CASE REPORT

Neuromuscular investigation in diabetic polyneuropathy

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Abstract

The aim of this paper is to present to new method for assessment diabetic polyneuropathy, before the moment of first clinical sign. Our working presents the method of tensiomyography (TMG) for assess the muscle composition rapports with muscle fibers types I and II. This composition can help to have an image regards the neuromusuclar potential of muscle during diabetic process. Tensiomyographic parameters included time contraction Tc, time delay Td, sustain time Ts, displacement Dm, and relax time Tr. All these parameters give information regards muscle fatigue in correlation with muscle composition. Muscle composition regards fibers type I or II is in relation with Tc, increase of these parameters means decrease of muscle fibers type I that means muscle fatigue. Also, values of Dm help us to assess the muscle tonus, elasticity and response to electrostimulus. We consider that this method helps the clinicians to have a prediction of a future polyneuropathy at diabetic patients.

***Keywords*:** tensiomyography, muscle fatigue, muscle composition, diabetic, polyneuropathy.

Introduction

Within the structure of the skeletal muscle, there are fascicles of muscular fibers that are made up of serially distributed contractile elements. These elements are controlled by the nervous system, control which results in obtaining the muscular strength required for movement and its control [1].

The intervention of the nervous system in motor control is possible due to the motor neurons within the spinal cord marrow or cerebral trunk, whose axons come out of the spinal cord marrow through the anterior root of the spinal nerve and then becomes part of the peripheral nerves that are distributed in the muscles whose innervations they ensure [2].

Skeletal muscles are made up of three types of fibers: I, IIa, IIb; the proportion in which each of these fibers is represented varies according to muscle activity. Apart from these types of muscular fibers, there are also type IIc muscle fibers, usually considered intermediate fibers that have a high potential to turn into type I, IIa or IIb fibers; this transformation is supposed to happen during the regeneration period, this phenomenon representing muscle plasticity. This structural diversity is the result of the description of a large number of phenotypes whose functional significance is unclear [3]. The factors that influence these variable structural aspects could be genetic programs, hormonal influences, usage (particularly important from the point of view of functional recovery).

The total number of striated muscular fibers cannot change; only the percentage of muscular fibers (fast and slow twitch) within skeletal muscles can vary and this is influenced by muscular plasticity, as previously mentioned [4]. This property of skeletal muscle is affected in the pathological processes that regard either the nervous or the neuroendocrine, muscular or vascular systems; this influence is expressed within the muscular fiber metabolism. The transformation of the muscular fiber metabolism is an aspect that can be controlled through a complex medical intervention, following complex evaluation of the structure and contractile properties of the muscular fibers [4]. Such changes exist and they are noted by many authors in type 2 diabetes, more precisely in the context of diabetic neuropathy that these subjects develop.

Diabetic neuropathy can take different forms, if we are to refer to its anatomic and physiopathological substrate. Diabetic polyneuropathy is almost constantly present in the clinical evolution of type 2 diabetes. The prevalence of this neuropathy in diabetic patients is 30%. This study is based on a series of questions about the evaluation of the structural functional potential that the skeletal muscle has in diabetic neuropathy and it can lead to more objective, less invasive estimates that patients would accept more easily. These questions are:

1. What is the residual morphofunctional substrate in diabetic neuropathies?
2. What is the response of the muscle to a stimulus that produces an isometric contraction within the anti-gravitational muscle groups?
3. Are there changes in the muscle composition related to the changes in the receptors on the surface of the muscular fiber, which modulate the behavior of the muscle fibers to insulin? (In literature there is data that highlight this aspect, but without presenting a rigorous approach to its objectification, from the point of view of the muscle fiber).

4. What are the parameters that can quantify the muscular behavior in diabetic neuropathies?

5. Is any rapport between muscle fatigue and level of muscle disorder included in diabetic neuropathies?

Patient and Methods

We think that the investigation of the contractile properties of muscle fibers in these cases and even the attempt to determine the muscle composition are ways to estimate the functional behavior of the muscle, thus allowing for the modulation of the complex therapeutic intervention beyond the drug therapy specific to type 2 diabetes. These investigations need to provide information about contraction speed, muscle endurance, recruitment of motor units [5–7].

Density of the muscle fibers (DF) could be obtained through needle electromyography, method useful for the asessment of reinervation. This method is tension-myography (TMG), whose protocol we will present below.

