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CLINICAL AND ELECTROPHYSIOLOGICAL SIGNS OF DIABETIC POLYNEUROPATHY – EFFECT OF GLYCEMIA AND DURATION OF DIABETES MELLITUS

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SUMMARY – Diabetic polyneuropathy occurs in around 50% of diabetic patients. Its pathophysiological mechanism is not completely clarified and major occurrences boil down to the change in neural phenotype and vasa nervorum. As glucose neurotoxicity has been suggested by plenty of evidence, the aim of the study was to assess the effect of glycemia on the severity of diabetic polyneuropathy. Considering that some practical experiences point to serious complications in patients suffering from diabetes of shorter duration, another aim was to assess the effect of diabetes duration on the severity of related neuropathy. Clinical and electromyoneurographic examinations were performed in 100 patients with diabetic polyneuropathy free from any laboratory signs of renal failure. The effect of HbA_{1c} value and duration of disease on clinical symptoms, signs and electrophysiological indicators of polyneuropathy was analyzed. Study results indicated that 78% of patients with diabetic polyneuropathy did not have well-regulated glycemia. Diabetes duration was associated with a growing number of sensory symptoms, among which the sensation of pain similar to electric shock was present in 63% of patients. In addition, it also had negative impact on the sensory and motor nerve conduction velocity. HbA_{1c} influenced the whole range of electrophysiological indicators of diabetic polyneuropathy.

Key words: *Diabetes mellitus; Hemoglobin glycosylated A_{1c}; Signs and symptoms; Diabetic neuropathy; Electromyography*

Introduction

It is known that there is a multiple (up to four times) increase of glucose concentration in the blood of patients with diabetes mellitus (DM), which is then associated with glucose neurotoxicity. Recent studies show that diabetic neuropathy will begin to develop at significantly lower levels of glycemia than it was thought previously[1]. The understanding of the pathophysiological activities in the neurons of diabetic patients gives way to new possibilities of therapeutic interventions to ensure better quality of life for these patients. The example can be found in the proof from animal testing of the effect of poly adenosine ribose polymerase (PARP) inhibitors on the control of the motor and sensory neural fiber velocity reduction[2], as well as the use of inhibition of the 12/15 lipoxygenase mediating in the pathological metabolism of amino acids during nitrous stress induced by hyperglycemia[3]. The biomarkers are used that correlate to clinical presentation of polyneuropathy and allow for monitoring its progression, such as increased level of γ-glutamyltransferase (GGT) and nitrates[5,6]. The pathogenesis of diabetic neuropathy is still controversial and not completely understood. Multiple trigger-

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ing factors are mentioned, such as metabolic, vascular or autoimmune disorders, oxidation and nitrous stress, as well as deficiency of neurohumoral growth factors[5,6]. Prolonged stress hyperglycemia in patients with ischemic stroke increases even the mortality rate of nondiabetic patients[7]. The protective activity of the blood-brain barrier is absent on peripheral nerves, and the abnormally high level of the inserted insulin-dependent intracellular glucose activates various metabolic paths that damage the myelin and axon and result in neuron degeneration[6,8,9]. This leads to complete breakdown of neuron function, loss of the protective function of senses, trauma insensitivity, and poorly treated wounds resulting in amputations. Hyperglycemia damages the microcirculation structure and function, as well as the blood-brain barrier, which results in ischemia[10,11]. The toxicity of glucose leads to damage to axon regeneration, ruins the excitability and conduction of neural impulses, and generates pain of the allodynia or hyperalgesia type[6]. Neuropathic pain demands treatment with antidepressants and anticonvulsants. Sometimes, poly-pharmacotherapy is needed[12,13]. It is known that the current blood glucose level does not reflect the constant value of glycemia that can be responsible for the pathophysiological processes. The value of glycosylated hemoglobin is considered to be a good indicator of the average blood sugar levels. It is recommended to maintain it at <6.5% by therapeutic measures. We estimated the effect of hemoglobin A_{1c} (HbA_{1c}) values on clinical and electrophysiological indicators of polyneuropathy in DM patients. Since, according to some studies, HbA_{1c} does not always correlate with the level of polyneuropathy, it was also investigated whether the duration of DM contributed to the accumulation of peripheral neurologic damage. It was considered interesting since there is no unique attitude in the literature towards the impact of DM duration on the manifestation and intensity of electrophysiological and clinical signs of polyneuropathy[15-17].

