

# Lumos for the long trail: Strategies for clinical diagnosis and severity staging for diabetic polyneuropathy and future directions

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Baba's classification, Diabetic polyneuropathy, DPNCheck

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## ABSTRACT

Diabetic polyneuropathy, which is a chronic symmetrical length-dependent sensorimotor polyneuropathy, is the most common form of diabetic neuropathy. Although diabetic polyneuropathy is the most important risk factor in cases of diabetic foot, given its poor prognosis, the criteria for diagnosis and staging of diabetic polyneuropathy has not been established; consequently, no disease-modifying treatment is available. Most criteria and scoring systems that were previously proposed consist of clinical signs, symptoms and quantitative examinations, including sensory function tests and nerve conduction study. However, in diabetic polyneuropathy, clinical symptoms, including numbness, pain and allodynia, show no significant correlation with the development of pathophysiological changes in the peripheral nervous system. Therefore, these proposed criteria and scoring systems have failed to become a universal clinical end-point for large-scale clinical trials evaluating the prognosis in diabetes patients. We should use quantitative examinations of which validity has been proven. Nerve conduction study, for example, has been proven effective to evaluate dysfunctions of large nerve fibers. Baba's classification, which uses a nerve conduction study, is one of the most promising diagnostic methods. Loss of small nerve fibers can be determined using corneal confocal microscopy and intra-epidermal nerve fiber density. However, no staging criteria have been proposed using these quantitative evaluations for small fiber neuropathy. To establish a novel diagnostic and staging criteria of diabetic polyneuropathy, we propose three principles to be considered: (i) include only generalizable objective quantitative tests; (ii) exclude clinical symptoms and signs; and (iii) do not restrictively exclude other causes of polyneuropathy.

## SIGNIFICANCE OF DIAGNOSIS OF DIABETIC POLYNEUROPATHY FOR DIABETES PATIENTS

The International Diabetes Federation estimates 8.8% of adults in 2017 had diabetes mellitus and the prevalence will expand to 9.9% by 2045<sup>1</sup>. In the International Diabetes Federation report, the global prevalence of diabetic foot is estimated to be 6.4% among diabetes patients. We, clinician scientists, must provide freedom of choice to these patients to live as healthy lives as people without diabetes.

The present review focuses on typical diabetic polyneuropathy (DPN), which is a chronic, symmetrical, length-dependent

sensorimotor polyneuropathy, because it is thought to be the most common form of diabetic neuropathy. DPN is the most important risk factor for cases of diabetic foot, including foot ulcers and amputations. However, at present, diabetic foot and other complications, such as cardiovascular events, end-stage renal disease and blindness, have not been sufficiently prevented, regardless of how strictly patients control their blood glucose levels. Particularly in type 2 diabetes, various factors other than hyperglycemia often coexist and impair a healthy lifestyle, such as the following: eating habits including fast eating<sup>2</sup>, low frequency of breakfast intake<sup>3</sup>, higher intakes of red and processed meats<sup>4</sup>, low physical activity, and overworking including night shift work<sup>5</sup>. Therefore, it is mainstream in

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current diabetes care to simultaneously intervene in individual factors; that is, obesity, dyslipidemia, smoking, hyperuricemia and hypertension, to obtain an overall risk reduction. As a representative disease concept, a metabolic syndrome has been defined by a cluster of interconnected factors that increase the risk of cardiovascular atherosclerotic diseases and type 2 diabetes. The concept is used worldwide for enlightenment and prevention of arteriosclerosis. The strategy of enlightenment and prevention are authorized by various large-scale randomized clinical studies<sup>6–11</sup> in which an atherosclerotic change; that is, thickening of the intima-media thickness, occurs in metabolic syndrome patients, and the thickening significantly correlates with cardiovascular events. The multifactorial intervention is allowed in community-level populations without an assessment of the presence and progress/remission of atherosclerotic changes in individual practical cases because of the guarantee for the intervention to reduce the cardiovascular event rate in the entire population.

We assume that, like arteriosclerosis, DPN also requires early detection and prevention. A recent 5-year prospective study in the Japanese language reported that the severity of DPN can predict cardiovascular events<sup>12</sup>. In the report, Baba's classification (BC)<sup>13</sup>, the details of which are described later, was used to classify the severity of DPN based on a nerve conduction study (NCS; Figure 1). The study found that the severity of DPN had a compelling correlation with the prognosis of diabetes patients. A similar report from the 1990s also showed that the 10-year survival prognosis of 545 people with type 1 diabetes, including patients with pancreatic transplantation, is greatly affected by the degree of abnormalities in NCS and reduction of heart rate variability at the time of transplantation<sup>14</sup>. Furthermore, a recent study showed that the three-question set ("Are your legs numb?", "Have you ever had an open sore on your foot?" and "Do your legs hurt when you walk?") from the Michigan Neuropathy Screening Instrument (MNSI)<sup>15</sup> can be used as a prognostic factor for cardiovascular outcomes<sup>16</sup>. However, clinical trials have not been sufficiently accumulated to prove a causal sequence. As a result, no therapeutic method that assesses the pathogenesis of DPN has been widely accepted in the world. The final goal we aim for is to disseminate an outcome-oriented treatment of DPN, which can be continued without individual regular assessment of DPN based on the verified benefits. The following four steps are required to achieve this goal. First, we will establish an objective evaluation method for DPN. Second, we will show the correlation between the severity of DPN and prognosis, including mortality and cardiovascular events, in large clinical studies, and verify DPN as a prognostic indicator. Third, parallel to the previous two steps, disease-modifying treatment(s) of DPN should be developed. Fourth, the efficacy of the treatment of DPN and the improvement of prognosis should be verified in large-scale clinical trials.

