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ORIGINAL ARTICLE

Bilateral atrophy of the extensor digitorum brevis muscle might be a useful sign for diagnosing diabetic polyneuropathy in Japanese men who do not sit in the traditional "*seiza*" style

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ABSTRACT

Aims/Introduction: As the extensor digitorum brevis muscle is a small muscle in the most distal part of the legs, its atrophy (EDBA) might reflect symmetric polyneuropathy (SPN). We aimed to clarify the EDBA-related factors and the usefulness of bilateral EDBA detection for diagnosing SPN, especially diabetic SPN (DSPN).

Materials and Methods: In 1,893 participants from the Japanese general population (investigation I) and 133 established diabetes patients (investigation II), relationships between EDBA and various factors including the traditional sitting style called "*seiza*" (kneeling and sitting on one's heels) were investigated. Analyses were carried out by univariate and multivariate analysis, and SPN or DSPN was diagnosed by the criteria of "Probable DSPN" of the Toronto Consensus. The validity of EDBA detection for diagnosing SPN/DSPN was also evaluated.

Results: Investigation I: EDBA was more prevalent in women than men (44% vs 20%). Significant EDBA-related factors were aging and *seiza* habit regardless of sex. Male-specific EDBA-related factors were SPN and known diabetes. In men without *seiza* habit, EDBA was significantly associated with SPN regardless of diabetes, so EDBA seemed to be a useful sign for diagnosing SPN/DSPN. Investigation II: In men, DSPN was more prevalent in the EDBA group than the non-EDBA group (71% vs 33%). Sensitivity, specificity, positive predictive value and kappa coefficient of EDBA detection for diagnosing DSPN were 44, 87, 67% and 0.323, showing fair agreement.

Conclusions: EDBA detection might be a useful method to screen for distal symmetric polyneuropathy, such as DSPN in men, although the exclusion of individuals with *seiza* habit is necessary to improve accuracy.

INTRODUCTION

Diabetic polyneuropathies, which consist of diabetic symmetric polyneuropathy (DSPN) and diabetic autonomic neuropathy, are the most prevalent diabetic complications. DSPN has been diagnosed clinically by the existence of neuropathic symptoms, decreased Achilles tendon reflexes (ATR) and decreased sensation in the distal part of the legs[1]. Muscle atrophy in the distal part of the legs, which are signs of motor neuropathy, are seen in advanced DSPN and might be involved in the development of diabetic foot lesions. Therefore, early diagnosis of motor neuropathy is desired, but there is no simple and appropriate diagnosis method. In contrast, in Germany, a high prevalence of

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distal symmetric polyneuropathy similar to DSPN has been reported in the general population regardless of diabetes[2]. We also reported a low prevalence of DSPN-like neuropathy in non-diabetic regional residents[3]. The etiology and pathological background of DSPN-like neuropathy in these non-diabetic participants are undetermined, and it is doubtful whether they correspond to one disease concept. In the present study, we call DSPN-like neuropathy in non-diabetic participants distal symmetric polyneuropathy (SPN) for convenience.

The extensor digitorum brevis muscle (EDB) is a small muscle located on the dorsum of the foot in the front of the lateral malleolus innerved by the deep peroneal nerve. EDB atrophy (EDBA) is easily detected in <30 s when EDB bulk cannot be identified by inspection and palpation at the position of toe extension. EDBA has been reported to be a sign of anterior tarsal tunnel syndrome[4], L5 radiculopathy[5], lumbar canal stenosis[6] and DSPN[7]. EDBA is also reported to be due to the traditional habit of sitting on the floor, cross-legged or kneeling and sitting over one's feet[8]. In Japan, this traditional sitting style, known as "*seiza*" (kneeling and sitting over one's heels on the floor), might cause EDBA. Because EDB is one of the most distal muscles of the lower legs, EDBA might also be a sign of SPN. Actually, Baba *et al.*[9] reported that EDBA reflects the clinical and electrophysiological severity of DSPN in Japanese people. Therefore, EDBA seems to be a pathophysiologically multifactorial condition. Nevertheless, EDBA might be a simple and useful sign showing moderate motor nerve fiber loss in SPN, especially DSPN.

In cross-sectional observation studies, we aimed to clarify the factors associated with EDBA and the usefulness of bilateral EDBA for diagnosing SPN/DSPN. First, we examined the relationship between EDBA and demographic, clinical, neurological factors and lifestyle (such as a *seiza* habit) in the regional residents who underwent a health checkup program (investigation I). The program was carried out as a part of the Wakayama Health Promotion Study. Second, we investigated the relationship between EDBA and many quantitative nerve functions in hospital-based established diabetes patients (investigation II).

As is known, muscle mass is physiologically different between men and women due to endocrinological characteristics. For example, the diagnostic criteria for muscle mass in sarcopenia differ between men and women[10]. Therefore, the clinical significance of EDBA was investigated separately for men and women in our studies.

METHODS

Ethics statement

These protocol and consent procedures were carried out in accordance with the World Medical Association's Declaration of Helsinki and were approved by the ethics board of the Wakayama Medical University (approval number 92 and 2852).

Investigation-I: Factors associated with EDBA in the general population and validity of EDBA detection for diagnosing polyneuropathy

Research design and participants

We recruited 1,893 participants (794 men, 1,099 women, aged 40–75 years) who underwent an annual health checkup program from 2014 to 2016. Those with a positive history for cerebral infarction sequela, renal failure, hypothyroidism or alcoholism were excluded. All participants were examined for EDBA by visual inspection and palpation at the foot position with extended toes. On visual inspection, EDBA was defined when the tendon of extensor hallucis longus was visible, but no bulge of the EDB muscle was visible. On palpation, EDBA was defined when the tendons of the extensor digitorum longus were palpable, but the EDB muscles were not palpable. Figure 1 shows the *seiza* sitting style, the normal appearance of EDB and atrophic EDBs found in a man with a daily *seiza* habit, or in a male DSPN patient. Unilateral atrophy was not enrolled as EDBA, because we aimed to examine the relationship between EDBA and symmetric polyneuropathy. Data of demographics (age, sex), anthropometry (height, weight, waist circumference), lifestyle (*seiza* habit, smoking, drinking) and lifestyle-related diseases (diabetes, hypertension, dyslipidemia) were also collected from all participants.

Regarding lifestyle-related diseases, all participants were stratified by glucose tolerance, blood pressure (BP) and serum lipid level, as in our previously report[3]. Specifically, four groups (normal, prediabetes, newly diagnosed diabetes, known diabetes), three groups (optimal/normal BP, elevated blood pressure, hypertension) and two groups (normolipidemia, dyslipidemia) were constructed according to glucose tolerance, BP and serum lipids, respectively.

Evaluation of neurological functions

Neuropathic symptoms, ATR and quantitative vibration threshold (QVT) were evaluated in all participants. Symptoms of peripheral neuropathy were determined by asking whether there were any positive symptoms (numbness, pricking sensation, pain) on their feet/toes. Bilateral ATRs were examined at the knee standing position. QVT at 125 Hz was assessed on both big toe tips using a vibratory sensation meter (AU-02B™; RION Inc, Tokyo, Japan). The method of QVT measurement has been described previously[11].

