【 ORIGINAL ARTICLE 】

Relationship between the Diabetic Polyneuropathy Index and the Neurological Findings of Diabetic Polyneuropathy

Shoji Hemmi[1], Katsumi Kurokawa[2], Taiji Nagai[3], Keiichi Yokoi[1], Toshio Okamoto[4],
Akio Asano[4], Tatsufumi Murakami[1], Masahito Mihara[1] and Yoshihide Sunada[1]

Abstract:
Objective To achieve an accurate quantification in diabetic polyneuropathy (DPN), we developed a new electrophysiological index that we called the DPN index. The relationship between the DPN index and the neurological findings in diabetic patients was assessed.

Methods The DPN index was calculated by the mean value of percentages of four parameters (tibial compound muscle action potential amplitude / F wave minimum latency, sural sensory nerve action potential amplitude / sensory nerve conduction velocity) against the mean normal values. Twenty healthy subjects were recruited as a control group.

Patients A total of 348 diabetic patients who were hospitalized in our hospital during the period from December 2016 to August 2019 were retrospectively studied. The correlations between the DPN index and five neurological findings (subjective sensory symptoms, diminished or absent Achilles tendon reflex, impaired tactile and vibration sense, low coefficient of variation of R-R interval) were evaluated.

Results The DPN index in healthy subjects was 129.3±32.7%. The DPN index in diabetic patients with one or more neurological findings was significantly lower than that in diabetic patients without any neurological findings (p<0.01: 89.3±27.8% vs. 118.4±21.2%). For each of the five neurological findings, the DPN index in the group with an abnormality was significantly lower than that in the group without any abnormality (each p<0.01). Spearman's correlation coefficients indicated that a greater number of neurological findings resulted in a lower DPN index (r=-0.711, p<0.01).

Conclusion Our study suggested that the DPN index is useful for evaluating the severity of DPN.

Key words: diabetes, diabetic polyneuropathy index, compound muscle action potential, F wave minimum latency, sensory nerve action potential, sensory nerve conduction velocity

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Introduction

Diabetic polyneuropathy (DPN) is the most common type of distal symmetric sensorimotor polyneuropathy and it is a frequent complication of both type 1 and type 2 diabetes (1). Since DPN is a major risk factor for the development of diabetic foot complications (2, 3) and one of the risk factors of other life-threatening events, it is very important to evaluate the condition of the peripheral nervous system in diabetic patients.

A nerve conduction study (NCS) is considered to be the most sensitive diagnostic tool for DPN (4). Several electrophysiological scores for assessing DPN have been developed including Nerve Conduction Sum score (5), Σ 5 NC nds (6), and Baba's Diabetic Neuropathy classification (BDC) (7). These are severity grading systems that select and evaluate several nerves by NCS. For example, the Nerve Conduction Sum score includes four motor nerves (median, ulnar, tibial, and common fibular nerves) and three sensory nerves (median, ulnar, and sural nerves) and consists of seven stages ranging from 0 (all normal) to 7 (all abnormal). In the Σ 5

NC nds, five parameters are selected from three nerves (common fibular, tibial, and sural nerves) and scored. The BDC includes two nerves (tibial and sural nerves) and consists of five stages ranging from BDC-0 (normal) to BDC-4 (ultimately abnormal). In addition to these severity grading systems, we thought that a quantitative evaluation system by NCS could provide more objective findings and also be useful for clinical research in diabetic patients.

The aim of this study was to develop a new quantitative evaluation index for NCS in diabetic patients. We called this index the DPN index. In order to confirm the usefulness of the DPN index, the relationship between the DPN index and the neurological findings in diabetic patients was retrospectively assessed in this study.

Materials and Methods

Subjects

A total of 348 diabetic patients who were hospitalized in our hospital during the period from December 2016 to August 2019 and were referred to the electrodiagnostic laboratory were retrospectively investigated. No previous history of other diseases known to induce peripheral neuropathy was confirmed by a medical chart review and routine NCS. The routine NCS included motor and sensory NCS of the median and ulnar nerves, motor NCS of the tibial nerve, sensory NCS of the sural nerve, and F-wave studies of the median and tibial nerves.

