365 (96.8)	153 (94.5)	257 (95.2)	288 (97.0)	480 (96.2)	72 (96.0)
Unilateral	6 (1.6)	1 (0.5)	5 (1.3)	1 (0.6)	6 (2.2)	1 (0.3)	7 (1.4)	0 (0)
Bilateral	4 (1.1)	11 (5.1)**	7 (1.9)	8 (4.9)*	7 (2.6)	8 (2.7)	12 (2.4)	3 (4.0)
Coldness in legs								
No symptom	89/125 (71.2)	28/46 (60.9)	67/93 (72.0)	30/45 (66.7)	48/67 (71.6)	58/93 (62.4)	97/142 (68.3)	14/22 (63.6)
Symptomatic	36/125 (28.8)	18/46 (39.1)	26/93 (28.0)	15/45 (33.3)	19/67 (28.4)	35/93 (37.6)	45/142 (31.7)	8/22 (36.4)
Painful leg cramp								
No symptom	261/348 (75.0)	132/194 (68.0)	251/358 (70.1)	113/146 (77.4)	191/257 (74.3)	198/275 (72.0)	340/469 (72.5)	50/68 (73.5)
Symptomatic	87/348 (25.0)	62/194 (32.0)	107/358 (29.9)	33/146 (22.6)	66/257 (25.7)	77/275 (28.0)	129/469 (27.5)	18/68 (26.5)
Dizziness on standing								
No symptom	293/365 (80.3)	144/210 (68.6)	301/375 (80.3)	101/158 (63.9)	222 (82.2)	205/291 (70.4)	388/495 (78.4)	47/74 (63.5)
Symptomatic	72/365 (19.7)	66/210 (31.4)**	74/375 (19.7)	57/158 (36.1)***	48 (17.8)	86/291 (29.5)**	107/495 (21.6)	27/74 (34.5)**
Sweating restricted to face/trunk								
No symptom	301/366 (82.2)	152/208 (73.1)	311/376 (82.7)	107/156 (68.6)	227 (84.1)	218/291 (74.9)	403/493 (81.7)	47/74 (63.5)
Symptomatic	65/366 (17.8)	56/208 (26.9)**	65/376 (17.3)	49/156 (31.4)***	43 (15.9)	73/291 (25.1)**	90/493 (18.3)	27/74 (36.5)***
Frequent constipation/diarrhea								
No symptom	335/366 (91.5)	172/208 (82.7)	339/376 (90.2)	128/156 (82.1)	247 (91.5)	247/291 (84.9)	444/493 (90.1)	58/74 (78.4)
Symptomatic	31/366 (8.5)	36/208 (17.3)**	37/376 (9.8)	28/156 (17.9)**	23 (8.5)	44/291 (15.1)*	49/493(9.9)	16/74 (21.6)**

Table 2 | (*Continued*)

	Probable DSPN		Confirmed DSPN		Possible CAN		Advanced CAN	
	No	Yes	No	Yes	No	Yes	No	Yes
	n = 367 (%)	*n* = 214 (%)	*n* = 377 (%)	*n* = 162 (%)	*n* = 270 (%)	*n* = 297 (%)	*n* = 499 (%)	*n* = 75 (%)
Objective nerve function test								
Achilles tendon reflex								
Normal	175/351(49.9)	0 (30.4)	158/358 (44.1)	11 (6.8)	120/258 (46.5)	48/283 (17.0)	162/475 (34.1)	8/71(11.3)
Unilaterally decreased	7/351 (2.0)	0 (0)*	6/358 (1.7)	1 (0.6)	2/258(0.8)	4/283 (1.4)	5/475 (1.1)	1/71(1.4)
Bilaterally decreased	169/351 (48.1)	214 (100.0)***	194/358(54.2)	150 (92.6)***	136/258 (52.7)	231/283 (81.6)***	308/475 (64.8)	62/71 (87.3)***

Relationships between symptoms or Achilles tendon reflex and defined types of diabetic symmetric polyneuropathy (DSPN) and cardiovascular autonomic neuropathy (CAN) according to the statement of American Diabetes Association were evaluated. Unilateral and bilateral symptoms were separately analyzed. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ analyzed by chi-squared-test for 2 × 2 contingency table.

