

# Muscle Modification in Asymptomatic Diabetic Neuropathy: a Surface Electromyographic Study

Carmelo Chisari, Alberto Piaggese<sup>(1)</sup>, Fabio Baccetti<sup>(1)</sup>, Rosaria Licitra and Bruno Rossi

*Neurorehabilitation, Department of Neuroscience and (1) Chair of Metabolic Disease, Department of Endocrinology and Metabolism, University of Pisa*

## Abstract

In 24 non insulin-dependent diabetic patients [NIDDM-12 with (ND+) and 12 without (ND-) asymptomatic polyneuropathy] in stable metabolic control, and in 12 age-matched controls (C), we studied the functional properties of tibialis anterior muscle (TA) through an electrically elicited contraction. We recorded the surface EMG signal and analysed the median frequency of power spectrum (MDF), the average rectified value of amplitude (ARV) and the muscle fibers conduction velocity (CV).

At the beginning MDF, ARV and CV were significantly decreased in ND+ compared both to ND- and controls. After 23 and 43 sec from the beginning of the stimulation a statistically significant decrease in CV was observed in ND+ compared to ND- and controls (-26% and -49% in ND+, -9% and -28% in ND-, -12% and -30% in C  $p < 0.01$ ). No significant differences emerged as regard MDF and ARV among three groups, either after 23 and 43 sec of electrical stimulation.

Our main findings are consistent with a decrease in mean size of muscle fibers in ND+ respect to ND- and controls. This data suggest a muscle fibers hypotrophy even in non denervated ones. Moreover we can suppose a shift of fiber composition toward the type II fibers in asymptomatic neuropathic diabetic patients.

In conclusion, we observed a myopathic involvement in TA of asymptomatic NIDDM patients. So, it seems very important to early detect muscle function impairment in these patients in order to advise them appropriate rehabilitative program.

**Key words:** diabetic neuropathy, muscle fatigue, surface electromyography.

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Peripheral neuropathy (PN) is perhaps the most prevalent chronic complication of diabetes mellitus: a recent study, confirming previous findings, evidenced a prevalence of 8% at onset of type II diabetes and of 42% after 10 years of duration of disease [15].

Diabetic polyneuropathy in its most frequent clinical presentation has, beside sensory impairment, a definite motor fiber involvement of peripheral nerves, with a prevalent localization at lower limbs, with muscle wasting and reduction of strength.

Motor symptoms of polyneuropathy are not as frequent as sensory ones, and are often misinterpreted as of osteoarticular origin. Still, is not clear if a intrinsic muscle alteration may play a role in motor functional impairment [23].

Actually, diagnostic procedures are essentially based on electrophysiological evaluation of motor component of peripheral nerves, which cannot identify specific muscle abnormalities in muscle structure and functioning [1].

Over the past few years the relevance of the surface myoelectric signal for the qualitative and quantitative understanding and documentation of muscle physiopathology has been demonstrated [9, 12-14].

During sustained contraction at a constant force level, the metabolic processes and the changes in sarcolemma ion permeability modify the sarcolemmal electrical properties. This, in turn, produces alterations in amplitude, shape and width of the action potential resulting in changes of the surface myoelectric signal [5]. Quantitative indicators of such changes are estimates of the mean conduction velocity (CV), median frequency of the power spectrum (MDF) and average rectified value (ARV).

This method may help to investigate muscle impairment in the earlier stages of PN presentation [15].

## Patients and methods

We evaluated a group of NIDDM outpatients affected by peripheral polyneuropathy (ND+), selected among those who underwent the screening for diabetic neu-

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ropathy of the diabetologic clinic according to the following inclusion criteria: age comprised between 35 and 65 years, known duration of diabetes longer than 5 years, presence of peripheral neuropathy as ascertained by bilateral involvement of nerve conduction velocity (NCV) of both peroneal and sural nerves, absence of symptoms of neuropathy evaluated with Michigan Neuropathy Screening Instrument (MNSI), stable metabolic control as evidenced by glycated haemoglobin (HbA1c: normal range 4.1%-6.1%) less than 9% and without variation exceeding 1.5% in the last six months.

Exclusion criteria were: presence of other forms of neuropathy (like mononeuropathies, radiculopathies) or anamnesis indicative of exposure to conditions predisposing to the development of forms of polyneuropathies other than diabetes; presence of osteoarthritis or other clinically relevant rheumatologic disturbances at lower limbs, regular or recent training exercise, presence of clinical peripheral macroangiopathy or absence of peripheral pulses, alcohol consumption heavier than 10 g/die, plasma creatinine higher than 2 mg/dl, presence of other evolved diabetes' chronic complications, recent episodes of ketoacidosis or of hypoglycemic crises requiring others' intervention.

