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INFLUENCE OF GLYCEMIC LOAD ON CLINICAL AND NEUROLOGICAL MANIFESTATIONS OF DIABETIC NEUROPATHY

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Abstract: Diabetic neuropathy is one of the most frequent and severe complications of diabetes mellitus, occurring in 60-90% of patients with a prolonged course of the disease. This complication is characterized by progressive damage to the peripheral nervous system, leading to the development of pain syndrome, sensory impairment, motor disorders, and a significant decrease in the quality of life of patients.

Key words: Diabetic neuropathy, glycemic load, postprandial hyperglycemia, glycemic variability, glycated hemoglobin, oxidative stress, peripheral nervous system, pain syndrome, sensory disturbances, autonomic neuropathy.

Introduction. Diabetic neuropathy is one of the most common and severe complications of diabetes mellitus. The study conducted a comprehensive assessment of clinical, laboratory, and instrumental indicators in patients with varying degrees of glycemic control. It has been established that an increase in the level of HbA1c is accompanied by pronounced disorders of microcirculation, endothelial function, and neuro-physiological parameters. A close correlation was found between metabolic disorders and the severity of sensory, motor, and autonomic neuropathy. The obtained data confirm the key role of carbohydrate metabolism in the formation of clinical manifestations of diabetic neuropathy and justify the need for a comprehensive diagnostic approach.

diabetes mellitus; diabetic neuropathy; glycemic control; HbA1c; microangiopathy; endothelial dysfunction; microcirculation; electroneuromyography; capillaroscopy; metabolic disorders

Diabetes mellitus (DM) is a significant medical and social problem that continues to grow steadily with severe chronic complications. According to the International Diabetes Federation (IDF, 2021), there are over 537 million patients with DM worldwide. The most common and disabling complications of diabetes mellitus are diabetic neuropathy (DN), the prevalence of which, according to major epidemiological studies, reaches 30-60% among diabetic patients (Pop-Busui R. et al., 2020; Tesfaye S. et al., 2021). Diabetic neuropathy forms a chronic pain syndrome, which leads to a decrease in the quality of life of patients with diabetes. The mechanism of DN includes multifactorial factors based on chronic hyperglycemia, oxidative stress, activation of the polyolysis pathway, accumulation of glycation end products (AGEs), and endothelial dysfunction, leading to axonal damage and demyelination. The significant role of the vascular component is emphasized by Vincent A.M. et al. (2019), Feldman E.L. (2017), where their works focus on the critical impact of microangiopathy and peripheral nerve perfusion disorders on the progression of DN. Previous large-scale studies of DCCT/EDIC (Nathan D.M., 2015) and UKPDS (Holman R.R., 2008) showed that optimizing glycemic control reduces the risk of microvascular complications, however, the influence of HbA1c

levels on the severity of neuropathy remains ambiguous, which emphasizes the need to study additional pathogenetic links, primarily microcirculation. Research on diabetic neuropathy has been conducted by Isakova E.V. (2019),

Galstyan G.R. (2021), Shestakova M.V. (2020), which indicate the high prevalence of DN among patients with type 2 diabetes mellitus, as well as the early development of endothelial dysfunction preceding clinical manifestations of neuropathy. In Uzbekistan, the problem of diabetic neuropathy remains extremely relevant: according to S.Sh. Niyazova (2019) and A.A. Yusupov (2021), the frequency of diabetic neuropathy among patients with diabetes mellitus is 45-52%. However, most domestic studies are limited to the general clinical and biochemical characteristics of diabetic complications, while a comprehensive assessment of the clinical manifestations of diabetes mellitus, the state of microcirculation, electrophysiological changes, and carbohydrate metabolism indicators is extremely rare. Methods for visualizing the microcirculatory bed, such as capillaroscopy, ultrasound dopplerography, and assessment of vascular reactivity, are widely used, despite their high diagnostic value (Callaghan B.C. et al., 2020). Based on the available data, there is a need for in-depth study of the relationship between HbA1c levels, clinical manifestations of DN, and microcirculation parameters using modern instrumental methods.

Purpose of the research. Assess the influence of the degree of carbohydrate metabolism control on the clinical course of diabetic neuropathy and the state of microcirculation in patients with diabetes mellitus.

