What is the ideal biological marker in diagnosis of diabetic neuropathies?

As diabetes mellitus rapidly increases worldwide, diabetic neuropathy is the most common long-term debilitating complication of diabetes, and is the main initiating factor for foot ulceration and amputation without trauma. Foot ulceration and amputation is much more common in neuropathic patients, with the annual incidence rising from <1% in those without neuropathy to more than 7% in those with established neuropathic deficits. As the reversible change in nerve-loss repair only occurs in small peripheral nerve fibers, earlier detection, accurate diagnosis and early treatment of diabetic neuropathy are important strategies to induce reversible change in small nerve fibers.

Small peripheral nerve fibers, which constitute 70–90% of peripheral nerve fibers, regulate several main functions, such as tissue blood flow, temperature, pain perception and sweat production[1]. Many clinical trial data show that small fiber damage might precede large fiber damage in diabetic neuropathy. Damage to small nerve fibers causes the characteristic symptoms of painful diabetic neuropathy, which are typically distal symmetrical and associated with nocturnal exacerbation. The symptoms are very variable in each patient, and are described in various terms such as, prickling, aching, numbness and burning pain with intermittent sharp stabbing electric shock-like pains. Recently, Tesfaye *et al.*[2] proposed that "If nerve conduction is normal, a validated measure (with class 1 evidence) of small fiber neuropathy may be used" to define and quantify the severity of diabetic neuropathies. Nerve conduction study is based on relative ease of quantification, reproducibility, and reasonable sensitivity and specificity, which are regarded as gold standard methods to assess all types of fiber damage. However, it cannot accurately evaluate small nerve fibers, which are the earliest to be damaged and show repair even in advanced diabetic neuropathy. THIS was supported by recent data from many studies that reported minimal worsening and improvements in nerve conduction velocity results with little relationship to other methods of small fiber function in diabetic neuropathy patients. Other diagnostic methods of neurological symptoms and deficits questionnaires, and neurological examinations have been shown to have less reproducibility and low to moderate sensitivity. However, quantitative sensory tests have an advantage of evaluating both small and large nerve fiber function, but they require specific equipment and show low reproducibility. Furthermore, quantitative sensory tests require the cooperation and alertness of the patients. Table 1 shows classifications and characteristics for the diagnosis of diabetic neuropathies by the invasiveness, interpretation, advantages and disadvantages.

As seen in Table 1, ideal biological markers for diabetic neuropathies should be easy to use, reliable, sensitive and non-invasive to enable repeated assessment as often or as long as necessary to define diagnosis and progression or response to therapeutic intervention. However, to date, we have not had the aforementioned gold standard and single novel complete biomarker for diagnosis, progression and treatment of diabetic neuropathies. Many researchers have tried to find the ideal biomarker for diabetic neuropathies.

When we evaluate the efficacy of a new treatment modality, an improvement and aggravation of diabetic neuropathic symptoms and signs has to appear and be monitored during the intervention period. Although current methods have a good ability to diagnose diabetic neuropathies, their usefulness to define a therapeutic response and observe clinical outcome parameters might have significant limitations. These are major reasons why many clinical trials examining the therapeutic effects in human diabetic neuropathies have failed to reach predetermined primary end-points, such as neuropathic deficit symptoms, electrophysiological results and clinical outcome improvements.

Nerve fiber morphology in sural and peroneal nerve biopsies, and recently developed skin punch biopsies, which observe and monitor intra-epidermal nerve fiber density, can be accurately used as quantifying tools for nerve fiber damage and repair, but both are invasive procedures and require a pathology laboratory. In diabetic patients, there are many problems associated with invasive procedures, such as small wound healing complications, and non-reiterative and painful methods.