In the present review, we clarify the current environment for DPN diagnosis and suggest directions for future research.

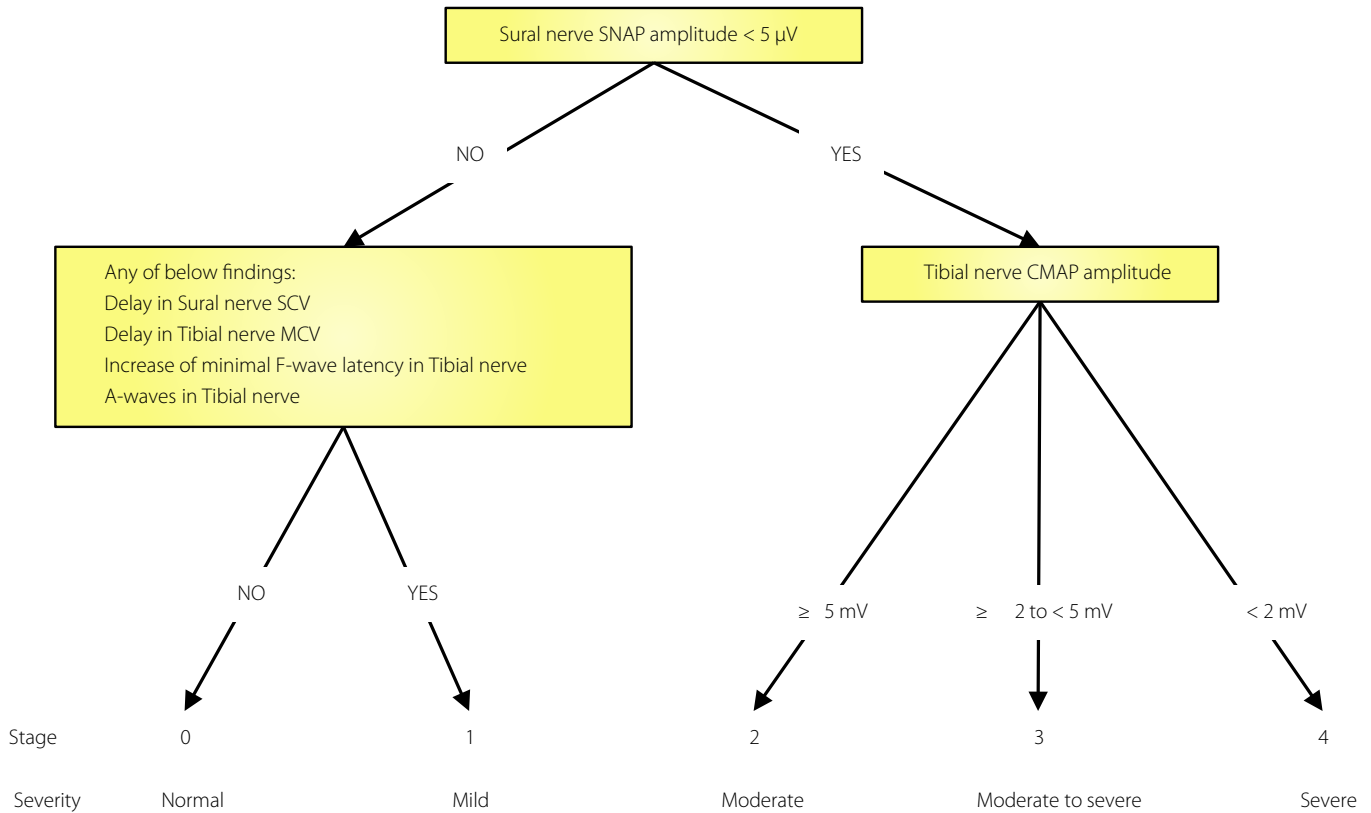
## DIAGNOSTIC CRITERIA AND SCORING SYSTEMS CONSIST OF CLINICAL SIGNS, SYMPTOMS AND QUANTITATIVE TESTS

### Toronto consensus

The Toronto Expert Panel on Diabetic Neuropathy<sup>17</sup> published their consensus for a definition of DPN, which was subsequently cited by several reviews and guidelines<sup>18–20</sup> including the position statement of the American Diabetes Association (Table 1)<sup>21</sup>. The Toronto Consensus classifies DPN into four categories: (i) possible clinical diabetic sensorimotor polyneuropathy (DSPN); (ii) probable clinical DSPN; (iii) confirmed clinical DSPN; and (iv) subclinical DSPN. Neurological symptoms and signs that can be assessed in actual clinical settings define only "possible" or "probable" clinical DSPN. "Confirmed" clinical DSPN cannot be diagnosed unless any abnormality is proven in NCS or evidenced by examinations of small nerve fiber impairments, which is included based on the suggestion that the earliest nerve fiber damage is to the small fibers. Although their purpose is not clearly shown in the report, "possible", "probable" and "confirmed" are clearly defined for clinical use, and "confirmed" or "subclinical" for research use. Although the definition for clinical use is divided into three categories expressing the certainty of diagnosis, in terms of stage progression, "confirmed" is not necessarily the most advanced, but rather "probable", which requires signs and symptoms, and thus likely contains the most advanced disease state. Although the consensus states that the severity can only be assessed in the "confirmed" group, the problem is that it is difficult for non-specialists to understand that "probable" contains many severe cases. However, this consensus helps to highlight the fact that early diagnosis of DPN is difficult, and clarifies that it is necessary to develop a diagnostic method.

