Corneal Confocal Microscopy as a Measure of Diabetic Neuropathy

Roni M. Shtein[1] and Brian C. Callaghan[2]

Distal symmetric polyneuropathy is the most common pattern of nerve injury in patients with diabetes (1,2). In fact, up to 50% of patients with diabetes will develop distal symmetric polyneuropathy at some point during their illness (3). Currently, the only effective treatment to prevent this prevalent condition is glucose control (4). Unfortunately, demonstrating an improvement in neuropathy over time has been much more difficult to achieve than preventing progression (5). Possible explanations for the lack of improvement in outcome measures include a lack of an effective treatment and/or a lack of a sensitive test for nerve fiber repair.

No consensus exists as to which neuropathy outcomes should be obtained after a therapeutic intervention, and all currently available options have advantages and disadvantages. Clinical assessments and scales have the advantage of taking into account patients' symptoms and neurologic examination, but recent work has indicated that this approach may have poor reproducibility (6). Nerve conduction studies have long been used in studies of glucose control in type 1 and type 2 diabetes, and they have the advantage of being quantitative. However, improvement in nerve conduction studies may take years to manifest, and these studies do not assess small fiber nerve function, which are often the first nerves to be injured and perhaps the first to be repaired. Intraepidermal nerve fiber density (IENFD), measured by counting nerves that cross the dermal-epidermal junction, is a newer technique that is a measure of small fiber nerves and may be more sensitive to change (7) (Fig. 1). However, this technique is invasive, requiring a skin biopsy at one or two places each time it is measured. Quantitative sudomotor axon reflex testing is another measure of small fiber nerves, but it has the advantage of being noninvasive. However, the reproducibility of this study has been called into question (8). Quantitative sensory testing is another noninvasive, quantitative neuropathy outcome measure that has the potential to measure both large and small fiber function. This approach has been shown to be reproducible; however, it requires an alert, attentive, and motivated subject and there is no way to distinguish those with real from those with feigned sensory loss (9). Given the advantages and disadvantages of commonly used outcome measures, a need for a noninvasive, sensitive measure of neuropathy exists.

Several groups have reported the use of corneal confocal microscopy (CCM) evaluation of corneal nerve structures as a reliable measure of diabetic neuropathy (10–12) (Fig. 1). CCM has been shown to be effective as a rapid, noninvasive, repeatable evaluation that allows detection of neuropathy in patients with diabetes (10). Tavakoli et al. (13) have previously shown CCM evidence of early regeneration of corneal nerves in 20 patients with type 1 diabetes following simultaneous pancreas-kidney transplantation (SPK). In this issue of *Diabetes*, Tavakoli et al. (14) present longer-term data on 15 patients with significant neuropathy who underwent successful SPK. In this well-designed and carefully executed study, patients were evaluated at baseline and at 6 and 12 months after surgery with a detailed assessment of their neurologic status, including nerve conduction studies, quantitative sensory testing, and skin biopsies as well as CCM and corneal sensitivity testing (14). Evaluation of the recovery of diabetic neuropathy following SPK has been difficult to assess, but in this study the authors show that corneal nerve fiber density, corneal nerve branch density, and corneal nerve length as measured by CCM all improve significantly by 1 year after SPK. A major strength of this study is the simultaneous evaluation of peripheral nerve function using traditional examination methods, which showed no improvement at either the 6-month or 12-month postoperative visit. The authors conclude that CCM provides a more sensitive measure of assessing nerve repair than other currently used methods of evaluating neuropathy. Despite the small number of subjects, the lack of a randomized control group or blinding, and the relatively large number of comparisons performed, this study provides compelling evidence of the utility of CCM as a measure of early nerve regeneration.

It should be noted that the current study did not evaluate IENFD in thigh skin biopsy specimens (7), upper extremity nerve conduction studies (15), or sudomotor testing (16)—measures that have previously been shown to improve in studies of the recovery of neuropathy. Further, since no other peripheral nerve measures studied showed improvement over the time course of this study, it is unclear how the early nerve regeneration seen in the cornea relates to functional improvements of peripheral neuropathy.

Overall, the results of this study provide further evidence for the role of CCM as a biomarker to evaluate potential therapies in future clinical trials of human diabetic neuropathy. Importantly, CCM is a noninvasive technique that is fast, reproducible, quantitative, and measures small fiber nerves. However, many important questions need to be addressed. First, future studies need to determine if improvements in CCM parameters predict improvements in traditional neuropathy outcome measures such as clinical assessments and nerve conduction studies, as well as patient-oriented outcomes such as pain, disability, and quality of life. The possibility remains that corneal nerves and sensory/motor nerves in the feet are unrelated.

From the [1]Department of Ophthalmology, University of Michigan, Ann Arbor, Michigan; and the [2]Department of Neurology, University of Michigan, Ann Arbor, Michigan.
Corresponding author: Brian C. Callaghan, bcallagh@med.umich.edu.
DOI: 10.2337/db12-1114

See accompanying original article, p. 254.