Patients and Methods

The study included 100 patients with type 2 DM treated at Diabetes Center, Vukovar General Hospital, from January to July 2009. There were 59 women and 41 men, average age 61 (range, 29-75) years and suffering from DM for 2 to 35 (average, 11) years. Patients with signs of impaired renal function, determined by increased laboratory values of creatinine clearance, urea and creatinine, patients regularly taking alcohol drinks, those suffering from systemic and malignant diseases, and patients with clinical and electrophysiological signs of compressive mononeuropathies (e.g., carpal canal syndrome) were excluded.

Patient HbA_{1c} value was recorded and then each patient was classified according to glycemia regulation as measured by HbA_{1c} into one of the following groups: "good" if HbA_{1c} <6.5%, "acceptable" if HbA_{1c} ≤7.0%, and "poor" if HbA_{1c} >7.0%. The HbA_{1c} values obtained by the method of microcolon determination were taken as reference values[1].

The existence of clinical symptoms of polyneuropathy that were integrated and evaluated by use of the Neuropathy Total Symptom Score (NTSS-6), a scale usually employed for this purpose, was recorded in all study patients. The existence of 6 sensory symptoms was recorded, adding one point for the existence of a single symptom (up to a maximum of 6 points): deep pressuring, kneading pain; burning pain in feet and legs; pinching and pricking pain; being benumbed; loss of senses in legs ("numbness"); sudden harsh pain resembling electric shocks that come in waves lasting for a couple of seconds to a minute; hypersensitivity of legs to touch or when the legs touch the ground while walking.

Clinical signs of polyneuropathy were diagnosed in all patients: crude muscular strength (CMS) in legs and arms, trophics of feet and hand muscles, muscle-tendon reflex (MTR), touch sensation in feet and lower legs as well as in hands and forearms, and vibration detection by means of tuning fork[19].

All patients underwent detection electromyography (EMG) and neurographic analysis including measurement of conduction velocity as the so-called "gold standard" for assessment of polyneuropathy (conduction velocity of motor fibers of ulnar nerve, median nerve, deep peroneal nerve, tibial nerve, conduction velocity of sensory fibers of ulnar nerve, median nerve, sural nerve), determination of distal latency, minimal latency of F-wave in legs and arms, as well as the amplitudes of sensory potentials and muscular response[20,21]. All patients were examined by the Synergy model ISO-1000VA electromyoneurography (EMNG) instrument.

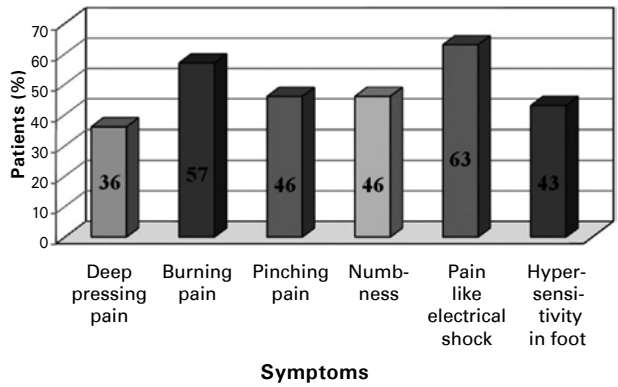
Detection electromyography was carried out by use of pin-electrodes. The degree of polyneuropathy was assessed according to the degree of denervation in muscles of feet and lower legs as well as of hands and forearms. Mildly reduced pattern with milder reduction in motoneurons was designated as mild polyneuropathy, the pattern with moderate reduction in motoneurons was designated as moderate polyneuropathy, whereas the pattern with severe reduction was designated as severe polyneuropathy. Neurographic analyses were performed by use of standard techniques. The mean temperature of the room in which the electrophysiologic analysis was conducted was 23 °C. Skin temperature in patient feet ranged from 26 °C to 28 °C, and in hands from 30 °C to 32 °C.

Each patient was given the information form explaining the procedure and the informed consent form to sign, in line with the principles and standards of Good Clinical Practice, which includes assurance of personal integrity and welfare of patients in accordance with the Declaration of Helsinki.

