Diabetic polyneuropathy (DPN) is a serious complication of both type 1 and type 2 diabetes. The major clinical manifestations of DPN are neuropathic pain, diabetic foot (which is associated with ulcers, gangrene and amputation) and autonomic neuropathy. Diabetic sensorimotor peripheral neuropathy (DSPN) is the most common form of DPN and affects approximately 50% of people with type 1 or 2 diabetes during their lifetime. Despite its major clinical impact, DSPN remains underdiagnosed and undertreated. To reduce the burdens of DPN, there is an urgent need to develop both novel diagnostic procedures that enable improvement in the early detection of the disease and new treatments that address multiple mechanistic pathways (Figure 1).

Nerve conduction studies are the current gold standard for diagnosing DSPN, but they are labor intensive, time-consuming, costly and impractical to implement in routine clinical care. Therefore, DSPN is primarily diagnosed by a clinical examination that uses simple evaluation tests. They consist of assessing both small and large nerve fiber function, including temperature and pinprick perception (small fiber function); vibration sensation (with a 128-Hz tuning fork) and Achilles tendon reflexes (large fiber function); and protective sensation (with a 10-g monofilament; large fiber function).

Recently, some new diagnostic point-of-care devices that enable early detection of DPN have been developed. DPNCheck is a handheld point-of-care device that measures sural nerve amplitude and conduction velocity without the need for physiologist expertise or expensive equipment. DPNCheck measurements of sural nerve amplitude show strong agreement with standard nerve conduction studies. Kamiya et al. showed that parameters of the sural nerve obtained by DPNCheck were significantly associated with the severity of DSPN categorized by the Baba classification, suggesting that DPNCheck could provide comprehensive management of DSPN. However, further research is required to determine whether routine use can be used as a reliable assessment for DSPN, and whether it can prevent clinical outcomes, such as foot ulcers, amputation and cardiovascular disease.

I anticipate that future research will establish novel biomarkers for DSPN, painful neuropathy and autonomic neuropathy. Novel biomarkers derived from the current pathogenic concepts show promise in the early detection of DPN, and in predicting its development and progression, with biomarkers of oxidative stress and inflammation being very promising candidates. Other biomarkers, such as serum bilirubin, platelet size and complement C1q tumor necrosis factor-related protein 9, are promising candidates for diagnosing DSPN and cardiovascular autonomic neuropathy (CAN). However, large prospective studies are required to further validate whether these biomarkers can predict the unwanted outcomes of diabetic neuropathy, such as neuropathic pain, ulcers, amputations or even death.

Diabetic autonomic neuropathy affects the autonomic neurons (parasympathetic and/or sympathetic) and is associated with a variety of organ-specific symptoms. Clinical manifestations of autonomic neuropathy include hypoglycemia unawareness, resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea and fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction.

CAN is associated with the development of cardiovascular disease, and has a high risk of lethal arrhythmias and sudden death. A post-hoc analysis of the Action to Control Cardiovascular Risk in Diabetes trial showed beneficial effects of intensive glycemic or blood pressure control on the development of CAN in high-risk patients with type 2 diabetes. Identifying CAN by assessing heart rate variability as early as possible is important and clinically relevant, because it allows physicians to decide when and how to implement optimal strategies for risk factor management.

A review article mentioned the possibility that continuous glucose monitoring could help improve hypoglycemia awareness, because it is effective in reducing hypoglycemia and severe hypoglycemic episodes in patients with type 1 diabetes and hypoglycemia unawareness. Management of DSPN consists of three major principles: (i) causal treatment, including lifestyle modification, intensive glucose control and multifactorial cardiovascular risk intervention; (ii) pathogenesis-based therapy; and (iii) relief of pain. A better understanding of the underlying pathophysiology is required to enable new diagnostic and treatment approaches to be developed.

Some drugs derived from research on the pathogenetic concepts of DSPN are being used in several countries around the world. Aldose reductase is a key enzyme of the polyol pathway, which has been shown to be enhanced and a possible factor in DSPN (Figure 1). Aldose reductase inhibitors aim to inhibit the activation of the polyol pathway induced...
by chronic hyperglycemia. In a 3-year randomized study, the aldose reductase inhibitor, epalrestat, was well tolerated, and hindered the deterioration in median motor nerve conduction velocity, minimum F-wave latency and vibration sensation seen in an untreated group of patients with DSPN. A growing body of evidence suggests that oxidative stress resulting from enhanced free-radical formation and/or defects in anti-oxidant defense is implicated in the pathogenesis of DSPN. Several meta-analyses suggested that anti-oxidative therapy with α-lipoic acid might be effective in treating DSPN, and it has been used to treat symptomatic DSPN for a couple of decades.

For the initial symptomatic treatment of neuropathic pain, α2δ ligands for voltage-dependent Ca2+ channels, such as pregabalin, and norepinephrine reuptake inhibitors, such as duloxetine, are the two classes of analgesic drugs recommended, and they can also be used in combination. In a study of Asian patients with diabetic neuropathy, mirogabalin, a new α2δ ligand, relieved neuropathic pain in a dose-dependent manner and showed statistically significant pain relief (vs placebo) at a dose of 30 mg/day. However, the efficacy of symptomatic treatments for neuropathic pain is limited, so there is a continuing need for novel drugs to be developed for painful neuropathy that target the pathogenesis.

The current management strategy for diabetic neuropathy is focused on its early diagnosis, and prevention of diabetic foot and cardiovascular disease. In future, novel diagnostic techniques and criteria for classifying the severity of diabetic neuropathy might be developed, and their usefulness in evaluating the prognosis of diabetic neuropathy might be examined in large-scale clinical studies. I also expect that basic research will lead to the development of new, more efficacious compounds (drugs) that ideally address multiple mechanistic pathways.

**DISCLOSURE**

The author declares no conflict of interest.

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