Twenty healthy volunteers were recruited as normal controls and underwent routine NCS. Individuals with a previous history of diabetes, and other diseases known to induce peripheral neuropathy were excluded. All healthy volunteers gave their signed informed consent form before evaluation. However, we did not obtain informed consent from diabetic patients because all clinical and nerve conduction data were investigated retrospectively from medical chart reviews. The Ethics Committee of Kawasaki Medical School and Hospital approved this study.

DPN index

All NCSs for diabetic patients and normal controls were performed using an electromyography machine (Neuropack MEB-2216; Nihon Kohden, Tokyo, Japan). The subjects lay in a supine position with a relaxed posture. Skin temperature was maintained at ≥32℃. The skin of the recording sites was cleaned with alcohol to decrease impedance.

To obtain the DPN index, the following four parameters from two nerves (tibial and sural nerves) were used: amplitude of distal tibial compound muscle action potential (CMAP), tibial F wave minimum latency, amplitude of sural sensory nerve action potential (SNAP), and sural sensory nerve conduction velocity (SCV). Peak-to-peak amplitude was used for the amplitude measurement, and sural SCV was calculated using the onset latency. The DPN index was calculated as the mean value of the percentages of these four parameters against the mean normal values. Values of 19.06 mV for distal tibial CMAP (8) and 43.26 m/s for sural SCV (9) were used as mean normal values. F wave latencies are proportional to height. Therefore, the values should be compared with height-adjusted normal values. We calculated the value of F wave latencies using the following formula: tibial F wave latency (ms)=0.436×height (cm)-27.01 (10). Since the sural SNAP amplitude decreases with aging (11, 12), age-adjusted mean normal values (13) were used: 14.0 μV for 15-24 years of age, 13.0 μV for 25-34 years of age, 12.0 μV for 35-44 years of age, 10.0 μV for 45-54 years of age, 9.0 μV for 55-64 years of age, 8.0 μV for 65 years of age or older. If tibial CMAP or tibial F wave or sural SNAP was absent, the parameter was considered to be 0%.

We calculated the DPN indexes in all diabetic patients and normal controls. When NCSs had been performed bilaterally, the results from the left and right sides were averaged for the analysis. Fig. 1 shows examples of actual calculations for the DPN index.

Neurological examinations

All diabetic patients were asked whether they had subjective sensory symptoms (numbness, tingling, burning, and pain) and they received the following neurological examinations: Achilles tendon reflex (ATR), tactile and vibration sense, and coefficient of variation of R-R interval (CVR-R). All neurological examinations were performed by experienced physicians. For a diagnosis of an impaired tactile sense, the 4-g Semmes Weinstein monofilament was used according to a previously reported study (14) and was tested on the hallux and little finger. A decreased vibration sense was assessed on the medial malleolus by a 128-Hz tuning fork (<7 s). Impairment of the autonomic nervous system was assessed by CVR-R on an electrocardiogram (<2.0%). Strictly, CVR-R is not a neurological examination, but we included it in the neurological examinations because it is routinely used to evaluate autonomic nervous systems in diabetic patients.

Grouping of diabetic patients on the basis of clinical findings

To evaluate correlations with the DPN index, diabetic patients were divided into groups with various conditions: (1) a group with one or more neurological findings and a group without neurological findings, (2) two groups according to the presence and absence of each of the neurological findings, and (3) a group with a duration of diabetes of more than 10 years and a group with a duration of diabetes of less than 10 years. Furthermore, diabetic patients were divided into six groups according to the total number of neurological findings (0 to 5).

