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Natural course of diabetic neuropathy: a tale of four phenotypes

***Aims*.** To assess the clinical and neurological features associated with different neuropathic phenotypes defined by quantitative sensory testing (QST); and establish their evolution over a period of 3 years in relation to diabetic sensorimotor polyneuropathy (DSPN).
***Methods*.** In this prospective longitudinal study, n=316 and n=250 adults with type 1 or 2 diabetes were assessed at baseline and follow-up, respectively. DSPN was defined according to 1) clinical criteria comprising Neuropathy Disability Score (NDS) ≥6 or a combination of Neuropathy Symptom Score (NSS) ≥5 and NDS=3-5; and 2) the Toronto criteria for confirmed DSPN based on sural nerve amplitude or conduction velocity (NCV) <1st percentile, combined with at least one motor nerve abnormality and NDS and/or NSS ≥3. Participants were categorized into four neuropathic phenotypes namely healthy state, thermal hyperalgesia (TH), mechanical hyperalgesia (MH), and sensory loss (SL) based on 13 QST domains.
***Results*.** At baseline, 80 participants were classified as healthy, 91 as TH, 77 as MH, and 68 as SL. Signs (P<0.001) and symptoms (P<0.001) of DSPN worsened gradually with increasing neuropathic severity across healthy, TH, MH, and SL groups, respectively. Neurophysiological findings of sural, peroneal, and tibial nerves (all P<0.001) followed a similar trend with the SL and MH groups being the most affected compared to healthy and TH counterparts. DSPN prevalence based on clinical/Toronto criteria respectively was highest in the SL group (79.8%/61.8%) followed by MH (39%/22.1%), TH (23.1%/18.7%), and healthy (8.8%/6.3%) groups. At follow-up, 135 (54%) participants had a change of phenotype. Overall, there was a decrease in the healthy cluster (-41.2%) and increase in the SL (+29.4%) followed by the MH (+10%), and TH (+8.8%) clusters. There was a predominant pattern of change from healthy to TH (62.5%, P<0.005), from TH to MH (58.5%, P<0.05), from MH to SL/TH (46.2%/43.6%, P<0.05), and from SL to MH (66.7%, P<0.01). Baseline MH phenotype and higher HbA1c carried an increased risk for SL occurrence at follow-up (HR=5.19 and 1.37, P=0.002 and 0.018). By contrast, the highest rates of reversion to healthy state at follow-up were observed from the baseline TH group (HR=6.14, P=0.016). Regression modelling showed a significantly higher risk of progression for patients at the highest vs. lowest HbA1c (8.4% vs. 5.9%, P=0.008) quantile. Finally, baseline SL phenotype was associated with a 3-fold risk for development of clinically defined DSPN whereas the other 3 phenotypes were not.
***Conclusions*.** QST-based phenotyping may be useful in determining the course of DSPN and assist clinical decision making.

Comments. DSPN is characterized by progressive degeneration of small and large nerve fibers, however a more precise model to describe its natural evolution is needed. Using QST, a measure of small and large fiber function, the authors elegantly demonstrate four distinct sensory phenotypes underpinned by gradually increasing neuropathic severity, each associated with a different likelihood of progression or regression over time. SL, representing the end of this neuropathic spectrum, was associated with the lowest probability for reversion whereas TH, indicating milder disease, with the highest. During this dynamic process, higher baseline HbA1c was the main driver of phenotypic switch and DSPN occurrence at follow-up. These results imply that QST may identify patients in intermediate sensory states at risk of developing clinically evident DSPN; and assist in assessing effectiveness of different treatment and preventive strategies. Further phenotyping studies incorporating objective small fiber measures like corneal confocal microscopy and intra-epidermal nerve fiber density are warranted.
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Reference. Tsilingiris D, Schimpfle L, von Rauchhaupt E, Sulaj A, Seebauer L, Herzig S, Szendroedi J, Kopf S, Kender Z. Sensory Phenotypes Provide Insight Into the Natural Course of Diabetic Polyneuropathy. Diabetes. 2024 Jan 1;73(1):135-146. doi: 10.2337/db23-0271. PMID: 37862374.
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