Diabetic polyneuropathies are a group of heterogeneous peripheral neuropathies, and are roughly classified into polyneuropathy and focal neuropathy. Diabetes-specific neuropathy is polyneuropathy, which is pathophysiologically associated with metabolic disorders as a result of hyperglycemia and microangiopathy. Recently, classification1,2 of the spectrum of diabetic polyneuropathy (DPN) based on the different types of nerve fiber involved has grown (e.g., myelinated, unmyelinated, autonomic, somatic). DPN is divided into diabetic distal sensory neuropathy (DSN), diabetic small-fiber neuropathy (DSFN) and diabetic autonomic neuropathy2. The most common type is DSN, which mainly affects the large myelinated fibers, more often sensory than motor. DSN shows a length-dependent, primarily sensory neuropathy of large nerve fibers, while often being asymptomatic. DSFN mainly affects the unmyelinated small nerve fibers, not the large fibers, and occasionally carries the phenotype of burning feet syndrome. DSFN occurs early in metabolic disorders associated with hyperglycemia. Subsequent neurodegeneration through uncontrolled diabetes might promote DSFN to DSN, but it is not clear whether DSFN consistently progresses to DSN. Diabetic autonomic neuropathy occurs when the widespread involvement of autonomic unmyelinated fibers occurs, and patients can suffer from unpleasant autonomic dysfunction. We will not describe diabetic autonomic neuropathy here due to a limited word count. As severe DSN or DSFN causes severe neuropathic pain, or foot ulcer, and morbidity might significantly deteriorate, early diagnosis is important.

This commentary describes the diagnostic strategy for DSN and DSFN based on recent advances in neurodiagnostic technology. Table 1 shows the classification, manifestations, validated examinations of each nerve fiber types and their implication for the phenotypes of DPN. Nerve fiber types involved in DSN and DSFN consist of sensory small fiber (c-, Aδ-fiber) to large fiber (Aβ-, Aα-fiber), and motor large fiber (Aα-fiber). As the intra-epidermal terminal end of c- and Aδ-fibers is unmyelinated small fibers, disorder of these two fibers is called small-fiber neuropathy. DSN is actually considered to be a mixed small- and large-fiber neuropathy, as an obvious loss of intra-epidermal nerve fibers has been reported in DSN or advanced DSN. In advanced DSN, small muscle atrophies in the distal legs are caused by large motor fiber impairment.

In daily practice, DSN is diagnosed by the presence of voluntary sensory symptoms and/or neuropathic signs, including decreased Achilles tendon reflex and symmetric decreased distal sensation in both legs. All of these clinical symptoms/signs other than neuropathic pain, such as burning, electric shock-like, stabbing and tingling, are due predominantly to large myelinated fiber disorders. Therefore, definitive diagnosis of DSFN was difficult until effective diagnostic methods for small nerve fiber damage had been established. Even for DSN, it was not easy to make a definitive diagnosis, because symptoms are not objective, and the accuracy of evaluating these signs depends on the skill of the examiner. Therefore, an objective, quantitative and reliable neurological examination is required to accurately diagnose DPN. Neurological examinations that satisfy these requirements include quantitative sensory testing (QST), nerve conduction study (NCS), pathological/morphological examination and magnetic resonance (MR) neurography.

As sensory impairment significantly harms the patients’ quality of life, various QSTs have been developed to evaluate each sensory dysfunction. In small nerve fibers, unmyelinated C- and Aδ-fibers transmit dull pain and warm sensations, and sharp pain and cold/hot sensations, respectively. Sensory thresholds are determined by various computer-based thermal testers and pinprick testing. In large nerve fibers, Aβ-fibers transmit vibratory and pressure sensation, and Aα-fibers transmit proprioception and modulate tendon reflex. Perception thresholds are evaluated by various tuning forks, monofilaments or quantitative vibration meters. Decreased Achilles tendon reflex also indicates large-fiber neuropathy. The results of QST are not completely objective, as they depend on the patient’s response. However, QST appears to be the most sensitive method for individually assessing different types of sensory nerve fibers.

Nerve conduction study has been considered the gold standard for DSN diagnosis because of its high objectivity. However, most of the results obtained
Table 1 | Characteristics, manifestations and examinations of each class of nerve fiber, and phenotypes of diabetic polyneuropathy

