A novel method to assess small and large fiber properties in painful and painless diabetic neuropathy

Aim: This study aimed to validate a novel method for evaluating the function of small sensory nerves in diabetes to give insights into the differences between painless (DPN) and painful diabetic polyneuropathy (PDPN).

Methods: The function of large and small fibers was assessed using a novel perception threshold tracking technique (able to preferentially activate Aδ and C fibers in the epidermis and Aβ fibers in the dermis by using a low-current electrical stimulation by a patch and a pin electrode, respectively) in three well-characterized groups (n=60) with type 1 diabetes and PDPN (T1DM+PDPN), DPN (T1DM+DPN), no DPN (T1DM-DPN), and healthy controls (n=20). Electrical currents with different shapes, duration, and intensities were applied by two different skin electrodes activating large and small fibers, respectively. The minimal current needed to activate the fibers were analyzed as the rheobase of the stimulus-response function. Nerve fiber selectivity was measured by accommodation properties of stimulated nerves.

Results: The rheobase of both fiber types were highest for T1DM+PDPN, followed by T1DM+DPN, T1DM-DPN and healthy controls, indicating that the nerve properties are specific in individuals with diabetes and pain. There was an overall significant difference between the groups ($p<0.01$). The accommodation properties of stimulated fibers differed between the two electrodes ($p<0.05$) in all groups apart from in T1DM+PDPN, where both electrodes stimulated nerves with properties similar to large fibers.

Conclusions: Perception threshold tracking shows differences in large- and small nerve fiber function between groups with and without diabetes, DPN, and neuropathic pain, suggesting potential applications of the method in screening DPN and differentiating painful from painless DPN.

Comments. PDPN is a major cause of mortality and morbidity in patients with diabetes, thus there is an urgent need to better understand its pathogenesis. Small fibers are primary responsible for peripheral nociception. Conventional diagnostic methods like electrophysiological testing, which assess large fiber function, and also corneal confocal microscopy and skin biopsy, which measure only structural changes, cannot detect small fiber function. The novel perception threshold technique used in the present study can assess the function of both small and large nerve fibers individually in patients with type 1 diabetes. Rheobase of large and small fibers showed a sensitivity and specificity >80% for a diagnosis of large and small fiber neuropathy, based on sural nerve conduction study and thermal thresholds, respectively. In addition, this method seemed able to distinguish patients with PDPN and DPN whereas other small fiber function measures as thermal thresholds could not. Thus, these findings may provide further understanding of the differences in sensory nerve fiber properties in patients with/without neuropathic pain. The study is limited in its sample size and the lack of skin biopsies.

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Reference. Røikjer J, Croosu SS, Frøkjær JB, Hansen TM, Arendt-Nielsen L, Ejskjaer N, Mørch CD. Perception threshold tracking: validating a novel method for assessing function of large and small sensory nerve fibers in diabetic peripheral neuropathy with and without pain. Pain. 2022 Sep 19. doi: 10.1097/j.pain.0000000000002780. Epub ahead of print. PMID: 36130086.

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