After having obtained their informed consent, patients were taught to self-monitor capillary glucose six times per day in the two days preceding the muscle fatiguing test: any value out of the range comprised between 80 and 250 mg/dl, would postpone the test. Patients were taught also to stop taking drugs which possibly interfere with muscular activity, like  $Ca^{2+}$  antagonists and  $\beta$ -blockers, two days before the test. They were sitting quietly for two hours before testing and then underwent the surface EMG evaluation according to the following procedure: the patient laid supine with his/her non-dominant leg placed in an isometric brace. The brace assured that the position of the ankle joint is fixed with the foot forming an angle of  $110^\circ$  with the tibia bone. The motor point of (TA) were found by means of electrical stimulation and that point, with the lowest stimulation threshold providing the highest muscle contraction, visually registered, was chosen for the stimulation protocol. Stimulation consisted of pulse trains (each stimulus 0.1 msec in width, lasting 43 seconds, delivered at 35 Hertz). A supramaximal stimulation 10-15% above the level generating the maximum amplitude motor-evoked potential was applied. The myoelectric signal was detected with the 4-bars electrode technique described by Broman et al. (1985) [4].

The following items were recorded at the beginning, after 23 and 43 sec of the stimulation: Median Frequency of the Power Spectrum (MDF - Hz), Muscle Fiber Conduction Velocity (CV-m/s), Average Rectified Value of the amplitude (ARV -  $\mu$ V).

A single differential output is obtained from the two central bars, and is used to compute the MDF parameter. The detection technique provided double differential output from which the average muscle fibers CV was estimated. The myoelectric signals were low-pass

filtered with a cut-off frequency of 480 Hz and were digitised by a 12-bit analogue-to-digital converter and stored on the PC hard disk. The spectral variables and the CV were then computed with numerical algorithms according to the methods outlined respectively by Mc Gill and Dorfman (1984) [13], and Merletti and De Luca (1989) [14], tabulated and plotted versus time for each stimulated contraction.

The normalized mean values ( $\pm$ SD) of MDF, ARV and CV at 23<sup>th</sup> and 43<sup>th</sup> seconds of stimulation were plotted.  $\Delta^{11-12}$  was defined as percentage change in value from one time to the next, with  $\Delta^{23}$  being the difference between  $t=23$  and onset and  $\Delta^{43}$  being the difference between  $t=43$  and onset.

After 20 minutes from the end of the fatiguing test, deep peroneal and sural nerves conduction velocities (NCV) and potential amplitudes were determined on the same side from the same operator.

Skin temperature and capillary glucose were verified before and after the performances of both fatigue and NCV tests: if skin temperature was lower than  $33^\circ$  C the limb was heated with a blanket, if capillary glucose was lower than 100 mg/dl extra sugar (15 g) was administered.

Patients were compared with a group of non neuro-pathic non-insulin dependent diabetic patients superimposable for clinical and demographic features (ND-), and with an age and sex matched non diabetic control group (C). Statistical analysis of data, which are expressed as mean  $\pm$  standard deviation, was performed with analysis of variance (ANOVA) and linear regression, using a commercially available software (Statview 512<sup>TM</sup>) running on Macintosh SE computer.

### Results

47 patients fulfilled the inclusion criteria for entering the study, but only 12 were enrolled; in tab. 1 are reported their characteristics as well those of control subjects.

Neuro-electrophysiological evaluation confirmed a significant reduction of both nerve conduction velocities and M-wave amplitudes of deep peroneal and sural nerves in ND+, compared to ND- and controls, as showed in tab. 2.

#### Mean MDF

Absolute value at the beginning of stimulation was significantly lower in ND+ compared with ND- and controls (fig. 1, tab. 3). No significant difference was found in three groups for  $\Delta^{23}$  (-33% in ND+, -33% in ND- and -32% in controls) and  $\Delta^{43}$  (-44% in ND+, -42% in ND- and -46% in controls) (fig. 2).

#### Mean ARV

Absolute value at the beginning of stimulation was significantly lower in ND+ compared with ND- and controls (fig.1, tab. 3). No significant difference was found in three groups for  $\Delta^{23}$  (25% in ND+, 24% in

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*Tabella 1. Characteristics of neuropathic (ND+) and non-neuropathic (ND-) diabetic patients and of control subjects.*

	ND+	ND-	Controls	p*
N° (F/M)	12 (5/7)	12 (6/6)	12 (6/6)	n.s.
Age (yrs)	52.4±9.8	54.6±5.3	53.8±4.1	n.s.
Duration of diabetes (yrs)	8.7±2.5	10±3.9	-----	n.s.
HbA1c (%)	8.5±1.9	8.9±1.2	-----	n.s.
BMI	25.6±3.4	26.4±4.2	26.1±2.1	n.s.
MNSI	2.2±0.8	1.9±1.1	2.0±1.2	n.s.

