

Atrophy of foot muscles in diabetic patients can be detected with ultrasonography.

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**Running title: Ultrasonography of atrophic diabetic foot muscles.**

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Received for publication 25 January 2007 and accepted in revised form 17 August 2007.

Additional information for this article can be found in an online appendix at <http://care.diabetesjournals.org>.

## **Abstract**

**Objective:** To establish a bedside test with ultrasonography for evaluation of foot muscle atrophy in diabetic patients.

**Research Design and Methods:** Thickness and cross sectional area of the extensor digitorum brevis muscle (EDB) and of the muscles of the first interstitium (MIL) were determined in 26 diabetic patients and in 26 matched control subjects using ultrasonography. To estimate the validity findings were related to the total volume of all foot muscles determined at magnetic resonance imaging (MRI-FM<sub>vol</sub>). Furthermore, the relations of ultrasonographic estimates to nerve conduction, sensory perception thresholds and clinical condition were established.

**Results:** In diabetic patients the ultrasonographic thickness of EDB (U-EDB<sub>t</sub>) was  $6.4 \pm 2.1$  mm (mean  $\pm$  SD) vs.  $9.0 \pm 1.0$  mm in controls ( $p < 0.001$ ), thickness of MIL (U-MIL<sub>t</sub>) was  $29.6 \pm 8.3$  mm vs.  $40.2 \pm 3.6$  mm in controls ( $p < 0.001$ ) and the cross sectional area of EDB (U-EDB<sub>CSA</sub>) was  $116 \pm 65$  mm<sup>2</sup> vs.  $214 \pm 38$  mm<sup>2</sup> in controls ( $p < 0.001$ ). The MRI-FM<sub>vol</sub> was directly related to U-EDB<sub>t</sub> ( $r = 0.77$ ), U-MIL<sub>t</sub> ( $r = 0.71$ ) and to U-EDB<sub>CSA</sub> ( $r = 0.74$ ). U-EDB<sub>t</sub> and U-MIL<sub>t</sub> were thinner in neuropathic than in non-neuropathic diabetic patients ( $5.8 \pm 2.1$  mm vs.  $7.5 \pm 1.7$  mm ( $p < 0.05$ ) and  $28.3 \pm 8.8$  mm vs.  $35.6 \pm 4.3$  mm ( $p < 0.03$ ), respectively).

**Conclusions:** Atrophy of intrinsic foot muscles determined at ultrasonography is directly related to foot muscle volume determined by MRI and to various measures of diabetic neuropathy. Ultrasonography seems to be useful for detection of foot muscle atrophy in diabetes.

## **Abbreviations:**

US (Ultrasonography), MRI (Magnetic Resonance Imaging), EDB (the Extensor Digitorum Brevis muscle), MIL (the muscle group between the 1st and 2nd metatarsal bone), CSA (Cross Sectional Area) MNCV (Motor Nerve Conduction Velocity), CMAP (Compound Motor Action Potential), SNCV (Sensory Nerve Conduction Velocity), SNAP (Sensory Nerve Action Potential), MRI-FM<sub>vol</sub> (Total foot muscle volume determined with MRI and stereological techniques), U-EDB<sub>t</sub> (Thickness of EDB determined with US), U-MIL<sub>t</sub> (Thickness of MIL determined with US), U-EDB<sub>CSA</sub> (CSA of EDB determined with US)

Motor dysfunction is an established part of diabetic polyneuropathy resulting in distal atrophy and weakness. At the clinical examination foot deformities clearly indicate muscle atrophy whereas detection of atrophy at earlier stages is difficult.

Atrophy of small foot muscles has been reported using magnetic resonance imaging (MRI) (1-3). Due to excellent soft-tissue contrast MRI enables detection of even subtle changes in size and structure of foot muscles (1-3). In a previous study we found substantial atrophy in neuropathic patients without any foot deformity (1), whereas muscle volume was preserved in non-neuropathic diabetic patients. Recently, a study using  $^{31}\text{P}$  MRI at 3 Tesla observed minor loss of muscle tissues in non-neuropathic patients, also (3).

MRI is the golden standard for visualization of soft tissue structures in the foot due to its high spatial resolution enabling identification of the individual small foot muscles (2). However, MRI is time consuming, can not be performed bedside and is more expensive than ultrasonography (US). US is an established method for examination of various musculoskeletal structures in children and adults with chronic neuromuscular diseases and traumatic muscle injuries (4-6). Also, animal experiments in acute muscle denervation indicate consistency between MRI, EMG and US one to 64 days after denervation (7).