### Simple diagnostic criteria proposed by the Japanese Study Group on Diabetic Neuropathy

In Japan, the simple diagnostic criteria proposed by the Japanese Study Group on Diabetic Neuropathy<sup>22</sup> have been popularized for daily use in medical clinics and hospitals (Table 2). These criteria consist of a prerequisite condition and three neurological examination items. The prerequisite condition includes two items: (i) diagnosed with diabetes mellitus; and (ii) neuropathies other than DPN can be excluded. The criteria require any two or more of the following three items: (i) the presence of symptoms considered to be due to DPN; (ii) decreased vibratory threshold in the bilateral medial malleoli; and (iii) the decrease or disappearance of bilateral Achilles tendon reflexes. Additionally, the criteria include important references with which, if either one of the following reference items is met, even if the above criteria are not met, DPN can be diagnosed: (i) the presence of any abnormality in two or more nerves in NCS; and (ii) the presence of clinically apparent diabetic autonomic nerve dysfunction. These criteria narrowed down the survey items to enable a rapid bedside diagnosis, while at the same time realizing high consistency with findings in NCS.



**Figure 1** | Baba's classification: a diagnostic and staging algorithm for diabetic polyneuropathy based on nerve conduction study. Stage 0: normal without any nerve conduction study abnormalities; stage 1: mild neuropathy with the presence of any delay in tibial motor nerve conduction velocity, sural sensory nerve conduction velocity (SNCV), tibial minimal F-wave latency or the presence of A wave; stage 2: moderate neuropathy with a decrease in sural SNAP, sensory nerve action potential (SNAP) amplitude <5 μV; stage 3: between moderate-to-severe neuropathy with a decrease in sural SNAP amplitude <5 μV and a decrease in tibial compound muscle action potential (CMAP) amplitude ≥2 to <5 mV; stage 4: severe neuropathy with a decrease in sural SNAP amplitude <5 μV and a decrease in tibial CMAP amplitude <2 mV. MCV, motor nerve conduction velocity.

**Table 1** | Toronto consensus: definitions of minimal criteria for diabetic symmetric polyneuropathy

1. Possible clinical DSPN  
Symptoms or signs of DSPN. Symptoms may include: decreased sensation, positive neuropathic sensory symptoms (e.g., "asleep numbness," "prickling" or "stabbing," "burning" or "aching" pain) predominantly in the toes, feet or legs. Signs may include: symmetric decrease of distal sensation, or unequivocally decreased or absent ankle reflexes.
2. Probable clinical DSPN  
A combination of symptoms and signs of distal sensorimotor polyneuropathy with any two or more of the following: neuropathic symptoms, decreased distal sensation, or unequivocally decreased or absent ankle reflexes.
3. Confirmed clinical DSPN  
An abnormal nerve conduction study and a symptom or symptoms or a sign or signs of sensorimotor polyneuropathy. If nerve conduction is normal, a validated measure of small fiber neuropathy (with class 1 evidence) may be used. Severity of DSPN can be assessed by staged or continuous approaches described above, and by dysfunction and disability scores.
4. Subclinical DSPN (stage 1a)  
No signs or symptoms of polyneuropathy. Abnormal nerve conduction, as described above, or a validated measure of small fiber neuropathy (with class 1 evidence) is present

Class 1 evidence: corneal confocal microscopy, intra-epidermal nerve fiber or nerve biopsy. DSPN, diabetic symmetric polyneuropathy.

**Scoring systems**

Scoring systems, such as the Neurological Disability Score and Neurological Symptom Score (NSS)<sup>23,24</sup> are mainly used by

neurologists to evaluate peripheral neuropathy. As the Neurological Disability Score consists of 35 items and the Neurological Symptom Score consists of 17 items, which were optimized

**Table 2** | Simple diagnostic criteria for distal symmetric polyneuropathy proposed by the Japanese Study Group on Diabetic Neuropathy (original version was made in 2004 and revised in 2005)

## Prerequisite condition

Must meet the following two items

1. Diagnosed as diabetes
2. Other neuropathies than diabetic neuropathy can be excluded

## Criteria

Meet any two of following three items

1. Presence of symptoms considered to be due to diabetic polyneuropathy
2. Decreased vibration in bilateral medial malleoli
3. Decrease or disappearance of bilateral ankle reflex

## Notes

1. "Symptoms considered to be due to diabetic polyneuropathy" include following:

- (1) Bilateral
- (2) Numbness, pain, paresthesia or decreased sensation in the tips of toes and bottom of feet

Meet above two items

Exclude symptoms in only upper extremities or only cold sense in the cases with peripheral vascular disease

2. Ankle reflex is examined on standing position on the knees
3. Decreased vibration is considered as  $\leq 10$  s by 128 Hz tuning fork, but varied if aged
4. Take age into consideration in elderly individuals

