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Editorial

Nerve ultrasound – A screening tool for diabetic neuropathy

Diabetes mellitus is a global epidemic, probably the largest of the 21st century (Tabish, 2007). The 2021 report of the International Diabetes Federation (IDF) estimated a prevalence of 537 million (10.5% of the world population) of adults aged 20–79 years and stated that "Without sufficient action to address the situation, we predict 643 million people will have diabetes by 2030 (11.3% of the population) (International Diabetes Federation, 2021). If trends continue, the number will jump to a staggering 783 million (12.2%) by 2045".

Peripheral neuropathy is the most prevalent complication of diabetes, affecting up to 50% of all patients, with significant morbidity and mortality and disastrous social and economic consequences (Feldman et al., 2019).

Prevention and new therapeutic interventions demand sensitive biological markers that allow early diagnosis of the neuropathy and reliable monitoring of its severity and progression. To be widely applied, screening and monitoring tests should also be easily applicable (preferably at point-of-care), reasonably fast and, relatively inexpensive.

Electrodiagnostic tests are currently used in the investigation of diabetic neuropathy by neuromuscular physicians for both diagnosis and assessment of severity. The downsides are that these tests are generally not available in primary centres, are uncomfortable and do not test small nerve fibres.

In recent years, several studies have investigated ultrasound of single or multiple nerves in diabetic neuropathy. In this volume of *Clinical Neurophysiology Practice*, Tóth et al. report a prospective comprehensive nerve ultrasound study in a large cohort of 103 patients affected by diabetes mellitus, 26 with type 1 (DM1) and 76 with type 2 (DM2). Patients were compared with 50 controls, divided in two equal groups of 25 individuals whose mean age was matched with the mean age of the DM1 and DM2 groups. The cross-sectional areas (CSAs) of multiple mixed (median, ulnar, fibular and tibial) and sensory (superficial radial and sural) nerves were measured at 14 points in the upper and lower limbs, including compression and non-compression sites. The data was comprehensively analyzed according to several categories, including anatomical distribution, type of diabetes, presence and severity of polyneuropathy, presence of demyelination and clinical characteristics. Electrophysiological studies were used to both diagnose polyneuropathy and assess its severity. It should be noted that signs of polyneuropathy were not present in the subgroups with normal electrophysiology.

On group analysis, significant mild/moderate diffuse nerve enlargement was found in patients with DM2. This was more pronounced at compression sites versus non-compression sites, and in the upper limbs versus the lower limbs. In DM1, nerve enlargement was found only in the median nerve at the wrist. No major difference was found between subgroups with or without polyneuropathy and subgroups with or without demyelination. Median and ulnar nerve forearm CSAs showed a gradual increase from polyneuropathy of mild severity to polyneuropathy of moderate/medium severity with no further significant changes in severe polyneuropathy. No correlation was found between the duration of diabetes, mean HbA1c level and CSA.

This article makes several important points. Firstly, structural changes of the nerves pre-date clinical and/or electrophysiological manifestations of the neuropathy. This confirms previous nerve ultrasound reports (Pitarokoili et al., 2016; Breiner et al., 2017; Borire et al., 2018; Tandon et al., 2021), one of which (Borire et al., 2018) also demonstrated changes of axonal membrane function in the early pre-clinical stage of the neuropathy.

Tóth et al. (2023) showed a progression of the ultrasound abnormality from the mild to the clinically moderate polyneuropathy with no further change in severe polyneuropathy, supporting the argument that the most significant nerve damage occurs in the initial stages. This stresses the importance of screening for neuropathy from diagnosis, or even earlier at the pre-diabetic stage, when intervention is expected to be most effective.

In the Tóth et al. (2023) study there were interesting differences between the subgroups separated according to the diabetes type. Type 2 exhibited significant CSA changes, both diffuse and at multiple compression points, whereas Type 1 had significant changes only in the median nerve at the wrist. Differences between type 1 and type 2 diabetes were also reported in an earlier study with regard to correlations between nerve CSA and functional nerve excitability, which were demonstrated in type 1 but not type 2 (Borire et al., 2018). This provides further evidence for distinct pathophysiological mechanisms in the neuropathies associated with type 1 and type 2 diabetes, despite the similarities in clinical presentation and electrophysiology. Features of metabolic syndrome, such as dyslipidaemia, hypertension, visceral adiposity and increased insulin resistance are risk factors for type 2, but not type 1. Glucose control is highly effective in controlling the progression of the neuropathy in type 1, but not type 2 diabetes mellitus (Feldman et al., 2019). Interestingly, an earlier ultrasound study reported changes in both type 1 and type 2, which were more marked in patients with type 2 (Breiner et al., 2017). It is possible that nerve thickness in type 1 is affected by the glycaemic values and may fluctuate accordingly. This could explain the different ultrasound findings reported by Breiner et al. (2017) and Tóth et al.

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(2023) in patients with type 1 diabetes. Further ultrasound studies may address this issue on larger cohorts of patients.

The Tóth et al. (2023) study also confirms previous reports that nerve abnormality is present both at compression and non-compression points (Pitarokoili et al., 2016; Breiner et al., 2017). The latter is likely to reflect an increased susceptibility to compression neuropathy and was previously observed in both symptomatic and asymptomatic patients (Pitarokoili et al., 2016). This raises the question of what is relevant in everyday clinical practice. As the nerves of the diabetic patients can also be diffusely enlarged, it is important in the investigation of entrapment neuropathy in a patient with diabetes mellitus, to compare the compression site with a non-compression site in the same nerve, to distinguish the truly focal abnormalities. This is particularly true for ulnar mono-neuropathy in the diabetic patient in which the nerve abnormality, unlike that in the non-diabetic population, may not be at the usual compression sites (elbow or wrist), but could be diffuse or most pronounced in the forearm or upper arm. Ultrasound is particularly useful in the investigation and management of ulnar mono-neuropathy in these patients (Pelosi et al., 2020).

There is clearly a role for ultrasound in the investigation of focal mono-neuropathies in the everyday clinical setting alongside routine nerve conduction studies (Pelosi et al., 2021; 2022), and this seems particularly useful in the diabetic patient (Pelosi et al., 2020). The study by Tóth et al. (2023), alongside earlier ultrasound studies, suggests an even larger scope for the use of ultrasound in screening and possibly also monitoring diabetic neuropathy. Nerve ultrasound seems highly suited for screening diabetic neuropathy. It is painless, applicable at point-of-care, allows non-invasive examination of multiple nerves in a short time, doesn't require patient cooperation or warming up, is relatively inexpensive and, most of all, is capable of detecting subclinical changes, which none of the current screening methods can do.

Most screening tools/methods used for diabetic neuropathy search for the presence of clinical symptoms and/or signs, or abnormalities on electrophysiological testing (Feldman et al., 2019). This means that they are incapable of detecting early sub-clinical changes, at a stage when serious nerve damage is still potentially preventable. A tool with that ability could make a significant difference to the history of the diabetic neuropathy.

With a projected alarming number of people estimated to be affected by diabetes mellitus over the next decades with the current trend, there is an urgent need for early detection to reduce the increasing prevalence of diabetic neuropathy. Ultrasound could serve this purpose. However, current research findings by multiple groups are fragmented and cannot be translated into the use of nerve ultrasound in the clinical setting without clear guidelines. Tóth et al. (2023) suggest that their results "may contribute to the delineation of an ultrasonography protocol for the assessment of nerves in patients with diabetes." The next step would seem to be the creation of a screening protocol agreed by neuromuscular ultrasound physicians based on a systematic review (and *meta*-analysis if appropriate) of the literature.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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