Emergence of a Predictive Clinical Biomarker for Diabetic Neuropathy

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Diabetes is often complicated by the development of neuropathy, with up to a third of the direct costs of diabetes attributed to neuropathy-related morbidity (1). The incidence of diabetic neuropathy increases with duration of diabetes, affecting up to 50% of diabetic patients after 25 years of disease (2). To date, the development of neuroprotective and disease-modifying approaches for diabetic neuropathy has been disappointing. Therapeutic approaches with aldose reductase inhibitors and nerve growth factors have so far proved unsuccessful (3). Despite the promise of positive outcomes in research animal models, clinical trials of neuroprotective therapies have failed to yield significant benefit. In part, this lack of success reflects the absence of sensitive and robust methods for early detection of neuropathy (4). It is perhaps not surprising that initiation of therapy when axonal degeneration is advanced—well after the horse has left the gate—has resulted in trials that have been negative to date.

When considering the design of large-scale clinical trials for diabetic neuropathy in the future, development of biomarkers that facilitate both early detection and monitoring of disease progression remains the Holy Grail. Results from standard clinical electrodiagnostic techniques such as nerve conduction studies and quantitative sensory testing are determined based on detection of axonal loss. By definition, this approach renders these conventional measurements of limited use in detecting early changes and thereby the prevention of neuropathic injury. As a consequence, diabetic neuropathy often becomes apparent only after irreversible nerve injury has occurred, leading in turn to foot infections, ulceration, and in severe cases, amputation (5).

Even in today's modern era and despite the availability of advanced technologies, the mechanisms underlying diabetic neuropathy remain poorly defined. Nerve biopsies in diabetic neuropathy have demonstrated microangiopathy with multifocal fiber loss, most prominent distally and similar in nature to the abnormalities observed in experimental ischemic neuropathy (6). Diabetic nerves also exhibit an increased pathological vulnerability to ischemia (7). As part of an overarching ischemic hypothesis, considerable attention has focused on the role of metabolic derangements in diabetic neuropathy, mediated by decreased activity of the energy-dependent Na^+/K^+ pump present on the axonal membrane (7,8).

Although ischemia per se may lead to alterations in nerve activity, the abnormalities in Na^+/K^+ pump function in diabetic neuropathy have also been linked to metabolic changes occurring as a result of hyperglycemia and C-peptide deficiency (9). Reduced function of the Na^+/K^+ pump may also reflect the effects of activation of the polyol pathway, insulinopenia, and perturbations in insulin signal transduction (10). These changes in Na^+/K^+ pump function lead to intra-axonal Na^+ accumulation and a reduction in transmembrane Na^+ conductances (11,12).

Regardless of the cause, impairments of Na^+/K^+ pump function would be expected to produce an alteration in membrane potential, specifically membrane depolarization, due to retention of intra-axonal Na^+ (13,14). The importance of these changes is underscored by the fact that chronic alteration in ion channel function is capable of initiating a cascade of processes that ultimately result in axonal death (15). Given the intrinsic connection between membrane ion channel dysfunction and axonal loss, the development of clinical biomarkers that could identify the presence of early changes in ion channel function would clearly facilitate early detection of neuropathy thereby enabling treatment to be initiated well before irreversible nerve injury has set in.

With this in mind, the study by Sung et al. (16) in this month's issue of *Diabetes* presents novel axonal excitability findings from a sample of 108 type 2 diabetic patients with results compared with age-matched healthy control subjects (16). These potentially landmark studies have not only demonstrated prominent changes in axonal membrane function that are detectable even in diabetic patients without neuropathy, but they also show that changes become progressively greater with development of neuropathy and increasing neuropathy severity. Using an array of specialized nerve excitability parameters that reflect both nodal and internodal function, the abnormalities (specifically, reductions in threshold electrotonus, superexcitability, and subexcitability) were indicative of progressive depolarization of the axonal membrane. Perhaps more critically, changes in excitability that were evident among diabetic patients without neuropathy were capable of differentiating these patients from healthy control subjects, suggesting that these abnormalities have the potential to be further developed and validated as a clinical biomarker of neuropathy onset.

Although these results are intriguing, information regarding the relevance of these changes in relation to development of neuropathy will require longitudinal studies of larger population groups. However, these early studies hold the promise that identification of diabetic patients "at risk" of developing neuropathy is feasible in an objective clinical fashion. As a consequence, it may yet prove possible to initiate therapy in diabetic patients well before

See accompanying original article, p. 1592.

they manifest the symptoms and disability that inevitably reflect development of clinical neuropathy. Perhaps most importantly, the studies of by Sung et al. (16) suggest that pharmacological manipulation of axonal membrane channels may yet provide further new therapeutic approaches for treating patients with diabetic neuropathy.

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REFERENCES

1. Gordois A, Scuffham P, Shearer A, Oglesby A, Tobian JA. The health care costs of diabetic peripheral neuropathy in the US. Diabetes Care 2003;26: 1790–1795
2. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4400 patient observed between 1947 and 1973. Diabetes Care 1978;1:168–188
3. Habib AA, Brannagan TH 3rd. Therapeutic strategies for diabetic neuropathy. Curr Neurol Neurosci Rep 2010;10:92–100
4. Sima AAF, Kamiya H. Diabetic neuropathy differs in type 1 and type 2 diabetes. Ann N Y Acad Sci 2006;1084:235–249
5. Manes C, Papazolglou N, Sossidou EK, et al. Prevalence of diabetic neuropathy and foot ulceration: identification of potential risk factors—a population-based study. Wounds 2002;14:11–15
6. Sugimura K, Dyck PJ. Multifocal fiber loss in proximal sciatic nerve in symmetric distal diabetic neuropathy. J Neurol Sci 1982;53:501–509
7. Krishnan AV, Kiernan MC. Altered nerve excitability properties in established diabetic neuropathy. Brain 2005;128:1178–1187
8. Sima AA. Metabolic alterations of peripheral nerve in diabetes. Semin Neurol 1996;16:129–137
9. Sima AA, Zhang W, Li ZG, Murakawa Y, Pierson CR. Molecular alterations underlie nodal and paranodal degeneration in type 1 diabetic neuropathy and are prevented by C-peptide. Diabetes 2004;53:1556–1563
10. Grunberger G, Qiang X, Li Z, et al. Molecular basis for the insulinomimetic effects of C-peptide. Diabetologia 2001;44:1247–1257
11. Krishnan AV, Lin CS, Kiernan MC. Activity-dependent excitability changes suggest Na$^+$/K$^+$ pump dysfunction in diabetic neuropathy. Brain 2008;131: 1209–1216
12. Krishnan AV, Lin CSY, Park SB, Kiernan MC. Axonal ion channels from bench to bedside: a translational neuroscience perspective. Prog Neurobiol 2009;89:288–313
13. Kiernan MC, Bostock H. Effects of membrane polarization and ischaemia on the excitability properties of human motor axons. Brain 2000;123:2542–2551
14. Misawa S, Kuwabara S, Ogawara K, Kitano Y, Hattori T. Strength-duration properties and glycemic control in human diabetic motor nerves. Clin Neurophysiol 2005;116:254–258
15. Waxman SG. Sodium channel blockers and axonal protection in neuroinflammatory disease. Brain 2005;128:5–6
16. Sung J-Y, Park SB, Liu Y-T, et al. Progressive axonal dysfunction precedes development of neuropathy in type 2 diabetes. Diabetes 2012;61:1592–1598