Investigation 1. In the Nationwide survey, two questions, 'Do you feel numbness in your hand? Numbness in hand' and 'Do you feel pain in your hand? Pain in hand' were omitted, and sensory symptoms in the lower leg were limited to bilateral symptoms. Private information was not included for each question item.

Prevalence of the symptoms was compared between the WMUH and Nationwide, WMUC and Control, and Nationwide and Male control surveys. Statistical analyses were carried out by chi squared-test for a 2 × 2 contingency table using statistical software (Statview-J5.0; Hulinks).

RESULTS

Investigation 1. Characteristic Symptoms of DSPN

The prevalence of symptoms and diminished ATR by sex, age, diabetes duration, diabetic retinopathy and HbA_{1c} are shown in Table 1. Unilateral and bilateral symptoms were separately analyzed. Bilateral 'numbness in toe and sole', 'paresthesia in toe and sole', 'pain in foot' and 'sweating restricted to face/trunk' were significantly associated with duration and retinopathy. However, unilateral symptoms of these question items were not associated with duration and retinopathy. Bilaterally diminished ATR was significantly associated with age, duration and retinopathy. Although 'painful leg cramp' was significantly associated with duration, an increase in the prevalence in parallel with increasing duration was not observed.

Probable DSPN, confirmed DSPN, possible CAN and advanced CAN were observed at 36.8% (214/581), 30.1% (162/539), 52.4% (297/567) and 13.1% (75/574) in diabetic patients, respectively. The prevalence of symptoms and diminished ATR by probable DSPN, confirmed DSPN, possible CAN and advanced CAN are shown in Table 2. Bilateral 'numbness in toe and sole', 'paresthesia in toe and sole', 'pain in foot', 'dizziness on standing', 'sweating restricted to face/trunk' and 'frequent constipation/diarrhea' were significantly associated with all DSPN and CAN. Unilateral symptoms of sensory symptoms in the lower limb were not associated with DSPN and CAN at all.

Table 3 shows the data of seven quantitative nerve function tests in subdivided groups by symptoms and ATR. Data in the patients with bilateral 'numbness in toe and sole' were significantly deteriorated compared with those in asymptomatic patients in all nerve function tests. In contrast, data in the patients with unilateral 'numbness in toe and sole' were not significantly different from those in asymptomatic patients in all nerve function tests. Therefore, it was considered that not unilateral, but bilateral 'numbness in toe and sole' was significantly related to all nerve functions examined. In the same way, the relationships between other symptoms or ATR and nerve functions were examined. As a result, not unilateral, but bilateral 'numbness in toe and sole', 'paresthesia in toe and sole' and diminished ATR were significantly related to all nerve functions. Similarly, bilateral 'pain in foot' and 'sweating restricted to face/trunk' were significantly related to six of seven nerve functions. 'Frequent constipation/diarrhea', bilateral 'pain in hand' and 'dizziness on standing' were related to five, four and three

Table 3 | Difference in objective quantitative nerve functions between the patients with and without subjective symptoms or diminished Achilles tendon reflex