## Reference item

If either one of the following reference items is met, even if the above criteria are not met, diabetic polyneuropathy is diagnosed

1. Presence of any abnormality (nerve conduction velocity, amplitude or latency) in two or more nerves in electrophysiological test
2. Presence of clinically apparent diabetic autonomic disturbance (it is desirable to confirm obvious abnormality by autonomic function test)

for well-equipped medical institutions, it is cumbersome for general practitioners to use them on a daily basis. Thus, as diagnostic methods specialized for DPN, several scoring systems have been proposed; for example, the San Antonio Consensus<sup>25</sup>, a composite score in Rochester Diabetic Neuropathy Study<sup>26</sup>, the Toronto Neuropathic Clinical Score (TNCS)<sup>27</sup> and the MNSI<sup>15</sup>. The TNCS and MNSI have been recently used in clinical trials to determine the severity of DPN. In particular, as the correlation of the TNCS has been verified with the pathological findings in DPN<sup>27</sup>, as a result, several reports of clinical studies used the score to describe the severity correlated with the pathological findings of DPN<sup>28,29</sup>. However, in the original report of the TNCS<sup>27</sup>, no symptom or sign showed a significant correlation with NCS and pathological findings. Therefore, this scoring system should be carefully applied to interpret the progression of DPN. It is rather beneficial that both TNCS and MNSI reflect the seriousness of the subjective symptoms in diabetes patients, and that they can clarify objective physical findings to support these symptoms through physical assessments; for example, tendon reflexes, monofilament tactile test and tuning fork<sup>30</sup>.

As can be seen from the clinical trial that evaluated the Rochester Diabetic Neuropathy Study cohort using the Neuropathy Impairment Score of the lower limbs plus seven tests in which specialized equipment was used, a combination of physical findings and quantitative sensory tests requires at least 3 years to determine the effectiveness of the intervention, thus, it has been suggested that the duration of each clinical study might take longer time depending on the strength of intervention<sup>26</sup>.

**Problems of diagnostic methods based on symptoms and physical findings**

Both reports from the Toronto Consensus Panel and Diabetic Neuropathy Study Group have suggested using positive or negative subjective symptoms and neurophysiological findings, including tendon reflex and vibratory threshold, for diagnosis of DPN<sup>22,27</sup>. In addition, it is recommended in these diagnostic criteria to confirm a diagnosis by quantitative tests: nerve conduction test, corneal confocal microscopy, intra-epidermal nerve fiber density, and various quantitative sensory tests that require the attention and cooperation of participants. However, these simple diagnostic criteria are underutilized, and DPN is excluded from the end-points in clinical trials, even in clinically important large-scale trials; for example ADVANCE<sup>31</sup>, EMPA-REG OUTCOME<sup>32</sup>, Diabetes Prevention Program Research<sup>33</sup> and Japan Diabetes Optimal Integrated Treatment study for 3 major risk factors of cardiovascular diseases<sup>34</sup>. Considering these circumstances, it is time to rethink the purpose to make a diagnosis of DPN.

For each patient with painful DPN, his/her worry might be reduced if the doctor determines and explains that his/her symptoms are due to DPN. However, after that, no particular treatment will be provided, other than analgesics for positive symptoms. In other words, diagnosis to explain subjective symptoms is not very useful for improving the quality of life for each patient. We now should separately consider the treatment strategies of disease-modifying treatments and symptom relief treatments. Although many diagnostic criteria commonly emphasize subjective symptoms and physical findings, diagnosis

of symptomatic DPN has so far only epidemiological implications.

### QUANTITATIVE TESTS FOR LARGE NERVE FIBERS

Several studies have shown small fiber neuropathy in early-stage diabetes patients and even in impaired glucose tolerance (IGT) patients<sup>35–38</sup>. However, it is still controversial whether small nerve fibers are more susceptible in those situations compared with large nerve fibers. It was reported that low myelinated fiber density in the sural nerve predicted future nerve dysfunction. In addition, Ishibashi *et al.*<sup>35</sup> reported that a decrease in sensory nerve action potential (SNAP) and sensory nerve conduction velocity (SNCV) in the sural nerves, which means large-fiber dysfunction, has been shown in IGT patients. In addition, in patients who were newly diagnosed with type 2 diabetes, it has been confirmed that NCS had a higher abnormality rate compared with CCM and intra-epidermal nerve fiber (IENF)<sup>38</sup>. In contrast, there were also reports that IGT patients who had abnormal findings in CCM and IENF showed no significant findings in sural nerve SNAP and SNCV<sup>36,37</sup>. We should also consider the fact that the structural abnormalities of small nerve fibers in CCM or IENF are not necessarily in parallel with functional impairment in nerve conduction. It cannot be concluded whether pathology in large nerve fibers or in small nerve fibers precedes or simultaneously progresses in DPN.

