The diagnostic role of high-frequency ultrasound in diabetic neuropathy

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Abstract

Diabetic peripheral neuropathy (DPN) is a frequent complication of DM. Advanced DPN can lead to major problems such as diabetic foot ulcers. Early identification of DPN cases will benefit early therapy and motivate patients to participate in their care actively.

Early diagnosis is critical to improving prognosis and quality of life for people with DPN. This is due to the absence of symptoms in 50% of patients and the limited sensitivity of neuro-electrophysiology to small fibers. Many studies have shown that high-resolution ultrasound (HRU) is a good noninvasive method for diagnosing DPN. With modern technologies, HRU may be used to screen, diagnose, and monitor DPN, acting as a biomarker and giving novel diagnostic insights.

The electrodiagnostic alteration in DPN is preceded by morphological abnormalities on ultrasonography. High-resolution ultrasonography of peripheral nerves has the potential to become the first-line study for the diagnosis of DPN. This review work studies the diagnostic Role of High-Frequency Ultrasound in Diabetic Neuropathy.

Introduction

History, clinical examination, and electrodiagnostic (EDx) tests have examined peripheral neuropathies for decades. EDx investigations are the most reliable objective assessments of the neuromuscular system. However, EDx studies lack information on nerve anatomy, surrounding tissues, and tiny nerve fiber function. Ultrasound offers a higher value and effectiveness for diagnosing peripheral neuropathy than neuro-electrophysiology, but it also helps determine the kind of neuropathy based on morphological and structural alterations. It is also useful in the treatment and monitoring of peripheral neuropathy. High-resolution ultrasound (HRU) is increasingly utilized to assess peripheral nerve morphology, especially localized nerve entrapment and peripheral neuropathy [1,2]. In this review work, we explore HRU’s capacity to identify cross-sectional nerve area and blood flow and echo, and other image abnormalities in DPN patients to improve HRU diagnostic efficiency in peripheral neuropathy.

Diabetic peripheral neuropathy (DPN) is a frequent complication of DM. Advanced DPN can lead to major problems such as diabetic foot ulcers, gangrene, and amputation, lowering diabetes patients’ quality of life. The pathophysiology is unknown, but early in diabetes, enhancing glycemic control has been proven to successfully postpone or prevent the development of neuropathy [3]. A length-dependent “glove and sock” feeling is typical in DPN, and clinical symptoms are used to diagnose. Early diagnosis is critical to improving prognosis and quality of life for people with DPN. This is due to the absence of symptoms...
in 50% of patients and the limited sensitivity of neuro-electrophysiology to small fibers. Many studies have shown that high-resolution ultrasound (HRU) is a good noninvasive method for diagnosing DPN. With modern technologies, HRU may be used to screen, diagnose, and monitor DPN, acting as a biomarker and giving novel diagnostic insights [4].

The echotexture of normal peripheral nerves is distinct. Although most nerves are easily visible, nerves in the lower extremities are not always the case. Nerve enlargement and enhanced hypoechogenicity are the primary pathogenic alterations seen. Measurements should be taken and compared to reference values to indicate nerve expansion. Carpal tunnel syndrome is the most well-studied peripheral neuropathy, and ultrasonography appears to offer value when paired with nerve conduction investigations. Although widespread nerve thickening might be seen, the relevance of sonography in various genetic and inflammatory neuropathies remains unknown [4].

Normal nerves have a visible architecture comprised of fascicles and a surrounding epineurium on an ultrasound picture. The lower echo nerve bundles are encircled on the transverse axis by the (higher echo) nerve bundle membrane and the outside membrane, forming a honeycomb structure [5]. The nerves are thin and parallel to the linear structure generated on the longitudinal axis by the gap between the high and low echo lines.

