LOWER / UPPER EXTREMITY F-WAVE RATIO FOR DETECTING EARLY DIABETIC NEUROPATHY

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Background and purpose – Results of conventional nerve conduction studies may be within normal limits in early diabetic neuropathy. Previous studies demonstrated that F-wave latency should be used to detect this early neuropathic process. The aim of this study is to evaluate the sensitivity of lower/upper extremity F latency ratios in detecting the early neuropathy in patients with diabetic neuropathic pain.
Methods – 44 patients with diabetic neuropathic pain (DNP) and 44 control subjects whose both conventional nerve conduction studies and F-wave latencies were within normal limits were included to the study. We compared the nerve conduction parameters and lower/upper extremity (tibial/ulnar) F latency ratios of the groups.
Results – Tibial F latency was significantly prolonged and tibial/ulnar F latency ratio was significantly higher in DNP group. Our results support that F-waves are useful for detecting early diabetic neuropathy and suggest that comparison with a control group will demonstrate a difference even when the individuals' F-wave latencies are within the normal limits. The difference was significant for tibial but not for ulnar F latency values supporting the length dependent involvement. The tibial/ ulnar F-wave latency ratio was significantly higher in the DNP group, suggesting that it might also be useful to detect early neuropathy and to demonstrate that the underlying process was predominant in lower extremity.
Conclusion – Further studies may provide additional information about the utility of this ratio for detecting early neuropathy even when F-wave latencies are within normal limits.

Keywords: *F wave, diabetes melitus, diabetic neuropathy, electrophysiology*

ALSÓ/FELSŐ VÉGTAGI F-HULLÁM-ARÁNY ALKALMASSÁGA A DIABETESES NEUROPATHIA KORAI KIMUTATÁSÁRA

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Háttér és cél – A konvencionális idegvezetési vizsgálatok eredményei a normális határokon belül lehetnek korai diabeteses neuropathia esetén. Korábbi vizsgálatok bizonyították, hogy az F-hullám-latencia alkalmas lehet a korai neuropathiás folyamatok kimutatására. A jelen vizsgálat célja, hogy igazoljuk: az alsó/felső végtagi F-hullám-latenciák aránya alkalmas a diabeteses neuropathiás fájdalommal küzdő betegek körében a neuropathia korai kimutatására.
Módszerek – 44, diabeteses neuropathiás fájdalommal (DNP) küzdő beteget és 44 olyan kontrollszemélyt vontunk be a vizsgálatba, akiknél a konvencionális idegvezetési vizsgálatok és az F-hullám-latenciák vizsgálata egyaránt a normális határokon belüli eredményt adott. Összehasonlítottuk a csoportok idegvezetési paramétereit és az alsó/felső végtagi (tibialis/ulnaris) F-hullám-latenciák arányait.
Eredmények – A kontrollcsoporttal összehasonlítva, a DNP-csoportban szignifikánsan megnyúlt a tibialis F-hullám-latencia és szignifikánsan magasabb volt a tibialis/ulnaris F-hullám-latencia-arány. Eredményeink azt mutatják, hogy az F-hullámok mérése használható a korai diabeteses neuropathia kimutatására, és értékeinek kontrollcsoport értékeivel való összehasonlítása akkor is képes különbséget detektálni, amikor az egyének F-hullám-latenciái a normális határértékeken belül vannak. A tibialis F-hullám-latencia-értékek különbsége szignifikáns volt, azonban az ulnaris értékeké nem, ami azt támasztja alá, hogy az idegrostok hossza lényeges tényező. A tibialis/ulnaris F-hullám-latenciák aránya szignifikánsan magasabb volt a DNP-csoportban, ami azt mutatja, hogy ez a mérőszám is hasznos lehet a neuropathia korai diagnosztizálásában, és hogy a háttérben álló kórfolyamat az alsó végtagon kifejezettebb.
Következtetés – További vizsgálatok kiegészítő eredményekkel szolgálhatnak ennek az aránynak a neuropathia korai diagnosztizálásában való hasznosságával kapcsolatban, még olyan esetekben is, amikor az F-hullám-latenciák a normális határértékeken belül vannak.

Kulcsszavak: *F-hullám, diabetes mellitus, diabeteses neuropathia, elektrofiziológia*

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Diabetes mellitus (DM) is one of the most common chronic diseases with high morbidity and its incidence increases day by day[1]. Diabetic peripheral neuropathy (DPN) is a complication of diabetes which can be detected even in newly diagnosed diabetics[2]. The most common form of neuropathy is distal symmetric polyneuropathy in which lower and distal extremities are involved earlier due to length dependent process. It reduces the patient's quality of life and is an important cause of limb amputations[2, 3]. Diabetes Mellitus is also a main cause of neuropathic pain.

