The Role of Muscle Thickness and Echogenicity in the Diagnosis of Diabetic Peripheral Neuropathy

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Abstract

Objectives: This study aims to find the thickness of muscles of lower limbs in patients with diabetic peripheral neuropathy (DPN) along with echogenicity and applying these two findings in the diagnosis of the disease.
Methods: This is a case-control study conducted in the clinical neurophysiology unit in Merjan medical city. It includes 73 patients diagnosed to have DPN based on characteristic history and physical examination and documented by nerve conduction study. These patients are matched to 73 control that has matched age and sex to the patient group. Patient and control are examined by high-resolution ultrasound (12 MHz linear probes). We assess muscle thickness and echogenicity of the tibialis anterior, biceps femoris, and abductor halluces brevis.
Results: The study showed that there was a statistically significant decrease in muscle thickness and increase in echogenicity in all tested muscles when compared to the control group. Also, we calculated the cut-off value with sensitivity and specificity of muscle thickness in the diagnosis of DPN.
Conclusion: Muscle ultrasound is a useful complementary test for the diagnosis of DPN.

Key Words: Diabetic Peripheral Neuropathy, Neuromuscular Ultrasound, Muscle Thickness, Echogenicity.

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Introduction

Diabetic peripheral neuropathy (DPN) is the most common neuropathy caused by diabetes mellitus (M.R. Khdour, 2020). Its diagnosis relies mainly on history and physical examination which is supported by electrophysiological studies mainly nerve conduction study (NCS). NCS is very helpful in confirming the presence of polyneuropathy, exclude its mimics, and identify its symmetrical length-dependent fashion. But it is unable to provide information about the morphological assessment of the muscles or state of surrounding tissues and structures (J. Miller, 2021). Ultrasound imaging has a very good yield in evaluating muscle size, thickness, shape, and echogenicity. In polyneuropathies, nerve damage will result in decreased muscle thickness and increase muscle echogenicity supplied by that nerve (S. Pillen, 2008). Motor nerve dysfunction is an established part of DPN, resulting in muscle changes like muscle atrophy and weakness which are pronounced distally more than proximally (Severinsen, 2007).

Materials and method.

This case-control study was conducted at the Neurophysiology unit and diabetes clinic of Al-Imam Al Sadeq teaching Hospital and Merjan medical city in Al-Hilla Governorate and through the period from October 2020 till March 2021. Seventy-three patients (44 males and 29 females) with type 2 diabetes mellitus (DM) were included as the patient group.

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These were selected to have a complaint of pain, paresthesia, and/or a sense of weakness at their extremities, especially lower limbs, with abnormal nerve conduction study. The age of DPN patients ranged from 40 to 65 years. Additional 73 adults (26 males and 47 females) were also included as the control group who's their age was consistent with those of the patient group. This group was subdivided into two subgroups; 33 were diabetic patients without neuropathy and the rest 40 were normal healthy adults. Verbal informed consent was obtained from the participants. A full history was taken from each patient, body mass index (BMI) was calculated, biochemical investigations Include HbA1c and FBS were obtained, and general examination was done for the participants including full neurological examination of both upper and lower limbs. Each participant had four motor nerves tested (median, ulnar, tibial, and peroneal), and three sensory nerves (median, ulnar and sural nerves). Limb temperatures were maintained between 33- 36C° by using the radiant heater when needed, and the skin was prepared when necessary using an abrasive skin cleanser. Maximal responses were applied using electrical stimuli. Multiple parameters were measured for each nerve including waveform amplitude, distal latency, and conduction velocity (Z. M. M. Al-Deen and I. A. Ajeena, 2015). Ultrasound examination was performed in the ultrasound unit using GE LOGIQ P6 pro ultrasound machine and Philips US device. The sonographic examination was performed on the same day of the electrophysiological study Linear transducer with frequency 3-12 MHz was used to examine the muscles and adjusted on a high frequency of 12-MHz (C. Y. Tan, 2018). A large amount of ultrasound gel should be used to remove any air between the probe and the skin. Muscle thickness and echogenicity were evaluated for tibialis anterior, short head of biceps femoris, and abductor bollicus longus muscle. The depth was adjusted according to the muscle thickness and the distance of the inferior border from the skin. Muscle thickness was determined on a transverse view by using the US distance measurement function (A. Abraham, 2019). The thickest or largest muscle diameter represents muscle thickness (C. Caresio, 2016). Put on minimal pressure to avoid muscle compression. The mean value of two consecutive measurements was determined (A. Abraham, 2019). Muscle echogenicity was assessed according to the Heckmatt scale. This is a subjective scale that looks at the echogenicity of muscle compared to a nearby bone shadow (D. C. Preston and B. E. Shapiro, 2021).