Statistical analysis was carried out using the Statistica for Windows, version 6.0 (StatSoft, Inc. Tulsa, OK) statistical package. For description of continuous variables, arithmetic mean, standard deviation and range were used if variables were of normal range or median, and otherwise, interquartile range and range. Categorical variables were presented as frequency (%). The χ^2-test was used to compare categorical variables among the groups. To assess the correlation between specific variables, regression analysis (linear, Spearman's Rank Correlation) was applied, i.e. χ^2-test depending on the type of specific variables. Discrimination multivariate analysis by use of step-added variables (forward stepwise) was used for identification of independent predictors of polyneuropathy as well as electrophysiological parameters that best represented differentiation between polyneuropathy subgroups by the degree of severity. The level of statistical significance was set at $P<0.05$.

Results

Three-quarters (78%) of our patients had poorly regulated glycemia with HbA_{1c} values over 7%; 16% had acceptably regulated glycemia with HbA_{1c} less than or exactly 7%; and only 6% had well regulated glycemia with HbA_{1c} less than 6.5%.

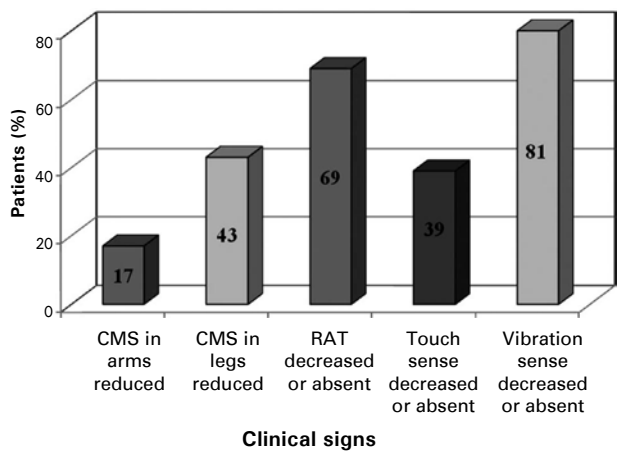


NTSS-6 = Neuropathy Total Symptom Scores 6

Fig. 1. Prevalence of individual clinical symptoms of polyneuropathy in patients with diabetes mellitus according to NTSS-6.

The most common clinical symptom of sudden harsh pain resembling electric shocks was recorded in 63% of study patients; 57% of patients complained of annealing pain in legs, whereas deep pressuring pain of the allodynia type was recorded in the lowest percentage of patients (36%). Figure 1 shows the prevalence of clinical symptoms of polyneuropathy in our patients according to NTSS-6.

The most prominent clinical sign was lowered or absent sensation of vibration (81%), followed by lowered or absent reflex of Achilles tendon (RAT) in legs (69%), whereas lowered crude muscle strength in arms was the least common, recorded in 17% of cases (Fig. 2).



CMS = crude muscular strength; RAT = reflex of Achilles tendon

Fig. 2. Prevalence of clinical signs of polyneuropathy in patients with diabetes mellitus.

Table 1. Classification of patients according to duration of disease and severity of diabetic polyneuropathy

Degree of polyneuropathy (according to the degree of denervation detected in the muscles of arms and legs)	Disease duration (yrs) χ±SD	Number of patients
Mild	7.93±6.06	25
Moderate	9.78±5.70	45
Severe	15.90±8.72	30
χ±SD for disease duration	11.15±7.48	100

P<0.0005

The duration of DM was found to significantly influence the severity of denervation detected in the muscles of arms and legs. Table 1 shows the severity of polyneuropathy to have increased with longer duration of diabetes (*P*<0.0005); 25 patients with mild polyneuropathy and low level of denervation had an average diabetes duration of 8 years (7.93), whereas in 30 patients the development of severe polyneuropathy characterized by severe denervation took 16 (15.9) years. The signs of moderate polyneuropathy characterized by moderate loss of motoneurons were present in almost half of our patients (45%), 30% had severe polyneuropathy with a higher grade of axon damage, and 25% had mild polyneuropathy.

A significant link was found between the duration of DM and the intensity of clinical symptoms and signs of polyneuropathy; according to the NTSS-6 scale, a higher sum of sensory symptoms was recorded in patients with longer duration of DM. They experienced higher hypersensitivity to touch in feet, lowered GMS of arms and legs, lower or absent RAT reflex, lower sense of touch and vibration compared to the patients with shorter DM duration. Elderly patients were not recorded with a significantly higher sum of sensory symptoms (NTSS-6) compared to young patients.

The patients with longer DM duration had slower conduction velocity of motor fibers in arms and legs, i.e. motor nerve conduction velocity (MNCV) of ulnar nerve, peroneal nerve and tibial nerve, as well as lower sensory nerve conduction velocity (SNCV) of median nerve in arms and of sural nerve in legs. Almost all indicators tested in relation to DM duration yielded a mild biologic correlation (Table 2).