Ding *et al.*[3] measured microvascular dysfunction with quantitative and qualitative retinal photographic grading and computer-based evaluation methods in patients with diabetic neuropathies. They also carried out quantitative sensory testing, such as 10-g monofilament and hand-held neurothesiometer for vibration perception threshold measurement. They reported that individuals with a suboptimal arteriolar caliber and larger arteriolar branching coefficient, as well as diabetic retinopathy and focal arteriolar narrowing, were more likely to have diabetic neuropathy than those without these signs. Diabetic patients with two or more signs were six times more likely to have

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Table 1 | Diagnostic methods of diabetic neuropathies

Invasiveness	Interpretation	Methods	Advantage	Disadvantage
Non-invasive	Subjective (require patient's responses)	Clinical/neurological exam	Simple, easy to use	Less sensitive and reproducible
		Questionnaire	Simple, easy to use	Less sensitive
		Monofilament	Rapid	Non-quantitative
		Quantitative sensory test	Evaluate small and large fibers	Low reproducibility
	Objective	Nerve conduction study	High sensitivity, objective	Assess only large fibers
		Autonomic test	Quantitative	Moderate sensitivity
Minimally invasive	Objective	Corneal confocal microscopy	Rapid, quantitative, high reproducibility	Expensive
		Retinal photographic grading	Rapid, quantitative, high reproducibility	Expensive
Invasive	Objective	Skin biopsy (intra-epidermal fiber density)	Quantitative, high sensitivity	Non-reiterative
		Sural nerve biopsy	Quantitative, high sensitivity	Non-reiterative

diabetic neuropathy than those without any signs. Furthermore, diabetic patients have an association with these retinal arteriolar changes, which are present even in people without the traditional signs of diabetic retinopathy. From their results, Ding *et al.* suggested that early microvascular dysfunction in the retina is an independent risk factor for diabetic neuropathy and concluded that a range of early retinal microvascular abnormalities can be used as a new biological marker. However, as they mentioned in their study, although they used quantitative and qualitative methods to measure the geometry of the retinal microvasculature, as well as the assessment of diabetic retinopathy and arteriolar wall signs by standardized grading protocols, a relevant limitation of that study was the application of sensory tests, such as the 10-g monofilament test and the vibration perception threshold test, to diagnose subjects' diabetic neuropathies. This is because these tests are used for evaluating large nerve fiber functions, not small nerve fibers. Therefore, their result could exclude the subjects with only small nerve fiber diabetic neuropathy. In fact, the prevalence rate of diabetic neuropathy in study participants was 25.5%, relatively lower than other clinical trials. Therefore, we should also more precisely validate the earlier changes of retinal microvascular abnormalities in small fiber neuropathy patients. Because this study used a cross-sectional protocol, longitudinal evaluation for relationships of retinal microvascular abnormalities and diabetic neuropathy development is required to obtain more clear information in clinical use.

Adams *et al.*[4] introduced an opposite viewpoint compared with the hypothesis of Ding *et al.* They suggested that there was substantial neural dysfunction across the retina of patients with diabetes before relevant diabetic retinopathy was observed. They measured peripheral neural dysfunction by the use of multifocal electroretinogram for diabetic patients, and they recommended that it could be used as a non-invasive early detector to quantitatively predict new diabetic vasculopathy within a year, even in eyes that had no prior retinopathy. So, we compared these two study results of the sequence of retinal vasculopathy, retinal neuropathy and diabetic peripheral neuropathy, respectively. Furthermore, we should validate the association between corneal nerve density loss, retinal neural dysfunction and diabetic neuropathy development.

Recently, many researchers[1,5] have introduced ophthalmic markers, such as corneal nerve structure and function, retinal nerve structure, and vision loss. These methods had been used to demonstrate that diabetic neuropathy associated with morphological degradation of corneal nerves, reduced corneal sensitivity, retinal nerve fiber layer thinning and peripheral visual field loss. Also, they suggest that with further validation with other direct and indirect modalities, they can be used as new ideal biological markers, which are quick, painless, non-invasive, sensitive, reiterative, cost-effective and clinically useful means of screening for early detection, diagnosis, staging severity and monitoring progression of diabetic peripheral neuropathy, as well as assessing the effectiveness of possible therapeutic interventions[5].

Because of the rapid increase in diabetic patients, effective management of diabetic neuropathy has become more important than before. However, we do not have a complete biomarker yet, like microalbumin in diabetic nephropathy, for diagnosis and progression of diabetic neuropathy.

In addition to the methods already in use, the recently discovered methods, such as corneal nerve change and retinal microvascular abnormalities, need to be confirmed by large prospective clinical trials for diabetic neuropathy biological markers.

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