Regardless, NCS has been reported to be able to detect one or more abnormal findings in 60–90% of diabetes patients, and thus can be applied to the diagnosis of early DPN<sup>14,39,40</sup>. Although poor reproducibility and lack of measurement standardization are highlighted as the limitations of NCS<sup>41</sup>, the intraclass correlation coefficient, the index of reliability for continuous variables, of NCS is as high as 0.85–0.91 for the sural SNAP and peroneal nerve conduction velocity in the cohort of DPN patients<sup>42</sup>. Furthermore, NCS has been verified to present as monotonous worsening over time in the development of DPN<sup>42</sup>, and to be useful for the evaluation of the response to interventions<sup>43,44</sup>. For example, Kennedy *et al.*<sup>45,46</sup> found that some parameters of NCS improved 42 months to a decade after cotransplantation of the pancreas and kidney. Similar improvements have been reported by another group<sup>47</sup>. In addition, Malik *et al.*<sup>48</sup> showed that the angiotensin-converting enzyme inhibitor, trandolapril, improved peroneal nerve conduction velocity, M-wave amplitude, F-wave latency and sural nerve SNAP. Given these results, it is plausible that NCS can show functional improvement of large fibers when a sufficiently strong interventional impact is provided.

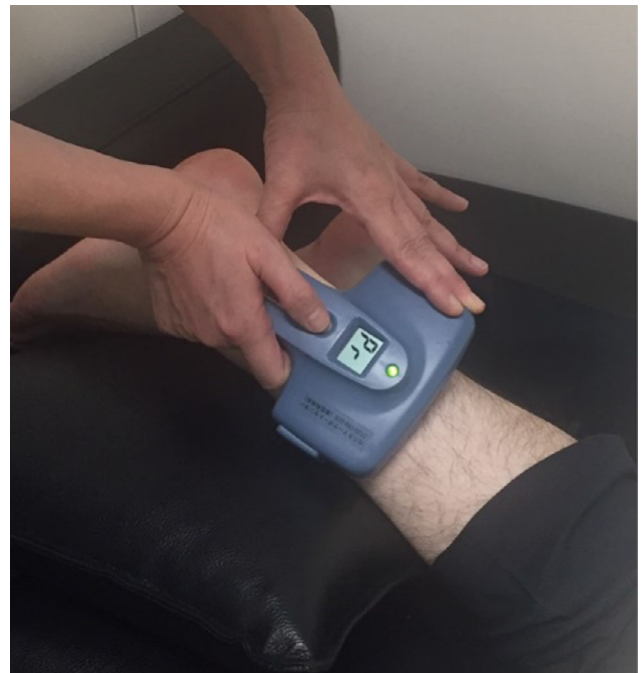
Although there are interinstitutional or interexaminer differences in NCS results, researchers are working to reduce those differences. The recently developed simple NCS equipment, DPNCheck<sup>TM</sup> (Neurometrix Inc, Waltham, MA, USA), can establish a homogeneous measurement method (Figure 2). Furthermore, the correlation with the standard NCS is sufficiently high (Spearman's correlation coefficient of sural SNCV = 0.95)<sup>49</sup>. The interrater intraclass correlation coefficient is 0.83 in sural

SNAP, and 0.79–0.97 in SNCV<sup>50,51</sup>, which are comparable or superior to the performance of standard NCS (sural SNAP 0.74, SNCV 0.79)<sup>52</sup>. DPNCheck<sup>TM</sup> has already been disseminated worldwide, and real-world data of the device in Caucasians and Asians are being accumulated<sup>149,53,54</sup>.

### QUANTITATIVE TESTS FOR SMALL NERVE FIBERS

Quantification of pathological changes in IENF and corneal nerve fibers has been established as objective quantitative examinations to evaluate degeneration in small nerve fibers at the very early stage of DPN<sup>55–58</sup>. The density of IENF (IENFD) is assessed by collecting 3-mm diameter skin, visualizing nerve fibers using immunological staining and measuring its density in the epidermis. IENFD has been shown to correlate well with the sural nerve fiber density<sup>59,60</sup>. Although the evaluation of IENFD has been clinically applied in some medical institutions, the procedure is accompanied by mild invasiveness, and the procedure and quantification of fixation and staining of tissue are complicated. Thus, it is difficult to say if the examination is widely used in general clinics and hospitals<sup>61</sup>.

As another non-invasive morphological examination, many findings have been reported on the quantitative evaluation of corneal nerve fibers using corneal confocal microscopy (CCM) (Figure 3)<sup>56,58,62–65</sup>. As the examination using CCM enables rapid observation of the morphology and distribution of the sensory nerve fibers in the cornea without invasive tissue sampling, the usefulness of CCM has been repeatedly confirmed. It has been shown that corneal nerve fibers were already



**Figure 2** | Examination scene of DPNCheck<sup>TM</sup>. The device should be aligned to the sural nerve and firmly pushed down.

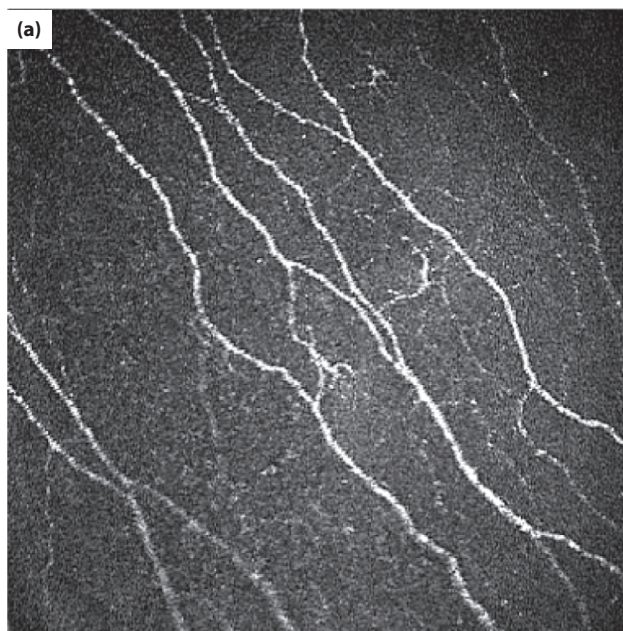
degenerated in patients with IGT<sup>37</sup>, and corneal nerve fiber lengths improved after simultaneous pancreas and kidney transplantation<sup>66</sup>. However, this examination has not yet been standardized for analysis and evaluation of the obtained images. Although the problem is still to be solved, CCM is expected to play an important role as an objective evaluation method of DPN.

