RESPONSE TO COMMENT ON BREINER ET AL.

Does the Prevailing Hypothesis That Small-Fiber Dysfunction Precedes Large-Fiber Dysfunction Apply to Type 1 Diabetic Patients? Diabetes Care 2014;37:1418–1424

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Diabetes Care 2014;37:e242 | DOI: 10.2337/dc14-1587

We read with interest the comments of Vas et al. (1) regarding our article (2), which used noninvasive tests of small-fiber structure and function to demonstrate the presence of small-fiber dysfunction prior to large-fiber change in patients with type 1 diabetes. We would like to respond to the following points.

Vas et al. (1) raised concerns regarding low laser Doppler imaging of heat-evoked flare (LDI_{flare}) sensitivity for detection of polyneuropathy. In our study, LDI_{flare} was measured using the moorLDI2 instrument (Moor Instruments Ltd., Axminster, U.K.), according to published techniques (3). In a previous study, we have shown that LDI_{flare} shows potential as a biomarker for early nerve fiber dysfunction and is able to distinguish between healthy control subjects and type 1 diabetic patients with and without polyneuropathy (4). However, using the England et al. (5) criteria to define diabetic sensorimotor polyneuropathy (DSP), the receiver operating characteristic curve demonstrated an area under the curve of 0.72 and optimal sensitivity of 70% for detection of DSP, indicating that LDI_{flare} is relatively sensitive but insufficiently so to serve as a "stand-alone" measure.

One possibility raised in Vas et al. (1) is that lower sensitivity may be due to use of an older technique used to perform LDI_{flare} studies. We are indeed very grateful to the group of Vas et al. for the excellent work they have done in improving the reliability and shortening study time via an updated LDI_{flare} protocol (6). It is important to note that our patients were accrued and tested between 2008 and 2012, prior to the validation of these new techniques in 2013. In our hands, we indeed did observe substantial coefficient of variation for LDI_{flare}: 52.7% for healthy volunteers, 60.1% for all type 1 diabetic patients, 55.9% for type 1 diabetic patients without DSP, and 50.1% for type 1 diabetic patients with DSP. Such variation may arise from error variability or the inherent distribution of the neurogenic vasodilatation in response to cutaneous heating.

We are in agreement that there is a need for established standards for small-fiber neuropathy methodologies. However, these methods may continue to evolve over time, as illustrated above. Even with rigorous methodology, we do not believe that any singular noninvasive test has been established as the gold standard for diagnosis of small-fiber neuropathy. As a research community, we must commit to the development of a test—or a combination of tests—that can accurately predict the development of future polyneuropathy in asymptomatic patients. Such an attribute would be of greatest value for the clinical research into natural history and putative neuropathy interventions, as well as to screening in clinical practice. As reflected in our recent publication (7), our own belief is that corneal confocal microscopy (a morphological measure of small-diameter nerve fiber integrity) may be the ideal marker; however, we believe that the issue requires further study before definitive conclusions are drawn.

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

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