Statistical Analysis

Statistical analysis of this study was conducted using SPSS version 17. Categorical variables are expressed as percentages while continuous variables are expressed as mean and standard deviation (M ± SD). The independent t-test was achieved to compare the data between DPN and control groups. Pearson's (r) correlation coefficients were calculated to measure the association of continuous data; also the receiver operating characteristic (ROC) curves were used to define optimal cut-off values of muscle thickness for DPN diagnosis.

Results

The results of this study were shown and expressed as three groups: diabetic patients with diabetic peripheral neuropathy (DPN), diabetic patients without DPN, and healthy subjects as a control group. Gender had a statistically significant impact on the study parameters so that each study group was subdivided into males and females. There were statistically insignificant differences ($p>0.05$) in the age and body mass index (BMI) between the study groups as shown in table1. Patients with DPN had higher fasting blood sugar (FBS) and glycated hemoglobin (HbA1c) (table 1) with a longer duration of diabetes mellitus (figure 1).

Table 1. Characteristics of study participants

variable	Patients with DPN		Patients without DPN		Normal subjects	
	Male	female	male	female	male	female
Age(years)	53.0±2.7	52.2±2.3	52.3±2.6	53.0±3.7	52.3±1.8	51.7±2.1
BMI(Kg/m^2)	30.7±1.8	30.8±1.4	30.9±1.6	30.4±1.4	31.0±1.6	30.3±1.2
FBS mg/dl	224±67**	247±57**	139±28	146±30	-	-
HbA1c %	8.6±1.2**	9.5±1.8**	6.7±0.9	7.3±0.4	-	-

Values are mean ± standard deviation. DPN= diabetic peripheral neuropathy, BMI= body mass index. FBS= fasting blood sugar, HbA1c= glycated hemoglobin. ** Highly significant p<0.001 between patients with DPN and those without DPN

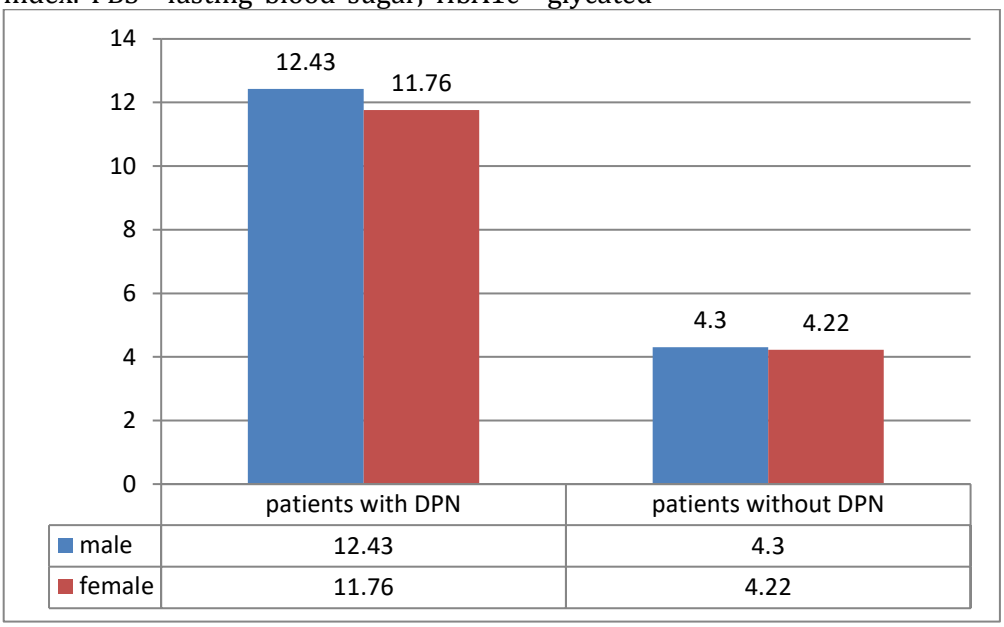

Figure 1. Distribution of diabetic patients according to the duration of diabetes mellitus

Muscle thickness was measured for three muscles in the lower limb, they were: tibialis anterior, short head of biceps femoris, and Abductor halluces brevis. There were significant differences in tibialis anterior and abductor halluces brevis thickness between males with DPN and males of the other study groups. While only abductor halluces brevis thickness was significantly different between females with DPN and females of the other study groups (table 2).