	MCV (ulnar n: m/s)				FCV (ulnar n: m/s)				SCV (median n: m/s)				SNAP (median n: μV)				CVdb (%)				ΔBP (mmHg)				VPT125 (dB)			
	N	M	SD	*P*-value	*n*	M	SD	*P*-value	*n*	M	SD	*P*-value	*n*	M	SD	*P*-value	*n*	M	SD	*P*-value	*n*	M	SD	*P*-value	*n*	M	SD	*P*-value
Subjective symptoms																												
Numbness in toe and sole				**<0.0001**				**<0.0001**				**<0.0001**				**<0.0001**				**<0.0001**				**<0.0001**				**<0.0001**
No symptom	381	51.6	5.0		340	59.4	4.7		355	57.7	5.3		337	20.9	13.1		386	4.2	2.8		386	9.9	15.0		392	19.9	9.7	
Unilateral	26	50.2	4.8		21	58.7	4.8		21	57.2	4.5		20	17.9	11.5		26	3.5	2.2		26	4.4	8.6		26	24.5	11.7	
Bilateral	154	47.7	5.6	****	142	55.7	5.4	****	139	54.0	6.0	****	140	14.1	14.0	****	160	2.8	2.0	****	157	16.1	17.4	****	160	26.5	10.4	****
Paresthesia in toe and sole				**<0.0001**				**<0.0001**				**<0.0001**				**<0.0001**				**<0.0001**				**<0.0001**				**<0.0001**
No symptom	453	51.3	5.2		406	59.1	4.9		418	57.3	5.5		402	20.2	13.8		464	4.0	2.8		461	9.9	15.5		468	20.7	10.3	
Unilateral	13	50.9	5.4		9	60.9	3.3		12	56.6	5.0		10	20.2	14.2		13	3.4	1.6		13	11.1	9.0		13	23.7	8.2	
Bilateral	95	47.2	5.5	****	88	54.2	4.8	****	85	53.3	5.6	****	85	12.6	10.9	****	95	2.9	2.2	****	95	18.2	16.4	****	97	27.4	9.6	****
Numbness in hand				0.23				0.06				0.12				0.18				0.17				0.07				**0.0332**
No symptom	470	50.5	5.3		418	58.4	5.0		432	56.9	5.4		415	19.3	13.6		475	3.8	2.7		472	10.4	15.5		482	21.5	10.3	
Unilateral	27	51.5	6.1		25	59.0	6.2		24	55.7	6.6		25	15.9	12.1		27	3.9	3.3		28	8.4	14.0		28	22.2	10.3	
Bilateral	64	49.5	6.4		60	56.9	6.0		59	55.4	6.9		58	16.5	13.9		70	3.2	1.9		69	15.2	17.7		68	25.0	10.8	*
Pain in foot				**<0.0001**				**0.0006**				**0.0003**				**0.0229**				**0.0148**				0.26				**<0.0001**
No symptom	473	50.9	5.2		427	58.7	5.0		441	57.1	5.5		424	19.4	13.3		488	3.9	2.8		484	10.9	16.6		498	21.0	10.3	
Unilateral	12	48.8	6.0		10	56.6	6.3		10	55.3	6.9		9	20.6	12.9		13	3.2	1.6		11	15.7	23.9		12	26.7	8.9	
Bilateral	71	47.9	6.2	****	66	56.1	6.0	***	64	54.0	6.5	***	65	14.5	14.8	*	71	2.9	1.8	****	74	13.6	15.3		73	27.3	9.3	****
Pain in hand																												
No symptom	540	50.5	5.4	**0.0174**	482	58.4	5.2	**0.0202**	495	56.7	5.7	**0.0240**	477	19.1	13.7	**0.0174**	550	3.8	2. 7	0.36	547	11.3	15.9	0.21	557	21.7	10.5	0.13
Unilateral	6	53.3	6.5		6	58.4	5.9		6	58.8	6.5		6	23.2	16.4		7	5.1	4.0		7	3.6	8.7		6	25.0	7.7	
Bilateral	15	46.9	5.6	*	15	54.6	5.7	*	14	52.8	5.1	*	15	9.3	4.8	*	15	3.2	1.7		15	16.3	13.8		15	26.9	6.9	
Coldness in legs				0.06				0.10				**0.0118**				0.76				0.17				0.17				0.62
No symptom	101	49.8	5.1		70	59.0	4.7		81	57.2	4.7		67	24.7	17.7		114	3.3	2.1		103	10.6	14.6		111	19.1	9.8	
Symptomatic	49	48.1	5.2		31	57.2	6.1		36	54.1	5.2		31	23.5	19.0		57	2.8	1.7		50	14.2	16.7		51	19.9	11.3	
Painful leg cramp				0.25				0.56				0.39				0.38				0.61				0.34				0.05
No symptom	383	50.3	5.5		340	58.4	5.2		349	56.9	5.5		337	19.2	13.7		392	3.8	2.7		387	10.8	16.0		394	21.2	10.4	
Symptomatic	143	50.9	5.3		130	58.7	5.2		134	56.4	5.8		128	20.4	13.8		147	3.7	2.6		143	12.3	15.6		145	23.2	10.2	
Dizziness on standing				0.07				0.11				**0.0234**				0.18				0.10				**0.0001**				**0.0186**
No symptom	422	50.8	5.3		377	58.6	5.2		385	57.0	5.7		370	19.4	13.6		432	3.9	2.7		430	9.8	13.9		435	21.3	10.0	
Symptomatic	133	49.8	5.4		120	57.7	5.3		124	55.7	5.4		122	17.5	13.5		135	3.4	2.6		133	15.8	20.3		137	23.7	11.4	
Sweating restricted to face/trunk				**0.0008**				**0.0273**				**0.0062**				0.22				**0.0031**				**0.0018**				**0.0146**
No symptom	436	51.0	5.3		397	58.6	5.0		405	57.1	5.5		393	19.3	13.6		449	4.0	2.7		446	10.3	15.1		451	21.3	10.0	
Symptomatic	119	49.1	5.5		100	57.3	5.8		104	55.4	6.2		99	17.5	13.8		117	3.1	2.4		116	15.4	17.6		120	23.9	11.5	
Frequent constipation/ diarrhea				**0.0432**				**0.0188**				0.06				0.41				**0.0173**				**0.0011**				**0.0005**
No symptom	487	50.7	5.4		433	58.6	5.0		446	56.9	5.5		429	19.2	13.8		499	3.9	2.7		497	10.5	15.2		504	21.3	10.3	
Symptomatic	68	49.3	5.6		64	57.0	6.0		63	55.5	6.4		63	17.7	12.2		67	3.1	2.2		65	17.3	18.9		67	25.9	10.5	