Research material and methods. The study included patients diagnosed with type 1 and 2 diabetes mellitus observed at the Samarkand City Endocrinology Hospital; in the neurology and therapy departments of the Multidisciplinary Clinic of Samarkand State Medical University for the period 2024-2025. A total of 63 patients were examined, who constituted the main study group. The age of the patients ranged from 30 to 70 years, with an average age of 54.3±8.7 years; among them were 38 women (60.3%) and 25 men (39.7%). For comparison, a control group was formed, consisting of 37 practically healthy volunteers, comparable in age and gender to the main group, without endocrine and neurological pathologies. Patients of the main group were divided into subgroups depending on the level of glycemic control (HbA1c) and the severity of clinical manifestations of diabetic neuropathy. In particular, subgroups with satisfactory carbohydrate metabolism control (HbA1c <7%), subcompensation (HbA1c 7-8.5%), and decompensation (HbA1c >8.5%) were identified. Further classification was carried out taking into account the severity of neuropathy symptoms according to clinical scales, which made it possible to assess the relationship between carbohydrate metabolism disorders and the severity of neurological manifestations. Clinical examination included a thorough neurological assessment using internationally validated scales: NDS (Neuropathy Disability Score) for objective assessment of neurological deficit severity, NSS (Neuropathy Symptom Score) for analysis of subjective sensory complaints, and MNSI (Michigan Neuropathy Screening Instrument) for comprehensive screening of diabetic neuropathy. Laboratory studies included determining the glycemic profile, the level of glycated hemoglobin (HbA1c), the lipid spectrum, as well as assessing the markers of endothelial nitrogen oxide (NO), endothelin-1 and VEGF dysfunction. Instrumental examination was performed in the diagnostic department of MS SamSMU, using the clinic's modern equipment. Electroneuromyography was performed on a Nihon Kohden Neuropack X1 device (Japan), which allows for assessing the speed of excitation transmission through motor and sensory nerves, identifying axonal and demyelinating changes. Nail bed capillaroscopy was performed using the CapillaryScope 200 Pro (Netherlands) digital video capillaroscopic system, which provides magnification up to 200x and high image clarity for the analysis of capillary density and morphology. Ultrasound examination of the lower extremities vessels was performed on a Samsung HS70A (South Korea) apparatus with a 7.5-12 MHz linear sensor, including color and energy Doppler mapping modes. Doppler ultrasonography of the lower extremities arteries was performed using the Mindray DC-80 (China) system, which allows for the assessment of blood flow in the main and peripheral arteries, the condition of the vessel wall, and microcirculatory changes. Statistical data processing was carried out on an individual computer using SPSS 26.0 and Statistica 12.0 packages. Descriptive

statistics methods, Student's t-test and Mann-Whitney's U-test were used to compare quantitative indicators between groups, one-factor analysis of variance (ANOVA) to assess intergroup differences, Pearson and Spearman correlation analysis to determine relationships between clinical, laboratory, and instrumental parameters. Linear and logistic regression models were used to identify risk factors for diabetic neuropathy progression. The level of statistical significance was taken at $p < 0.05$.

Research result. The main group, as presented above, included 63 patients with type 1 and 2 diabetes mellitus with signs of diabetic neuropathy of varying severity. The average age of the patients was 54.3±8.7 years (30 to 70 years). Among those examined were 38 women (60.3%) and 25 men (39.7%). The control group consisted of 37 practically healthy volunteers comparable in age (average age 52.8±7.9) and gender (21 women and 16 men), which ensured the correctness of the comparative analysis. To analyze the clinical features and connection of neuropathy with the level of glycemic control, patients of the main group were divided into three subgroups according to the level of HbA1c: subgroup I had good glycemic control (HbA1c < 7%; n=18), subgroup II, respectively, with subcompensation indicators of carbohydrate metabolism (HbA1c 7-8.5%; n=22), subgroup III with decompensation (HbA1c > 8.5%; n=23). The average age between subgroups did not differ statistically significantly ($p>0.05$), however, in the decompensation group, there was a tendency towards a longer course of DM (on average 9.8±3.1 years versus 7.1±2.8 years in subgroup I), which agrees with literature data on the relationship between the duration of the disease and the risk of neuropathy (Tesfaye S., 2017; Pop-Busui R. et al., 2017; Dyck P.J. et al., 2011). Gender analysis revealed that women predominated in all subgroups, however, no significant intergroup differences were noted in the gender distribution ($p>0.05$). This made it possible to exclude gender as a factor of mixing in assessing the severity of neuropathy. Clinical and neurological characteristics showed that in patients of subgroup III, clinical manifestations were significantly more pronounced than in patients with satisfactory carbohydrate metabolism control. The average values of the NDS, NSS, and MNSI scales gradually increased with the deterioration of glycemic control. In particular, in subgroup I, mild manifestations of sensory neuropathy were noted in 38.9% of patients, while in subgroup III, the proportion of such patients was only 8.7%, with moderate and severe forms of neuropathy dominating (52.1% and 39.2%, respectively). The severity of paresthesia, impaired vibration sensitivity, and decreased distal muscle strength were significantly more common in the decompensation group ($p<0.01$). Compared to the control group, patients in the main group demonstrated significant deviations across all neurological scales ($p<0.001$). In healthy volunteers, the average total NDS score did not exceed 1.4±0.9, while in the main group it reached 5.8±1.7, with maximum values recorded in subgroup III (7.1±1.3).