Table 2. Comparison in muscle thickness between study groups

Muscle thickness(cm)	Patients with DPN		Patients without DPN		Normal subjects	
	male	female	male	female	male	female
TA muscle	2.42±0.12**	2.50±0.19	2.66±0.15	2.51±0.15	2.72±0.19++	2.57±0.24
BF muscle (short head)	2.02±0.28	1.97±0.15	2.12±0.22	2.03±0.34	2.14±0.17	2.04±0.22
AHB muscle	0.80±0.11**	0.81±0.07**	1.14±0.15	1.05±0.12	1.20±0.09++	1.10±0.11++

Values are mean ± standard deviation. TA= tibialis anterior, BF= biceps femoris, AHB= abductor halluces brevis. ** Highly significant differences (p<0.001) between patients with DPN and those without DPN. ++ Highly significant differences (p<0.001) between patients with DPN and normal subjects.

Muscle echogenicity was assessed according to the Heckmatt scale and divided into four grades. Muscle echogenicity was normal in both the normal group and patients without the DPN group (Grade 1). The next table (table 3) shows the frequency of each grade for tibialis anterior, biceps femoris, and abductor halluces brevis muscles in patients with DPN.

ROC curve analysis was applied to obtain the optimal cutoff value of abductor halluces brevis muscle thickness to diagnose DPN which was (0.955 cm) with AUC 98%, sensitivity 93%, and specificity of 100%.

Table 3. Muscle echogenicity in patients with DPN

echogenicity / muscle	Grade 1	Grade 2	Grade 3	Grade 4
Tibialis anterior	2.7%	61.6%	35.6%	0%
Biceps femoris	68.5%	31.5%	0%	0%
Abductor halluces brevis	28.8%	68.5%	2.7%	0%

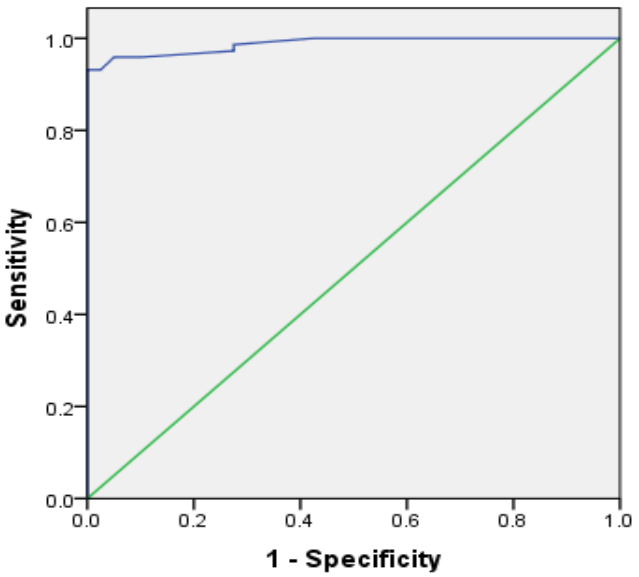

Figure 2. The ROC curve analysis for the identification of DPN in symptomatic patients by measurement of muscle thickness of abductor halluces brevis (cm)

There was a highly significant (p<0.001) negative correlation between tibialis muscle and abductor halluces brevis muscle thickness and diabetes duration, FBS, and HbA1c, while biceps femoris thickness was not significantly correlated with the same parameters (table 4).

Table 4. Correlation of muscles thickness and diabetes duration, fasting blood glucose, and glycated hemoglobin

Muscle thickness (cm)	Duration of DM		FBS		HbA1c	
	r	p	r	p	r	p
Biceps femoris muscle	-.100	.227	-.005	.957	-.074	.372
Tibialis anterior muscle	-.367**	P<0.001	-.367**	P<0.001	-.378**	P<0.001
Abductor halluces brevis muscle	-.752**	P<0.001	-.669**	P<0.001	-..655**	P<0.001

DM= diabetes mellitus, FBS= fasting blood sugar, HbA1c= glycated hemoglobin.
** Highly significant (p<0.001)

Regarding the correlation with NCS parameters, there was a highly significant positive correlation between tibialis anterior muscle thickness and, amplitude and conduction velocity of the peroneal nerve, while there was no correlation between the thickness and peroneal latency as shown in table 5.

