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RESPONSE TO COMMENT ON MALIK

Which Test for Diagnosing Early Human Diabetic Neuropathy? Diabetes 2014;63:2206–2208

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We thank van der Heyden et al. (1) for their thoughtful comment in response to the commentary by author Malik (2). We totally agree there is a need to develop better surrogate markers if we are to translate clinically meaningful new therapies for diabetic peripheral neuropathy (DPN).

Therefore, we read with interest their recent study (3) showing reduced motor nerve axonal excitability, measured using threshold-tracking techniques, in young type 1 diabetes patients with normal compound muscle action potential scan measures of axonal loss and reinnervation as well as conventional electrophysiology. This is not surprising given that minor perturbations in glucose can lead to anaerobic glycolysis, tissue acidosis, and reduced Na^+/K^+ATPase activity with alterations in voltage-gated potassium (Kv) and sodium (Nav) channels and hence nerve excitability. This may well seem to challenge the belief that small sensory nerves, as evidenced by a loss of intraepidermal nerve fiber and corneal nerves, are the earliest to be affected in DPN. However, nerve dysfunction likely precedes fiber degeneration, and damage to small sensory fibers has direct clinical relevance because they mediate neuropathic pain paradoxically via increased rather than decreased sodium channel hyperexcitability (4), as well as blood flow and inflammation leading to foot ulceration and amputation.

Clinically relevant motor deficits on the other hand are late manifestations. Furthermore, the fact that motor nerve excitability is acutely reversible by correcting hyperglycemia surely suggests this is an acute metabolic phenomenon rather than a progressive neurological deficit (5). Moreover, the utility of motor nerve axon excitability should be interpreted with caution given that the study (3) used crude clinical measures, which can only reliably identify advanced DPN, as opposed to skin biopsy, which can detect early neuropathy. We understand the authors' ethical concern for undertaking an invasive skin biopsy and would indeed argue that corneal confocal microscopy (CCM), a validated, noninvasive alternative to skin biopsy, could easily be deployed to stratify DPN severity in children. Thus, CCM is a rapid, well-tolerated, reproducible, and highly sensitive technique to diagnose early nerve damage in children and adults with type 1 and type 2 diabetes, impaired glucose tolerance, and a range of other peripheral neuropathies (6). Importantly, it shows a reduction in corneal nerve fiber density in subjects without symptoms, signs, or neurophysiologic abnormalities and axonal regeneration following simultaneous pancreas and kidney transplantation in patients with type 1 diabetes, fulfilling many of the criteria for a viable surrogate end point.

We believe that altered motor axonal excitability may also eventually become a surrogate end point, but it needs validation. This will require longitudinal and interventional studies comparing it against standard neurophysiology and quantitative sensory testing as well as measures of structural pathology such as intraepidermal nerve fiber density and CCM in patients with and without DPN.

Undoubtedly, there is an urgent need to establish better functional and structural surrogate end points of DPN. Otherwise, we will not translate the ever-dwindling pipeline of experimental therapies because of failure after failure of potential treatments in phase 2/3 studies. The consequences are stark. We will drive both basic investigators and pharmaceutical companies away from

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investing in and developing viable treatments for our patients with DPN.

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