Statistical analysis

A statistical analysis using the Mann-Whitney U test was carried out to compare the values in two groups of diabetic
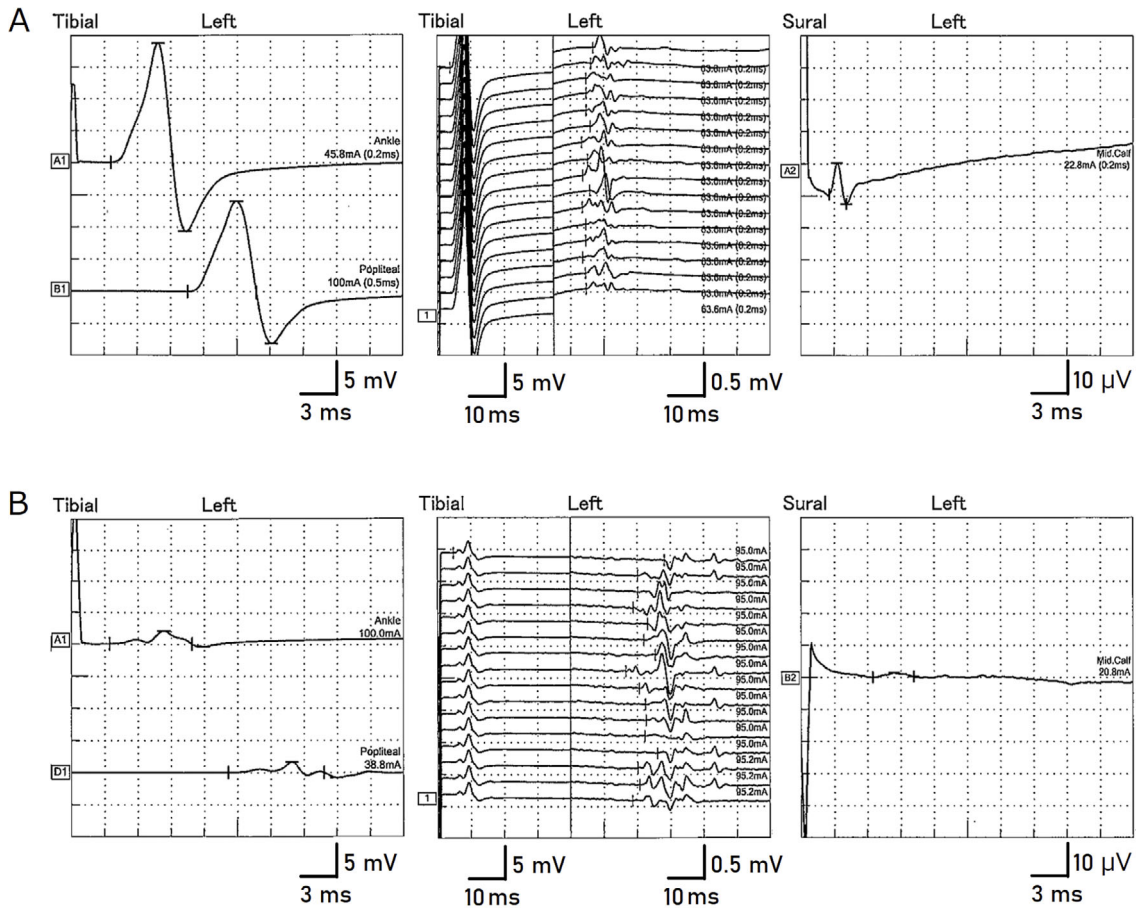
Figure 1. Examples of calculating the DPN index in a normal control (A) and a diabetic patient (B). Normal control: a 46-year-old woman with a height of 158 cm. Distal tibial CMAP amplitude was 29.9 mV, tibial F wave minimum latency was 43.5 ms, sural SNAP amplitude was 15.0 µV, and sural SCV was 54.3 m/s. Height-adjusted normal tibial F wave latency (ms)=0.436×158 (cm)-27.01=41.9. DPN index (%)=(29.9/19.06+41.9/43.5+15.0/10.0+54.3/43.26)/4×100=132.2. Diabetic patient: a 56-year-old man with a height of 179 cm. Distal tibial CMAP amplitude was 2.5 mV, tibial F wave minimum latency was 56.6 ms, sural SNAP amplitude was 1.7 µV, and sural SCV was 24.1 m/s. Height-adjusted normal tibial F wave latency (ms)=0.436×179 (cm)-27.01=51.0. DPN index (%)=(2.5/19.06+51.0/56.6+1.7/9.0+24.1/43.26)/4×100=44.5. DPN: diabetic polyneuropathy, CMAP: compound muscle action potential, SNAP: sensory nerve action potential, SCV sensory nerve action potential

patients or normal controls. Spearman's correlation coefficients were used to evaluate the correlations between the DPN index and the number of neurological findings. For descriptive statistics, the mean and standard deviations were calculated. P values <0.05 were considered to be statistically significant.