BMI = Body Mass Index

MNSI = Michigan Neuropathy Symptoms Instrument

\*p<0.05

*Tabella 2. Amplitude of M-wave and nerve conduction velocity (NCV) of peroneal and sural nerves in neuropathic (ND+) and non-neuropathic (ND-) diabetic patients and in control subjects.*

	ND+	ND-	Controls
Peroneal nerve NCV (m/sec)	39.4±5.3*	44.6±4.8	45.8±3.7
Peroneal nerve Amplitude (mV)	3.9±2.1^	8.8±3.8	9.2±2.4
Sural nerve NCV (m/sec)	38.5±4.4*	44.1±4.1	44.9±2.3
Sural nerve Amplitude (µV)	6.2±3.3^	16.3±2.4	16.8±3.1

^ p<0.01 ND+ vs ND- and Controls

\* p<0.05 ND+ vs ND- and Controls

*Tabella 3. Median Frequency of the Power Spectrum (MDF), Muscle Fiber Conduction Velocity (CV), Average Rectified Value (ARV), at the beginning, after 23 and 43 sec of stimulation in neuropathic (ND+) and non-neuropathic (ND-) diabetic patients and in control subjects.*

	ND+	ND-	C
ARV-Bas. (µV)	355.1±151.3^	606.1±230.5	634.6±221.7
MDF-Bas. (Hz)	71.8±22.4*	119.8±27.9	124.6±32.8
CV-Bas. (m/sec)	4.07±0.5*	5.1±0.5	5.4±0.5
ARV-23'' (µV)	434.9±188.6^	702.5±212.9	711.6±266.3
MDF-23'' (Hz)	48.3±13.9^	80.9±19.7	85.2±24.4
CV-23'' (m/sec)	3±0.4^	4.6±0.4	4.8±0.4
ARV-43'' (µV)	287.5±177.9^	443.2±213.1	465.1±219.9
MDF-43'' (Hz)	40.4±15.2^	69.8±17.6	68.3±20.8
CV-43'' (m/sec)	2.1±0.4^	3.7±0.6	3.8±0.3

\*p<0.05 and ^p<0.01 ND+ vs ND- and Controls

ND- and 12% in controls) and  $\Delta^{43}$  (20% in ND+, 27% in ND- and 27% in control) (fig. 2).

### *Mean CV*

Initial absolute values were significantly lower in ND+ compared to ND- and controls (fig. 1, tab. 3). The  $\Delta^{23}$  in ND+ (-26%) was significantly different (p < 0.01) from that of ND- and controls (-9% and -12%, respectively). Also  $\Delta^{43}$  in ND+ (-49%) was significantly different (p < 0.01) from that of ND- and controls (-28% and -30%, respectively), as showed in fig. 2.

### **Discussion**

The presence of intrinsic muscle alterations in asymptomatic neuropathic NIDDM has been further corroborated by the findings reported in this study.

CV and MDF parameters have been shown to be indirect measurements of the size of muscle fibers and an indirect tool for inferring about the fiber type composition of muscle. In fact, Hakansson (1956) documented a direct relationship between muscle action potential CV and fiber circumference in isolated frog

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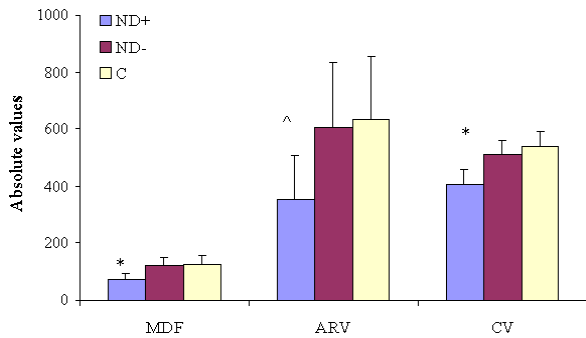


Figure 1. Basal values of MDF, CV and ARV, in neuropathic (ND+) and non-neuropathic (ND-) diabetic patients and in control subjects; \* $p < 0.05$ , ^ $p < 0.01$  ND+ vs ND- and C.

muscle fibers [8]; Pedrinelli et al. (1998) demonstrated a positive correlation between MDF and fiber diameter in human skeletal muscle [16].