In the present study the size of individual foot muscles was examined with US in diabetic patients with and without neuropathy and in matched control subjects as compared with the total volume of all foot muscles determined by MRI.

### **Research design and methods**

Twenty-six diabetic patients (22 type 1, 4 type 2) and 26 control subjects matched for age, gender, height and

weight were included in the study. Demographic and baseline clinical data are shown in Table 1. Patients were recruited from the out-patient diabetes clinic and controls were recruited among hospital staffs. All patients were able to walk unsupported, and none had a history of foot surgery or had symptoms or signs of arterial insufficiency of the lower extremities.

Patients with severe cardiac or lung disease, cancer, alcoholism, acute or chronic musculoskeletal disease, other neurological disease, other endocrine disorders or symptomatic peripheral artery disease were excluded. All subjects gave informed consent to the study which was approved by the local ethics committee.

All ultrasonographic (US) examinations were made by the same examiner (KS) using a scanner with a linear array real-time-ultrasonic probe (Toshiba Powervision 6000 duplex®). The subjects were placed in a supine position with the non-dominant foot placed on a plastic ramp to keep the ankle joint in a neutral position.

At ultrasonographic evaluation the extensor digitorum brevis muscle (EDB) and the muscle group between the 1st and 2nd metatarsal bone (MIL) including the first dorsal interosseus muscle, the adductor hallucis muscle and the first lumbrical muscle could be unambiguously identified. The EDB thickness (U-EDB<sub>t</sub>) and cross sectional area (U-EDB<sub>CSA</sub>) was determined by scanning transverse to the muscle fibres (fig. 1), whereas the MIL (U-MIL<sub>t</sub>) was scanned longitudinal to the fibres (fig. 1). The frequency of the ultrasonic beam was 15 MHz for the EDB and 8 MHz for the MIL. In each case the position of the ultrasound probe was marked externally on the skin using easily defined bone landmarks.

For evaluation of the EDB muscle a line drawn perpendicular to the mid-point of a straight line between the

lateral malleolus and the tuberositas of the fifth metatarsal bone defined the scanning plane. The exact position along this line for maximum cross sectional muscle thickness differs between individuals and was defined at each scanning procedure.

For examination of the MIL the distal position of the ultrasound probe was defined by a line between the 1st and 2nd metatarso-phalangeal joint and two lines marking the 1st and 2nd metatarsal bone.

The US measurements were performed with the ultrasound probe perpendicular to the muscle surface, gently placed on the skin to avoid any pressure induced alterations of muscle tissue dimension using generous amounts of gel (ULTRA/PHONIC Conductivity Gel, Pharmaceutical Innovations, Inc, NJ, USA). During US scanning the patients were initially asked to perform a voluntary contraction of the muscles facilitating the definition of the borders of the muscle. Then the patient was asked to relax while the US image was recorded. For each parameter 5 measurements were made. The images were saved on a magneto-optical media for digital storage for later analysis on a PC. Afterwards the lowest and highest values were excluded and the average of the remaining values was used for further analysis. The average time spent for US was five minutes for preparation of the scanning session and identification and demarcation of the bone landmarks followed by 10-15 minutes for making the 15 US measurements.

The non-dominant foot of all patients and control subjects was visualised by magnetic resonance imaging (MRI) using a 1.5 Tesla scanner (Sigma GE, USA) adopting the principles for MRI estimation of foot muscle size as described in earlier studies (2). All MR-scans were obtained with a conventional T1 weighted Spin-Echo sequence (Echo

time = 20 ms, Repetition time = 540 ms) using cross-sectional MR-images with a slice thickness of 1.5 mm and an intersection interval of 10 mm. A 256 x 256 matrix and two excitations were used. The images were stored on a PC and transferred from the 256 x 256 matrix to a 512x512 bitmap colour picture (BMP). The identity of MR-images was blinded to the observer. Within the muscle compartments an upper level of signal intensity for muscle tissues was defined for each patient by the examiner because a fixed limit could not be applied due to autoscaling. Signal intensities above the upper level were defined as signal intensities of fat allowing separation of muscle tissues from "non-muscle tissues" within the muscle compartments. Muscle fasciae, tendons and blood vessels were excluded. At each image, the CSA of all muscles was estimated using a stereological point counting technique described elsewhere (1,8,9). The total volume of all foot muscles (MRI-FM<sub>vol</sub>) was calculated by multiplying the distance (10 mm) between the sections by the total CSA, the first section being randomly placed within the first interslice interval. It was not possible to study the same muscles at MRI and US because the largest CSA could not be determined at beforehand at MRI. Furthermore, it was difficult to obtain enough slices to ensure a reliable estimate using the point-counting technique (9).