Results

Subjects

The diabetic patients included 204 men and 144 women with a mean age of 60.5±14.6 years and age range of 16 to 90 years. There were 29 patients with type 1 diabetes and 319 patients with type 2 diabetes. Diabetes had been present for 0.5 to 50 years with a mean duration of 12.5±10.1 years. The duration of diabetes was more than 10 years in 198 pa-

tients (56.9%). The mean body mass index (BMI) in the diabetic patients was 25.5±5.7.

There were 250 diabetic patients (71.8%) with one or more neurological findings. The mean age of those patients was 63.1±13.6 years and the mean duration of diabetes was 14.3±10.5 years. Of those 250 patients, 128 patients (36.8%) had one or more subjective sensory symptoms, 150 patients (43.1%) had diminished or absent ATR, 130 patients (37.4%) had an impaired tactile sense, 87 patients (25.0%) had a decreased vibration sense, and 113 patients (33.7%) had low CVR-R.

There were 98 diabetic patients (28.2%) without any neurological findings. The mean age of those patients was 53.9 ±15.2 years and the mean duration of diabetes was 7.7±7.4 years. There were statistically significant differences in the mean age and mean duration of diabetes between those patients and diabetic patients with one or more neurological

Table.   DPN Indexes in Diabetic Patients and Normal Controls.

		Diabetic patients			p value		
		Controls (1) (n=20)	Symptomatic (2) (n=250)	Asymptomatic (3) (n=98)	1 vs. 2	1 vs. 3	2 vs. 3
Tibial CMAP	(mV)	26.1±11.6	17.2±7.8	23.3±7.2			
	(%)	136.8±61.0	90.1±41.1	122.3±37.5	<0.01	0.54	<0.01
Tibial F latency	(ms)	44.7±4.1	49.7±6.1	46.4±3.9			
	(%)	97.8±8.8	86.3±16.4	94.8±7.2	<0.01	0.2	<0.01
Sural SNAP	(μV)	16.6±9.8	7.6±5.6	14.3±6.5			
	(%)	168.3±91.8	84.1±58.3	146.3±64.5	<0.01	0.49	<0.01
Sural SCV	(m/s)	49.5±3.8	41.8±12.6	47.7±5.2			
	(%)	114.5±8.8	96.5±29.0	110.2±12.1	<0.01	0.09	<0.01
DPN index	(%)	129.3±32.7	89.3±27.8	118.4±21.2	<0.01	0.65	<0.01

Data are means±standard deviation. DPN: diabetic polyneuropathy, CMAP: compound muscle action potential, SNAP: sensory nerve action potential, SCV: sensory nerve conduction velocity
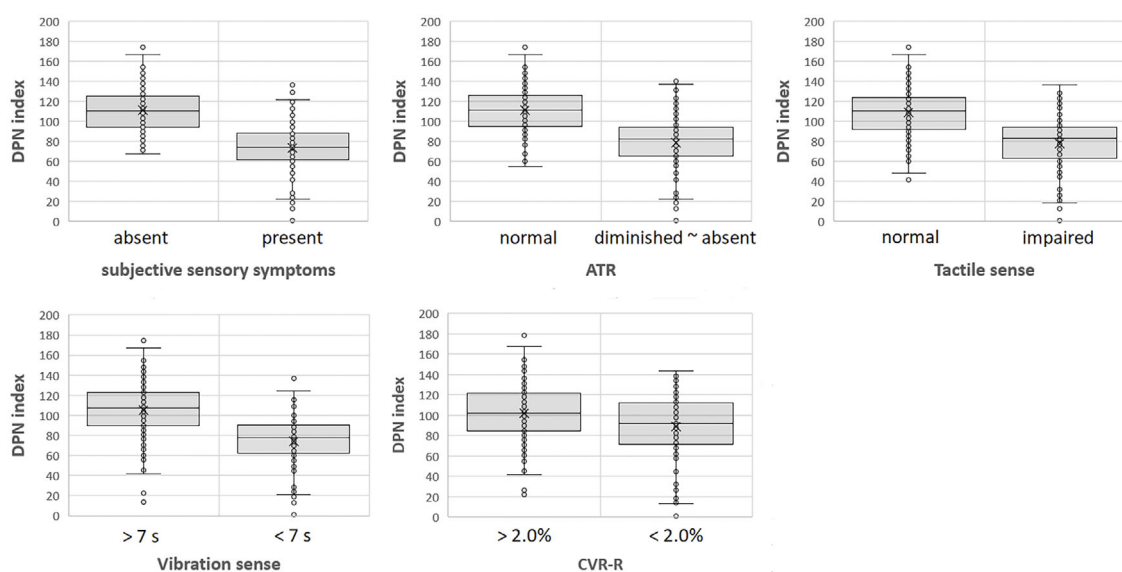
Figure 2.   Correlations between the DPN index and neurological findings. The DPN index in the group with an abnormality was significantly lower than that in the group without any abnormality (each p<0.01). DPN: diabetic polyneuropathy, ATR: Achilles tendon reflex, CVR-R: coefficient of variation of R-R interval