Table 3 | (*Continued*)

	MCV (ulnar n: m/s)				FCV (ulnar n: m/s)				SCV (median n: m/s)				SNAP (median n: μV)				CVdb (%)				ΔBP (mmHg)				VPT125 (dB)			
	N	M	SD	*P*-value	*n*	M	SD	*P*-value	*n*	M	SD	*P*-value	*n*	M	SD	*P*-value	*n*	M	SD	*P*-value	*n*	M	SD	*P*-value	*n*	M	SD	*P*-value
Objective nerve function test																												
Achilles tendon reflex				<0.0001				<0.0001				<0.0001				<0.0001				<0.0001				<0.0001				<0.0001
Normal	162	53.1	4.6		142	61.1	4.0		152	59.3	4.3		145	26.2	13.9		171	4.9	2.7		167	7.1	13.6		169	17.6	9.1	
Unilaterally decreased	7	50.0	4.1		4	57.4	4.9		6	55.8	5.8		4	21.7	9.8		5	2.9	1.8		7	11.4	9.6		7	17.1	12.4	
Bilaterally decreased	365	49.4	5.4	****	330	57.1	5.3	****	331	55.4	5.9	****	323	15.2	11.3	****	369	3.2	2.5	****	368	13.9	16.2	****	375	24.0	10.3	****

Figures of *P*-value indicate *P*-value between two or three groups by ANOVA, and statistically significant *P*-value was shown by boldfaced type, and $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$ vs No symptom or Normal Achilles tendon reflex by a *post-hoc* test. Statistical analyses were carried out by ANOVA followed by Scheffé's method as a *post-hoc* test. There was no significant difference between the data in unilateral and no symptom groups. ΔBP, a fall in systolic blood pressure during head-up tilt; CVdb, coefficient of variation of R-R intervals in electrocardiogram during deep breathing; FCV, F wave conduction velocity; M, mean values; MCV, motor nerve conduction velocity; SCV, sensory nerve conduction velocity; SD, standard deviations, SNAP, sensory nerve action potential; VPT125: 125 Hz quantitative vibratory perception threshold at the big toe.

functions, respectively. Other symptoms were related to only a few functions. Table 4 shows the summarized relationships between symptoms, ATR and background characteristics, probable and confirmed DSPN, possible and advanced CAN, and seven nerve function data.