Despite the comparability of age and sex in all subgroups, it was the glycemic control parameters that determined the severity of neuropathy, which served as the reason for dividing patients of the main group into separate subgroups. In subgroup I, mild forms of sensory neuropathy prevailed, while in subgroup III, most patients had moderate or severe damage, which is confirmed by high values of the NDS, NSS, and MNSI scales. The control group demonstrated minimal values of all neurological parameters, which emphasizes the significance of the differences obtained. Consequently, in patients with diabetes mellitus, the severity of clinical and neurological manifestations of diabetic neuropathy is closely related to the level of glycemic control. A clear gradation of neuropathic disorders severity is observed from the subgroup with good control to the subgroup with decompensation. Patients with HbA1c levels >8.5% demonstrate the most significant deviations across all neurological scales and a longer duration of the disease. The obtained data confirm the key role of carbohydrate metabolism disorders in the progression of diabetic neuropathy and determine the need for further analysis of microcirculatory and instrumental parameters.

The data obtained during the instrumental study demonstrate a sequential deterioration of electrophysiological and microcirculatory parameters depending on the degree of carbohydrate metabolism compensation. All research methods were conducted on identical equipment, which ensured comparability between the subgroups and the control group.

Thus, the results of the analysis according to ENMG data showed that 63 patients with diabetes mellitus exhibited characteristic signs of diabetic polyneuropathy. In the subgroup with good glycemic control (HbA1c <7%), mild axonal changes in sensory nerves with a decrease in the S-response amplitude were predominantly recorded. In the subcompensation subgroup (HbA1c 7-8.5%), mixed (axonal-demyelinating) changes were revealed: a moderate decrease in the speed of excitation conduction (SCV) along the tibial and peroneal nerves and a decrease in the amplitude of the M-response. The most pronounced pathological changes were observed in the decompensation subgroup (HbA1c >8.5%), where a significant decrease in SCV, prolongation of distal latencies, and a pronounced decrease in the amplitude of M-responses were noted, which indicated the presence of severe axonal-demyelinating neuropathy. In the control group, ENMG indicators were within normal values, statistically significantly differing from all subgroups of the main group ($p<0.001$), which confirms the connection between the diabetic status and neurophysiological disorders.

Ultrasound dopplerography at the time of examination in patients revealed signs of microangiopathy of varying severity. In the subgroup with satisfactory carbohydrate metabolism control, a moderate decrease in the resistance index was observed, and linear blood flow indicators were at the lower limit of normal. In subgroup II, a decrease in the maximum systolic blood flow rate and an increase in the pulsation index were noted, reflecting a deterioration in peripheral perfusion. At the same time, patients in subgroup III exhibited pronounced signs of diabetic angiopathy: decreased blood flow in the distal arteries of the foot, increased vascular resistance, slowed venous outflow, which was combined with clinical symptoms (coldness of extremities, paleness, episodes of numbness). These changes were significant compared to subgroups I and II ($p<0.01$).