Patients with higher HbA_{1c} values suffered from severe polyneuropathy assessed according to the severity of denervation or axon damage in arms and legs; in patients suffering from mild polyneuropathy (mild level of denervation), moderate polyneuropathy (moderate level of denervation) and severe polyneuropathy, the mean HbA_{1c} value was 7.79%, 8.43% and 9.09%, respectively.

Table 3 shows that patients with higher levels of HbA_{1c} also had significantly worse neurographic parameters of diabetes polyneuropathy: they had lower conduction velocity of motor fibers of peroneal and

Table 2. Influence of disease duration on electrophysiological parameters in patients with diabetic polyneuropathy (N=100)

	Total patients	Spearman	t (N-2)	*P* value
Disease duration and polyneuropathy – degree of denervation	100	0.389	4.169	0.000
Disease duration and MNCV of ulnar nerve	100	-0.252	-2.575	0.012
Disease duration and MNCV of peroneal nerve	100	-0.286	-2,960	0.003
Disease duration and MNCV of tibial nerve	100	-0.290	-3.110	0.002
Disease duration and SNCV of median nerve	100	-0.214	-2.166	0.033
Disease duration and SNCV of sural nerve	100	-0.213	-2.156	0.033
Disease duration and peroneal nerve distal latency	100	-0.279	-2.877	0.004
Disease duration and amplitude of peroneal nerve evoked muscle response	100	-0.369	-3.931	0.000

MNCV = motor nerve conduction velocity; SNCV = sensory nerve conduction velocity; *P*<0.05

Table 3. Influence of glycosylated hemoglobin values (HbA_{1c}) on electrophysiological parameters in diabetic patients (N=100)

	Total patients	Spearman	t (N-2)	*P* value
HbA_{1c} and ulnar nerve distal latency	100	-0.237	-2.414	0.017
HbA_{1c} and MNCV of peroneal nerve	100	-0.217	-2.197	0.031
HbA_{1c} and peroneal nerve distal latency	100	-0.346	-3.648	0.000
HbA_{1c} and amplitude of peroneal nerve evoked muscale response	100	-0.233	-2.372	0.010
HbA_{1c} and CMAP of peroneal nerve	100	-0.242	-2.465	0.015
HbA_{1c} and MNCV of tibial nerve	100	-0.239	-2.439	0.016
HbA_{1c} and tibial nerve distal latency	100	-0.260	-2.667	0.000
HbA_{1c} and amplitude of tibial nerve evoked muscale response	100	-0.228	-2.319	0.022
HbA_{1c} and CMAP of tibial nerve	100	-0.246	-2.508	0.014
HbA_{1c} and F-wave in arms	100	0.222	2.251	0.027
HbA_{1c} and F-wave in legs	100	0.300	3.115	0.002
HbA_{1c} and SNCV of ulnar nerve	100	-0.337	-3.548	0.000
HbA_{1c} and amplitude of ulnar nerve evoked sensory potential	100	-0.217	-2.203	0.020
HbA_{1c} and SNCV of sural nerve	100	-0.245	-2.498	0.014

MNCV = motor nerve conduction velocity; SNCV = sensory nerve conduction velocity; CMAP = compound motor action potential; $P<0.05$

tibial nerve (MNCV), and of sensory fibers (SNCV) of ulnar and sural nerve compared to DM patients with lower HbA_{1c}. Patients with higher levels of HbA_{1c} had longer distal latency of peroneal, ulnar and tibial nerves, and lower amplitude of evoked muscle response after stimulation of peroneal and tibial nerve, as well as lower amplitudes of the compound motor action potential (CMAP) after stimulation of peroneal and tibial nerves. Patients with higher levels of HbA_{1c} had longer wave latencies in arms and legs, and lower amplitude of evoked sensory potential after stimulation of fibers of ulnar nerve.

Table 4 shows the most sensitive electrophysiological parameters, which were significantly worse in the groups of patients with poorly regulated glycemia (HbA_{1c} ≥7%): MNCV and SNCV of ulnar nerve, SNCV of sural nerve and middle latencies of F wave in arms and legs. For example: the middle SNCV of sural nerve in the group with best regulated HbA_{1c} was 39.45 m/s; in the group with acceptably regulated HbA_{1c} it was slower than 34.09 m/s, and in the group of poorly regulated diabetes with HbA_{1c} >7% it was slowest, 29.74 m/s (P=0.02).