### MAGNETIC RESONANCE IMAGING AND ULTRASONOGRAPHY

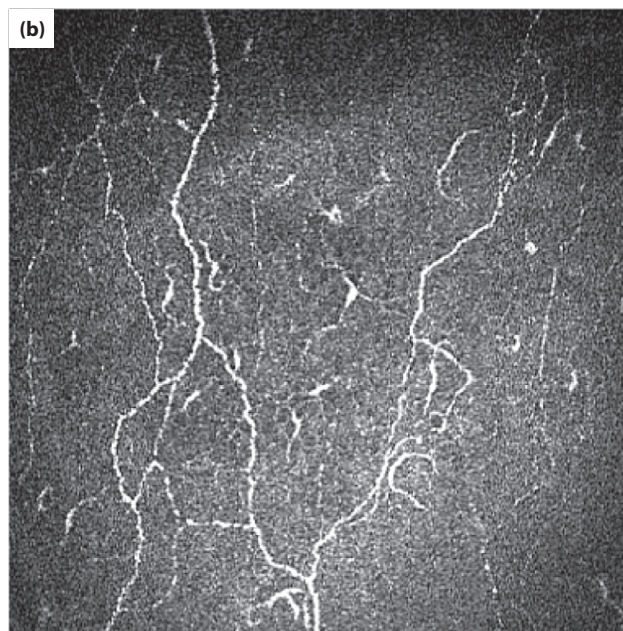
Recently, the development of high-performance imaging using echocardiography or magnetic resonance imaging has shown abnormal findings in the peripheral nerves of diabetes patients. In magnetic resonance imaging, as it has been shown that structural changes in peripheral nerves can be detected using equipment with a magnetic field of  $\geq 3$  Tesla, abnormal findings in various peripheral nerve diseases have accumulated<sup>67–73</sup>. Pathological changes in DPN are conventionally evaluated at distal sites of the legs. However, surprisingly, abnormal findings, such as hypertrophy of nerve bundles, are remarkable at the proximal sites of the sciatic nerves in magnetic resonance imaging (Figure 4)<sup>73</sup>. This novel finding could provide additional insights into the pathophysiology of DPN. Ultrasonography of peripheral nerves has shown an increased cross-sectional area in DPN patients<sup>74–77</sup>. However, it has also been reported that the contraction of the median and ulnar nerves is recognized in young patients with type 1 diabetes who had no clinical DPN<sup>70</sup>. Further investigations are required to clarify the natural history of morphological changes in peripheral nerves of DPN. Additionally, in some reports, elastography, another approach using ultrasonography, which can evaluate the stiffness of nerves, showed an increase in stiffness in patients with subclinical or clinical DPN, suggesting that elastography might reproduce consistent findings in DPN<sup>77–79</sup>.

### BABA'S CLASSIFICATION ON THE SEVERITY OF DPN USING NCS

As mentioned in earlier, the use of BC, the novel severity classification of DPN using NCS, proposed by Baba *et al.*<sup>13</sup>, has been rapidly increasing and is now popular in Japan. Baba *et al.* proposed a staging system for DPN severity defined by abnormalities of NCS in the lower limbs. They divided DPN severity into five stages: stage 0 – normal without any NCS abnormalities; stage 1 – mild neuropathy with the presence of any delay in tibial motor nerve conduction velocity, sural SNCV, tibial minimal F-wave latency or the presence of A wave; stage 2 – moderate neuropathy with a decrease in sural SNAP amplitude  $< 5 \mu\text{V}$ ; stage 3 – between moderate-to-severe neuropathy with a decrease in sural SNAP amplitude  $< 5 \mu\text{V}$  and a decrease in tibial CMAP amplitude  $\geq 2$  to  $< 5 \text{ mV}$ ; and stage 4 – severe neuropathy with a decrease in sural SNAP amplitude  $< 5 \mu\text{V}$  and a decrease in tibial CMAP amplitude  $< 2 \text{ mV}$  (Figure 1).