Additionally, the amplitude of the sensory nerve action potential (AMP) and sensory nerve conduction velocity (CV) of both sural nerves were measured by a point-of-care sural nerve conduction device (DPNCheck™; Neurometrix Inc, Waltham, MA, USA) according to the test manual[12] by trained clinical laboratory technicians. Impairments of QVT, AMP and CV were judged by Japanese age-specific reference values[13].

Diagnosis of SPN/DSPN was made according to the criterion of "Probable DSPN" of the Toronto Consensus[1], which is widely used worldwide. "Probable DSPN" is diagnosed in participants who have two or more of three bilateral signs/

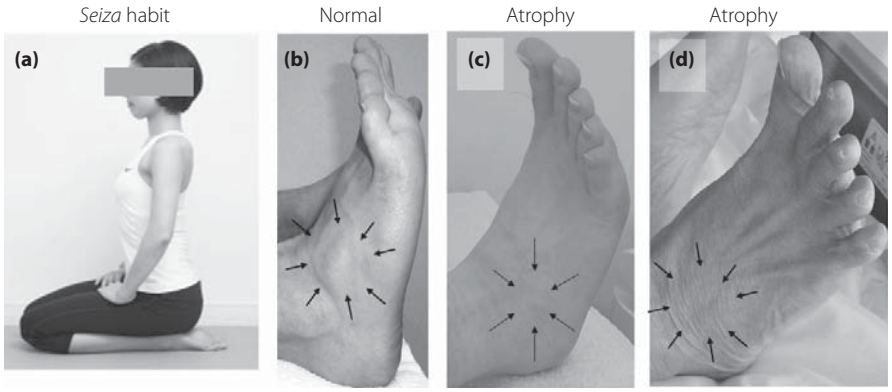

Figure 1 | (a) The Japanese traditional sitting style, *seiza* (kneeling and siting over one's heels on the floor), is shown. The normal appearance of (b) the extensor digitorum brevis and atrophic (c) extensor digitorum brevis found in a man with a daily *seiza* habit or in (d) a male diabetic symmetric polyneuropathy patient are shown.

symptoms (positive symptoms, ATRs reduction and decreased sensation in toes, feet or legs). In the present study, bilateral impaired QVTs were used as decreased sensation in the toes.

Statistical analysis

Various clinical parameters related to EDBA were analyzed. Continuous and categorical variables were analyzed by ANOVA and the χ^2-test, respectively. Multivariate logistic regression analyses were also carried out by using EDBA as a dependent variable, and demographics, anthropometry, lifestyle, lifestyle-related diseases and neurological functions as independent variables, respectively.

Validity and reliability of EDBA detection for diagnosing SPN/DSPN was examined separately in participants with and without diabetes by assessing sensitivity, specificity, positive and negative predictive values, and the Cohen's kappa coefficient.

Statistical analyses were carried out by using statistical software (Statview-J5.0™; Hulinks, Tokyo, Japan, and Excel statistics 2010; Social Survey Research Information Co, Ltd, Tokyo, Japan).

Investigation II: Usefulness of EDBA detection for diagnosing DSPN in established diabetes patients

Research design and participants

As diabetes is the most common disease to elicit SPN[14], the relevance between various neurological dysfunctions and EDBA was evaluated.

A total of 133 diabetes patients who had undergone medical interviews, physical examinations, QVT and quantitative autonomic function tests at Wakayama Medical University Hospital (Wakayama, Japan) from 2010 to 2012 were enrolled. Conventional nerve conduction tests were carried out in just 65 of the patients because of the tests' time-consuming nature. Clinical data, such as age, sex, height, weight, hypertension, dyslipidemia, diabetic retinopathy, proteinuria, and smoking or drinking habits, were also collected. Unfortunately, we did not ask about the *seiza* habit. The patients who had a positive history for cerebral infarction sequela, renal failure, peripheral arterial disease, hypothyroidism or alcoholism were excluded. Hypertension was diagnosed with BP ≥140/90 mmHg and/or under antihypertensive treatment. Dyslipidemia was diagnosed on the same criteria as investigation I. Proteinuria was defined as micro- or macroalbuminuria. Diabetic retinopathy was diagnosed as simple or preproliferative or proliferative retinopathy by the ophthalmologists.

Evaluation of neurological functions

The quantitative vibration threshold was examined and determined to be impaired the same as in investigation I. As autonomic nerve functions, the coefficient of variation in R-R intervals of an electrocardiogram at resting (CVrest) and during deep breathing (CVdeep), and a fall in systolic BP during 70° head-up tilt test (ΔBP) were examined. As nerve conduction studies, motor nerve conduction velocity (MCV) and compound muscle action potential (CMAP) in the bilateral ulnar and tibial nerves, and sensory nerve conduction velocity and sensory nerve action potential in both median nerves were examined. All tests were carried out as in our previous report[11]. Tibial MCV <42 m/s and CMAP <5 mV were judged as impaired according to Baba's classification for diagnosing DSPN[15]. The other neurological parameters were judged as impaired by the same criteria as our previous report[11]. Bilaterally impaired QVT or nerve conduction data were considered as impaired as a result of DSPN. Diagnosis of DSPN was based on the "Probable DSPN" criteria, as in investigation I.

Statistical analysis

Clinical and neurological factors associated with EDBA, and validity and reliability of EDBA detection for diagnosing DSPN were analyzed as in investigation I. Because of the small

number of participants, multivariate logistic regression analysis was carried out on the sum of men and women.

RESULTS

Investigation I: Factors associated with EDBA in the general population, and validity of EDBA detection for diagnosing polyneuropathy

EDBA prevalence, and relationships between EDBA and other factors

The prevalence of EDBA in men (20%) was significantly lower than in women (44%; Table 1). The proportion of participants with *seiza* habits was also significantly lower in men than women. The daily *seiza* habit in men, and daily and previous *seiza* habits in women were significantly more prevalent in the EDBA (+) groups compared with the EDBA (−) group. No participants were identified who had local paresthesia in the EDB area or difficulty in toe extension, regardless of EDBA.

In male participants, significant EDBA-related factors were age, height, weight, waist circumference, diabetes, hypertension, neuropathic symptoms, ATR reduction, QVT, SPN, both AMP values and AMP impairment. In women, diabetes, neuropathic symptoms and AMP impairment were excluded from the factors significant in men.

Associated factors with EDBA by multivariate logistic regression analysis in total participants or participants without daily and previous seiza habits

Even in the limited number of participants without daily or previous *seiza* habits, EDBA prevalence in men (19%) was also significantly lower than that in women (39%; Table 2).

In total participants, aging, *seiza* habit and SPN were significant EDBA-related factors regardless of sex. As a *seiza* habit could be confirmed as an independent related factor of EDBA, the same analysis was carried out in the participants without daily and previous *seiza* habits. The results showed that the significant EDBA-related factors in men were aging, small waist circumference, previous smoking, known diabetes and SPN, and those in women were aging, short stature and overweight, respectively.