Discussion

In three-quarters of our patients, glycemia was not well regulated. This result is not in discrepancy with the European (Code 2 – The cost of diabetes in Europe) and American data (NHANES, National Health and Nutrition Examination Survey), according to which almost two-thirds of patients do not reach the target level of HbA_{1c} of 6.5% or less[22].

The findings of the most prominent symptoms of polyneuropathy in patients with DM are different, making it difficult to determine its diagnosis, severity and progression. According to Rubino *et al.*, the most common clinical sign of polyneuropathy in patients with DM was the feeling of pricking, as recorded in France, Italy and Spain; in Great Britain, numb-

Table 4. Influence of HbA_{1c} regulation categories on electrophysiological parameters in patients with diabetic polyneuropathy

Electrophysiological parameters	HbA_{1c} value %			*P* value
	Good <6.5 χ±SD	Acceptable ≤7.0 χ±SD	Poor >7.0 χ±SD	
MNCV of ulnar nerve (m/s)	59.13±4.48	51.47±7.53	50.9±7.74	0.04
SNCV of ulnar nerve (m/s)	36.41±9.24	34.60±8.23	30.44±7.21	0.03
SNCV of sural nerve (m/s)	39.45±3.28	34.09±11.50	29.74±9.74	0.02
F-wave in arms (ms)	27.61±1.66	28.43±2.81	30.56±3.83	0.02
F-wave in legs (ms)	40.91±21.44	50.68±3.06	54.86±11.9	0.01
Total patients N=100	6	16	78	

MNCV = motor nerve conduction velocity; SNCV = sensory nerve conduction velocity; $P<0.05$

ness was the leading symptom[23]. The most prominent clinical sensory symptom in our patients was pain resembling electric shock. The vibration disorder in legs is the sign of such neuropathy in which ulcerations in legs will appear soon, and which is the most important clinical sign according to Kanji *et al.*[24]. The vibration disorder in legs was experienced by 81% of our patients, while Young *et al.* demonstrated this disorder to show positive correlation with the scale of neurologic disorders in patients with diabetic polyneuropathy[25]. De Wytt *et al.* recommend the use of neurographic methods as the "gold standard" to specify the diagnosis[19], whereas Liu *et al.* claim that electrophysiological changes do not always correlate with the clinical signs of polyneuropathy[26]. Said *et al.* (2008) conclude that detection of pain and sense and temperature disorders is the best method for its detection, since non-myelinated fibers sustain damage earlier, whereas motor deficiency, which can be detected by clinical examination and EMNG testing, appears later[27]. Since early detection of the sense disorder and pain is not easy in practice, it is more acceptable for us to apply the experiences reported by Karsidag *et al.* (2005), which confirm that testing of electrophysiological parameters is very reliable in the detection of early neuropathy, even in patients with stable neurologic status[17].

In a study published at the beginning of 2010, the authors report that, in order to specify the diagnosis, the sensitivity of vibration sensation testing needs to be 86%, the scale of neurologic examination (Diabetic Neuropathy Examination, DNE) 85%, and the study of conduction velocity 71%[28]. Keeping this in view, we consolidated the clinical symptoms, clinical signs and electrophysiological parameters when evaluating our patients and concluded that it was the most convincing way of early detection of polyneuropathy and evaluation of its severity.

Although the course of diabetes is rather individual and depends on different disease control factors, hereditary factors and environmental influences, De Block *et al.* conclude, based on the research of the factors possibly influencing diabetic neuropathy and retinopathy, that the duration of diabetes and HbA_{1c} are the most important and most influential ones[29]. Our study was directed towards finding the symptoms, signs and electrophysiological parameters of polyneuropathy that are influenced by these measurable factors: HbA_{1c} and duration of diabetes. Patients with longer duration of DM had a greater number of sensory disorders; they had more often the feeling of feet hypersensitivity generated by damage to thick myelinated fibers that transfer the sense of vibrations. The duration of disease also influences the neuropathy pain to appear more often, thus lowering the patient quality of life[30]. All clinical signs of polyneuropathy appear more often in patients with longer DM duration; they develop weakness in legs and arms more often, their walk is unstable, and the EMNG testing reveals severe loss of peripheral motoneurons due to axon damage, as well as the reduced conduction velocity of the peripheral motor and sensory nerves due

to the loss of myelin. It appears that, in patients with DM, polyneuropathy will appear sooner that retinopathy. According to De Block *et al*., the patients who develop diabetic complications in terms of retinopathy have been suffering from DM for 25 years on an average[29]. On the other hand, our patients with mild polyneuropathy had suffered from DM for 8 years on an average, and those with severe neuropathy for 16 years. Besides, retinopathy is to appear less frequently than polyneuropathy. According to a study conducted in Sweden, retinopathy developed in 29% and neuropathy in 67% of 156 patients suffering from type 2 DM for 7 years on an average[31].