| Classification | Manifestations | Validated examinations | Possible clinical course of DPN |
|----------------|----------------|-----------------------|-------------------------------|
| Fiber type     | Functions      | Symptoms | Signs | QST | Pathology | Magnetic resonance neurography | Pre-DM => DM =>⇒ longstanding DM |
| DSN small-fiber neuropathy (DSFN) | Diabetic sensory neuropathy (DSN) | Advanced DSN |
| C-fiber       | Unmyelinated   | Burning pain | Electric | Warmth detection | IENFD | T2w-high lesion |
|               | Warmth receptor |                      | Pinprick | Hot/cold detection | CCM | T2w-low lesion |
| Aβ-fiber      | Myelinated     | Burning pain | Mechanoreceptor | Number | Tuning fork | MF (10-g) |
|               | Cold/hot receptor |                      | Tingling | Tuning fork | MF | T2w-high lesion |
| Aβ-fiber      | Myelinated     | Burning pain | Mechanoreceptor | Number | Tuning fork | MF |
|               | Vibration      |                      | Tingling | Tuning fork | MF | T2w-low lesion |
| MeÁš-fiber    | Myelinated     | Burning pain | Mechanoreceptor | Number | Tuning fork | MF |
|               | Cold/hot receptor |                      | Tingling | Tuning fork | MF | T2w-high lesion |
| Aβ-fiber      | Myelinated     | Burning pain | Mechanoreceptor | Number | Tuning fork | MF |
|               | Vibration      |                      | Tingling | Tuning fork | MF | T2w-low lesion |
| Ax³-fiber     | Myelinated     | Burning pain | Mechanoreceptor | Number | Tuning fork | MF |
|               | Cold/hot receptor |                      | Tingling | Tuning fork | MF | T2w-high lesion |
| Ax³-fiber     | Myelinated     | Burning pain | Mechanoreceptor | Number | Tuning fork | MF |
|               | Vibration      |                      | Tingling | Tuning fork | MF | T2w-low lesion |
| Ax³-fiber     | Myelinated     | Burning pain | Mechanoreceptor | Number | Tuning fork | MF |
|               | Cold/hot receptor |                      | Tingling | Tuning fork | MF | T2w-high lesion |
| Ax³-fiber     | Myelinated     | Burning pain | Mechanoreceptor | Number | Tuning fork | MF |
|               | Vibration      |                      | Tingling | Tuning fork | MF | T2w-low lesion |
| Ax³-fiber     | Myelinated     | Burning pain | Mechanoreceptor | Number | Tuning fork | MF |
|               | Cold/hot receptor |                      | Tingling | Tuning fork | MF | T2w-high lesion |
| Ax³-fiber     | Myelinated     | Burning pain | Mechanoreceptor | Number | Tuning fork | MF |
|               | Vibration      |                      | Tingling | Tuning fork | MF | T2w-low lesion |

Nerve fibers are classified by the Erlanger-Gasser classification. High or low lesion means hyperintense or hypointense lesion, respectively. ATR, Achilles tendon reflex; CCM, corneal confocal microscopy; DM, diabetes mellitus; DPN, diabetic polyneuropathy; IENFD, intra-epidermal nerve fiber density; MF, monofilament; MNCS, motor nerve conduction study; MRN, magnetic resonance neurography; NCS, nerve conduction study; QST, quantitative sensory testing; QVT, quantitative vibration threshold; SNCS, sensory nerve conduction study; T2w, T2 weighted.
number of T2w high-intensity signals. As a result, the load of nerve lesions increased in parallel with DPN severity, highest in the mid sciatic nerve at thigh level and lower in the distal tibial nerve with a strong proximal-to-distal gradient. The authors speculated that the accumulation of microstructural nerve alterations at the thigh level, which might represent a vulnerable region for ischemic and/or metabolic injury, could precede and possibly trigger distal fiber loss in a length-dependent manner.

In 2018, Jende et al.1 evaluated T2w-hyperintense and T2w-hypointense lesions of the sciatic nerve by MRN in type 1 and type 2 diabetes patients, and the association between MRN findings, and clinical, serological and electrophysiological data. The results showed, in both type 1 and type 2 diabetes patients, T2w-hyperintense and T2w-hypointense lesions increased with DPN, but T2w-hypointense lesions were more prevalent in type 2 diabetes patients than in type 1 diabetes patients. T2w-hyperintense lesions were associated with nerve conduction function and glycated hemoglobin, and T2w-hypointense lesions correlated positively with triglyceride and negatively with high-density lipoprotein cholesterol. Therefore, the etiology of DPN in type 1 diabetes patients might be mainly due to poor glycemic control, and that of type 2 patients diabetes might be related to dyslipidemia.

In 2020, Groener et al.5 reported the association of T2w-hyperintense or hypointense lesions in MRN of the sciatic nerve, and impairments of various types of nerve fiber in type 2 diabetes patients and healthy controls. The function of each type of nerve fiber was evaluated using NCS and QST. In large nerve fibers, Aα- and Aβ-fibers were evaluated by NCS and the mechanical detection threshold. Aδ fibers were evaluated by the mechanical pain threshold, and the unmyelinated C-fibers were evaluated by the warmth detection or pain threshold. The results showed the T2w-hyperintense lesion load was significantly associated with decreased Aα-, Aβ- and Aδ-fiber function, but not C-fiber function. T2w-hypointense lesions were negatively correlated only with mechanical detection, peroneal conduction velocity and amplitude. The authors concluded that T2w MRN lesions in the sciatic nerve might be pathophysiologically associated with a decline in middle and large-fiber nerve function of DPN.

A summary of MRN studies is as follows: (i) the MRN lesion load in peripheral nerves and severity of the DPN correlate positively, and the most affected site is the sciatic nerve in the proximal thigh; (ii) the MRN lesion load reflects middle-to-large-fiber dysfunction, but not small C-fiber dysfunction; and (iii) differences in MRN lesions between type 1 and type 2 diabetes might reflect etiological differences in DPN. However, several problems exist as follows: (i) the pathophysiological condition of MRN lesions is unknown; (ii) the optimal MRN imaging method and cut-off value for evaluating lesions have not been established; and (iii) overlap with healthy controls is large, and it is difficult to distinguish normal from abnormal. MRN has the great advantage of being able to evaluate morphology, which is the most objective index, non-invasively, and might be extremely useful as a tool for evaluating DPN. Further studies including device innovation and longitudinal studies are desired.

DISCLOSURE
The authors declare no conflict of interest.

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Doi: 10.1111/jdi.13364