findings (each p<0.01).

The total number of neurological findings from 0 to 5 were 0 in 95 patients, 1 in 76 patients, 2 in 69 patients, 3 in 41 patients, 4 in 28 patients, and 5 in 26 patients (n=335). Thirteen patients were excluded from this analysis since CVR-Rs had not been obtained due to arrhythmia.

Normal controls included seven men and thirteen women with a mean age of 54.9±19.2 years and age range of 20 to 81 years. The mean BMI in the normal controls was 22.8± 3.3.

DPN index

The DPN index in the normal controls was 129.3±32.7%, and the 95th percentile cutoff value was 98.1%. The details of the DPN index in normal controls and diabetic patients are summarized in Table. The DPN index in diabetic pa-

tients with one or more neurological findings was significantly lower than that in diabetic patients without any neurological findings (p<0.01: 89.3±27.8% vs. 118.4±21.2%) and it was obviously lower than that in normal controls (p< 0.01). For each of the five neurological findings (subjective sensory symptoms, ATR, tactile and vibration sense, CVR-R), the DPN index in the group with an abnormality was significantly lower than that in the group without an abnormality (Fig. 2; each p<0.01). Spearman's correlation coefficients indicated that a greater number of neurological findings resulted in a lower DPN index (Fig. 3; r=-0.711, p< 0.01). The DPN index in the group with a duration of diabetes of more than 10 years was significantly lower than that in the group with a duration of diabetes of less than 10 years (p<0.01: 89.8±29.7% vs. 107.6±25.3%).
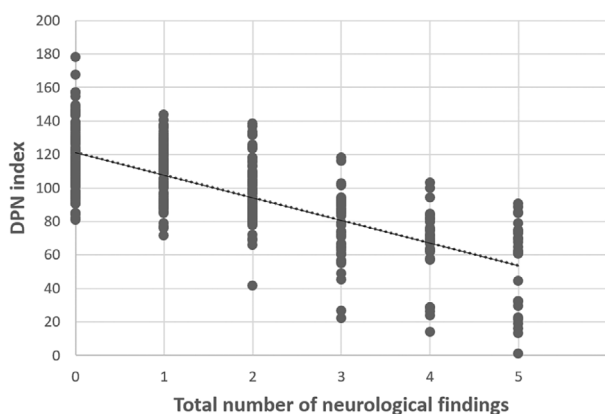
Figure 3.   **Correlations between the DPN index and the total number of neurological findings. Spearman's correlation coefficients indicated that a greater number of neurological findings resulted in a lower DPN index (r=-0.711, p<0.01). DPN: diabetic polyneuropathy**

Discussion

This study demonstrated that the DPN index has a strong relationship with the neurological findings of DPN. The DPN index in diabetic patients with neurological findings was significantly lower than that in diabetic patients without any neurological findings. The values of the DPN index correlated negatively with the number of major neurological findings and decreased with an increase in the number of neurological findings. Since the DPN index is a quantitative index, we regard it as a tool to accommodate serial evaluation for polyneuropathies which either become aggravated or improve over time.

NCS of the lower extremities seems to be more sensitive than that of the upper extremities for detecting DPN. This observation is consistent with the more pronounced clinical involvement of the legs in DPN (15). In accordance with a precedent (7), we decided to use two nerves (tibial and sural nerves) of the lower extremity for the analysis of the DPN index. Two nerves (median and ulnar nerves) of the upper extremity were excluded due to less sensitivity in the diagnosis of length-dependent neuropathy and vulnerability to entrapment neuropathies such as carpal tunnel syndrome and cubital tunnel syndrome.