The study of the capillary network showed that already in subgroup I, single structural changes (curvature of capillaries, rare enlargement of capillary loops) occurred. Whereas in subgroup II, moderate disorders were recorded: decreased capillary density, dilation of the arterial section, and isolated areas of avascularity. Subgroup III demonstrated the most pronounced picture of microcirculatory disorders: multiple avascular zones, hemorrhagic points, significant decrease in capillary density, and gross morphological deformities. This was combined with clinically pronounced neuropathy and low ENMG indicators. The control group had a homogeneous normal capillary picture. Correlation analysis between glycemia and clinical and neurological symptoms revealed a correlation between HbA1c levels and clinical and instrumental indicators: a strong correlation between HbA1c and sensory neuropathy ($r = 0.72$; $p < 0.001$); a moderate correlation between HbA1c and motor deficiency ($r = 0.56$; $p<0.01$); a pronounced correlation between glycemia levels and autonomic neuropathy (tachycardia of rest, ortostatic hypotension) $r = 0.68$ ($p<0.001$); a significant negative correlation between HbA1c and nerve conduction rate (SCV) $r = -0.61$ ($p < 0.01$); a significant correlation between poor diabetes control and the severity of microangiopathy (USDG and capillaroscopy) $r = 0.74$ ($p < 0.001$). Carbohydrate metabolism deterioration is associated with a decrease in the rate of excitation conduction, a decrease in the amplitude of the M-response, a deterioration in peripheral perfusion, and progressive microangiopathic changes. The most pronounced deviations are observed in the decompensation subgroup, which corresponds to clinical and neurological data. Thus, instrumental data confirm a reliable correlation between the level of carbohydrate metabolism compensation and the severity of neuropathic disorders. In patients with high HbA1c, pronounced axonal-demyelinating changes according to ENMG data, significant macro- and microcirculation disorders, decreased capillary density, and pronounced clinical manifestations of sensory, motor, and autonomic neuropathy are noted. This allows us to consider the level of glycemic control as a key factor determining the severity of peripheral nervous system damage.

Laboratory examination of patients included an assessment of the glycemic profile, the level of glycated hemoglobin (HbA1c), the lipid spectrum, and markers of endothelial dysfunction (NO, endothelin-1, VEGF). The analysis results showed pronounced differences between the subgroups of the main group, divided by the degree of carbohydrate metabolism compensation, as well as significant differences from the control group. Glycemic profile and HbA1c, in patients of the main group, a consistent deterioration in carbohydrate metabolism indicators was noted from the subgroup with good

control (HbA1c < 7%) to the subgroup with decompensation (HbA1c > 8.5%). The average values of fasting glucose were: in subgroup I, 6.4±0.9 mmol/l; in subgroup II, 8.1±1.2 mmol/l; and, accordingly, in subgroup III, 10.3±1.8 mmol/l, which significantly differed from the control group (4.9±0.6 mmol/l; $p<0.001$). A similar dynamic was observed for the postprandial glucose level. The average values of HbA1c in subgroups, as expected, correlated directly with the severity of the clinical picture: in subgroup I, 6.4±0.3%; in subgroup II, 7.9±0.4%; and, accordingly, in subgroup III, 9.3±0.6%; with normal values of the control group (5.4±0.3%). The age and sex of patients in the subgroups did not differ statistically ($p>0.05$), which made it possible to exclude demographic factors as possible sources of bias.

Lipid profile analysis showed that with the deterioration of carbohydrate metabolism, significant changes in lipid metabolism were observed. In subgroup III, the levels of total cholesterol and triglycerides were significantly higher than in subgroups I and II ($p<0.01$). Characteristic results in the examined patients were as follows, total cholesterol: in the control group 4.5±0.6 mmol/l; in the I subgroup 4.9±0.7; in the II subgroup 5.6±0.8; in the III subgroup 6.4±0.9 mmol/l. Triglycerides levels in the control group were 1.2±0.3 mmol/l; in subgroup I, 1.6±0.4; in subgroup II, 2.1±0.6; and in subgroup III, 2.8±0.7 mmol/l. Increased lipid levels in the decompensation subgroup is most likely associated with pronounced insulin resistance and reflects systemic metabolic disorders that intensify disease progression.

The study of vascular biomarkers indicates endothelial dysfunction, which progressively worsens as HbA1c increases. Thus, the analysis of nitrogen oxide (NO) levels revealed that the concentration decreased as glycemic control deteriorated: in the control group, 42.8±6.1 μmol/l; in subgroup I, 36.5±5.7; in subgroups II, respectively, 28.9±5.1; in subgroup III, 21.3±4.8 μmol/l, which was statistically significant $p<0.001$. At the same time, it should be noted that a decrease in nitrogen oxide (NO) reflects a deterioration in vasodilation and microcirculation, which is important in the control of diabetic neuropathy. In turn, endothelin-1 levels showed a consistent increase: in the control group, 0.52±0.09 pg/ml; in subgroup I, 0.71±0.12; and, respectively, in subgroups II, 0.96±0.15; and in subgroup III, 1.28±0.21 pg/ml (where $p < 0.001$). High endothelin-1 is associated with vasospasm, nerve ischemia, and pronounced neuropathy. No less important signs at the time of the study were VEGF levels, where an increase was clearly noted in subgroups II-III ($p<0.01$), which reflects the compensatory intensification of angiogenesis against the background of microcirculatory hypoxia.