All patients were clinically evaluated according to a neuropathy symptom score (NSS) (10) and a neurological impairment scale (NIS) (11). Vibratory perception thresholds (VPT) were evaluated at the dorsum part of the dominant index finger and the non-dominant great toe using the 4, 2, and 1 stepping algorithm (12) (CASE IV, WR Medical Electronics Co., Stillwater, MN, USA). The perception thresholds for each patient were compared with

results from a large group of healthy controls (CASE IV, unpublished data).

Nerve conduction studies were performed using an electromyograph (KeyPoint®, Medtronic, Skovlunde, Denmark) and standard methods as described elsewhere (13,14). Motor conduction velocity (MNCV) and amplitude of the compound muscle action potential (CMAP) were measured of the non dominant peroneal and tibial nerve. Sensory nerve conduction velocity (SNCV) and amplitude (SNAP) of the sensory nerve action potential were measured of the non-dominant sural nerve, skin temperatures ranging between 31 and 34 centigrades. Z-scores reflecting the degree of deviation from the expected mean were calculated for MNCV and SNCV using values of healthy volunteers obtained with similar techniques (13,14).

Patients were defined as neuropathics in accordance with the minimal criteria for diabetic neuropathy (15). For quantification of severity of neuropathy, a neuropathy rank sum score (NRSS) was calculated for each patient including rank scores of NSS, NIS, the VPT's and the average of the rank scores of the MNCV's and SNCV's (1).

Statistical comparisons of muscle size determined at US and at MRI between groups were made with unpaired t-tests and correlations were sought for using linear regression analysis. MS Excel® was applied for the statistical comparisons using a significance level of 0.05. Reproducibility analyses of the 5 US measurements were performed using ANOVA using STATA®.

## **Results**

According to the minimal criteria for diabetic neuropathy 17 patients were neuropathic and nine patients were non-neuropathic. Among the 17 neuropathic patients 13 patients were symptomatic. Patients with and without neuropathy

had a diabetes duration of 32 years (8-46) (median, range) and 31 years (14-49), respectively.

For all diabetic patients the neurological impairment score (NIS) was 13 (0-40) (median, range). The neuropathic and non-neuropathic patients had a NIS of 20 (2-40) vs. 2 (0-17), respectively ( $p < 0.001$ ). Furthermore, the neuropathic patients had significantly higher VPT, lower peroneal MNCV and lower peroneal CMAP as compared to the non-neuropathic patients (Table 1).

In patients mean U-EDB<sub>CSA</sub> was  $116 \pm 65 \text{ mm}^2$  vs.  $214 \pm 38 \text{ mm}^2$  in controls ( $p < 0.001$ ), U-EDB<sub>t</sub> was  $6.4 \pm 2.1 \text{ mm}$  (mean  $\pm$  SD) vs.  $9.0 \pm 1.0 \text{ mm}$  in controls ( $p < 0.001$ ) and U-MIL<sub>t</sub> was  $29.6 \pm 8.3 \text{ mm}$  vs.  $40.2 \pm 3.6 \text{ mm}$  in controls ( $p < 0.001$ ). For the neuropathic and non-neuropathic patients U-EDB<sub>CSA</sub>, U-EDB<sub>t</sub> and MRI-FM<sub>vol</sub> expressed as a percentage of individually matched control subjects were significantly reduced (Table 2). The reduction of U-MIL<sub>t</sub> reached significance in the neuropathic patients, only (Table 2). Comparing the neuropathic and non-neuropathic patients U-EDB<sub>CSA</sub>, U-MIL<sub>t</sub> and MRI-FM<sub>vol</sub> were significantly reduced in the neuropathic patients compared to the non-neuropathic diabetic patients (Table 2).

Close correlations were found between the distally placed U-MIL<sub>t</sub> and the proximally placed U-EDB<sub>CSA</sub> and U-EDB<sub>t</sub> in the neuropathic group and in the non-neuropathic group as well (Table 3, online appendix [available at <http://care.diabetesjournals.org>]).

For diabetic patients and healthy control subjects close relationships could be established between MRI-FM<sub>vol</sub> on the one side and U-EDB<sub>CSA</sub> ( $r=0.74$  and  $r=0.64$ ), U-EDB<sub>t</sub> ( $r=0.77$  and  $r=0.76$ ) and U-MIL<sub>t</sub> ( $r=0.71$  and  $r=0.58$ ) on the other side (Table 4, Fig. 2 and Table 3 online appendix). Reproducibility analysis of the 5 repeated US measurements using

ANOVA showed a Coefficient of Variation (CV) of U-EDB<sub>CSA</sub>, U-EDB<sub>t</sub>, and U-MIL<sub>t</sub> amounting to 0.031, 0.034 and 0.015, respectively, in controls and 0.046, 0.059 and 0.026, respectively, in diabetic patients.

