

### Can Glucagon-like peptide-1 receptor agonist treatment reverse diabetic neuropathy?

**Aims:** To investigate whether treatment with common Glucagon-like peptide-1 receptor agonists (GLP-1 RA) can improve structural and functional indices of diabetic peripheral neuropathy (DPN) in individuals with type 2 diabetes.

**Methods:** Clinical composite neuropathy scores including neuropathic signs and symptoms, nerve conduction studies (sural and tibial nerves), and tibial nerve ultrasonography to assess cross-sectional nerve area (CSA) were performed in 22 participants with type 2 diabetes and DPN before and 1 month after commencing weekly GLP-1 RA treatment with semaglutide or dulaglutide as part of standard clinical care.

**Results:** At 1 month of follow-up, a reduction in tibial CSA was observed in 19 out of 22 participants, with 7 out of 22 returning to the normal range. A 3 month follow-up study including a subgroup of 14 participants demonstrated further improvement in tibial CSA in 13 out of 14 individuals, accompanied by a slightly improved Total Neuropathy Score (TNS) outcome and higher sural sensory nerve conduction amplitude (SNAP), but no change in sural sensory nerve conduction velocity or tibial nerve conduction. Improved indices were not associated with changes in HbA1c or BMI.

**Conclusions:** GLP-1 RA treatment may exert beneficial short-term effects on nerve morphology and function in patients with type 2 diabetes and DPN.

**Comments.** While the efficacy of GLP-1 RA treatment on chronic complications of diabetes including cardiovascular endpoints, diabetic kidney disease, and diabetic retinopathy has been extensively studied, evidence on DPN and, more importantly, on reliable clinical endpoints of DPN remain scarce and without breakthrough results. In a commendable approach, the authors aimed to investigate the effects of GLP-1 RA treatment in a real-world setting including functional, morphological, and clinical indices of DPN. Despite the limitations of a single-arm observational study design, the results show several interesting aspects that warrant further, more elaborate randomized trials including small- and large-fiber neuropathy endpoints evaluating the effects of GLP-1 RA treatment effects on DPN. In the present study, both morphological (tibial nerve CSA) and functional (sural SNAP) indices, mainly reflecting large-fiber impairments, improved, while these effects could not be attributed to changes in glycemic control and weight. It deserves further investigation whether this may be influenced by other cardiovascular risk factors, changes in body composition, or inflammatory processes. According to the clinical scoring, the study participants had predominantly mild DPN, which may be more amenable to treatment than more advanced stages. Finally, it remains to be seen whether the observed beneficial effects reflect a transient state in the first few months of GLP-1 RA treatment or are sustained over time.

**Gidon J Bönhof**

**Reference.** Dhanapalaratnam R, Issar T, Lee ATK, Poynten AM, Milner KL, Kwai NCG, Krishnan AV. Glucagon-like peptide-1 receptor agonists reverse nerve morphological abnormalities in diabetic peripheral neuropathy. *Diabetologia*. 2024 Jan 8. doi: 10.1007/s00125-023-06072-6. Epub ahead of print. PMID: 38189936.

<https://link.springer.com/article/10.1007/s00125-023-06072-6>