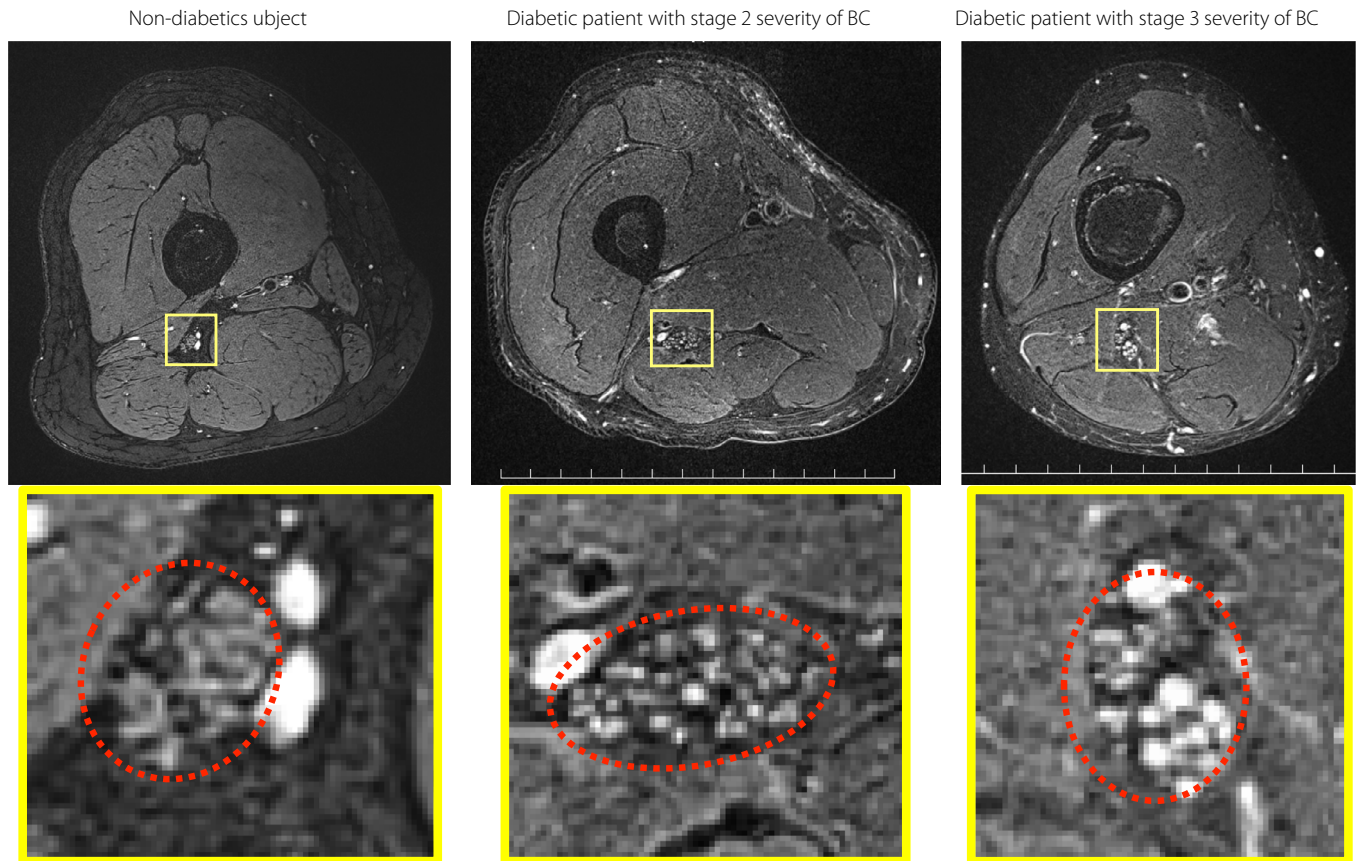
Non-diabetic subject



Diabetic patient

**Figure 3** | Images of corneal nerve fibers captured by corneal confocal microscopy. The (a) corneal nerve fiber length and density in a diabetes patient decreases compared with that (b) in a non-diabetic individuals. Images were provided by Takahiro Ishikawa, Aichi Medical University.

This BC showed that  $\geq 90\%$  of diabetes patients had one or more abnormal findings in the NCS<sup>12</sup>. This high prevalence is consistent with the reports from Dyck *et al.*<sup>39</sup> and Navarro *et al.*<sup>14</sup>, suggesting that NCS has excellent sensitivity of DPN. Given the high prevalence of NCS abnormality, the evaluation



**Figure 4** | Magnetic resonance images of sciatic nerves. The lower panels are insets of the upper panels. Red dotted circle shows a nerve area. The sciatic nerves have multiple larger high-intensity lesions in patients with diabetic polyneuropathy (middle and right panels). BC, Baba's classification. Images were provided by Makoto Endo, Aichi Medical University Hospital.

of peripheral nerve function in diabetes or prediabetes patients should be considered as important as, or more important than, the quantification of intima-media thickness in carotid arteries, in terms of evaluating systemic impairments in metabolic disorders and pathological developments of arteriosclerotic changes.

As it would be difficult to achieve clinical applications of BC due to the use of complicated standard NCS, more concise examinations that have similar diagnostic capabilities to BC should be developed. As an example, DPNCheck<sup>TM</sup>, which is the point-of-care device (POCD) of simple NCS, can easily and repeatedly evaluate the sural nerve SNAP and SNCV. As these two parameters are included in the BC, the POCD might reproduce a part of the staging of BC, especially in the early stage of DPN. Although real-world data of the POCD has not been accumulated, it is expected that this POCD might enable early detection of, and intervention in, the dysfunctions in the peripheral nervous system of diabetes patients.

### PROPOSAL FOR FUTURE RESEARCH

The novel quantitative examinations that we are struggling to establish take aim at an early diagnosis and intervention for DPN, which is different from the current conventional

diagnostic methods aiming to prevent diabetic foot in patients with overt physical symptoms and signs of DPN. Early diagnosis and treatment of DPN should be considered as important as prevention and treatment for diabetic foot. For instance, as all diabetes patients are recommended to be screened for foot care every year<sup>80</sup>, early diagnostic screening examination of DPN should be carried out for all diabetes and prediabetes patients.