In all patients close correlations were found between the neuropathy rank sum score (NRSS) and the US measurements of U-EDB<sub>CSA</sub> ( $r=-0.76$ ), U-EDB<sub>t</sub> ( $r=-0.73$ ) and U-MIL<sub>t</sub> ( $r=-0.71$ ). Results of regression analyses performed for the neuropathic and non-neuropathic subgroups are shown in fig. 2 and table 3, online appendix.

### **Conclusion**

In this study US could detect atrophy of individual foot muscles in a group of diabetic patients. Muscular atrophy was more pronounced in diabetic patients with clinical neuropathy. In addition, a significant reduction of muscle size was observed in non-neuropathic diabetic patients. Close relationships were found between US estimates of foot muscle size and MRI determined volume of all foot muscles. Furthermore, US measurements of foot muscle size were closely related to the clinical severity of neuropathy in diabetic patients when expressed with a neuropathy rank sum score.

In previous studies, substantial muscular atrophy has been found in diabetic patients with neuropathy (8,9). There was a proximal to distal gradient of atrophy at the leg (8) and pronounced atrophy of the foot muscles in diabetics with neuropathy have been found in recent studies using different MRI-techniques (1-3). Brash et al. observed increased fatty infiltration as well as indications of muscle fibre depletion of the intrinsic foot muscles at the 1<sup>st</sup> metatarsal joint in 19 patients suffering from diabetic neuropathy using MRI and Magnetization Transfer (MT) sequences (16). The quantitative techniques in that study are not comparable to the ones used in the present study because the

MT method provides an indirect estimate of muscle size. The method, however, has the potential to discover even subtle tissue changes in non-neuropathic diabetic patients. Using standard MRI techniques and analysis of single pixel relaxation times Bus et al found atrophy of the intrinsic foot muscles at the level of the metatarsal heads in 8 diabetic patients with neuropathy amounting to a 73% reduction of muscle CSA (2). In our study, less pronounced atrophy was observed, the U-MIL and MRI-FM<sub>vol</sub> muscle size amounting to 71 % and 42% of the matched controls, respectively. In a previous study, we found pronounced atrophy of all foot muscles with reduction in the total muscle volume of 15 patients suffering from diabetic neuropathy using traditional MRI-technique combined with unbiased stereological methods (1). Greenman et al. used <sup>31</sup>P RARE MRI and found significant foot muscle atrophy at the level of the metatarsal joint, not only in neuropathic patients but also in diabetic patients without clinical neuropathy (3). Their finding suggests that muscular atrophy may occur very early in the neuropathic process even before the minimal criteria of diabetic neuropathy are fulfilled. In accordance with their observation, we found a statistically significant reduction in total foot muscle volume in non-neuropathic patients. These observations suggest that even subtle changes in nerve function may lead to muscle loss and that the applied clinical criteria for neuropathy are too insensitive for detection of the earliest neuropathic changes.

In this study we have introduced US as a new method to estimate size of foot muscles. We found that the US method had high reproducibility with CV less than or equal to 0.06 for all muscles evaluated. US has been used in evaluation of muscular dystrophies (17-20) and other neuromuscular diseases in adults (21-23). Comparative studies of

US and MRI indicate that the lower spatial resolution in US is in part compensated for by its bedside availability and higher cost-effectiveness (20,24,25). In a study by Küllmer et al. in experimental denervated rabbits MRI and sonography were equally informative (7).

In our study the foot muscles were evaluated differently applying MRI and US. At US the thickness and cross sectional area of the whole muscle of interest was determined, whereas at MRI the tissue with increased signal intensity within the muscles reflecting degeneration was excluded from the analysis of the volume of the foot muscles. Therefore the US measurements might underestimate the degree of loss of muscle tissue.

In fig. 2 there is a close correlation between MRI-FM<sub>vol</sub> and U-EDB<sub>CSA</sub>, however, this does not necessarily imply that there is a high level of agreement comparing these two methods (26). In our study we applied two different visualization techniques on different muscle structures including a single foot muscle and all foot muscles, respectively. Since different muscular structures were evaluated a direct analysis of limits of agreement was not performed.

