

Serum neurofilament light chain: another step for a new future biomarker of diabetic peripheral neuropathy

Aims: To study the longitudinal change of serum neurofilament light chain (s-NfL) levels in type 2 diabetes (T2D) with and without diabetic peripheral neuropathy (DPN+/-) and its potential predictive role as a biomarker for DPN.

Methods: This is a retrospective longitudinal case-control analysis (data from ADDITION-Denmark 5- and 10-year follow-ups). 178 participants were included. S-NfL was analyzed at the 5-year and 10-year visits, and the results were compared with NfL z-scores, obtained from neurologically healthy individuals. Patients performed nerve conduction study (NCS), Michigan Neuropathy Screening Instrument questionnaire (MNSIq) and examination, Douleur Neuropathic en 4 questions questionnaire, and vibration detection threshold (VDT). DPN was diagnosed according to Toronto criteria (abnormal NCS with at least one symptom and/or symmetrical sign indicative of DPN) at the 10-year follow-up.

Results: Both in DPN+ group (n=39) and in DPN- group (n=139) s-NfL levels increased above normal z-scores during the follow up. Longitudinal s-NfL change was greater in DPN+ than in DPN- participants (17.4% or 0.31 SD higher s-NfL or NfL z-score increase in +DPN compared with -DPN). Moreover, s-NfL at the 5-year follow-up was positively associated with NCS at the 10-year follow-up (p=0.02 to <0.001) and areas under the curves (AUCs) for s-NfL were not inferior to AUCs for the MNSIq or VDT. Higher yearly s-NfL increase was associated with higher DPN risk (odds ratio 1.36 per 1 ng/L/year). Changes in s-NfL were associated with changes in weight, total cholesterol and eGFR but not with changes in HbA1c.

Conclusions: s-NfL changes trajectories could become a possible biomarker of DPN monitoring.

Comments. NfL is a cytoskeletal component of neurons that provides structural stability and is released into the circulation in presence of nerve injury (Gafson AR et al *Brain*. 2020;143:1975-1998). Widely used as a biomarker for peripheral nerve damage in several diseases, it is becoming very interesting in DPN. In fact, higher serum NfL levels are associated with DPN and nerve dysfunction in patients with short duration of T2D (Maalmi H et al *Diabetologia* 2023;66:579-589) and the TODAY (Treatment Option for Type 2 Diabetes in Adolescent and Young) study already described a steeper increase in NfL levels in patients developing DPN (Fridman V et al *J Peripher Nerv Syst*. 2023;28:460-470). This is the first longitudinal evaluation in adults with T2D. Despite some limitations, such as the absence of the exact time of DPN diagnosis and the lack of evaluation of small fibers dysfunction in DPN-, this is a challenging work that corroborates the potential role of s-NfL as a novel monitoring biomarker for DPN in routine clinical practice. However, its clinical implication needs to be investigated in future studies.

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Reference. Määttä LL, Andersen ST, Parkner T, Hviid CVB, Bjerg L, Kural MA, Charles M, Søndergaard E, Kuhle J, Tankisi H, Witte DR, Jensen TS. Longitudinal Change in Serum Neurofilament Light Chain in Type 2 Diabetes and Early Diabetic Polyneuropathy: ADDITION-Denmark. *Diabetes Care*. 2024 Mar 19;dc232208. doi: 10.2337/dc23-2208. Epub ahead of print. PMID: 38502878.

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