This protocol has been applied following the rules of the *Ethics Committee of the Research Centre* and is compliant with the *Helsinki Declaration* principles. In this respect, the investigated subject has been informed about the proceedings of this study.

We have attempted to obtain answers to these questions by using tensiomyography (TMG) as an evaluation method for the morphofunctional potential of the muscle, which allows for the detection for the muscular reaction to electrical stimulation.

Through this method we can appreciate the rapport between type I (fatigue-resistant) and type II (white, fast-twitch, with low resistance to fatigue – this phenomenon appearing before the completion of the electrical stimulation process) muscular fibers.

The current study is a case study of a 60-year-old patient who displays, within type 2, non-insulin dependant diabetes, diabetic polyneuropathy, rheumatoid polyarthritis evident in the lower limbs, with sensory-motor-type clinical manifestations within the muscular territory innervated by the common sciatic, femoral, tibial and peroneal nerves. The associated pathology was a right side herniated lumbar disk L4–L5 which required surgical intervention.

The clinical evaluation of the patient showed: ataxia, instability when walking, distal-proximal atrophy, decreased muscle strength, right-side cauda equina claudication, with a 20–25 m claudication index. Pain under the posterior side of thigh and shank on both lower limbs. Local assessment included: gross light touch and pinprick sensation, decrease of distal proprioception, decrease of Achillean reflex, vibratory sense (128-Hz tuning fork) at base of great toenail and monofilament (5.07) to test larger sensory fibers shows inability to perceive the 128-Hz tuning fork or to feel a 10-g (5.07) monofilament on the plantar surfaces of the foot identifies patients who are at increased risk (i.e., 60% in next 3 y) of developing a foot ulcer. The two tests should be performed at least every year, dorsal pedal and posterior tibial pulses normal, Tinel testing positive, strength testing and examination for distal intrinsic extremity muscle atrophy shows a lower level of muscle force. At the first moment of assessment, clinical assessment has been completed using also MRI results, because our patient has also herniated lumbar disk L4–L5. MRI shows hypertrophy of joint processes of spinal column and yellow ligaments. Other laboratory results show: lack of pulmonary disorders, normal cardiologic parameters, decrease of K^+ blood level, decrease of blood protein level.

In order to complete the data supplied by the clinical and paraclinical examination, we have suggested the use of TMG as an evaluation method for muscular fatigue and skeletal muscle composition, which have taken place within type 2 diabetes and have been necessary to establish the connection between the structure and morphofunctional properties of the muscle on the one hand, and its functional potential on the other side.

The evaluation of muscular fatigue can be made under intermittent electrical stimulation of the muscle. This stimulation is made with a TMG–S1 electrostimulator (Furlan & Co., Ltd.), using 5/5 cm Platinum-type electrodes. The stimulation is performed under increasing electrical current intensities, between 10–65 mA, the length of the stimulation being one millisecond. An isometric contraction is produced because of electrical stimulation. The detection of the muscular response to the electrical stimulus is performed with a G40, RLS Inc. sensor, perpendicular to the muscle surface, in the area in which the muscular geography is well displayed (this can be more precisely determined if the subject is requested to perform an isotonic contraction, if a muscle strength higher than 2 is possible). The sensor is placed at this level; it will exert a 0.7 N/mm^2 pressure on the contact surface. This pressure is called pretension [5] and its role is to increase the response to the applied electrical stimulus. Because of the electrical stimulation, a transversal movement of the muscular fibers will occur and the sensor will record this.

The amplitude of this transversal movement is proportional with the muscular force and the percentage of type I muscle fibers, which enables us, together with the data from the other parameter, to evaluate muscle fatigue and transmission speed. The measurement of the muscular response, and the data storage and analysis have been made with a dedicated TMG software.

Signal recording

The TMG signals are received by a Matlab Compiler Toolbox on a 1 kHz frequency. Two supra-maximal responses are stored and then the average is calculated. The supra-maximal stimulation [6] is regarded as corresponding to a minimal stimulation and it determines a maximal amplitude of muscular deformation, recorded as Dm.

The parameters evaluated through tensiomyography were:

- latency time (Tc) – the time elapsed from stimulation to obtaining 10% muscular contraction [ms];
- contraction time (Ts) – the time it takes the 10% muscular contraction to reach 90% [ms];

▪ sustaining time (Ts) – the time it takes a 50% contraction to reach 50% relaxation [ms];

▪ relax time (Tr) – the time between 50% muscular relaxation and 90% muscular relaxation [ms];

▪ the amplitude of the transversal muscle belly movement (displacement) – Dm [mm].