Pathophysiological mechanisms: It is intriguing to hypothesize why all diabetic individuals, regardless of diabetes type, demonstrate the moderate expansion of peripheral nerves, regardless of the evidence for the presence or absence of large-fiber neuropathy. Diabetes may cause decreased axonal flow [6] enabling materials to accumulate within the axon itself. It is possible that even minor axonal flow restriction might result in mild axonal elongation. The degree of enlargement does not compare to that seen in individuals with autoimmune or acquired demyelinating polyneuropathies [7], which have been demonstrated to cause significant and multifocal nerve swelling due to unsuccessful remyelination efforts. Small-caliber nerve fiber changes in pre-diabetic patients [8] have shown that damage to peripheral nerves clearly precedes both the onset of neuropathic symptoms and the formal diagnosis of DSP. So it’s possible that having a larger BMI causes nerve expansion, as seen on HRU, and BMI was higher in diabetic individuals with DS.

Routine ultrasound vs. high-frequency ultrasound: A conventional ultrasonic transducer uses a frequency range of 5 to 12 MHz; however, it has a high resolution that generates a frequency of 70 MHz [9]. High-resolution ultrasound, characterized by high resolution and large attenuation, can dynamically scan and continuously observe the morphological changes of tissues in real-time. This depicts the structure more correctly, raising the structural resolution ratio to 30 M. Quantifying changes in image echoes was done using ImageJ software combined with HRU. The echo intensity may effectively diagnose diabetic peripheral neuropathy, allowing for more precise and efficient diagnosis in clinical trials [10].

Diabetic sensorimotor polyneuropathy (DSP): DSP is the most prevalent consequence of diabetes mellitus (DM), affecting more than 60% of type 1 diabetic patients and 45% of type 2 diabetic individuals [11]. DSP is characterized by gradual axonal loss, which may be shown in EDx investigations as a decrease in the amplitudes of sensory nerve and compound muscle action potentials. DSP is diagnosed based on typical clinical symptoms and findings, validated by abnormalities on objective peripheral nerve testing, most often nerve conduction investigations (NCS).

Role of imaging in diabetic sensorimotor polyneuropathy: Although imaging tests haven’t been utilized to diagnose DSP, HRU might give another objective indicator of peripheral nerve health. Peripheral nerve expansion has been seen in individuals with Charcot–Marie–Tooth disease, multifocal motor neuropathy, and chronic inflammatory demyelinating polyradiculoneuropathy in previous HRU research [12]. Some exploratory investigations have revealed an increase in cross-sectional area (CSA) at non-compressive nerve locations due to peripheral nerve sonographic alterations in diabetes [13,14]. On the other hand, other investigations found no variation in nerve size or shape in individuals with axonal polyneuropathy (including diabetic polyneuropathy) [15].

HFU may be effective for the early detection of DPN, enhancing clinical results. In this regard, Xishun Ma et al. [16] investigated the use of high-frequency ultrasound (HFU) in the early detection of diabetic peripheral neuropathy (DPN). Based on electroneurophysiologic results, patients with type 2 diabetes (N = 60) were separated into diabetic nonperipheral neuropathy (group A) and diabetic peripheral neuropathy (group B). A healthy control group of 30 non-diabetic patients was included (group C). Based on measured width (W) and thickness (T), we computed the cross-sectional area (CSA) of the median nerve (MN) of the right upper limb at seven separate locations (MN1-7) (T). W, T, and CSA of the MN were higher in group A than in group C (P < 0.05), and were higher in group B than in group C (notably MN6 and MN7 (P = 0.05)). With a threshold value of 12.42 mm², ROC analysis revealed that CSA at the MN7 level provided the best diagnosis accuracy for DPN in group B. They suggested in DPN, ultrasound testing revealed that the MN had lost its internal sieve mesh structure and displayed diminished echo, a partial blood flow signal, and thicker epineurium; these findings were most noticeable at MN6 and MN7, which corresponded to the carpal tunnel. In group B, CSA was favorably connected with motor latency and F wave average latency and negatively correlated with motor conduction velocity, motor amplitude, and sensory conduction velocity.

