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From warmth to loss: sensory phenotypes and peripheral white matter integrity

***Aims*:** To investigate the relationship of sensory phenotypes in individuals with type 2 diabetes mellitus (T2D) using quantitative sensory testing (QST) with neuroanatomical alterations of the sciatic nerve using magnetic resonance neurography (MRN).
***Methods*:** In this prospective cross-sectional cohort study, 76 adults with T2D underwent laboratory tests, neuropathy symptom score (NSS), neuropathy disability score (NDS), nerve conduction studies (NCS) and high-resolution MRN of the right leg. QST was used to identify the sensory phenotypes of the right foot and allocate participants using a deterministic algorithm into four groups: healthy sensory profile (HSP), thermal hyperalgesia (TH), mechanical hyperalgesia (MH), and sensory loss (SL). A comparison of z transformed QST scores against 13 non-diabetic controls of the total cohort and sensory phenotype subgroups was also undertaken. Diagnosis of confirmed diabetic sensorimotor polyneuropathy (DSPN) was based on the definition of the Toronto Diabetic Neuropathy Expert Group (abnormal NCS and NDS≥3 and/or NSS≥3).
***Results*:** Relative to non-diabetic controls the T2D cohort had a loss of function to thermal, mechanical and vibration detection, a gain of function to heat pain (all P<0.001), an increased incidence of paradoxical heat sensations (p=0.009) and mechanical allodynia (p=0.005). The deterministic algorithm classified 16 participants as HSP, 24 as TH, 17 as MH, and 19 as SL. Signs of DSPN progressively worsen across HSP, TH, MH, and SL groups (NDS: P<0.001). Similarly, neurophysiological deficits increased progressively, with deficits more pronounced in MH compared to the HSP group (p=0.008), and the greatest decrements in the SL group relative to both HSP (P=0.005) and TH groups (p=0.003). The total T2D cohort DSPN prevalence was highest in the SL group (78.9%) relative to all the other groups (HSP: (6.3%), P<0.001; TH: (29.2%), P<0.01; MH: (41.2%), P<0.05). MRN of the sciatic nerve found a gradual decrease in fractional anisotropy (FA) from HSP to SL (p=0.005) with the greatest difference in FA in the SL group relative to the HSP (P=0.024) and TH (p=0.029) groups. A gradual increase of sciatic nerve cross sectional area (CSA) was found in MH and SL (P=0.011) which failed to reach significance in post-hoc testing. Multivariate regression modelling showed MH and SL groups were associated with lower sural nerve action potential (p<0.001), sciatic FA (p=0.004) and higher sciatic CSA (p=0.032). Lower sural nerve conduction velocity was associated with the SL phenotype (p=0.032), accounting for this the association between SL and lower sciatic FA was still significant (p=0.023), whilst the association of MH with FA became marginally non-significant (p=0.055).
***Conclusions*:** Progressive peripheral nerve damage in T2D precedes the SL phenotype and correlates with worsening DSPN signs and sensory phenotypes associated with a diagnosis of confirmed DSPN.

Comments. The SL phenotype likely indicates a critical juncture of irreversible axonal damage and neurodegeneration in peripheral nerves culminating in confirmed DSPN. This study is the first to associate neuroanatomical alteration using diffusion tensor imaging in the sciatic nerve with sensory phenotypes, highlighting the importance of integrating multimodal MRI techniques to understand pathophysiological mechanisms. Diagnostic methods are weighted towards large fibre abnormalities and may not account for the complex interplay between central and peripheral neuroanatomical changes in DSPN (*Selvarajah D et al Diabetes Care 2023;46:777-785***).** This study underscores the importance of integrated clinical diagnostic methods to identify the subclinical irritable nociceptor phenotype. Longitudinal studies, incorporating structural and functional measures of the peripheral and central nervous system in early T2D or high-risk individuals are warranted. Without disease-modifying treatment, assessment of the DSPN course would add value to recommendations for early identification and possible biomarkers suggestive of early worsening or improvement.
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Reference. Mooshage CM, Tsilingiris D, Schimpfle L, Seebauer L, Eldesouky O, Aziz-Safaie T, Hohmann A, Herzig S, Szendroedi J, Nawroth P, Heiland S, Bendszus M, Kurz FT, Kopf S, Jende JME, Kender Z. A diminished sciatic nerve structural integrity is associated with distinct peripheral sensory phenotypes in individuals with type 2 diabetes. Diabetologia. 2024 Feb;67(2):275-289. doi: 10.1007/s00125-023-06050-y. Epub 2023 Nov 29. PMID: 38019287; PMCID: PMC10789832.
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