The stimulation method and the reception of the mechanical muscular signal are rendered below (Figure 1), as well as the curve of the isometric stimulation (Figure 2) resulting because of electrical stimulation under the previously mentioned parameters.

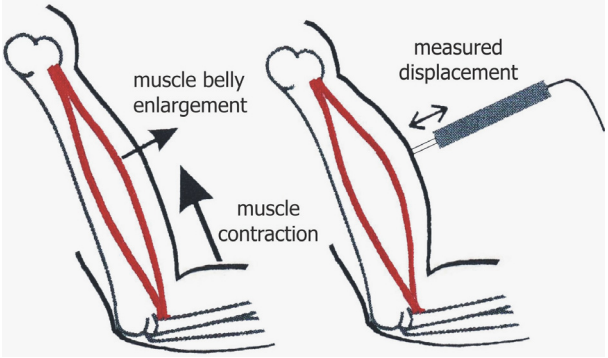

Figure 1 – ***The TMG measurement principle: the measurement of the amplitude of muscle movement because of stimulation (http://www.tmg-bmc.si).***

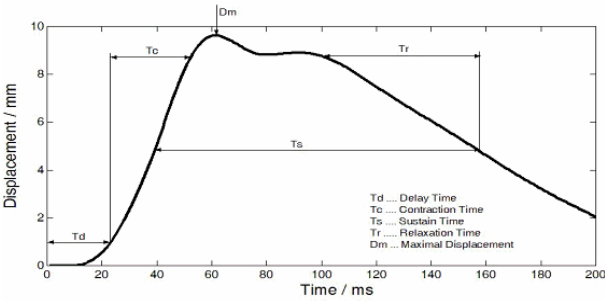

Figure 2 – ***The curve of the isometric muscular contraction obtained because of electro-stimulation: TMG parameters (http://www.tmg-bmc.si).***

In the case presented within this paper, the tensiomyographic parameters have been measured within the first muscular groups of the inferior limb: quadriceps, anterior tibial, sural triceps (gastrocnemius), and femoral biceps.

The evaluation was made at this level in order to obtain information about the muscular fatigue that accompanies muscular weakness, about transmission speed, lateral symmetry (left/right), which can explain the presence of equilibrium disturbances on the body, and then on the lumbar herniated disks, about functional symmetry (agonist/antagonist) at lower limb level – this ensures the stability and balance of the body. From a structural point of view, by measuring the tensiomyographic parameters, we can obtain data about muscle composition; this composition is modified in diabetic polyneuropathy. Knowing this correlation would allow us to create a complex therapeutic perspective that could include physical exercise [8], thus obtaining transformations of type IIc, intermediary, fibers that have this potential.

Results

The presentation of the results we have obtained has been made according to the percentages considered normal for lateral symmetry – 80%, and functional symmetry – 65%. Percentages lower than these values are related to muscular imbalances generated by morphofunctional properties of the muscles.

Apart form these estimates, the information related to the most relevant TMG parameters have been related to their normal values and to reference values we had obtained in a previous study on healthy subjects with similar ages, same sex, not taking part in systematic physical exercise.

The TMG parameter values are specific to every muscular group, being influenced by muscular composition. These values have a contraction time specificity – Tc, the reference value of which is 32.83 ± 4.5 ms, but some studies report few values for each muscle group to lower limb 30.25 ± 3.5 ms for the femoral biceps; 44.75 ± 4 ms for the gastrocnemius; 32.83 ms for the anterior tibial; 30.25 ± 3.5 ms for the quadriceps.

Td – latency time has a medium reference value of 28.7 ms, while that of Dm, the amplitude of the transversal movement, is 8.17 mm.

Tr and Ts are parameters whose values depend on the degree of muscular fatigue and on its pathological substrate, no reference values being so far available. It is for this reason that we have quantified these parameters taking into account healthy subjects.

The curvatures of the isometric contraction as a result of electrostimulation in the studied patient is presented for each muscle group (Figures 3–6) and show to us muscle behavior after electrostimulation. Each graphic presents TMG parameters.