Investigation 2. Prevalence of Symptoms in Diabetic and Non-Diabetic Subjects

Table 5 shows the prevalence of symptoms in all participants of Investigation 1 and 2. The first row is the prevalence of symptoms in the out- and inpatients of WMUH who attended Investigation 1 and whose symptoms were obtained by interview. Four rows from the second to fifth are the prevalence of symptoms in patients of the WMUH, Nationwide, Control and Male Control surveys, which were obtained by self-administered questionnaires, respectively. If possible, the prevalence of bilateral and unilateral symptoms was separately analyzed.

In the comparison between Investigation 1 and the WMUH survey, the prevalence of unilateral 'numbness in toe and sole', unilateral 'numbness in hand', uni- and bilateral 'pain in hand', 'painful leg cramp' and 'frequent constipation/diarrhea' in Investigation 1 was significantly lower than that in the WMUH survey. In contrast, the prevalence of bilateral 'numbness in toe and sole' and bilateral 'pain in foot' in Investigation 1 was significantly higher than that in the WMUH survey.

In the comparison between the WMUH survey and the Nationwide survey, all symptoms except for 'numbness in toe and sole' in the former survey were significantly more high-frequent than those in the latter survey.

Then, we compared the prevalence of symptoms between diabetic and non-diabetic subjects. Although a significantly higher prevalence of outpatients from the diabetes clinic (WMUH survey) compared with the non-diabetic subjects (Control survey) were observed with all bilateral sensory symptoms and other symptomatic items, the prevalence of unilateral symptoms of 'paresthesia in toe and sole', 'numbness in hand' and 'pain in foot' was not different between the two surveys. The prevalence of symptoms in male diabetic outpatients under primary-care physicians (Nationwide survey) was compared with that in male non-diabetic subjects (Male Control survey). Though the prevalence of 'painful leg cramp' and 'frequent constipation/diarrhea' in the Nationwide survey was not significantly different from that in the Male Control survey, all other symptoms were more frequently observed in the Nationwide survey than the Male Control survey.

Relatively common symptoms (>15%) in the WMUH or Nationwide surveys were bilateral 'numbness in toe and sole', 'paresthesia in toe and sole', 'coldness in legs', 'painful leg cramp', 'dizziness on standing', 'sweating restricted to face/trunk' and 'frequent constipation/diarrhea'.

DISCUSSION

In the present study, we examined which symptoms were suitable and helpful for diagnosis of DSPN among the 10

Table 4 | Significant association of subjective symptoms and Achilles tendon reflex with clinical background characteristics, defined types of diabetic symmetric polyneuropathy and cardiovascular autonomic neuropathy by American Diabetes Association statement and quantitative nerve functions

	Clinical background					Defined types of DSPN and CAN Probable Confirmed Possible Advanced				Quantitative nerve functions						
	Sex	Age	Duration	Retinopathy	HbA_{1c}	DSPN	DSPN	CAN	CAN	MCV	FCV	SCV	SNAP	CVdb	ΔBP	VPT125
Subjective symptoms																
Numbness in toes and soles			•	•		•	•	•	•	•	•	•	•	•	•	•
Paresthesia in toe and sole	•		•	•		•	•	•	•	•	•	•	•	•	•	•
Numbness in hands						•			•							•
Pain in feet			•	•		•	•	•	•	•	•	•	•	•		•
Pain in hands						•	•			•	•	•	•			
Coldness in legs												•				
Painful leg cramp			•													
Dizziness on standing						•	•	•	•			•			•	•
Sweating restricted to face/trunk			•	•		•	•	•	•	•	•	•		•	•	•
Frequent constipation/diarrhea						•	•	•	•	•	•			•	•	•
Objective nerve function test																
Diminished Achilles tendon reflexes		•	•	•		•	•	•	•	•	•	•	•	•	•	•