Relationships between neurological functions and EDBA, and validity of EDBA detection for diagnosing SPN/DSPN

Because a *seiza* habit was a significant associated factor for EDBA regardless of sex, the studies were carried out in participants with or without diabetes who did not have daily or previous *seiza* habits (Tables 3a, 3b).

In participants without diabetes, EDBA was significantly more prevalent in women (39%) than men (16%), but the difference was not significant in participants with diabetes. The prevalence of SPN/DSPN did not differ between men and women regardless of diabetes.

First, we examine the results for participants with diabetes. In men, the measured values of AMP, CV and QVT in the EDBA (+) group were significantly worse than those in the EDBA (−) group, whereas in women, only QVT values were worse in the EDBA (+) group compared with the EDBA (−) group. The prevalence of DSPN in the EDBA (+) group (21%) was significantly higher than that in the EDBA (−) group (1%) in men. Whereas the prevalence of DSPN in women was not different between the EDBA (+) group (8%) and the EDBA (−) group (6%). The results showed that the sensitivity, specificity, and positive and negative predictive value of EDBA detection for diagnosing DSPN in men were 89, 72, 21 and 99%, respectively. Cohen's kappa coefficient was 0.2467, which showed fair agreement[16]. In contrast, the sensitivity and specificity of DSPN diagnosis by EDBA in women were 50 and 56%, but there was not any significance.

Next, we examine the results for participants without diabetes. In men, the QVT values in the EDBA (+) group were higher than those in the EDBA (−) group. In women, AMP and QVT values and the frequency of AMP impairment and ATR reduction were significantly worse in the EDBA (+) group compared with the EDBA (−) group. In men, the prevalence of SPN in the EDBA (+) group (6%) was significantly higher than that in the EDBA (−) group (1%). Whereas the prevalence of SPN in women was not different between the EDBA (+) group (2%) and the EDBA (−) group (4%). The results showed that the sensitivity, specificity, and positive and negative predictive value of EDBA detection for diagnosing SPN in men were 46, 84, 6 and 99%, respectively. Cohen's kappa coefficient was 0.0747 (slight agreement). In contrast, the sensitivity and specificity of EDBA detection for diagnosing SPN in women were 52 and 61%, but there was not any significance.

Investigation II: Usefulness of EDBA detection for diagnosing DSPN in established diabetes patients

Clinical, neurological factors related to EDBA

Multivariate logistic regression analysis showed that EDBA was significantly associated with female sex, low body mass index and DSPN, but not with drinking, smoking, blood pressure or blood lipid levels (Figure 2; Table 4a).

The prevalence of EDBA in men (27%) was significantly lower than that in women (48%), whereas DSPN was more prevalent in men than in women (43% vs 22%). In men, aging, long diabetic duration, low bodyweight and low body mass index were significantly associated with EDBA, but not glycated hemoglobin, drinking or smoking habits, hypertension, dyslipidemia, retinopathy, or proteinuria. Regarding the relationship between nerve function and EDBA, many neurological indices, such as, CV rest, orthostatic hypotension, sensory nerve conduction velocity of median nerve, MCV and CMAP of tibial nerve, QVT, neuropathic symptoms, and ATRs, were significantly impaired in the EDBA (+) group. In contrast, in women, just two neurological dysfunctions (CV rest and tibial MCV) were significantly associated with EDBA.

Table 1 | Demographic, anthropometry, lifestyle, lifestyle-related diseases and neurological functions data by sex or the extensor digitorum brevis atrophy

	Male				Female			Male vs female
EDBA: (+) (*n*)	162/794 (20%)*				483/1,099 (44%)*			*P* < 0.0001*
Seiza: no/sometimes/daily/previously (*n*)	459/239/49/39 (59%▲/30%▼/6%▼/5%▼)*				279/490/209/115 (25%▼/45%▲/19%▲/11%▲)*			*P* < 0.0001*
	Total, *n* = 794	EDBA (–), *n* = 632	EDBA (+), *n* = 162	*P*-value	Total, *n* = 1,099	EDBA (–), *n* = 616	EDBA (+), *n* = 483	*P*-value
Seiza: no/sometimes/daily/previous (%)		61▲/29/5▼/5*	49▼/34/12▲/5*	0.0032*		28△/47/17▽/8▼*	22▽/42/22△/14▲*	<0.0001*
Age (years)	62.5 ± 9.1	61.6 ± 9.4*	66.4 ± 6.6*	<0.0001*	62.2 ± 9.3	60.9 ± 9.6*	64.0 ± 8.7*	<0.0001*
Height (cm)	167.7 ± 6.3	168.1 ± 6.3*	166.3 ± 6.1*	0.0012*	154.7 ± 5.8	155.4 ± 5.6*	153.9 ± 5.8*	<0.0001*
Weight (kg)	65.6 ± 9.7	66.1 ± 9.3*	63.8 ± 10.9*	0.0070*	53.3 ± 8.9	52.7 ± 8.7*	54.0 ± 9.0*	0.0157*
Waist circumference (cm)	86.6 ± 8.6	86.9 ± 8.3*	85.3 ± 9.5*	0.0331*	82.7 ± 9.1	81.8 ± 9.1*	83.8 ± 8.9*	0.0004*
Alcohol: no/social/daily (%)	35/15/50	35/14/51	38/16/46	0.4961	68/21/11	66/21/13	69/21/10	0.4359
Smoking: no/current/previously (%)	15/20/65	14/22/64	18/16/66	0.1560	60/3/37	58/4/38	61/3/36	0.5059
Diabetes: normal/preDM/NDM/KDM (%)	60/24/3/13	62▲/24/3/11▼*	51▼/23/4/22▲*	0.0015*	72/19/2/7	74/17/3/6	70/21/2/7	0.3340
Hypertension: ONBP/EBP/HT (%)	33/15/52	35△/16/49▼*	25▽/12/63▲*	0.0078*	48/11/41	52▼/10/38▼*	42▲/12/46▼*	0.0025*
Dyslipidemia (*n*)	438/793 (55%)	349/632 (55%)	89/161 (55%)	0.9895	632/1099 (58%)	350/616 (57%)	282/483 (58%)	0.6020
Bilateral neuropathic symptoms (*n*)	56/792 (7%)	36/631 (6%)*	20/161 (12%)*	0.0030*	100/1093 (9%)	56/614 (9%)	44/479 (9%)	0.9704
Diminished ATRs (*n*)	126/793 (16%)	86/631 (14%)*	40/162 (25%)*	0.0006*	156/1098 (14%)	65/615 (11%)*	91/483 (19%)*	<0.0001*
QVT right (dB)	20.4 ± 7.8	19.7 ± 7.9*	23.0 ± 6.8*	<0.0001*	18.6 ± 8.3	17.7 ± 8.6*	19.8 ± 7.9*	<0.0001*
QVT left (dB)	20.7 ± 8.1	20.0 ± 8.0*	23.5 ± 7.9*	<0.0001*	19.0 ± 8.5	18.1 ± 8.8*	20.2 ± 8.0*	<0.0001*
Both QVT impairment (*n*)	41/794 (5%)	32/632 (5%)	9/162 (6%)	0.8006	59/1098 (5%)	36/615 (6%)	23/483 (5%)	0.4258
SPN (*n*)	26/794 (3%)	8/632 (1%)*	18/162 (11%)*	<0.0001*	42/1099 (4%)	16/616 (3%)*	26/483 (5%)*	0.0168*
AMP right, μV (*n*)	15.0 ± 8.1 (253)	15.6 ± 8.1 (196)*	13.0 ± 7.8 (57)*	0.0308*	14.1 ± 7.3 (362)	15.2 ± 7.4 (233)*	12.0 ± 6.8 (129)*	<0.0001*
AMP left, μV (v)	14.3 ± 8.3 (255)	15.3 ± 8.6 (196)	11.2 ± 6.3 (59)	0.0008	13.6 ± 6.7 (361)	14.6 ± 7.0 (232)*	11.8 ± 5.7 (129)*	0.0002*
Bilateral AMP impairment (*n*)	16/258 (6%)	8/197 (4%)*	8/61 (13%)*	0.0104*	16/363 (4%)	8/232 (3%)	8/131 (6%)	0.2360
CV right, m/s (*n*)	51.9 ± 4.6 (252)	52.2 ± 4.3 (195)	51.2 ± 5.2 (57)	0.1868	56.4 ± 4.2 (361)	56.2 ± 4.3 (233)	56.8 ± 4.0 (128)	0.1968
CV left, m/s (*n*)	51.4 ± 4.4 (254)	51.7 ± 4.3 (196)*	50.3 ± 4.5 (58)*	0.0243*	55.3 ± 4.3 (357)	55.4 ± 4.3 (231)	55.3 ± 4.2 (126)	0.8626
Bilateral CV impairment (*n*)	27/257 (11%)	20/197 (10%)	7/60 (12%)	0.7377	8/365 (2%)	7/233 (3%)	1/132 (1%)	0.1590