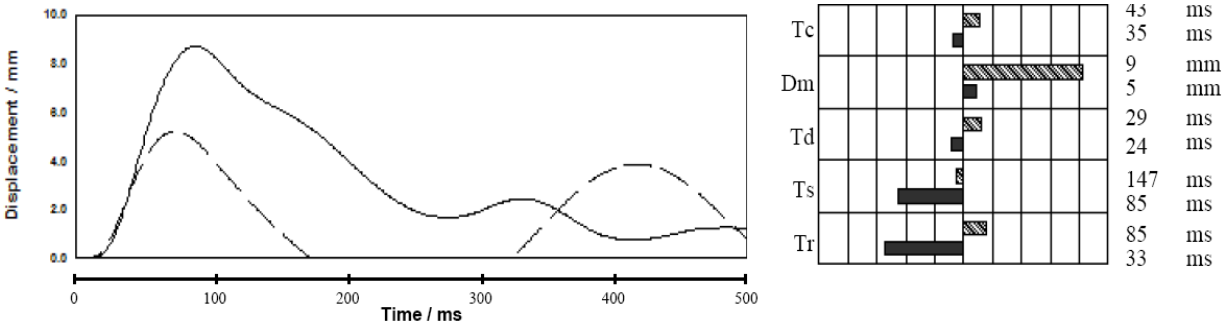

Figure 3 – ***Quadriceps TMG parameters.***

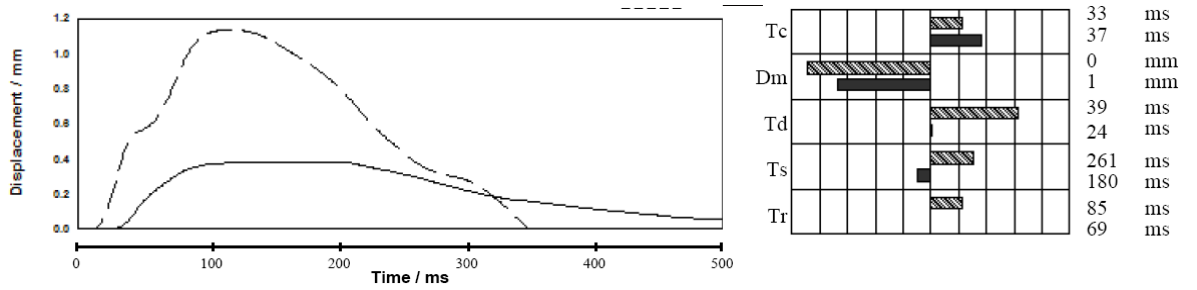

Figure 4 – ***Anterior tibial TMG parameters.***

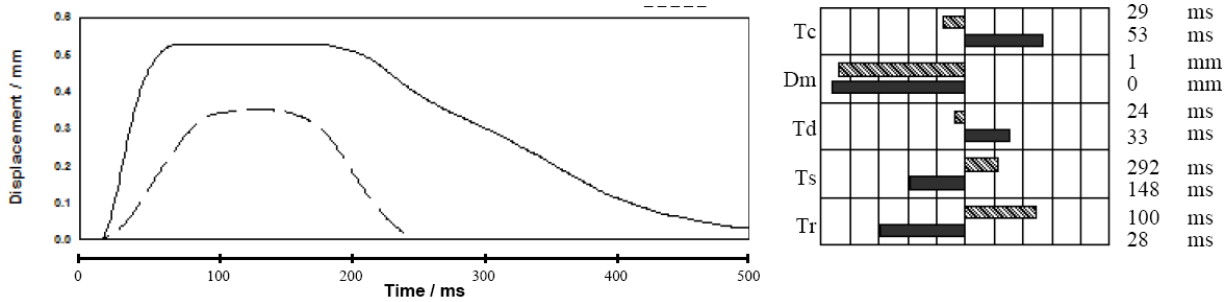

Figure 5 – ***Sural triceps (gastrocnemius) TMG parameters.***

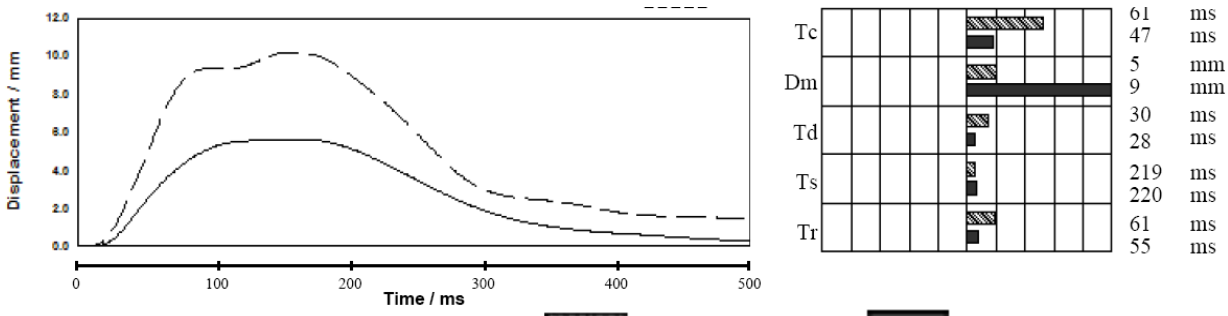

Figure 6 – ***Femoral biceps TMG parameters. Key:*** _____ ***right;*** ---------- ***left.***

Looking at the Figure 7, we can see the relationship between then values obtained by TMG exploration in the case of the patient with diabetic polyneuropathy associated with rheumatoid arthritis and operated herniated lumbar disk. We can notice that the Tc contraction time has higher than normal values. These values are less obvious in the case of the anterior tibial muscle.

The analysis of this Figure 8 shows that the muscular response to the electrical stimulus consists of a transversal muscle movement below the value considered normal.

The exceptions are the left femoral biceps and the right lower limb quadriceps.

Figure 9 shows a fall within the values that are equal with the reference value, an increase in the latency time being recorded in the right lower limb. Td values represent the latency time for obtain 10% from maximal muscle contraction amplitude.

As far as the contraction sustain time Ts and the relaxation time Tr are concerned, the value we have recorded have been compared to the average values obtained for the healthy subjects, in anterior study. In Figures 10 and 11, we presented Ts and Tr values that have been reported to references values for each muscle group.