(•) Significant association was observed. ΔBP: a fall in systolic blood pressure during head-up tilt; CAN, cardiovascular autonomic neuropathy; CVdb, coefficient of variation of R-R intervals in electrocardiogram; DSPN, diabetic symmetric polyneuropathy; FCV, F wave conduction velocity; MCV, motor nerve conduction velocity; SCV, sensory nerve conduction velocity; SNAP, sensory nerve action potential during deep breathing; VPT125; 125 Hz quantitative vibratory perception threshold at the big toe.

symptomatic items. The main results were as follows: significant relationships with probable DSPN, confirmed DSPN, possible CAN and advanced CAN defined by the criteria in the latest ADA statement[2] were observed in six symptoms – bilateral 'numbness in toe and sole', bilateral 'paresthesia in toe and sole', bilateral 'pain in foot', 'dizziness on standing', 'sweating restricted to face/trunk' and 'frequent constipation/diarrhea'; significant associations with duration of diabetes and diabetic retinopathy were observed in four symptoms – bilateral 'numbness in toe and sole', bilateral 'paresthesia in toe and sole', bilateral 'pain in foot' and 'sweating restricted to face/trunk'; significant relationships with all or six in seven objective quantitative nerve function tests were observed in four symptoms – bilateral 'numbness in toe and sole', bilateral 'paresthesia in toe and sole', bilateral 'pain in foot' and 'sweating restricted to face/trunk'; a higher prevalence in diabetic patients than in non-diabetic subjects was observed in many symptoms other than unilateral sensory symptoms, 'painful leg cramp' and 'frequent constipation/diarrhea'; common or not rare symptoms (<15%) were bilateral 'numbness in toe and sole', bilateral 'paresthesia in toe and sole', 'coldness in legs', 'painful leg cramp', 'dizziness on standing', 'sweating restricted to face/trunk' and 'frequent constipation/diarrhea'.

From the first, second and third results, bilateral 'numbness in toe and sole', bilateral 'paresthesia in toe and sole', bilateral 'pain in foot' and 'sweating restricted to face/trunk' were thought to correlate with the severity of diabetic chronic complication and nerve function deterioration. The fourth and fifth results confirmed the higher prevalence of the aforementioned four symptoms in diabetic patients compared with non-diabetic subjects, and clarified that bilateral 'pain in leg' was not frequent (approximately 10%). Taking into account all of the aforementioned findings, we might be able to conclude that bilateral 'numbness in toe and sole', bilateral 'paresthesia in toe and sole' and 'sweating restricted to face/trunk' are suitable symptoms useful for the diagnosis of DSPN, whereas bilateral 'pain in foot' is well associated with the severity of nerve dysfunctions in diabetic patients and a clinically important symptom. We also confirmed a close relationship between diminished ATR and severity of diabetic chronic complication and deterioration in quantitative nerve function tests. These findings are clinically well known; nevertheless, the reports that examine the characteristic symptoms of DSPN based on multiple objective neurological tests are rare.

At present, we can use the minimal criteria for DSPN proposed in the ADA statement[2], in which probable DSPN seems to be most usable in daily medical practice. Probable DSPN was defined by the presence of a combination of symptoms and signs of neuropathy including any two or more of the following: neuropathic symptoms, decreased distal sensation, or unequivocally decreased or absent ankle reflexes. Neuropathic symptoms were described as 'asleep numbness', prickling or stabbing, burning or aching pain in the toes, feet or legs. These are all bilateral sensory symptoms in the lower leg and concordant with our findings.