Table 5. Correlation of tibialis anterior muscle thickness and peroneal nerve conduction study parameters

	Tibialis anterior muscle thickness	
	r	p
peroneal motor latency	-.049	.558
peroneal motor amplitude	.351**	<0.001
peroneal motor CV	.338**	<0.001

** Highly significant (p<0.001)

There was a highly significant positive correlation between abductor halluces brevis muscle thickness and, amplitude and conduction velocity of the tibial nerve, while there was a significant negative correlation between the thickness and tibial latency as shown in table 6.

Table 6. Correlation of abductor halluces brevis muscle thickness and tibial nerve conduction study parameters

	Abductor halluces brevis muscle thickness	
	r	p
Tibial motor latency	-.173*	.036
Tibial motor amplitude	.634**	<0.001
Tibial motor CV	.625**	<0.001

* Significant (p<0.05). ** Highly significant (p<0.001)

Discussion

The results of our study showed a significant impact of gender on the study parameters, this difference between genders could be explained due to hormonal effects, as androgen has a role in the activation of the renin-angiotensin system that might cause endothelial cell injury, while estrogen plays a protective role from the microvascular disease (A. Kadhum, 2020), this finding in agreement with other studies (A. Tamer et al., 2006, O. Tabatabaei-Malazy, 2011). DPN patients had higher FBS and HbA1c and longer duration of DM, these findings agree with other studies (A. Kadhum, 2020). A long duration of diabetes and poor glycemic control is associated with increased production of glycosylation end products, metabolic derangements, endothelial injury, and oxidative products (M. U. Nisar et al., 2015). Distal muscle thickness (tibialis anterior and abductor halluces brevis muscles) was significantly lower in patients with DPN than the other group, while there was no significant difference in proximal muscle

thickness (biceps femoris muscle) between patients with DPN and the control group. This finding agrees with (Howayda F. et al., 2020, A. Abraham, 2019, Severinsen, 2007). Henderson and his coworker (2020) explained the cause behind muscular atrophy in patients with diabetic neuropathy was due directly to the degenerative effects of DPN. There was a topographical distribution of muscle atrophy with a proximo-distal gradient. Distal muscular atrophy most likely reflects the effect of a length-dependent neuropathic process within motor fibers. This agrees with (H. Andersen, 1997) who concluded that atrophy is most prominent in distal muscles of the lower leg. Muscle echogenicity in patients with DPN was more hyperechoic than that of the control group, this was more prominent in distal muscles. This finding consists of (H. Pan et al., 2014, S. B. Soliman et al., 2020, A. Abraham, 2019) who stated that muscle echogenicity increased in patients with DPN. Muscles appear hyperechoic in neurogenic disorders because muscle tissue undergoes atrophy, necrosis, inflammation, fatty infiltration, and fibrosis, all these changes result in many new planes of sound reflection in muscle, so that, diseased muscle become more echogenic, with loss of the normal heterogeneity of healthy muscle and its supporting fibrous stroma (D. Mayans, 2012). There was a highly significant ($p<0.001$) negative correlation between tibialis muscle and abductor halluces brevis muscle thickness and diabetes duration, FBS, and HbA1c. the correlations were more significant with abductor halluces brevis thickness than with tibialis anterior muscle thickness, these finding may be due to that abductor halluces brevis muscle is more distal than tibialis anterior muscle, this makes it prone for denervation, atrophy and other changes earlier than tibialis anterior due to dying back pattern of DPN. Biceps femoris thickness had no significant correlations with and diabetes duration, FBS, and HbA1c; again this may be due to its location proximally.

There was a highly significant positive correlation between tibialis anterior muscle thickness and, amplitude and conduction velocity of the peroneal nerve, while there was no correlation between the thickness and peroneal latency, these findings agree with (A. Abraham, 2019) who stated that there were significant correlations between tibialis anterior muscle thickness and NCS parameters. There were a highly significant positive correlation between abductor halluces brevis muscle thickness and, amplitude and conduction velocity of the tibial nerve, while there was a significant negative correlation between the thickness and tibial latency, these findings agree with (A. Abraham, 2019) who stated that there were significant correlations between abductor halluces brevis muscle thickness and NCS parameters.

Conclusion

Patients with DPN had lower muscle thickness and increase echogenicity compared with control groups, and a decrease in muscle thickness was correlated with nerve conduction study findings. Neuromuscular ultrasound can be used as a cheap, painless, and more available tool for the screening of DPN.

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