Continuous variables are expressed as the mean ± standard deviation, and analyzed by one-way ANOVA. Nominal variables were analyzed using the χ^2-test. Then the residual analysis was used as a post-hoc test. ▽ $P < 0.05$ (decreased), ▼ $P < 0.01$ (decreased), △ $P < 0.05$ (increased), ▲ $P < 0.01$ (increased). *Statistically significant *P*-value. AMP, amplitude of sensory nerve action potential; ATR, Achilles tendon reflex; CV, conduction velocity; EBP, elevated blood pressure; EDB, extensor digitorum brevis muscle; EDBA, extensor digitorum brevis muscle atrophy; HT, hypertension; KDM, known diabetes; NDM, newly diagnosed diabetes; ONBP, optimal/normal blood pressure; preDM, prediabetes; QVT, quantitative vibratory perception threshold; SPN, symmetric polyneuropathy.

Table 2 | Factors associated with extensor digitorum brevis atrophy analyzed by multivariate logistic regression analysis in total participants or in participants without daily and previous *seiza* habit

	Total participants				Participants without daily and previous 'Seiza' habit			
	Male		Female	Male vs female	Male		Female	Male vs female
Prevalence of EDBA (*n*)	162/794 (20%)*		483/1099 (44%)*	$P < 0.0001$*	133/698 (19%)*		302/766 (39%)*	$P < 0.0001$*
Dependent variable	EDBA (+) $P < 0.0001$, $R^2 = 0.210$, $n = 778$		EDBA (+) $P < 0.0001$, $R^2 = 0.057$, $N = 1078$		EDBA (+) $P < 0.0001$, $R^2 = 0.101$, $N = 691$		EDBA (+) $P = 0.0001$, $R^2 = 0.043$, $N = 754$	
Independent variables	OR (95% CI)	*P*-value	OR (95% CI)	*P* value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)	1.073 (1.039–0.108)*	<0.0001*	1.037 (1.018–1.056)*	<0.0001*	1.063 (1.028–1.099)*	0.0003*	1.045 (1.023–1.067)*	<0.0001*
Height (cm)	0.977 (0.938–1.017)	0.2540	0.950 (0.923–0.979)*	0.0006*	0.967 (0.926–1.010)	0.1299	0.953 (0.920–0.988)*	0.0081*
Weight (kg)	1.048 (0.994–1.105)	0.0831	1.061 (1.026–1.097)*	0.0005*	1.058 (1.000–1.119)	0.0509	1.063 (1.022–1.106)*	0.0024*
Waist circumference (cm)	0.946 (0.898–0.997)*	0.0393*	0.974 (0.944–1.004)	0.0903	0.944 (0.893–0.991)*	0.0421*	0.965 (0.930–1.002)	0.0602
Seiza, no vs sometimes	1.323 (0.868–2.016)	0.1928	1.293 (0.937–1.785)	0.1180				
vs daily	2.762 (1.369–5.571)*	0.0045*	1.818 (1.238–2.671)*	0.0023*				
vs previous	0.985 (0.417–2.326)	0.9725	2.134 (1.338–3.404)*	0.0015*				
Alcohol, no vs social	0.857 (0.471–1.560)	0.6143	1.020 (0.741–1.402)	0.9053	1.103 (0.586–2.076)	0.7622	0.938 (0.642–1.371)	0.7404
vs daily	0.833 (0.542–1.279)	0.4032	0.883 (0.581–1.342)	0.5602	0.996 (0.625–1.586)	0.9849	0.877 (0.534–1.439)	0.6031
Smoking, no vs current	0.611 (0.312–1.196)	0.1506	0.756 (0.355–1.607)	0.4669	0.623 (0.313–1.242)	0.1787	0.779 (0.310–1.953)	0.5939
vs previous	0.717 (0.429–1.198)	0.2038	0.857 (0.657–1.119)	0.2575	0.581 (0.340–0.993)*	0.0469*	0.878 (0.637–1.212)	0.4294
Diabetes, normal vs preDM	1.039 (0.650–1.662)	0.8716	1.022 (0.731–1.431)	0.8975	1.036 (0.624–1.720)	0.8912	0.995 (0.658–1.503)	0.9796
vs NDM	2.582 (0.956–6.973)	0.0613	0.498 (0.210–1.183)	0.1142	2.213 (0.788–6.220)	0.1318	0.306 (0.077–1.220)	0.0934
vs KDM	1.77 (1.028–3.05)*	0.0396*	0.81 (0.481–1.381)	0.4479	1.92 (1.094–3.394)*	0.0231*	1.15 (0.603–2.198)	0.6698
Hypertension, ONBP vs EBP	0.78 (0.410–1.514)	0.4749	1.20 (0.789–1.846)	0.3866	0.79 (0.388–1.614)	0.5196	1.12 (0.655–1.913)	0.6790
vs HT	1.27 (0.795–2.041)	0.3134	1.06 (0782–1.450)	0.6881	1.4 (0.841–2.348)	0.1941	1.01 (0.700–1.462)	0.9504
Dyslipidemia, NL vs DL	1. (0.670–1.493)	0.9989	0.82 (0.625–1.082)	0.1615	1.06 (0.692–1.648)	0.7677	0.72 (0.519–1.012)	0.0590
SPN	7.38 (2.957–18.454)*	<0.0001*	2.39 (1.181–4.848)*	0.0155*	6.85 (2.632–17.854)*	<0.0001*	1.47 (0.622–3.491)	0.3790

Statistical analyses were carried out by multivariate logistic regression analysis. *Statistically significant values. CI, confidence interval; DL, dyslipidemia; DM, diabetes mellitus; EBP, elevated blood pressure; EDBA, extensor digitorum brevis muscle atrophy; HT, hypertension; KDM, known diabetes; NDM, newly diagnosed diabetes; NL, normolipidemia; ONBP, optimal/normal blood pressure; OR, odds ratio; preDM, prediabetes; SPN, symmetric polyneuropathy.