Also, Narayan et al. evaluated the ultrasound examination of peripheral nerves’ cross-sectional area (CSA) in persons with suspected DPN [17]. The ulnar nerve in the lower arm, the median nerve proximal to the carpal tunnel, the common peroneal nerve proximal to the fibular head, the tibial nerve proximal to the tarsal tunnel, and the sural nerve in the lower third leg were all sonographically examined in 50 patients with probable DPN due to Type 2 diabetes and 50 age-matched healthy controls. When DPN patients were compared to healthy controls, their CSA levels were higher. With a demyelinating pattern, the area alterations were more pronounced. Compared to healthy controls, probable DPN cases with normal NCS exhibited more peripheral nerves with elevated CSA. A cut-off of +4 nerve thickening resulted in a sensitivity of 86% and a specificity of 56%. The lower limb neuropathy pattern was axonal, whereas the upper
Diabetic individuals have diffusely expanded peripheral nerves, including areas not vulnerable to bone compression.

Radiculoplexus neuropathy of the lumbar plexus can also be accurately detected, using high-resolution ultrasonography, indicating nerve thickness. The conventional diagnosis of lumbar radiculoplexus neuropathy (LRN) is based on a standard sequence of symptoms and a focused electrodiagnostic evaluation using electromyography. By measuring edema mesial to the site of compression, ultrasonography consistently predicts the degree of lumbar radiculopathy. Ravikanth studied the above idea on 15 diabetic patients with LRN symptoms [21]. The diameter (D) and transverse diameter (TD) of the L1 nerve root (L1NR), L2NR, L3NR, and L4NR were measured, and their cross-sectional areas (CSAs) were computed based on where the NRs were observed in the lateral zone. Furthermore, the CSA (calculated as CSA [mm²] = D TD)/4, diameter (mm), and transverse diameter (mm) of bilateral femoral nerves at the L3-L4 level was measured. At levels L1-L4, the difference attributable to CSAs between afflicted NRs in the LRN group and unaffected NRs in controls was considered statistically significant (p < 0.05). The mean values for L1NR were 8 mm² (CSA), 11.2 mm² (CSA), 13.6 mm² (CSA), and 17.8 mm² (CSA) according to receiver operating characteristic analysis. At L1 through L4 levels, there was a significant difference in CSA between LRN patients and controls (p < 0.05). On high-resolution ultrasonography, CSA measures of the lateral femoral cutaneous nerve (8 mm²) and femoral nerve (58 mm²) were substantially more significant on the afflicted side than on the unaffected side. Compared to controls, the laterality of impacted NRs was considerably higher in the LRN group.

HFU for diabetic foot: High-frequency ultrasound can effectively assess nerve-ending issues in diabetes foot. For Zheng et al. investigated the feasibility of employing US in nerve ending issue assessment for diabetic foot patients [22]. US probed the terminals of the medial branch of the deep peroneal nerves (mbDPN), and nerve conduction characteristics were investigated in 19 clinically diagnosed diabetic foot patients and a control group of healthy volunteers. Distinct echoic appearances were regularly found between the mbDPN nerves of diabetic foot patients and healthy volunteers. Hypoechoic bands were easily identified in healthy participants at the anatomical sites of mbDPNs. However, in diabetic foot patients, the hypoechoic bands of the mbDPNs were not evident, and the surfaces of the mbDPNs seemed opaque and uneven compared to healthy volunteers.

Furthermore, the US echoes of mbDPN in diabetic foot patients were more diverse than those in healthy individuals. The mean diameters of mbDPNs in diabetic foot patients were 1.30 ± 0.4 mm and 0.80 ± 2 mm in the control group (P < 0.05). Finally, nerve conduction studies (NCS) revealed anomalies in diabetic foot syndrome patients. They proposed that mbDPN enlargement, obscurity, surface irregularity, and echo heterogeneity can indicate nerve-ending issues in diabetic foot patients undergoing ultrasound examination.