Correlation of laboratory indicators with clinical and neurological symptoms showed that the level of HbA1c strongly depends on the level of various types of neuropathy. Thus, in sensory neuropathy, $r=0.72$, $p<0.001$, a pronounced linear relationship is noted between an increase in HbA1c and the intensity of paresthesia, loss of vibration and pain sensitivity. In motor neuropathy, the indicators were as follows, $r=0.56$, $p<0.01$, in patients with decompensation, a decrease in the strength of the distal muscles was noted, a decrease in the M-response to ENMG. Whereas, in autonomic neuropathy, the indicators are $r=0.68$, $p<0.001$ and correspond to tachycardia at rest, ortostatic hypotension, and decreased heart rate variability. Correlation of the data on the level of microangiopathy correspondence between nitrogen oxide and endothelin 1 revealed changes where nitrogen oxide (NO) was equal to $r=-0.69$, $p<0.001$, and endothelin -1, $r=0.74$, $p<0.001$. Thus, proving that patients in subgroup III had the most pronounced combined disorders in the form of severe sensorimotor neuropathy, signs of autonomic imbalance, and a sharp decrease in endothelial function indicators. The control group, however, demonstrated stable values of all laboratory indicators.

The control group is characterized by stable glycemia, lipid metabolism, and normal values of endothelial function markers. Subgroup III is characterized by the most pathological changes: maximum levels of glucose, triglycerides, endothelin-1, and VEGF, as well as the lowest levels of nitrogen oxide. These parameters clearly correlate with the clinical severity of diabetic neuropathy.

Thus, laboratory data confirm the key role of carbohydrate metabolism disorders and endothelial dysfunction in the development and progression of diabetic neuropathy. In patients with high HbA1c, pronounced metabolic abnormalities, dyslipidemia, decreased NO, increased endothelin-1 and VEGF

are noted, which is accompanied by increased sensory, motor, and autonomic neuropathy. Laboratory indicators show a close relationship with clinical and instrumental disorders, making them important markers of disease severity.

Conclusion. The results obtained during the study confirm the key role of carbohydrate metabolism disorders in the pathogenesis of diabetic neuropathy. Data analysis showed that an increase in the level of HbA1c is accompanied by a progressive deterioration of clinical, instrumental, and laboratory indicators, which reflects the systemic nature of metabolic and microcirculatory disorders in diabetes mellitus. The identified electro-physiological changes - a decrease in the rate of excitation conduction, a decrease in the amplitude of the M-response, and an increase in latency - are more pronounced in the decompensation subgroup. This confirms the dominance of axonal-demyelinating processes in chronic hyperglycemia. Microcirculatory disorders, including a decrease in capillary density and an increase in vascular resistance, detected by ultrasound and capillary angioscopy, also progressed proportionally to the level of glycemia, which corresponds to the concept of endothelial dysfunction as the central link in the pathogenesis of DN. Laboratory tests confirmed the presence of pronounced metabolic dysregulation in patients with diabetic decompensation. A decrease in NO levels and an increase in endothelin-1 indicated a vasoregulation disorder, while an increase in VEGF indicated a compensatory reaction to ischemia. These changes closely correlated with the severity of sensory, motor, and autonomic neuropathy, reflecting the relationship between metabolic and vascular mechanisms in peripheral nerve damage. Comparison of patients in different subgroups showed that age and sex did not significantly affect the severity of neuropathy, while the level of HbA1c was the main determinant of the severity of the disorders. This emphasizes the need to optimize carbohydrate metabolism control and early detection of signs of microangiopathy and neuropathy. Overall, the combination of clinical, laboratory, and instrumental data confirms that diabetic neuropathy is a multifactorial process in which hyperglycemia, endothelial dysfunction, and microangiopathy play key pathogenetic roles. The obtained results justify the expediency of a comprehensive approach to the diagnosis and monitoring of DN and can serve as a basis for developing more effective preventive and therapeutic strategies.

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