Table 3 | Relationships between neurological functions and extensor digitorum brevis muscle atrophy in the participants without daily and previous *seiza* habit by sex or the presence of diabetes

(a)	Participants with diabetes						Participants without diabetes					
	Male			Female		Male vs female	Male			Female		Male vs female
Prevalence of EDBA (+) (*n*)	38/117 (32%)			26/58 (45%)		*P* = 0.1103	95/581 (16%)	*		276/708 (39%)*		*P* < 0.0001*
Prevalence of SPN/DSPN (*n*)	9/117 (8%)			4/58 (7%)		*P* = 0.8501	13/581 (2%)			21/708 (3%)		*P* = 0.4167
	EDBA (–)	EDBA (+)	*P*	EDBA (–)	EDBA (+)	*P*	EDBA (–)	EDBA (+)	*P*	EDBA (–)	EDBA (+)	*P*
AMP right, μV (*n*)	13.5 ± 4.9 (23)*	8.9 ± 6.7 (15)*	0.02	13.1 ± 7.7 (16)	13.0 ± 6.5 (8)	0.9689	16.4 ± 8. (150)	15.3 ± 7.8 (35)	0.5	15.8 ± 7. (168)*	12.6 ± 7.7 (76)*	0.0017*
AMP left, μV (*n*)	13.3 ± 5.7 (23)*	8.1 ± 5.7 (17)*	0.0075*	13.0 ± 7.6 (15)	12.9 ± 5.2 (8)	0.9675	16.0 ± 8. (151)	12.9 ± 6.4 (35)	0.0509	14.8 ± 6.9 (168)*	12.1 ± 6.1 (77)*	0.0027*
AMP impairment (*n*)	2/23 (9%)	5/17 (29%)	0.0883	2/16 (13%)	1/8 (13%)	–	3/151 (2%)	3/37 (8%)	0.0576	3/167 (2%)*	6/77 (8%)*	0.0209*
CV right, m/s (*n*)	51.7 ± 4. (23)	48.1 ± 6. (15)	0.0520	55.8 ± 4. (16)	57.4 ± 3. (8)	0.3535	52.3 ± 4. (149)	52.8 ± 3. (35)	0.5133	56.4 ± 4. (168)	57.1 ± 4. (76)	0.2613
CV left, m/s (*n*)	50.5 ± 3.9 (23)*	47.1 ± 4. (16)*	0.0214*	53.4 ± 5.9 (15)	53.5 ± 4. (8)	0.9678	52.0 ± 4. (151)	51.7 ± 3. (35)	0.7265	55.5 ± 4.3 (167)	55.8 ± 4.1 (74)	0.6198
CV decline (*n*)	3/23 (13%)	6/17 (35%)	0.0957	1/16 (6%)	0/8 (0%)	0.4701	14/151 (9%)	0/36 (0%)	0.0575	6/168 (4%)	0 /78 (0%)	0.0911
QVT right (dB)	21.2 ± 7.6*	24.0 ± 6.4*	0.0492*	19.4 ± 8.3*	24.1 ± 6.2*	0.0182*	19.4 ± 8.0*	22.1 ± 7.3*	0.0023*	16.9 ± 8.5*	18.8 ± 8.4*	0.0038*
QVT left (dB)	21.9 ± 7.6*	25.9 ± 6.6*	0.0074*	19.5 ± 7.8*	23.4 ± 4.4*	0.0291*	19.5 ± 8.0*	22.0 ± 8.5*	0.0069*	17.4 ± 8.8*	19.1 ± 8.4*	0.0121*
QVT impairment (*n*)	3/78 (4%)	3/38 (8%)	0.3467	1/32 (3%)	0/26 (0%)	0.3632	25/486 (5%)	5/95 (5%)	0.9617	26/431 (6%)	12/276 (4%)	0.3326
Symptoms (*n*)	7/79 (9%)	8/38 (21%)	0.065	6/32 (19%)	5/25 (20%)	0.9055	25/486 (5%)	7/95 (7%)	0.3847	42/432 (10%)	23/276 (8%)	0.5325
Reduced ATRs: (*n*)	18/79 (23%)	15/38 (39%)	0.0603	4/32 (13%)	7/26 (27%)	0.1635	61/485 (13%)	18/95 (19%)	0.0979	38/432 (9%)*	50/276 (18%)*	0.0002*
DSPN/SPN (*n*)	1/79 (1%)*	8/38 (21%)*	2E-04*	2/32 (6%)	2/26 (8%)	0.8293	7/486 (1%)*	6/95 (6%)*	0.003*	10/432 (2%)	11/276 (4%)	0.2013

(b)	Sensitivity	Specificity	*P*	Positive predictive value	Negative predictive value	Kappa coefficients	*P*
Participants with diabetes							
Male	89%*	72%*	2E-04*	21%*	99%*	0.2467* (fair agreement)	0.0001*
Female	50%	56%	0.829	8%	94%	0.016	0.4147
Participants without diabetes							
Male	46%*	84%*	0.003*	6%*	99%*	0.0747* (slight agreement)	0.0016*
Female	52%	61%	0.201	4%	98%	0.02	0.1006

(a) Data of quantitative nerve functions tests, prevalence of impairment in each test and symmetric polyneuropathy (SPN)/diabetic symmetric polyneuropathy (DSPN) diagnosed by "Probable DSPN" criteria of the Toronto Consensus. (b) Sensitivity, specificity, positive and negative predictive values and reliability of extensor digitorum brevis muscle atrophy (EDBA) detection in diagnosing DSPN/SPN. Continuous variables were expressed as the mean ± standard deviation, and analyzed by one-way ANOVA. Nominal variables were analyzed by the χ^2-test and Cohen's kappa coefficient method. The participants with daily or previous *seiza* habit were excluded. *Statistically significant values. AMP, nerve action potential amplitude of the sural nerve; ATR, Achilles tendon reflex; CV, conduction velocity of the sural nerve; *n*, number; QVT, quantitative vibratory perception threshold.