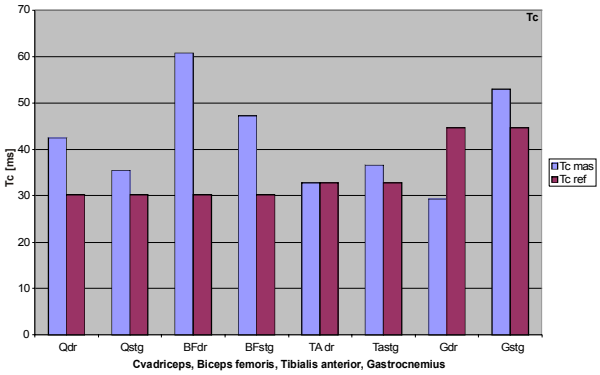

Figure 7 – ***Values of Tc contraction time [ms].***

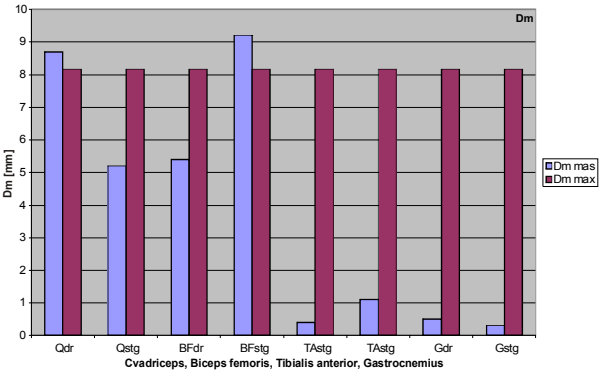

Figure 8 – ***Values of Dm movement amplitude [mm].***

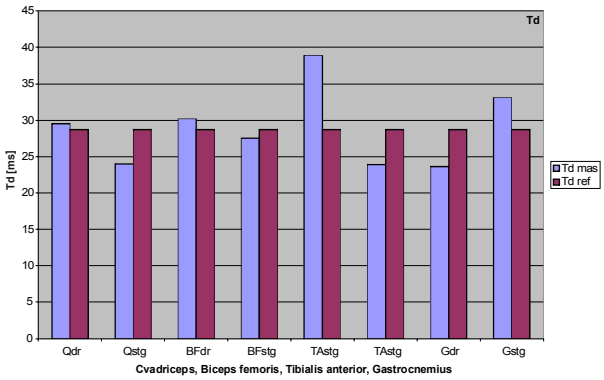

Figure 9 – ***Td values (latency time) [ms].***

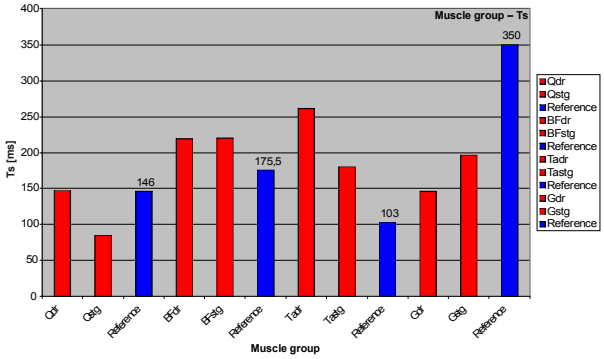

Figure 10 – ***Comparative Ts [ms] values.***

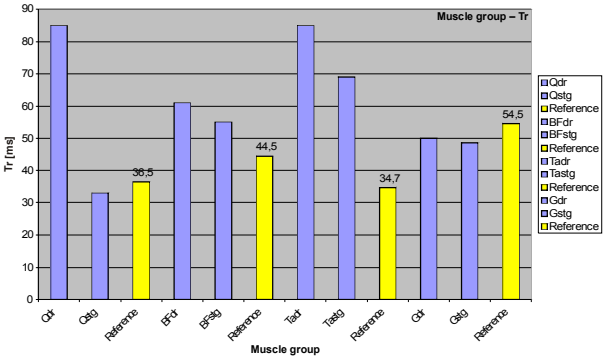

Figure 11 – ***Comparative Tr [ms] values.***

The diversity of the muscular behavior, also evident in the TMG evaluation, is due to the structural heterogeneity and the spatial disposition of the striped muscular fibers; these aspects influence the contraction speed, the muscular force and resistance, allowing us to obtain an image of the way in which muscular adaptation to effort happens. Most of the research was based around following the adaptation process of muscles in different pathologic processes or in muscle training.

The data analysis for the results was made for each muscle group, following the behavior of each TMG parameter. The purpose of the data analysis was to evaluate muscular fatigue, the lateral and functional symmetry.

Thus, for the thigh we have noticed that Tc is increased in the quadriceps, which shows the presence of muscular fatigue and the decrease in the percentage of slow-twitch type I muscular fibers, and this percentage is normally lower than 50% in the quadriceps. This increase of Tc correlated with the decrease in the Dm value, which in the case we have presented further shows an existing significant muscular imbalance between the agonists and the antagonists (quadriceps/femoral biceps), a compensatory mechanism being activated in the right lower limb for the quadriceps, and for the femoral biceps in the lower left limb. The Dm movement is a parameter than depends on the muscle tonus and volume, the decrease in Dm being an indicator of increased muscular tonus. Therefore, associating the decrease in Dm with the increase in Tc supports the hypothesis that muscular fatigue is present in the thigh.