The Michigan neuropathy screening instrument (MNSI)[9] and abbreviated diagnostic criteria proposed by the Diabetic

Table 5 | Prevalence of subjective symptoms in 593 diabetic out- and inpatients of Wakayama Medical University Hospital (WMUH): Investigation 1, 999 diabetic outpatients of WMUH survey, 1524 diabetic male outpatients in the Nationwide survey and 501 non-diabetic subjects in the Control survey (including 311 male non-diabetic subjects: Male Control survey)

	Investigation 1	WMUH survey	Nationwide survey	Control survey	Male control survey	Comparison between the surveys			
	(Interviewed DM patients) *n* = 593 (%)	(DM patients) *n* = 965 (%)	(Male DM patients) *n* = 1524 (%)	(Non-DM subjects) *n* = 500 (%)	(Male non-DM subjects) *n* = 311 (%)	Investigation 1 vs WMUH survey *P*-value	WMUH vs Nationwide *P*-value	WMUH vs Control *P*-value	Nationwide vs Male Control *P*-value
Numbness in toe and sole									
No symptom	402 (67.8)	705 (73.1)	1206 (78.1)	468/499 (93.8)	292 (93.9)				
Unilateral	26 (4.4)	78 (8.1)	ND	21/499 (4.2)	13 (42)	**0.0045**	NE	**0.0051**	NE
Bilateral	165 (27.8)	182 (18.8)	318 (20.9)	10/499 (2.0)	6 (1.9)	**<0.0001**	0.22	**<0.0001**	**<0.0001**
Paresthesia in toe and sole									
No symptom	480 (80.9)	765/950 (80.5)	1330 (87.3)	481/498 (96.6)	297/309 (96.1)				
Unilateral	13 (2.2)	32/950 (3.4)	ND	6/498 (1.2)	3/309 (1.0)	0.18	NE	0.46	NE
Bilateral	100 (16.9)	153/950 (16.1)	193 (12.7)	11/498 (2.2)	9/309 (2.9)	0.70	**0.0164**	**<0.0001**	**<0.0001**
Numbness in hand									
No symptom	494 (83.3)	748/954 (78.4)	ND	448 (89.6)	275 (88.4)				
Unilateral	29 (4.9)	83/954 (8.7)	ND	31 (6.2)	22 (7.1)	**0.0049**	NE	0.09	NE
Bilateral	70 (11.8)	123/954 (12.9)	ND	21 (4.2)	14 (4.5)	0.53	NE	**<0.0001**	NE
Pain in foot									
No symptom	505 (85.2)	829/938 (88.4)	1363 (89.4)	479/497 (96.4)	297/309 (96.1)				
Unilateral	13 (2.2)	36/938 (3.8)	ND	13/497 (2.6)	8/309 (2.6)	0.07	NE	0.23	NE
Bilateral	75 (12.6)	73/938 (7.8)	161 (10.6)	5/497 (1.0)	4/309 (1.3)	**0.0017**	**0.0327**	**<0.0001**	**<0.0001**
Pain in hand									
No symptom	571 (96.3)	856/951 (90.0)	ND	484/498 (97.2)	303/309 (98.0)				
Unilateral	7 (1.2)	34/951 (3.6)	ND	7/498 (1.4)	3/309 (1.0)	**0.0044**	NE	**0.0180**	NE
Bilateral	15 (2.5)	61/951 (6.4)	ND	7/498 (1.4)	3/309 (1.0)	**0.0006**	NE	**<0.0001**	NE
Coldness in legs									
No symptom	119/176 (67.6)	652/951 (68.6)	1250 (82.0)	420/499 (83.4)	286/310 (92.3)				
Symptomatic	57/176 (32.4)	299/951 (31.4)	274 (18.0)	79/499 (15.8)	24/310 (7.7)	0.80	**<0.0001**	**<0.0001**	**<0.0001**
Painful leg cramp									
No symptom	403 (72.7)	491/955 (51.4)	1130 (74.1)	338/498 (67.9)	218/309 (70.6)				
Symptomatic	151 (27.3)	464/955 (48.6)	394 (25.9)	160/498 (32.1)	91/309 (29.4)	**<0.0001**	**<0.0001**	**<0.0001**	0.15
Dizziness on standing									
No symptom	447/587 (76.2)	664/926 (71.7)	1277 (83.8)	399/496 (80.4)	273/308 (88.6)				
Symptomatic	140/587 (23.8)	262/926 (28.3)	247 (16.2)	97/496 (19.6)	35/308 (11.4)	0.06	**<0.0001**	**0.0003**	**0.0317**
Sweating restricted to face/trunk									
No symptom	464/586 (79.2)	713/925 (77.1)	1291 (84.7)	451/495 (91.1)	285/309 (92.2)				
Symptomatic	122/586 (20.8)	212/925 (22.9)	233 (15.3)	44/495 (8.9)	24/309 (7.8)	0.34	**< 0.0001**	**<0.0001**	**0.0006**
Frequent constipation/diarrhea									
No symptom	518/586 (88.4)	570/951 (59.9)	1262 (82.8)	362/494 (73.3)	244/309 (79.0)				
Symptomatic	68/586 (11.6)	381/951 (40.1)	262 (17.2)	132/494 (26.7)	65/309 (21.0)	**<0.0001**	**<0.0001**	**<0.0001**	0.09