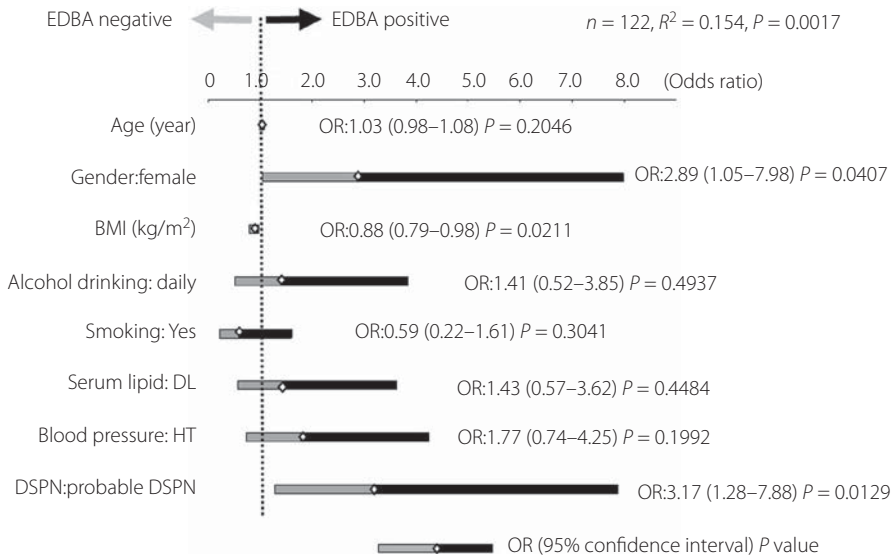

Figure 2 | Female sex, high body mass index (BMI) and diabetic symmetric polyneuropathy (DSPN)were significantly associated with extensor digitorum brevis atrophy (EDBA) in Japanese established diabetes patients by multiple logistic regression analysis. DL, dyslipidemia; HT, hypertension. OR, odds ratio.

Validity of EDBA detection to diagnose DSPN

In men, the prevalence of DSPN in the EDBA (+) group (71%) was significantly higher than that in the EDBA (−) group (33%; Table 4b). The sensitivity, specificity, and positive and negative predictive value of EDBA detection for diagnosing DSPN were 44, 87, 71 and 67%, respectively. The kappa coefficient was calculated as 0.3229 (fair agreement). In contrast, in women, the prevalence of DSPN in the EDBA (+) group (23%) was similar to that in the EDBA (−) group (21%). The sensitivity, specificity and the kappa coefficient were not statistically significant.

DISCUSSION

Investigation I was carried out on the Japanese general population and there were three findings. First, the prevalence of EDBA is clearly higher in women than in men, and the factors related to EDBA, regardless of sex, were aging, *seiza* habit and DSPN/SPN.

A previous Japanese study also reported that EDBA was more prevalent in women than men, and the authors speculated about the involvement of the customs to sit directly on a mat[17]. The cause of the high prevalence of EDBA in women seems be due to the *seiza* habit, which is common in women, but the sex difference in EDBA prevalence was also observed in the participants without *seiza* habits. Therefore, factors other than the *seiza* habit, such as the physiologically small muscle volume of women and a lifestyle of wearing tight shoes with high heels among women are thought to be involved.

The relationship between age and EDBA is not surprising, as the deterioration of EDB as a result of aging has been previously reported[18]. Also, in the *seiza* habit, the deep peroneal nerve and EDB are easily damaged because the dorsal aspect of the ankles is mechanically compressed by the floor or mat. Therefore, the *seiza* habit is thought to elicit EDBA by a similar mechanism to anterior tarsal tunnel syndrome.

Furthermore, EDBA has been reported to occur in distal symmetric polyneuropathy with acute intermittent porphyria[19] or diabetes[7], so a significant association between SPN/DSPN and EDBA is also reasonable.

Of note, all participants with EDBA in the present study were asymptomatic in the area of EDB. The reasons why EDBA is not accompanied by sensory deficits in the EDB region and clinical motor dysfunction are considered as follows. In the case of EDBA according to a *seiza* habit, it is supposed that the long extensor muscles can compensate for the loss of EDB function, and the sensory branch remains intact, like anterior tarsal tunnel syndrome[20]. In contrast, dysfunction of distal symmetric polyneuropathy progresses from the distal end to the proximal of nerve fiber, so the proximal site of the peroneal nerve, which innervates the long extensor muscles and the sensation of dorsal pedis, is preserved.

Second, when analyzed in the population without *seiza* habits, the male-specific EDBA-related factor was known diabetes, whereas the prevalence of SPN/DSPN in men with EDBA was higher than that of those without EDBA. Thus, EDBA could be a biomarker of distal symmetric polyneuropathy in men. In contrast, female-specific EDBA-related factors were short stature and overweight, and the association between EDBA and SPN/DSPN disappeared.

Table 4 | Associated factors with extensor digitorum brevis muscle atrophy and the validity of extensor digitorum brevis muscle atrophy detection to diagnose diabetic symmetric polyneuropathy

(a)	Male (*n* = 79)			Female (*n* = 54)		Male vs female
Prevalence of EDBA (n)	21/79 (27%)*			26/54 (48%)*		P = 0.0106*
Prevalence of DSPN (*n*)	34/79 (43%)*			12/54 (22%)*		*P* = 0.0132*
	EDBA (–)	EDBA (+)	*P*-value	EDBA (–)	EDBA (+)	*P*-value
n	58	21		28*	26*	
Age (years)	56.4 ± 9.7*	61.9 ± 9.2*	0.0293*	59.2 ± 11.0	62.7 ± 11.4	0.2539
Duration of diabetes (year)	12.8 ± 9.1*	20.9 ± 13.9*	0.0049*	15.2 ± 16.1	16.1 ± 11.0	0.7800
Height (cm)	168.1 ± 5.6	166.5 ± 5.7	0.2624	156.0 ± 4.9	154.1 ± 8.1	0.3358
Weight (kg)	73.8 ± 13.7*	64.0 ± 14.3*	0.0077*	63.7 ± 13.9	58.3 ± 13.2	0.1654
Body mass index (kg/m^2)	26.0 ± 4.1*	23.0 ± 4.6*	0.0078*	26.2 ± 5.3	24.5 ± 4.8	0.2438
Alcohol: daily (*n*)	23/53 (43%)	7/21 (33%)	0.4269	1/24 (4%)	4/24 (17%)	0.1563
Smoking: current or previous (*n*)	33/54 (61%)	12/21 (57%)	0.7528	4/24 (17%)	2/24 (8%)	0.3827
HbA1c (%)	8.9 ± 2.1	8.9 ± 2.7	0.9732	8.9 ± 1.9	8.2 ± 2.0	0.2821
Hypertension (*n*)	27/54 (50%)	12/21 (57%)	0.5728	11/24 (46%)	14/24 (58%)	0.3861
Dyslipidemia (*n*)	28/54 (52%)	10/21 (48%)	0.7420	15/24 (63%)	16/24 (67%)	0.7628
Retinopathy: NDR/SDR/PPDR< (%)	61/14/25	40/10/50	0.1387	76/14/10	50/21/29	0.1600
Proteinuria: no/micro/macro (%)	66/17/17	76/5/19	0.3957	83/4/13	75/17/8	0.3490
Autonomic nerve functions						
CV rest impairment (*n*)	18/56 (32%)*	12/19 (63%)*	0.0171*	6/27 (22%)*	16/26 (62%)*	0.0037*
CV deep impairment (*n*)	20/56 (36%)	10/19 (53%)	0.1934	7/27 (26%)	11/26 (42%)	0.2081
Orthostatic hypotension (*n*)	7/58 (12%)*	10/20 (50%)*	0.0004*	2/28 (7%)	4/26 (15%)	0.3356
Nerve conduction parameters						
Ulnar MCV impairment (*n*)	11/36 (31%)	6/11 (55%)	0.1473	1/12 (8%)	3/8 (37%)	0.1101
Ulnar CMAP impairment (*n*)	2/35 (6%)	1/11 (9%)	0.6924	IC	IC	IC
Median SCV impairment (*n*)	20/34 (58%)*	11/11 (100%)*	0.0103*	1/12 (8%)	2/7 (28)	0.2432
Median SNAP impairment (*n*)	8/33 (24%)	5/11 (45%)	0.1817	0/12 (0%)	1/7 (14%)	0.1786
Tibial MCV impairment (*n*)	18/34 (53%)*	10/11 (91%)*	0.0240*	3/13 (23%)*	6/7 (85%)*	0.0072*
Tibial CMAP impairment (*n*)	10/34 (29%)*	8/11 (73%)*	0.0108*	3/13 (23%)	2/7 (29%)	0.7866
QVT impairment (*n*)	6/58 (10%)*	10/21 (48%)*	0.0003*	1/28 (4%)	5/26 (19%)	0.0673
Neuropathic symptoms (*n*)	21/58 (36%)*	14/21 (67%)*	0.0161*	6/28 (21%)	10/26 (38%)	0.1708
Reduced ATRs: (*n*)	25/58 (43%)*	17/21 (81%)*	0.0029*	12/28 (43%)	12/26 (46%)	0.8075
DSPN (*n*)	19/58 (33%)*	15/21 (71%)*	0.0022*	6/28 (21%)	6/26 (23%)	0.8843