With regards to the other TMG parameters evaluated for the thigh musculature, we have noticed an increased Td latency time in the lower right limb, over the reference values, which falls within the clinical profile sequels for the operated lumbar herniated disks L4–L5, associated with the right cauda equine syndrome, the patient benefiting from an L4 right hemilamectomy. This increased latency time value also indicates a deficit in recruiting motor units because of electrostimulation. This latency time is correlated with increased values of the Tc contraction time, which again underlines the predominant type II muscular fibers.

The same aspects of both the agonist/antagonist and right/left muscular imbalance are also supported by the Ts and Tr values. Ts has lower values for the anterior muscular group (quadriceps) compared to the posterior muscular group (represented here by the femoral biceps), which can be correlated with Dm and with the increase in the muscle tonus which is probably highly increased under electrostimulation.

The Tr relaxation time is decreased in the quadriceps, which correlates closely with the values of the previous parameters, showing a faster depletion of the energy reserves. This aspect underlines again the dominance of type II muscle fibers, which have an anaerobic metabolism, based on glycolysis. For the femoral biceps, we have noticed a relative balance of the Tr values, compared with the reference values.

At thigh level, we have noticed values that are approximately normal for the lower right limb, while for the lower left limb we have noticed increased Tc values. Both lower limbs have registered a decrease in Dm, more prominent in the right lower limb, which shows that at this level we are facing a muscular fatigue phenomenon localized at thigh level.