Prevalence of symptoms was analyzed by chi-squared test for 2 × 2 contingency table. Bilateral and unilateral symptoms was separately analyzed in the comparisons of Investigation 1 vs Wakayama Medical University Hospital (WMUH) survey and WMUH survey vs Control surveys. DM, diabetes mellitus; ND, no data; NE, not examined because of no data.
Statistically significant *P*-values (<0.05) were shown by boldfaced type.

Neuropathy Study Group in Japan (DNSGJ-criteria)[10,11] are also used as convenient standards for DSPN screening. MNSI is used all over the world, and its survey sheet contains seven questions related to sensory disturbance in the legs. In the recent MNSI survey sheet distributed from the website of the Michigan Diabetes Research and Training Center, 'legs and/or feet numb', 'burning and/or pricking pain in legs and/or feet' and 'decreased sensation of temperature' were included, but 'muscle cramp in legs and/or feet' was excluded from neuropathic symptoms. Our data also showed that 'painful leg cramp' did not show a significant association with objective nerve functions.

Use of the DNSGJ-criteria is spreading in Japan. DSPN is usually diagnosed when two or more of three findings – sensory symptoms, bilaterally decreased ATR and bilaterally decreased vibratory sensation – are found. In the DNSGJ-criteria, bilateral numbness, pain, paresthesia or decreased sensation in toes and soles are used as symptoms considered to be as a result of DSPN; symptoms in only the upper extremities or only cold sense are excluded. These characteristics of the sensory symptoms of DSPN closely resembled with findings. The present study might provide supportive evidence to prove that the selection of sensory symptoms in the DNSGJ-criteria is warranted.

There are several problems or limitations in the present study. One problem is the accuracy of the response to the questions regarding neuropathic symptoms. We interviewed diabetic patients about symptoms in Investigation 1. The data are therefore thought to be more reliable than self-administered questionnaire surveys, because the interviewer explained the question in detail and might have excluded symptoms that were clearly of non-neuropathic origin. Although the degree of DSPN should be more severe in the patients of Investigation 1 than the patients who completed the surveys, the prevalence of unilateral sensory symptoms, 'painful leg cramp' and 'frequent constipation/diarrhea' were less frequent in patients of Investigation 1 than in those who completed the questionnaire surveys. We might have to take into account the possibility that the aforementioned symptoms are overestimated in a self-administered questionnaire survey.

Another problem is that the origin of the unilateral sensory symptoms is unknown. Because the nerve conduction and other quantitative nerve function data of the patients with unilateral sensory symptoms were not different from the data of asymptomatic patients, these symptoms seemed not to be caused by DSPN. The lower prevalence of unilateral symptoms in the interviewed patients than those in the patients who completed self-administered questionnaire surveys might suggest the possibility that these symptoms were caused by a disease other than peripheral neuropathy, such as inflammation or an orthopedic disorder. The interviewer might not have counted the unilateral symptom obviously caused by a disease other than DSPN as a positive response. Anyway, the unilateral sensory symptoms seem to not reflect the severity of DSPN.

We believe our data will contribute to devising simple, globally approved diagnostic criteria for DSPN.

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