Since early diagnosis of diabetic neuropathy increases the quality of patient's life, many studies have been conducted on this subject. Although electroneuromyography (ENMG) is the most important aid of the clinician in the diagnosis of DPN, it is insufficient in cases such as small fiber neuropathy or early stages of neuropathy[4]. When the patient has complaints and the results of routine nerve conduction studies are normal, it is still necessary to detect and prevent neuropathy at early stage.

With this purpose some studies were designed to demonstrate the neuropathy by calculating ratios of lower – upper extremity values like sural to radial amplitude ratio, in regard to the length dependent involvement[5]. Some used additional methods like cutaneous silent period, nerve excitability tests[6, 7].

F-wave studies provide additional information about the proximal segment of the peripheral nerve. And also due to the distance that the electric stimulation travels it seems to be more sensitive than routine nerve conduction studies in detecting neuropathy. So, it was used for detecting many neuropathies including diabetic neuropathy[8] and was demonstrated to be beneficial even when routine nerve conduction studies were within normal limits.

Some studies evaluated extra methods using F-wave study by calculating motor latency / F latency ratios[9], motor conduction velocity/ F-wave conduction velocity ratios[10], or by comparing the distal and proximal segment of peripheral nerve F-waves[11].

The aim of this study is to evaluate the sensitivity of lower/upper extremity F latency ratios in detecting early neuropathy in patients with diabetic neuropathic pain even when their conventional nerve conduction studies and F-wave latencies were both within normal limits.

Methods

This study was performed in Pamukkale University Department of Neurology between June 2020 and August 2020. 88 participants were included in the following groups: 44 patients (13 men and 31 women) with diabetes mellitus and neuropathic pain were in the diabetic neuropathic pain (DNP) group, and 44 non-diabetic participants (15 men and 29 women) without neuropathic pain were in the control group. All the research participants were between the age of 30 and 69 years old. Full neurological examination was performed on all patients. Patients with normal neurological examinations were included in the study. Controls with any positive or negative neuropathic pain symptoms were excluded. Also, all other conditions could cause neuropathic pain were ruled out.

The study was approved by the Clinical Research Ethics Committee of Pamukkale University. Informed consent was required from all participants included to the study.

Ulnar motor and sensory, median motor and sensory, tibial motor, peroneal motor and sural sensory nerves conduction studies were performed bilaterally. If these values were within limits then right tibial and right ulnar F responses were studied. The individual was included to the study if F-wave minimal latencies both were also within the normal limits. All patients included in DNP group had neuropathic pain diagnosed by using Douleur Neuropathique 4 Questionnaire (DN4). Patients included in the control group had no neuropathic complaints.

Medelec Nicolet EDX Synergy EMG device was used in the study. The tibial motor nerve was recorded from the Abductor Hallucis Longus (AHL) muscle and fibular motor nerve was recorded from Extensor Digitorum Brevis (EDB) muscle. The median nerve was recorded from Abductor Pollicis Brevis (APB) muscle and the ulnar motor nerve from Abductor Digiti Minimi (ADM) muscle. The same muscles at the conduction studies were used for tibial and ulnar F-wave latency. Minimal F latency was measured from minimum 20 stimulus and the values above 80% persistence were recorded. All motor nerve and F-wave recordings were studied with surface electrodes and conventional supramaximal stimulation. Sural nerve was studied with bar electrode and ulnar sensory nerve was studied with ring electrodes. Sural sensory nerve was recorded from the posterior of the lateral malleolus and was stimulated 14 cm proximally of the dorsal midcalf. Ulnar sensory nerve was recorded from proximal and distal interphalangeal joints of 5th finger and stimulated from the wrist. Upper and lower extremity F-wave latency ratio, sural and ulnar sensory velocity and amplitude ratios were calculated and recorded. The data analysis was performed with SPSS software version 25.0. Categorical data were compared with chi-square test and

T test. Mann–Whitney U test were used to compare group means.