The Td latency time is increased in the lower right limb, and as a result the muscular response to stimulation appears later, and the muscular group does not have the ability to respond through a maximal move because the conduction speed is significantly lowered and the muscular tonus is increased. We have noticed increased Ts values, more obvious in the right lower limb, which allows for its correlation with the existence of an increased muscular tonus, which is also supported by the previous statements referring to the Dm link-muscular tonus. The Tr values within the thigh muscles are close to the normal values for the lower right limb and for the lower left limb a significant decrease has been notes, showing rapid relaxation as a result of muscular relaxation evident in the lower left limb.

As a whole, from the point of view of the interpretation of the parameters evaluated at thigh level, we can notice an enhancement of the muscular fatigue phenomenon at this level, due to the decrease in the percentage of type I muscular fiber whose value, under physiologic conditions in the thigh, is 50%. Moreover, at this level we can notice a significant decrease in the Dm values, decrease which points to the existence of a muscular hypotrophy and increase in the percentage of type II muscular fibers and myopathic aspect.

The muscular fatigue phenomenon, its diagnosis through TMG [8], its correlation with the predominant type of muscular fibers, are also related to the density of muscular fibers, which is considerably decreased in the thigh, which can also explain the intensity of the muscular fatigue phenomenon that exists at this level.

Furthermore, the literature shows results of histological studies that show the percentile values of type II fibers, with a potential for transition to type I fibers. At thigh level, this percentage is 5.7% and at calf level, the percentage is between 1.8 and 2%, justifying the increased intensity in the fatigue phenomenon in the calf, compared to the thigh.

The lateral symmetry results both from comparing the left/right TMG parameters, and from following the morphology of the muscular contraction curves. Thus, at the anterior muscular calf level a biphasic response is recorded with the apparition of a contraction wave once the stimulus ceases to act, at the end of Tr. This means that there are probably aberrant reinnervation ways with longer latency and which give a lower amplitude motor response. At the same time, we have noticed that at the lower right limb level the motor response is more significant, with significantly modified TMG parameter values, which reflects a higher degree of muscular tiredness and therefore a higher percentage of type II muscular fibers, which works against type I muscular fibers. Lateral asymmetry is 76% in the anterior thigh muscular group.

For the posterior thigh muscular group we can notice a reverse situation, reflected in the morphology of the contraction curves, with lower Dm and Tc values on the right side, which also shows the existence of muscular fatigues resulting from structural modifications in the muscular composition. We can also notice left/right symmetry and harmonization, which is 77%, close to the value considered normal, 80%.

At calf level, by following the morphology of the contraction curvatures for the anterior tibial muscle, we can notice a lateral left/right asymmetry, shown by a motor response with low movement, and significantly increased of Ts on the right side; this aspect corresponds to a hypotrophy and the left/right lateral symmetry being 73%.

For the posterior muscular group of the calf, we can notice that the TMG parameters are present on a curve with a similar morphology with the one in the quadriceps, with a more ample response in the lower right limb, a lower latency time, higher Ts, and higher Tr. The latter proves the existence of a deficit in recruiting the motor units during stimulation. The lateral symmetry in this case is 59%.

We would like to point out that the lateral symmetry percentage is the result of an algorithm that the TMG contains.

Discussion

These neuromuscular aspects noted and evaluated through tensiomyography correspond with the laboratory data, the histopathological and biochemical data in literature and which can explain the morpho-functional changes that constitute the basis of the functional behavior of the skeletal muscle in type 2 diabetes.

We know that type 2 diabetes is associated with a disturbance in the response of the cellular membrane to insulin, attributed to the resistance to insulin of the skeletal muscle. Protein transporters named GLUT1 and GLUT4 mediate the transport of glucose in the membrane of the skeletal muscular fiber [9]. Within the skeletal muscle, the type I slow-twitch fibers are more receptive to insulin than fast-twitch fibers. Recent studies have shown that there is a relationship between the presence of the GLUT4 transporters and the type of muscular fiber, aspects that have been demonstrated through immunohistochemical and stereological analyses [10]. These studies have shown the existence of a high GLUT4 expression in the slow-twitch fibers, compared to their presence in the fast-twitch fibers [10]. The percentage of slow-twitch fibers is significantly decreased in patients with type 2 diabetes and inversely proportional with obesity grade [11]. Consequently, determining the percentage of slow-twitch fibers can represent an aid in establishing the diabetic phenotype and the connection with the presence of GLUT4 receptors. GLUT4 is significantly increased in slow-twitch fibers, compared to fast-twitch fibers in normal patients (2.4 ± 0.1 *vs.* 2.7 ± 0.1), while in the case of patients with type 2 diabetes this aspect is not encounters, GLUT4 being a lot lower in slow-twitch fibers, as studies show (2.4 ± 0.1 *vs.* 2.9 ± 0.1) [10].