HFU for special group: In some instances, such as pregnancy, HG-USG can be quite beneficial. Mirzaagari et al. performed HF US on 40 CTS patients and 40 matched controls. All subjects had their wrists HF-USG bilaterally, emphasizing the median
nerve cross-sectional area (MNCSA) at the carpal tunnel (CT) entrance. The difference in mean MNCSA between the CTS group (11.71 1.86 mm², range: 8 to 18 mm²) and the control group (6.75 1.38 mm², range: 4 to 11 mm²) was statistically significant (P 0.001). The receiver operating characteristic (ROC) curve was produced, and the cross-sectional area (CSA) cut-off point of 8.5 mm² demonstrated sensitivity and specificity of 98% and 93%, respectively. With the given point as the diagnostic threshold, the positive predictive value (PPV) and negative predictive value (NPV) were 95 and 98 percent, respectively. They proposed that HF-USG of the median nerve be employed as a preferable alternative to NCS (the current gold standard diagnosis procedure) in pregnant women because to its ease and reduced cost, or at the very least as a screening tool in pregnant women with suspicious symptoms [23].

Future studies

The presence of larger nerves in diabetic people who do not have DSP suggests that ultrasonic alterations may precede electrophysiological abnormalities. Future research should look at alterations in peripheral nerve blood flow and echogenicity in diabetes individuals and try to link peripheral nerve enlargement to an underlying pathophysiological mechanism. Furthermore, several neuropathies may be future indications of neuro-intervention and neuromodulation [24]. They might be combined by ultrasound and used with nerves or target organs in any location. Different pain-producing components, for example, can be ablated or manipulated by radiofrequency to reduce pain under the guidance of imaging [25].

Future studies in machine learning can also be useful in neuropathy diagnosis with HF-US. Liu et al. [26] investigated the diagnostic utility of high-frequency ultrasound imaging based on a fully convolutional neural network (FCN) for peripheral neuropathy in type 2 diabetic patients, for example (T2D). A total of 70 individuals with T2D mellitus were chosen and separated into two groups based on the type of peripheral neuropathy: lesion (n = 31) and nonlesion (n = 39). Furthermore, 30 healthy adults were utilized as controls. High-frequency ultrasound pictures based on hypervoxels and FCNs were utilized to investigate the three groups of patients to evaluate diagnostic performance and compare changes in peripheral nerves and ultrasound features. The Dice coefficient (92.7) and mean intersection over union (mIOU) (82.6) of the proposed technique after image segmentation were found to be the biggest. The segmentation algorithm-based high-frequency ultrasound had higher diagnostic accuracy (94.0 percent vs. 86.0 percent), sensitivity (87.1 percent vs. 67.7 percent), specificity (97.1 percent vs. 94.2 percent), positive predictive value (93.1 percent vs. 86.7 percent), and negative predictive value (94.4 percent vs. 84.0 percent) (P 0.05). The detection values of the three primary nerve segments of the upper limbs differed significantly between the control, lesion, and nonlesion groups (P 0.05). Patients in the lesion group were more likely to exhibit diminished nerve bundle echo, hazy reticular structure, thicker epineurium, and unclear boundaries of neighboring tissues (P 0.05) than those in the non lesion group. In conclusion, the high-frequency ultrasound processed using the algorithm described demonstrated a high diagnostic value for peripheral neuropathy in T2D patients. So high-frequency ultrasonography may be utilized to examine morphological alterations in peripheral nerves in T2D patients, and can be used for future studies

Conclusion

Early identification of DPN cases will benefit early therapy and motivate patients to participate in their care actively. The electrodiagnostic alteration in DPN is preceded by morphological abnormalities on ultrasonography. High-resolution ultrasonography of peripheral nerves has the potential to become the first-line study for the diagnosis of DPN.

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