A frequent objection to quantification of structures using US is the operator dependency. However, in a study by Bargfrede et al (21) investigating focal neuropathies an interobserver correlation of 0.85 of measurements of muscle size was obtained after scanning of several muscles. In accordance with this observation Maurits et al found an interobserver correlation of 0.845 at determination of the thickness of the biceps brachii muscles (27). Furthermore, Maurits et al found an intraobserver correlation coefficient of 0.93 confirming the observations made by Reimers et al in idiopathic

inflammatory myopathies (test-retest) (28).

In the present study five measurements at each of the various scanning positions were performed to obtain information about the variation of the estimate. In the clinical setting, however, one or two standardized measurements are sufficient for an experienced examiner. The costs for US evaluation are low because the equipment is affordable and needs one operator only.

In the present study we evaluated the size of small foot muscles at a proximal and at a distal position. The two muscles evaluated (EDB and MIL) are innervated from branches of the peroneal and tibial nerves. The examination of the two muscles with different nerve supply ensures that atrophy of the EDB muscle was not due to compression of the peroneal nerve at the fibular head. The close correlations between the size of the two muscle groups and the volume of all foot muscles suggest that all measures reflect the same pathophysiological process.

During US scanning of the MIL muscles, segmentation of individual muscles was not feasible. However, strong correlations were established between MRI-FM<sub>vol</sub> and the MIL muscle group, indicating that US estimates reflects atrophy of individual muscles. The US technique has the advantage that it can be performed in almost all patients. The technique is non-invasive and requires some experience of the examiner to obtain robust and reproducible results. The present study suggests that US is a reliable technique for screening and monitoring of muscle atrophy in the diabetic foot. Despite its lower resolution this method supplies the examiner with sufficient anatomical and functional information for evaluation of muscle size.

**Acknowledgments:**

The Danish Diabetes association (Diabetesforeningen) and the Danish Foundation of Neurological research (Neurologisk Forskningsfond) are acknowledged for economic support.

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**Table 1**

Clinical and electrophysiologic findings in diabetic patients and control subjects

	n	Age (years)	Weight (kg)	Height (cm)	Male/ female	Type 1/ Type 2	Diabetes duration (years)	HbA1c (%)	VPT 1st. Toe (JND)	NIS	Peroneal MNCV (m/s)	Peroneal CMAP (mV)
Diabetic-patients	26	50 (26-64)	73 (56-104)	176 (158-190)	16/9	21/4	32 (8-49)	8.9 (6.4-11.3)	22 (14-25)	13 (0-40)	36 (23-48)	3 (0-10)
+DNP	17	47 (26-64)	72 (60-95)	175 (158-190)	10/6	15/ 2	32 (8-46)	9.1 (6.4-11.3)	22 (14-25)	20 (2-40)	35 (23-41)	2 (0-4)
-DNP	9	49 (37-63)	72 (56-104)	175 (167-187)	6/3	7/ 2	31 (14-49)	8.1 (6.5-9.5)	19 (15-21)	2 (0-17)	44 (43-48)	6 (1-10)
Control subjects	26	49 (25-67)	78 (54-102)	176 (160-185)	16/9							

Values are median (range); VPT, vibratory perception threshold; JND, just noticeable difference; MNCV, motor nerve conduction velocity; CMAP, compound muscle action potential; DNP, diabetic neuropathy; NIS, neurological impairment score

**Table 2**

Muscle size (%) in diabetic patients with neuropathy and without neuropathy relative to muscle size of individually matched control subjects

	Diabetic patients with neuropathy		Diabetic patients without neuropathy		
<b>U-EDB<sub>csa</sub> (mm<sup>2</sup>)</b>	50 ±	33	79 ±	27	†
<b>U-EDB<sub>t</sub> (mm)</b>	66 ±	26	85 ±	21	ns.
<b>U-MIL<sub>t</sub> (mm)</b>	71 ±	22	90 ±	8.2	*
<b>MRI-FM<sub>vol</sub> (mm<sup>3</sup>)</b>	42 ±	30	74 ±	34	†

Values are mean (SD)

\* p<0.01, † p<0.05, diabetic patients with and without neuropathy are compared.

U-EDBCSA, cross-sectional area of extensor digitorum brevis muscle; U-EDBt, thickness of extensor digitorum brevis muscle; U-MILt, thickness of muscles of the first interstitium; MRI-FMvol, total volume of all foot muscles.

**Figure 1.** (A) Ultrasonographic image of cross sectional area of the EDB muscle (U-EDB-<sub>CSA</sub>) and thickness of the EDB muscle (U-EDB<sub>t</sub>). (B) Ultrasonographic image of thickness of the first dorsal interosseus muscle, the adductor hallucis muscle and the first lumbrical muscle (U-MIL<sub>t</sub>).

**Figure 1**