Since the feet are most commonly affected in length-dependent neuropathy, NCS of the more distal plantar nerves is more sensitive as an indicator of neuropathy than are sural studies (16-19). However, the small amplitude evoked response and difficult NCS procedure have limited the routine use of medial or lateral plantar NCS (19). Since we aimed to make the DPN index simple and easy to use and since both low amplitude SNAPs and slow SCVs in the sural nerve are major findings in DPN (20), we used the sural nerve instead of the medial or lateral plantar nerve for the analysis.

The F wave gives information about the whole length of

the motor nerve fiber. In mild neuropathies, in which nerve fibers are damaged uniformly, testing the total length of a nerve with the F wave should be beneficial for detecting a mild conduction abnormality (21-23). Since a prolonged tibial F wave minimum latency is the most sensitive nerve conduction parameter in DPN (24), we used it for the analysis of the DPN index.

Nerve conduction abnormalities are proportional to the duration of the disease (25). According to Gregerson (26), fibular MCV decreased with an increase in time since the onset of diabetes. Kraft et al. reported that fibular MCVs over a period of 1 to 8 years in diabetic patients decreased by a mean value of 8.8 m/s (27). Our study showed that the DPN index decreased with increase in time since the onset of diabetes. A comparison of patients with a long duration of diabetes and those with a short duration of diabetes clearly confirmed that patients with a long duration of diabetes had a lower DPN index. The difference in the DPN index was decisively significant when comparing a group with diabetes for more than 30 years (n=31) to a group with diabetes for less than 5 years (n=98) (p<0.01: 73.7±29.9% vs. 110.3±26.0%).

In our study, the DPN index in normal controls was 129± 32.7%, nearly 30% higher than the data calculated by the mean normal values. Although the values of conduction velocities (tibial F minimum latency, sural SCV) were almost the same as the mean normal values (97.8±8.8%, 114.5± 8.8%), the values of amplitudes (tibial CMAP, sural SNAP) were higher than the mean normal values (136.8±61.0%, 168.3±91.8%) (Table). We thought that the presence of supernormal values was one of the reasons for a higher DPN index. For example, the amplitude of sural SNAP was unusually high (38.5 μV) in a normal subject aged 48 years. Since the age-adjusted mean normal value is 10.0 μV for 45-54 years of age, the amplitude of SNAP was much larger than 100% (385%). This greatly affected the DPN index and the value in the subject became very high (190.5%). Unusually high amplitudes of CMAP or SNAP are not usually given consideration because the values are considered to be supernormal rather than pathological, but the presence of supernormal values should have caused a higher DPN index. In addition, the racial and physical differences between American and Japanese subjects might have influenced the values of DPN index since normal values differ depending on the country and region. In our study, we used values of the Neuromuscular Disease Clinic at the University of Alabama at Birmingham (UAB) as mean normal values (8-10, 13). Because of the widely ranging amplitudes of CMAP or SNAP, we recommend the use of the 95th percentile cutoff value as the lower limit of normal values in the DPN index rather than standard deviation.

Our method using the DPN index has some limitations in a clinical setting. First, the sensitivity for diagnosis might decrease in individuals in whom premorbid values are supernormal because the values of the DPN index are obtained by comparison with a mean normal value. Second, in elderly

people, the values of the DPN index might be smaller than the true values because the sural SNAP amplitude sometimes cannot be recorded even in healthy people over the age of 70 years (11, 12). Third, because known causes of small-fiber neuropathy include diabetes (28), it might not be possible to determine abnormalities by the DPN index in some DPN patients, even if they have subjective sensory symptoms.

Conclusion

Our study demonstrated that the DPN index provides more objective findings and it is useful for clinical evaluations in diabetic patients. The clinical utility of diagnostic tests depends on simplicity and reliability. The method described in this paper fulfils those criteria. Since prospective studies would be needed to evaluate the superiority of the DPN index to the others, we will next perform a detailed prospective investigation to confirm the effectiveness of our method for estimating the prognosis of DPN.

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

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