(b) DSPN	Sensitivity	Specificity	*P* value	P/N predictive value	Kappa coefficients	*P*
Male	44 (%)*	87 (%)*	0.0022*	71%/67%*	0.3229 (fair agreement)	0.0011*
Female	50 (%)	52 (%)	0.8843	23% /78%	0.0168	0.4421

(a) Relationships between clinical factors, neurological dysfunctions and EDBA in diabetic patients by gender. (b) Sensitivity, specificity, positive and negative predictive values, and reliability of extensor digitorum brevis muscle atrophy (EDBA) to diagnose diabetic symmetric polyneuropathy (DSPN) in established diabetic patients. Continuous variables were expressed as mean ± standard deviation, and analyzed by one-way ANOVA. Nominal variables were analyzed by the χ^2-test and Cohen's kappa coefficient methods. *Statistically significant values. ATR, Achilles tendon reflex; CMAP, compound muscle action potential; CV, coefficient of variation in R-R interval of electrocardiogram; EDB, extensor digitorum brevis muscle; IC, incalculable; Macro, macroalbuminuria; MCV, motor nerve conduction velocity; Micro, microalbuminuria; *n*, number; NDR, no diabetic retinopathy; No, no-albuminuria; P/N, positive/negative; PPDR<, proproliferative diabetic retinopathy or more; QVT, quantitative vibratory perception threshold; SCV, sensory nerve conduction velocity; SDR, simple diabetic retinopathy; SNAP, sensory nerve action potential.

Third, in male participants without a *seiza* habit, EDBA was significantly associated with SPN/DSPN in participants with and without diabetes, and EDBA detection was thought to be useful for diagnosing DSPN in individuals with diabetes or SPN in individuals without diabetes.

Although the sensitivity and specificity of EDBA detection for diagnosing DSPN or SPN were statistically significant, the positive predictive value was as low as 21% in men with diabetes, and 6% in men without diabetes. This is thought to be due to the low prevalence of DSPN in men with diabetes at 8%, and SPN in men without diabetes at 2%. Although the impression might be that the prevalence of DSPN is too low, we and Chinese researchers have reported similar results in a survey of the general population[3,21]. As for the reliability of EDBA detection for diagnosing polyneuropathies, the kappa coefficient of SPN (0.0747) was lower than that of DSPN

(0.2467), so, the validity of predicting SPN seems to not be sufficient because of the rarity of SPN.

Investigation II was carried out to confirm the validity of EDBA detection for diagnosing DSPN in established diabetes patients. The prevalence of EDB atrophy in women (48%) is higher than in men (27%), and multivariate logistic regression analysis showed that female sex is significantly associated with EDBA. When we examined the EDBA-related factors separately by sex, many factors were associated with EDBA in men, such as autonomic and nerve conduction dysfunctions, neuropathic symptoms/signs, and DSPN. However, just two factors were associated in women. Therefore, the effectiveness of EDBA detection for diagnosing DSPN appears to be sufficient in men but not women.

Regarding the reliability of EDBA detection for diagnosing DSPN, the specificity (87%) and positive predictive value (71%) were good, and a fair agreement was obtained (kappa coefficient 0.3229). The reason for the relatively low sensitivity (44%) might be that EDBA reflects moderate DSPN rather than early DSPN. Actually, the prevalence of EDBA (27%) was lower than that of DSPN (43%) or impaired nerve conduction velocities (ulnar MCV: 36%, median sensory nerve conduction velocity: 50%, tibial MCV: 62%, calculated from Table 4a). Impaired nerve conduction velocity is accepted as an indicator of early DSPN. The lack of association between prediabetes or newly diagnosed diabetes and EDBA in investigation I might also support that EDBA is not an early sign of DSPN. EDBA might be a sign of increasing diagnostic accuracy or determination of severity for DSPN.

Summary is as follows. First, in the Japanese general population, the factors significantly associated with EDBA were aging, female sex, *seiza* habit and distal symmetric polyneuropathy. Second, in the male general population without a *seiza* habit, EDBA was significantly associated with SPN in participants without diabetes or DSPN in participants with diabetes. Third, EDBA detection was useful for diagnosing moderate DSPN not only in the men with diabetes included in health checkup examinees, but also in established men with diabetes in a specialty clinic for diabetes.

The regular screening of sensations, such as temperature, pinprick, vibration and light touch with 10-g monofilament, has been recommended by the American Diabetes Association guidelines[22]. However, there is no convenient method to assess the motor neuropathy of the distal part of the legs in routine clinical practice. Studies using magnetic resonance imaging in patients with DSPN have found that muscle atrophy was more pronounced in the distal lower extremities, and that remarkable atrophy[23] was found in all the intrinsic muscles[24]. In addition, Severinsen *et al.*[25] reported that EDB and intrinsic muscle mass measured by ultrasonography had significantly correlated with magnetic resonance imaging findings, vibratory perception thresholds, and peroneal MCV and CMAP, and that ultrasonography might be useful for detection of foot muscle atrophy in diabetes patients. Although the method of using these diagnostic imaging devices are objective and accurate, they are not methods that can be easily carried out in daily clinical practice. In contrast, detection of bilateral EDBA by visual inspection and palpation can be easily carried out anywhere in a short time in daily practice. Therefore, we would like to conclude that EDBA detection is a useful method to screen for distal symmetric polyneuropathy, such as DSPN in men, but it is necessary to exclude individuals with daily or previous *seiza* habits to improve accuracy. Of course, to confirm the diagnosis, differential diagnosis is necessary by subjective symptoms, ATR test, vibration sensory test by tuning fork and preferably a nerve conduction test.

