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

Prashanth R.J. Vas, Sanjeev Sharma, and Gerry Rayman

Diabetes Care 2014;37:e240–e241 | DOI: 10.2337/dc14-1258

We read with great interest the article by Breiner et al. (1) demonstrating the presence of small-fiber dysfunction in type 1 diabetes of significant duration in the absence of perceptible abnormalities in large-fiber function, and we congratulate the authors for their simple, clear, and elegant study design. We also agree with the authors that this study "has made an important contribution to the literature" in understanding the development of early neuropathy in type 1 diabetes. As reviewed by the authors, the association of small-fiber dysfunction prior to large-fiber change is already an established concept in the neuropathy of type 2 diabetes and, indeed, in impaired glucose metabolism. It is also commendable that the authors derived their own normative values for the small-fiber parameters tested.

However, we would like to point out that using the laser Doppler imaging of heat-evoked flare (LDI_{flare}) methodology, we have already demonstrated impaired small-fiber function in type 1 diabetic subjects in whom clinical neuropathy had been excluded using the well-validated Neuropathy Disability Score (2). Furthermore, we have also shown that small-fiber function assessed by the LDI_{flare} method declines with age, established normative reference ranges, and highlighted the need for individual patients to be assessed using decade-specific normative values (3). Additionally, we have modified the original LDI_{flare} technique used by Breiner et al., significantly shortening the study time and improving its reliability (4). We believe that the LDI_{flare} methodology used by the authors could be another reason for the relatively low sensitivity of LDI_{flare} in diabetic sensorimotor polyneuropathy patients. In our experience, it has excellent sensitivity for the detection of clinical neuropathy (3). It would be helpful to know the coefficient of variation for the methodology used in their study. The mean values reported by Breiner et al. (1) are quite different to those we have obtained.

This brings us to our most important two points. *1*) There is a clear need for researchers in small-fiber neuropathy to agree on one specific methodology per test as currently promoted by the German Research Network on Neuropathic Pain for nerve conduction studies and quantitative sensory testing and also to develop shared "normative" values for small-fiber indices in a similar vein to the one developed by Lauria et al. (5) for intraepidermal nerve fiber density. Likewise, we believe it is important to set standards for techniques such as corneal confocal microscopy. *2*) Although skin biopsy is considered the gold standard, future studies looking at etiopathogenesis and putative drug regulatory studies should consider using corneal confocal microscopy, LDI_{flare}, and quantitative sensory testing as benchmarks for defining small-fiber abnormalities, perhaps in a composite way as identified in this article. We agree that there is significant heterogeneity between the markers of small-fiber structure and function, and no test is singularly indicative. The LDI_{flare} has great promise for determining small-fiber function; however, its future application and utility will depend on its ability to produce reliable and discriminating results. We would encourage future adopters to use the modified technique we have published, which, when applied with the precision required, demonstrates good reproducibility and high sensitivity and specificity in detecting small-fiber dysfunction.

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

References

1. Breiner A, Lovblom LE, Perkins BA, Bril V. Does the prevailing hypothesis that small-fiber dysfunction precedes large-fiber dysfunction apply to type 1 diabetic patients? Diabetes Care 2014;37:1418–1424
2. Vas PR, Green AQ, Rayman G. Small fibre dysfunction, microvascular complications and glycaemic control in type 1 diabetes: a case-control study. Diabetologia 2012;55:795–800
3. Vas PR, Rayman G. The rate of decline in small fibre function assessed using axon

Diabetes Research Centre, Ipswich Hospital National Health Service Trust, Suffolk, U.K.

Corresponding author: Gerry Rayman, gerry.rayman@ipswichhospital.nhs.uk.

reflex-mediated neurogenic vasodilatation and the importance of age related centile values to improve the detection of clinical neuropathy. PLoS One 2013;8:e69920

4. Vas PR, Rayman G. Validation of the modified LDIFlare technique: a simple and quick method to assess C-fiber function. Muscle Nerve 2013; 47:351–356

5. Lauria G, Bakkers M, Schmitz C, et al. Intraepidermal nerve fiber density at the distal leg: a worldwide normative reference study. J Peripher Nerv Syst 2010;15:202–207