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Lost in Translation? Measuring Diabetic Neuropathy in Humans and Animals (*Diabetes Metab J* 2021;45:27-42)

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We are grateful for the opportunity to respond to the letter received by *Diabetes and Metabolism Journal* from Dr. Hernandez Fustes concerning our recent review "Lost in translation? Measuring diabetic neuropathy in humans and animals" [1]. We would also like to thank Dr. Hernandez Fustes for his comments about our review.

We agree with Dr. Hernandez Fustes that the techniques he highlights, high resolution ultrasound (HRU) and pain-related evoked potentials (PREP), may offer additional options for diagnosis of diabetic neuropathy. There is a striking concordance amongst recent HRU studies in diabetic patients that nerve cross-sectional area (CSA) is increased compared to the nerves of control subjects [2]. Reference values have been established [3] and this technique offers the additional advantage of allowing measurement of nerve blood flow by Doppler shift [4], changes in which have been implicated in the pathogenesis of diabetic neuropathy [5]. Unfortunately, the current technical limitations of HRU do not allow detailed visualization of nerve or vascular pathology so that any pathophysiology implied by increased CSA remains speculative. A study by Breiner et al. [6] is of particular interest to us in that increased CSA was detected in multiple nerves of type 1 and type 2 diabetics, both with and without neuropathy, with slightly greater CSA in those with neuropathy. The authors suggested that this diffuse enlargement of nerves was a sensitive indicator of early neuropathy, given that it occurred in patients with signs and symptoms, but not electrodiagnostic confirmation. However, they also cautioned against sole use of HRU as a screening test and noted that it did not improve diagnosis of neuropathy beyond what is provided by the less complex assessment of quantitative vibration perception thresholds. In time, HRU may well find its place as part of the battery of early diagnostic tests that precede full eletrodiagnostic work up.

Like HRU, use of PREP is emerging as a non-invasive diagnostic test, in this case to identify small fibers, specifically A δ fiber, neuropathy [7]. Advantages of PREP over other forms of peripheral stimulation such as LEP and CHEP include the relative ease of use that facilitates low cost and low stress to patients. Such benefits would certainly be welcomed by patients. However, all such tests record activity across the full length of the somatosensory system and therefore represent the summation of pathological contributions from radiculopathy and myelopathy [8], with attendant conduction slowing [9] that occurs in diabetes as well as peripheral sensory nerves. This does not diminish the value of PREP but should always inform interpretation of findings and diagnosis.

One intent of our review was to reassess the alignment between indices of neuropathy currently used in preclinical studies investigating novel therapeutic approaches to diabetic neuropathy and the correlates used in a clinical setting for both diagnosis of diabetic neuropathy and assessment of treatment efficacy in clinical trials. Continued failure to translate therapies

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stems, at least in part, from disconnects in efficacy readouts that, while present in both animals and humans with diabetes, may derive from distinct nerve pathologies. Our particular focus on the emergence of skin biopsy and corneal confocal microscopy stems not only from the diagnostic capacity to identify early small fiber neuropathy, but also from the presence of similar pathologies in both rodent and human diabetes that may allow a more robust translational bridge between species. In the absence of an obvious gold standard, our current stance on preclinical studies is to suggest that potential therapeutics pass through a development funnel that includes multiple assays in multiple test systems before proceeding to clinical trial [1]. It may be equally important to expand the repertoire of acceptable efficacy endpoints in clinical trials. As Dr. Hernandez Fustes eloquently reminds us, emerging techniques such as HRU and PREP have potential for inclusion in such a battery of objective tests.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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