Results

44 diabetic patients with neuropathic pain (DNP) and 44 healthy controls were included to our study. 31 patients in the DNP group were female (70.5%) and 13 were male (29.5%). In the control group 29 participants (65.9%) were female, 15 were male (34.1%). The mean age was 56.8 ± 9.12 years in the DNP group and 53.4 ± 13.06 in the control group. There was no any significant difference in age and gender characteristics between the groups. The demographical and clinical features are given in **Table 1.**

Table 1. *Demographical features*

Characteristics	DNP Group (n=44)	Control Group (n=44)	p value
Age (mean ± SD),	56.84 ± 9.12	53.43 ± 13.06	0.647
Gender (n, %)			
Female	31 (70.5%)	29 (65.5%)	0.160
Male	13 (29.5%)	15 (35.5%)	

DNP: diabetic neuropathic pain

All participants were questioned for DN4 scale. The mean score of all 44 participants in the control group was 0.25. All 44 participants' DN4 score in the diabetic group was under 4. The mean DN4 score of the diabetic group was 0.48. The difference between the two groups was statistically insignificant (p>0.05). The duration since the diagnosis of diabetic patients included in the study ranged from 1 to 10 years. Average duration since diagnosis was 4.25 year.

There was no significant difference between the motor nerve conduction parameters of the groups. The mean sural sensory nerve action potential (SNAP) amplitude was 11.27 ±6.5 μV in the DNP group, and 13.36 ± 6.45 μV in the control group. The difference was not significant (p>0.05). The mean ulnar SNAP amplitude was 14.37 ± 6.84 μV in the DNP group and 15.46 ± 5.6 μV in control group, the difference was not significant. (p>0.05). We calculated the sural to ulnar SNAP amplitude ratio which was 0.91 for the DNP group and 0.94 for the control group. The difference between the groups was not significant (p>0.05). The mean sural sensory nerve conduction velocity (NCV) was 46.96 m/s ± 8.17 in the DNP group and was 50.00 ± 8.79 m/s in the control group. There was no any significant difference between two groups (p>0.05). The mean ulnar sensory NCV values were 44.8 m/s ± 8.36 in DNP and 45.2 ± 6,23 in the control group. The difference was not significant (p>0.05). The sural to ulnar sensory NCV ratio was 1.09 for the DNP group and 1.13 for the control group, and there was no any significant difference between the two groups (p>0.05).

The mean F-wave minimal latency (FWML) was 54.55 ± 4.43 milliseconds (ms) and 27.12 ± 2.82 ms for tibial and ulnar nerves in the DNP group. The mean FWML values were 49.28 ± 3.52 ms for tibial nerve and 26.8 ± 2,35 ms for ulnar nerve in the control group. The difference between the groups was only statistically significant for the tibial nerve FWML, but not for the ulnar nerve FWML ($p < 0.001$, $p = 0.769$). The tibial to ulnar FWML ratio was 2.01 in the DNP group and 1.84 in the control group. The difference was significant ($p < 0.001$). The electrophysiological findings are given in **Table 2**.

Table 2. *The electrophysiological findings of the groups*

NCS	DNP Group (n=44) Mean ± SD	Control Group (n=44) Mean ± SD	p-value
Sural nerve SNAP amplitude (μV)	11.27 ± 6.5	13.36 ± 6.45	0.072
Ulnar nerve SNAP amplitude (μV)	14.37 ± 6.84	15.46 ± 5.6	0.022
Sural/ulnar amplitude ratio	0.91 ± 0.77	0.94 ± 0.54	0.348
Sural nerve sensorial velocity (m/s)	46.96 ± 8.17	50.66 ± 8.79	0.146
Ulnar nerve sensorial velocity (m/s)	44.85 ± 8.36	45.22 ± 6.23	0.732
Sural/ulnar velocity ratio	1.09 ± 0.24	1.13 ± 0.19	0.244
FWML tibial nerve (ms)	54.55 ± 4.43	49.25 ± 3.52	0.0001*
FWML ulnar nerve (ms)	27.12 ± 2.82	26.8 ± 2.35	0.769
FWML tibial/ulnar ratio	2.01 ± 0.21	1.84 ± 0.14	0.0001*

NCS: nerve conduction studies, FWML: F wave minimal latency, m/s: meter/second, ms: milisecond, SNAP: sensory nerve action potential, μV: microvolt

*p< 0.0005

Discussion

Diabetes mellitus is the most common cause of neuropathy and neuropathic pain worldwide. It may cause all types of neuropathies but the most frequent type is distal, symmetrical neuropathy (DSP). Neuropathic pain is one of the main factors effecting the patients quality of life and could be obvious in every period of diabetes even in prediabetic stage.

Routine nerve conduction studies may be within normal limits in the early stages of neuropathy or if small fiber involvement is predominant which causes difficulties in detecting neuropathy even when the patients suffer from neuropathic pain.