The study shows the existence of a reduced density in the GLUT4 transporters in the slow-twitch fibers, therefore lower resistance to insulin, but also a reduction in the slow-twitch fibers in the patients with type 2 diabetes. These changes are attributed to perturbed glucose metabolism in the skeletal muscle. This is as we know made up of two types of muscle fibers; slow-twitch fibers are more receptive to insulin and are characterized by a high level of oxidative processes, with reduced glycolysis and an increase in the level of oxidation of fatty acids [12]. For this reason, we can talk about the existence of specific changes in the muscular fibers, which can outline the phenotype of type 2 diabetes.

Over the last decade, numerous studies have proved the connection between GLUT4 and insulin-resistance of skeletal muscles. Thus, the reduction of the GLUT4 expression probably contributes to the development of insulin-resistance. It has also been demonstrated that the incidence of neuropathy in people with type 2 diabetes is varied, ranging between 10–50%. This variability results from the absence of clear criteria to define

diabetic neuropathy in the context of a diabetic phenotype [13, 14]. Many diabetics show a symptomatic neuropathy, but there are a considerable percentage of people who are asymptomatic.

Resistance to insulin encountered in the case of the patient investigated within this study is an essentially muscular resistance to insulin, based mainly [15] on the synthesis if glycogen and it explains the evolution of the TMG parameters. This resistance to insulin appears on a genetic background, as we encounter it in children with normal glycemic load tolerance, but with two parents with type 2 diabetes. The genes involved in this are, however, not known yet [16].

On a metabolic level, resistance to insulin is secondary to fat excess at muscular and visceral adipose tissue (AT) level, which releases a high quantity of free fatty acids (FFA). The FFA portal flux favors hepatic triglyceride (TG) synthesis and stimulates the hepatic gluconeogenesis. At muscular level, there is a real competition between FFA and glucose for oxidation: FFA are oxidized as a priority, involving an increased production of acetylcoenzyme A, which inhibits glycolytic enzymes. On the other hand, the muscular energy is supplied mainly by the FFA oxidation; the supply of muscle glycogen [17] remains intact, which results in a decrease in its synthesis.

The storage and usage of glucose are therefore decreased at muscular level while there is an increase in gluconeogenesis at hepatic level.

The main clinical factors for insulin resistance that we estimated for the studies patient:

- obesity: body mass index (BMI) over 30;
- abdominal and visceral fat distribution: distribution of the gynoid type adipose tissue (AT), predominantly distributed in the lower side of the body, on the buttocks and thighs.
- sedentary lifestyle;
- genetic factor: resistance to insulin, explained by an increase in the number of fast-twitch muscle fibers, much more resistant to insulin than the slow-twitch fibers;
- age: aged subjects accumulate more insulin-resistance factors.

Conclusions

Through this study, we have tried to present a way of paraclinic investigation in diabetic polyneuropathy, a neuromuscular investigation whose results can represent prediction factors for the evolution of a diabetic polyneuropathy.

The use of this system of neuromuscular investigation [18] allows the monitoring of the drug treatment but also the conserving recuperating treatment, which have allowed the limitation of the clinical manifestations appearing within the context of polyneuropathy.

In this respect, we would like to mention the studies on groups of sports people, where we have observed that the different types of physical effort can induce changes in the stripy muscular fibers; it has thus been demonstrated that sustained endurance physical effort over a determined period of time determines the transformation of a specific number of type IIb, IIc fibers into type IIa fibers.

It is also possible that the type II fibers [19] can show increases in the oxidative capacity after high-intensity endurance training, which makes them reach a level where they are able to perform oxidative metabolism in the same way as stripy muscle fibers in patients not participating in training; this leads to an increase in the dimensions and the number of mitochondria associated to the mentioned changes, not to a change in the type of muscular fibers [20].

The correlation of the muscular fiber type with the action of the GLUT4 transporters, or more precisely, determining the type I muscular fiber deficit, flagged up in many studies [21, 22], allows for a modulation in the type II diabetes specific therapy.

The applicability of the TMG method in evaluating the neuromuscular parameters that define muscular contraction and strength represents a novelty element in the expansion of such a type [23] of evaluation in pathology, taking into account the fact that this method has not been applied so far in the pathological area.

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