During sustained contraction, in normal subjects, CV and MDF gradually decrease. This decrement, which is related to modifications in muscle membrane excitability and represents the direct effect of the electrical fatigue phenomenon, has a different time course in phasic (type II) and tonic (type I) fibers, the decrease in the phasic fibers being greater [14, 17].

Our work showed significantly lower CV and MDF basal values in ND+ compared to ND- and controls. This result indicates that the mean TA fiber size is reduced in ND+. Furthermore the percent decrement of CV, both after 23 and 43 sec, is significantly greater in ND+ respect to ND- and controls. This pattern suggests a modified TA myofibril composition: an increased percentage of type II fibers. In conditions with insulin resistance in muscle, a shift in muscle fiber composition has been demonstrated, with a higher proportion of white at the expense of red fibers [10, 11, 18]. This evidence suggested that insulin may regulate myosin synthesis in muscle in the direction of the change observed [12]. Nevertheless, our results suggest a myofibril modification related to polyneuropathy rather than to hyperinsulinemia.

On the other hand, the MDF percent decrement in ND+ is not different than that in ND- and controls. This apparent discordance with CV decrement could depend on the very low basal value of MDF.

The significantly lower value observed for ARV in ND+ compared to ND- and controls both at the beginning, after 23 and 43 sec suggests a reduction in the number of active muscle fibers. This datum is, of course, analogous to the reduced M-wave amplitude observed with the neuro-electrophysiological evaluation. On the other hand, the superimposable trend observed in ARV curve among groups reveals a normal membrane excitability of muscle fibers in ND+ [6].

The very interesting finding emerged in this study is referred to a myopathic involvement of TA. In fact, our stimulation protocol is not able to activate denervated

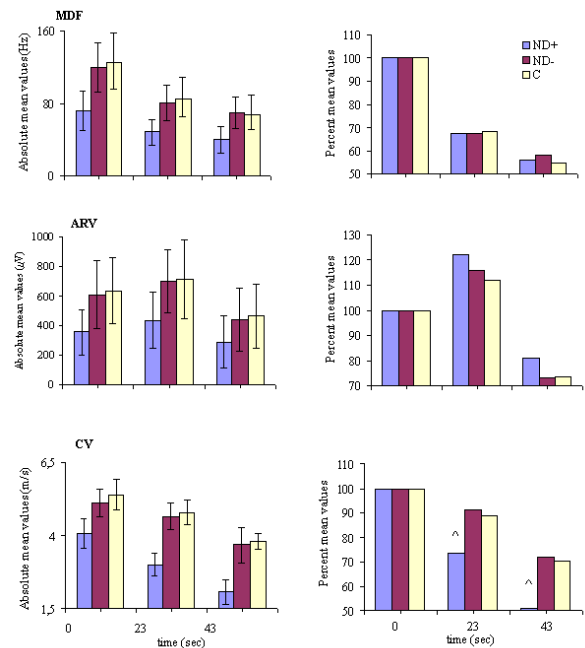


Figure 2. Absolute (left column) and percent (right column) variations of MDF, ARV and CV in neuropathic (ND+) and non-neuropathic (ND-) diabetic patients and in control subjects at the beginning, after 23 and 43 seconds of stimulation, respectively; ^ $p < 0.01$  ND+ vs ND- and C.

fibers, so we can affirm that the data obtained directly imply a modification of the innervated ones.

TA muscle contributes to postural stability both in static and dynamic conditions [2]. Many recent papers evidenced a high degree of postural instability in neuropathic diabetic patients, predisposing to accidents and injuries [20, 21]. Although sensory impairment has been judged as the major responsible for postural instability, motor component, either secondary to polyneuropathy and directly as myopathic involvement, may play a role as well, reducing the possibilities of automatic and efficacious postural adaptation through differential muscle contraction [7]. In dynamic conditions, insufficiencies of anterior limb muscles, which normally decelerate the ankle plantar flexion, has been associated with higher forefoot pressure, a condition which predispose to the development of plantar ulcerations in neuropathic patients [19, 22].

In conclusion, it seems very important to early detect a functional impairment of TA in order to design rehabilitative protocols specific for the muscle alterations observed in this study. This to try to retard or to avoid the severe and compromising complication at lower limbs. Moreover we consider remarkable to dispose of an useful and no invasive tool to accurately evaluate the muscle function also in asymptomatic NIDDM patients.

### Address correspondence to:

Carmelo Chisari, Neurorehabilitation, Department of Neuroscience, University of Pisa, via Paradisa, 2 Cisa-

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nello, 56100 Pisa, Italy, tel. +39 50 996964, fax +39 50 995166, Email [c.chisari@ao-pisa.toscana.it](mailto:c.chisari@ao-pisa.toscana.it).

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