One limitation of the present study was that the effect of a *seiza* habit in established diabetes patients was not evaluated. For established diabetes patients, further studies are required, including question on a *seiza* habit. Another limitation was that our investigations were carried out in Japanese people who have a unique traditional sitting style called *seiza*. Therefore, the results might be different in other groups of different races or traditional lifestyles. A report from Sweden also showed that EDBA was useful for screening DSPN[7]. Therefore, the difference among races might not be important. In contrast, traditional habits of sitting on the floor, cross-legged or kneeling that might cause EDBA are also seen in Asia and the Middle East[8]. Also, a report from Korea showed a correlation between traditional sitting on mats and thinner EDB on ultrasonography[26]. Therefore, it might be necessary to consider the traditional customs of each country and community when evaluating the validity of EDBA detection for screening distal symmetric polyneuropathies, such as DSPN.

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DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Tesfaye S, Malik RA, Boulton AJ, *et al*. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010; 33: 2285–2293.
2. Ziegler D, Strom A, Lobmann R, *et al*. High prevalence of diagnosed and undiagnosed polyneuropathy in subjects with and without diabetes participating in a nationwide educational initiative (PROTECT study). *J Diabetes Complicat* 2015; 29: 998–1002.
3. Kurisu S, Sasaki H, Kishimoto S, *et al*. Clinical polyneuropathy does not increase with prediabetic or metabolic syndrome in the Japanese general population. *J Diabetes Investig* 2019; 10: 1565–1575.
4. Krause KH, Witt T, Ross A. The anterior tarsal tunnel syndrome. *J Neurol* 1977; 217: 67–74.

5. Sinanovic O, Custovic N. Musculus extensor digitorum brevis is clinical and electrophysiological marker for L5/S1 radicular lesions. *Med Arh* 2010; 64: 223–224.
6. Munakomi S, Kumar BM. Wasting of extensor digitorum brevis as a decisive preoperative clinical indicator of lumbar canal stenosis: a single-center prospective cohort study. *Ann Med Health Sci Res* 2016; 6: 296–300.
7. Lithner F, Bergenheim T, Borssén B. Extensor digitorum brevis in diabetic neuropathy: a controlled evaluation in diabetic patients aged 15–50 years. *J Intern Med* 1991; 230: 449–453.
8. Al-Hashel JY, Rousseff RT, Khuraibet AJ, *et al*. Isolated asymptomatic atrophy of the extensor digitorum brevis muscle. *Muscle Nerve* 2020; 61: E10–E11.
9. Baba M, Suzuki C, Arai A, *et al*. Extensor digitorum brevis muscle in diabetic patients. *J Peripher Nerv Syst* 2009; 14(S2): 10–11.
10. Limpawattana P, Kotruchin P, Pongchaiyakul C. Sarcopenia in Asia. *Osteoporos Sarcopenia* 2015; 1: 92–97.
11. Yamasaki H, Sasaki H, Ogawa K, *et al*. Uncoupling protein 2 promoter polymorphism-866G/A affects peripheral nerve dysfunction in Japanese type 2 diabetic patients. *Diabetes Care* 2006; 29: 888–894.
12. Neurometrix. NC-stat DPNCheck™ User Manual, 2013. Available from: http://www.dpncheck.com/wp-content/uploads/2017/08/nc-stat_dpncheck_user_manual_pn2203282_rev_g.pdf. Accessed May 27, 2020.
13. Hirayasu K, Sasaki H, Kishimoto S, *et al*. Difference in normal limit values of nerve conduction parameters between Westerners and Japanese people might need to be considered when diagnosing diabetic polyneuropathy using a Point-of-Care Sural Nerve Conduction Device (NC-stat®/DPNCheck™). *J Diabetes Investig* 2018; 9: 1173–1181.
14. Hanewincke R, Van Oijen M, Ikram MA, *et al*. The epidemiology and risk factors of chronic polyneuropathy. *Eur J Epidemiol* 2016; 31: 5–20.
15. Baba M, Suzuki C, Ogawa Y. Severity grading system of diabetic neuropathy in type-2 diabetes by nerve conduction study: five-year prospective study on occurrence of diabetic foot, macroangiopathic events, and eventual death. *Japn J Clin Neurophysiol* 2018; 46: 71–77 [Japanese].
16. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33: 159–174.
17. Mimura E, Hasegawa O, Kirigaya N, *et al*. Isolated extensor digitorum brevis involvement in the population of normal systemic nerve conduction velocities. *No To Shinkei* 2000; 52: 969–972 [Japanese].
18. Campbell MJ, McComas AJ, Petito F. Physiological changes in ageing muscles. *J Neurol Neurosurg Psychiatry* 1973; 36: 174–182.
19. Wikberg A, Andersson C, Lithner F. Signs of neuropathy in the lower legs and feet of patients with acute intermittent porphyria. *J Intern Med* 2000; 248: 27–32.
20. Logullo F, Ganino C, Lupidi F, *et al*. Anterior tarsal tunnel syndrome: a misunderstood and a misleading entrapment neuropathy. *Neurol Sci* 2014; 35: 773–775.
21. Lu B, Hu J, Wen J, *et al*. Determination of peripheral neuropathy prevalence and associated factors in Chinese subjects with diabetes and pre-diabetes – ShangHai diabetic neuRopathy Epidemiology and Molecular Genetics Study (SHDREAMS). *PLoS One* 2013; 8: e61053.
22. American Diabetes Association. 11. Microvascular complications and foot care: standards of medical care in diabetes. *Diabetes Care* 2020; 43(Suppl. 1): S135–S151.
23. Andersen H, Gadeberg PC, Brock B, *et al*. Muscular atrophy in diabetic neuropathy: a stereological magnetic resonance imaging study. *Diabetologia* 1997; 40: 1062–1069.
24. Bus SA, Yang QX, Wang JH, *et al*. Intrinsic muscle atrophy and toe deformity in the diabetic neuropathic foot: a magnetic resonance imaging study. *Diabetes Care* 2002; 25: 1444–1450.
25. Severinsen K, Obel A, Jakobsen J, *et al*. Atrophy of foot muscles in diabetic patients can be detected with ultrasonography. *Diabetes Care* 2007; 30: 3053–3057.
26. Seok JI, Walker FO, Kwak SG. Evaluation of extensor digitorum brevis thickness in healthy subjects: a comparative analysis of nerve conduction studies and ultrasound scans. *Clin Neurophysiol* 2016; 127: 1664–1668.