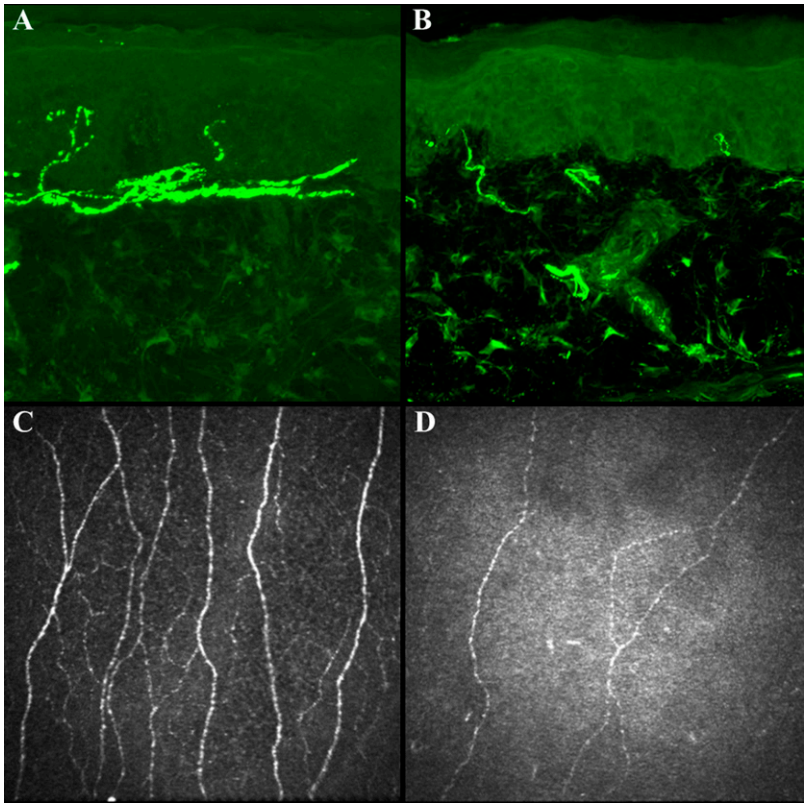

FIG. 1. Quantitative measures of small fiber nerves. Quantitative measures of small fiber nerves include immunohistochemical stain (PGP 9.5, magnification ×40) of skin biopsy specimens from the distal leg to illustrate IENFD in a healthy subject (*A*) and a patient with severe diabetic neuropathy (*B*), and representative CCM images from a healthy subject (*C*) and a patient with severe diabetic neuropathy (*D*).

Furthermore, if there is no connection between CCM and clinically meaningful outcomes, then this measure cannot be a useful biomarker in clinical trials. Second, all of these studies have been conducted in patients with type 1 diabetes receiving SPK. More studies are needed to investigate how CCM performs in those with type 2 diabetes and in those receiving other interventions, especially considering recent evidence pointing to type 1 and type 2 diabetes neuropathy being distinct entities (4,17). Finally, the relationship between CCM and other neuropathy outcome measures needs to be defined in a larger cohort of patients. CCM has the potential to be a game changer in neuropathy outcome assessment, but much more research is needed.

ACKNOWLEDGMENTS

R.M.S. is supported by a National Institutes of Health/National Eye Institute K23 Award (EY017885). B.C.C. is supported by a Junior Faculty Award from the American Diabetes Association.

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Martyn CN, Hughes RA. Epidemiology of peripheral neuropathy. J Neurol Neurosurg Psychiatry 1997;62:310–318
2. Palumbo PJ, Elveback LR, Whisnant JP. Neurologic complications of diabetes mellitus: transient ischemic attack, stroke, and peripheral neuropathy. Adv Neurol 1978;19:593–601
3. Pirart J. [Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973 (3rd and last part) (author's transl)]. Diabete Metab 1977;3:245–256 [in French]
4. Callaghan BC, Little AA, Feldman EL, Hughes RA. Enhanced glucose control for preventing and treating diabetic neuropathy. Cochrane Database Syst Rev 2012;6:CD007543
5. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
6. Dyck PJ, Overland CJ, Low PA, et al.; Cl vs. NPhys Trial Investigators. Signs and symptoms versus nerve conduction studies to diagnose diabetic sensorimotor polyneuropathy: Cl vs. NPhys trial. Muscle Nerve 2010;42:157–164
7. Smith AG, Russell J, Feldman EL, et al. Lifestyle intervention for pre-diabetic neuropathy. Diabetes Care 2006;29:1294–1299
8. Peltier A, Smith AG, Russell JW, et al. Reliability of quantitative sudomotor axon reflex testing and quantitative sensory testing in neuropathy of impaired glucose regulation. Muscle Nerve 2009;39:529–535
9. Freeman R, Chase KP, Risk MR. Quantitative sensory testing cannot differentiate simulated sensory loss from sensory neuropathy. Neurology 2003;60:465–470
10. Ahmed A, Bril V, Orszag A, et al. Detection of diabetic sensorimotor polyneuropathy by corneal confocal microscopy in type 1 diabetes: a concurrent validity study. Diabetes Care 2012;35:821–828
11. Rosenberg ME, Tervo TM, Immonen IJ, Müller LJ, Grönhagen-Riska C, Vesaluoma MH. Corneal structure and sensitivity in type 1 diabetes mellitus. Invest Ophthalmol Vis Sci 2000;41:2915–2921
12. Tavakoli M, Quattrini C, Abbott C, et al. Corneal confocal microscopy: a novel noninvasive test to diagnose and stratify the severity of human diabetic neuropathy. Diabetes Care 2010;33:1792–1797
13. Mehra S, Tavakoli M, Kallinikos PA, et al. Corneal confocal microscopy detects early nerve regeneration after pancreas transplantation in patients with type 1 diabetes. Diabetes Care 2007;30:2608–2612
14. Tavakoli M, Mitu-Pretorian M, Petropoulos IN, et al. Corneal confocal microscopy detects early nerve regeneration in diabetic neuropathy following simultaneous pancreas and kidney transplantation. Diabetes 2013;62:254–260
15. Allen RD, Al-Harbi IS, Morris JG, et al. Diabetic neuropathy after pancreas transplantation: determinants of recovery. Transplantation 1997;63:830–838
16. Navarro X, Sutherland DE, Kennedy WR. Long-term effects of pancreatic transplantation on diabetic neuropathy. Ann Neurol 1997;42:727–736
17. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol 2012;11:521–534