We, clinician scientists, have some important points to consider for the establishment of new diagnostic methods (Table 3). First, quantitative examinations have low repeatability. The Chronic Kidney Disease Epidemiology Collaboration equation, which is already widely used to estimate glomerular filtration rate (GFR) in the world, has 69% of concordance with measured GFR and 84.1% of P30, a percentage of estimated GFR (eGFR) that is within 30% of measured GFR<sup>81</sup>. The correlation between estimated and measured GFR values is not excellent, and the limitation on its accuracy is widely recognized. However, although the formula of eGFR uses age, which is a non-specific physiological value, eGFR showed excellent correlation with cardiovascular events and all-cause mortality<sup>82,83</sup>. As a result, eGFR has been trusted by many healthcare professionals,

**Table 3** | Principles for a new diagnostic criteria and staging system

1. Include only generalizable objective quantitative tests. Minimal reliability of the objective quantitative tests should be verified; do not pursue high reproducibility and predictivity.
2. Exclude clinical symptoms and signs. Clinical findings should be separately employed only to define and evaluate a painful diabetic polyneuropathy.
3. No restrictive exclusion diagnosis for other-caused polyneuropathy; especially, aging-related neuropathy cannot be distinguished.

and has become an important end-point in many large-scale clinical trials<sup>84,85</sup>. Given the shortage of eGFR in accuracy and the magnitude of eGFR in clinical trials, we should aim for a simple and easily understandable method of diagnosis and evaluation of DPN, which ensures moderate accuracy.

Second, the examinations of sensory functions poorly correlate with pathophysiological changes of DPN. It has long been known that nerve conduction abnormalities are detected even in patients who had no impairment in quantitative sensory examinations<sup>86–90</sup>. In addition, the TNCS has shown that the symptoms were uncorrelated with the nerve fiber density in the sural nerve and the neural function determined by NCS<sup>27</sup>. The TNCS has also failed to verify a significant correlation between sensory test scores consisting of pinprick, vibration, temperature, light touch, and position to nerve fiber density or NCS. The corneal nerve fiber density and length evaluated by CCM, which have been suggested as non-invasive pathological parameters for small fiber neuropathies in metabolic disorders, such as IGT and dyslipidemia, have shown no significant difference between painful and non-painful DPN patients<sup>91</sup>. As many studies have clarified no significant correlation between neuropathophysiological changes and subjective symptoms<sup>92,93</sup>, the limitations of these subjective and non-quantitative examinations must be considered.

Third, a perfect differential diagnosis of polyneuropathy is too ambitious. A great deal of epidemiological data have been collected about the development of aging-related dysfunction in the peripheral nervous system; as it is called, age-related polyneuropathy (ARPN), chronic idiopathic polyneuropathy or cryptogenic sensory polyneuropathy<sup>94–98</sup>. In a cohort study in the Netherlands, the prevalence of peripheral neuropathy was 5.5% (95% confidence interval 4.4–6.9) in the 70-year-old population, of which 31% had diabetes and 49% were deemed a so-called ARPN<sup>99</sup>. The prevalence or incidence rates increased with aging, and the tendency was common to the diabetes and the ARPN groups. In that study, all participants were selected using a physical examination by neurologists and NCS, followed by general laboratory examinations including fasting/casual blood glucose, vitamin B<sub>1</sub>, vitamin B<sub>12</sub>, protein electrophoresis and thyroid hormones. As the participants were also interviewed about alcohol consumption and history of antidiabetic medication, a diagnosis of peripheral neuropathies could be confidently established. However, as

approximately half of the peripheral neuropathies are classified in ARPN, it is not realistic in clinical settings to distinguish ARPN from DPN and exclude it from DPN treatments. Although it is necessary to strictly exclude ARPN to progress the understanding of the pathology in DPN, given that aging itself is also included as a risk factor for diabetic foot lesions or DPN<sup>100,101</sup>, it would not be reasonable to exclude elderly people from the diagnosis of DPN, or to hesitate recommending an intervention to DPN due to an inability to distinguish whether aging or diabetes is the main etiology of the peripheral neuropathy.

Finally, it should be noted that quantitative tests that will be applied to clinical trials should be as simple as possible. For example, as it has been shown that the reproducibility between left and right nerves using the standard NCS is sufficient<sup>102</sup>, we should also verify the reproducibility between the two sides using the simple NCS device, DPNCheck<sup>TM</sup>, to guarantee the one-side leg examination. In addition, as quantitative parameters of cardiac autonomic neuropathy are also candidates for indicators of DPN, which show a monotonous deterioration, we should simplify and verify these parameters<sup>42,103–106</sup>.

## CONCLUSION

Future novel diagnostic and severity classification criteria consisting of simple NCS of one or two nerves and parameters of cardiac autonomic neuropathy might be used for large-scale clinical studies to evaluate the prognosis of DPN. In contrast, more accurate examinations, including CCM and IENFD, should be used for the development of therapeutic agents. We must carefully select appropriate evaluation methods according to the situation and purpose of each clinical study.

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## DISCLOSURE

The authors declare no conflict of interest.



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