Studies to demonstrate small fiber involvement like biopsy or laser evoked potentials are expensive and hard to access. So many studies were designed to detect the early stage neuropathy in patients whose routine nerve conduction studies were within normal limits.

Some of these studies focused on additional methods like autonomic tests[12], cutaneous silent period testing[6] and nerve excitability properties[7, 13]. Some others tried to compare the ratios of lower and upper extremity nerve conduction values based on the fact that length dependent involvement is expected in DSP[14, 15].

F-wave responses reflect the action potentials triggered by the stimulation on peripheral nerve which cross the way to nerve root and come all the way back after stimulating anterior horn cells. So it may give additional information about the proximal part of the nerve. Also, as it crosses the peripheral part of the nerve almost twice it may also help to make clear the underlying neuropathic process in the peripheral nerve. These observations supported the idea to use F-wave responses to detect early neuropathy in many different neuropathies even in diabetic polyneuropathy[16]. Moreover, some studies mentioned that tibial or fibular F-wave studies might be the most sensitive tests in detecting early diabetic polyneuropathy[17].

A retrospective study compared the sensitivities of routine nerve conduction studies and F-wave studies for detecting neuropathy in diabetic neuropathic pain[18]. Examining the records, they found out that the prolongation of F-wave latencies were more obvious than any other prolongation of routine nerve conduction studies. And this finding was more obvious in tibial F responses (95%) than in ulnar F responses (82%). They mentioned that these results suggested that F-wave studies were more suited to predict than routine nerve conduction studies in detecting DPN. They also mentioned that, as it was predictable in a length dependent polyneuropathy, lower extremity (tibial) F-wave studies might be the most suitable choice to detect early DPN. Another study focused on the comparison of diabetic neuropathy and the control group by examining the F-waves in the proximal and distal segments of the same peripheral nerve[11].They demonstrated that F latencies were prolonged in both distal and proximal segments of the nerve which suggests that the involvement due to polyneuropathy affects the whole peripheral nerve. They also mentioned that proximal to distal F latency ratio was smaller in the diabetic group which supported the idea that the involvement was more predominant in the distal segment of the nerve. A study designed to compare the motor conduction velocities and F-wave conduction velocities among the diabetic neuropathic, non-diabetic neuropathic and control groups[10], mentioned that motor conduction velocity / F-wave conduction velocity ratio might be significant even when there is no significant difference between diabetic and control groups. And also this ratio could be used for the differential diagnosis of diabetic neuropathy. Another study aimed to compare the diabetic and the control groups[9] reported that distal motor latency and F-wave latency seemed to be prolonged in the diabetic group but the difference was significant only when the motor /F-wave latency was calculated for some peripheral nerves.

When these and similar studies are reviewed, data suggests that F-wave studies are useful for detecting early diabetic neuropathy and this is more sensitive if lower extremities are studied or compared with upper extremities. Another fact about the F response studies: if the F-wave studies are not within normal limits it supports the underlying neuropathic process; but if it is within normal limits, the only way to demonstrate the pathology is to compare the values of different groups. But it can not help to determine the pathology by using an individual's own values. For this purpose we included individuals whose routine nerve conduction and F-wave response studies were within normal limits. First of all we wanted to see the difference among the groups if it existed. The only significant difference among the groups was between the tibial F wave latencies. This supported the idea that even when the individuals' F-wave latencies were within the normal limits, the comparison between the groups might be useful to demonstrate the difference among the groups. This finding was compatible with the studies suggesting that F responses are suitable for detecting early neuropathy in diabetic neuropathic pain. But sometimes, as in our study, where all individuals' F wave latencies were

within normal limits, this difference could only be demonstrated by comparing different groups' values. To comment in case of individuals' values, alternative laboratory normal limits are needed for different cases such as diabetes.

Also, with respect to previous studies and the nature of DSP, our results suggested that the difference between tibial F responses was significant, while ulnar was not. When we compared the lower / upper extremity values between the groups, we found that the tibial / ulnar F-wave latency values were significantly high. This finding also supports the idea that the underlying process is predominant in lower extremity and distal segments.

Our findings suggests that the ratio between lower / upper extremity F-wave latencies would be useful for both detecting early neuropathic process and for demonstrating that the underlying process is predominantly distal. Further studies examining the repeatability and the utility of this ratio may provide additional information.

As mentioned above for F latency values, by using this ratio, demonstrating a difference could only be possible when different groups' values were compared. On the other hand, this ratio is individually calculated and reflects a number which have a smaller range than F latency values, so further studies may also help to discuss a possibility for a future warning cut-off value that suggests early neuropathy based on each individuals own values.

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