In our patients, the values of HbA_{1c} showed no statistically significant correlation with the significance and frequency of sensory symptoms, and nearly no correlation with the occurrence of clinical signs of polyneuropathy. Only the lower or absent sense of vibration correlated significantly with the higher values of HbA_{1c} in 88% of the patients with poorly regulated glycemia. A study from 1998 showed the severity of diabetic polyneuropathy to be related to poor glycemia control, having in mind that the HbA_{1c} cut-off value discriminating good and poor glycemia control was set to less or more than 9%[32]. In our study, the higher levels of glycemia determined by HbA_{1c} influenced the reduction of conduction velocity of all the measured motor and sensory fibers in legs, and they worsened other electrophysiological parameters in legs (F wave latency, distal latency, etc.). Reports of prominent denervation on EMG in patients with higher levels of HbA_{1c} show that not only the myelin of peripheral nerves was damaged, but there was also axonal damage. In our categories of patients with acceptably and poorly regulated HbA_{1c}, we observed a statistically significant worsening of the F wave latency and conduction velocity of sensory fibers in arms and legs as compared to patients with well-regulated HbA_{1c}. This proves that these are the most sensitive electrophysiological indicators of the effect of glycemia regulation on the severity of polyneuropathy and therefore very convenient for its monitoring. This is consistent with other authors who emphasize the value of F wave and conduction velocity of sensory nerves in diagnosing and monitoring the progression of polyneuropathy in patients with DM[21,33].

In conclusion, the higher values of glycemia determined by HbA_{1c} are a significant predictor of electrophysiological changes of peripheral nerves in case of diabetic polyneuropathy, and the longer presence of type 2 DM is the most convincing factor that, besides causing worsening of electrophysiological parameters in peripheral nerves, it also contributes to greater prominence of uncomfortable sensory symptoms and disabling clinical signs.

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Sažetak

KLINIČKI I ELEKTROFIZIOLOŠKI ZNACI DIJABETIČNE POLINEUROPATIJE – UTJECAJ GLIKEMIJE I TRAJANJA ŠEĆERNE BOLESTI

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Dijabetična polineuropatija javlja se u oko 50% bolesnika s dijabetesom. Njezin patofiziološki mehanizam nastanka nije u potpunosti razjašnjen, a glavna zbivanja svode se na promjenu neuralnog fenotipa i vasa nervorum. Kako postoje mnogi dokazi o neurotoksičnosti glukoze, cilj studije bio je ispitati utjecaj glikemije na težinu dijabetične polineuropatije. Budući da neka iskustva u praksi upućuju na prisutnost teških komplikacija u bolesnika koji imaju dijabetes kraćeg trajanja, ispitao se utjecaj dužine trajanja dijabetesa na težinu pridružene neuropatije. Klinički i elektromioneurografski je ispitano 100 bolesnika s dijabetičnom polineuropatijom. Uvjet je bio da bolesnici nemaju laboratorijske znakove bubrežnog oštećenja, a analizirao se utjecaj vrijednosti HbA_{1c} i trajanja bolesti na kliničke simptome, znakove i elektrofiziološke pokazatelje polineuropatije. Rezultati su pokazali da 78% bolesnika s dijabetičnom polineuropatijom nema dobro reguliranu glikemiju. Trajanje dijabetesa utječe na pojavu većeg broja senzornih simptoma, od kojih se osjećaj boli poput udara struje javlja u 63% bolesnika, a utječe i na pogoršanje brzine provodljivosti senzornih i motornih živaca. HbA_{1c} utječe na čitav niz elektrofizioloških pokazatelja dijabetične polineuropatije.

Ključne riječi: *Dijabetes melitus; Hemoglobin glikozilirani A_{1c}; Simptomi i znakovi; Dijabetična neuropatija; Elektromiografija*