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# DIABETIC PERIPHERAL NEUROPATHY IN TYPE 2 DIABETES MELLITUS: ISSUES OF PATHOGENESIS, PREVALENCE, AND PREVENTION

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**Abstract.** This article analyzes the epidemiological aspects and modern pathogenetic mechanisms of the development of diabetic peripheral neuropathy (DPN) in patients with type 2 diabetes mellitus (T2DM). The main objective of the study is to determine the prevalence of DPN and to assess the role of metabolic syndrome components in its development. The article substantiates that the development of DPN is associated not only with chronic hyperglycemia, but also closely linked with metabolic factors such as abdominal obesity, dyslipidemia, and arterial hypertension. In addition, the role of oxidative stress, inflammatory processes, and mitochondrial dysfunction in damaging nerve fibers is highlighted. The study results indicate that glycemic control alone is not sufficient for the prevention and treatment of DPN; rather, comprehensive metabolic correction and early screening are essential for improving patients' quality of life and reducing the risk of severe complications (amputation, disability).

**Keywords:** Type 2 diabetes mellitus, diabetic peripheral neuropathy, metabolic syndrome, abdominal obesity, dyslipidemia, hyperglycemia, oxidative stress, risk factors, neuropathic pain.

**Introduction.** Diabetic neuropathies are a group of disorders that develop as a consequence of diabetes mellitus, characterized by diverse clinical and pathomorphological manifestations. They affect the peripheral and autonomic nervous systems and negatively influence the function of multiple organs and systems in the body [1]. As a result of these pathological changes, organ function becomes impaired, patients' quality of life deteriorates, and the risks of disability and mortality increase [1, 2]. Diabetic peripheral neuropathy (DPN) is the most common form of diabetic neuropathy and is characterized by dysfunction of the peripheral nervous system [1, 3]. It presents with positive symptoms such as pain, burning, tingling (paresthesia), and dysesthetic sensations, as well as negative symptoms including reduced sensitivity, loss of reflexes, and muscle weakness [3]. DPN typically develops in a distal symmetric pattern, initially affecting the feet and gradually progressing proximally; in severe cases, it may also involve the hands [1, 4]. According to some scientific sources, DPN is considered one of the most prevalent microangiopathic complications of diabetes [2]. It may occur in up to nearly 50% of patients living with diabetes [1, 5]. The disease is characterized by the gradual (progressive) degeneration of nerve fibers, a process largely dependent on nerve length [3]. Consequently, patients experience pain syndrome, sensory impairment, and loss of balance, which can lead to falls, foot ulcers, infections, and amputations [2, 4]. Diabetic neuropathy is not only a clinical issue but also a significant socio-economic problem. It contributes to increased treatment costs, reduced work capacity, and a substantial burden on healthcare systems [1, 6]. Therefore, early detection and preventive measures are of great importance [2]. Studies indicate that the prevalence of DPN varies across different populations [5]. For instance, peripheral neuropathy is identified in 10–

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15% of patients with newly diagnosed type 2 diabetes mellitus [1]. As the duration of the disease increases, so does the risk of its development; after 10 years of diabetes, nearly half of the patients may develop DPN [5, 7]. Glycemic control is a key factor in preventing diabetic complications. Particularly in type 1 diabetes, strict glucose control slows the progression of neuropathy [8]. However, in type 2 diabetes, glycemic control alone is insufficient to completely prevent the development of DPN [9]. This suggests that additional factors play an important role in the pathogenesis of the disease [2, 7]. One of these important factors is metabolic syndrome (MetS). Metabolic syndrome includes a cluster of interrelated disorders: obesity (especially abdominal obesity), dyslipidemia (reduced HDL levels and elevated triglycerides), arterial hypertension, and insulin resistance [2, 10]. These factors are important not only for cardiovascular diseases but also for the development of diabetic neuropathy [7, 10]. Scientific studies demonstrate a significant association between metabolic syndrome and DPN [7, 10]. In particular, observations from the Danish arm of the ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment of Diabetes in Primary Care) study showed that increased waist circumference and low levels of high-density lipoprotein (HDL) cholesterol are important risk factors for the development of DPN [11]. Additionally, elevated levels of methylglyoxal, an indicator of oxidative stress, confirm metabolic alterations associated with nerve damage [11]. Furthermore, it has been found that statin medications, which affect lipid metabolism, do not have a significant impact on the development of DPN [12]. This suggests that not general hyperlipidemia, but rather specific lipid fractions and metabolites, play a more critical role [12]. At the same time, the exact metabolites or lipid components primarily responsible for neuropathy development have not yet been fully identified [7]. According to modern scientific perspectives, the development of diabetic peripheral neuropathy is a multifactorial process involving the interaction of hyperglycemia, oxidative stress, inflammatory processes, mitochondrial dysfunction, and metabolic disturbances [2, 4, 7]. This indicates that the disease cannot be explained by a single factor alone [1]. Therefore, studying the prevalence of diabetic peripheral neuropathy, identifying its underlying mechanisms, and especially controlling modifiable risk factors (such as obesity, dyslipidemia, and hypertension) are of significant scientific and practical importance [2, 7]. This approach contributes to the prevention of the disease, early diagnosis, and the development of effective treatment strategies [1, 6].

**The aim of this study** is to determine the prevalence of diabetic peripheral neuropathy in patients with type 2 diabetes mellitus and to assess the factors influencing its development, particularly evaluating metabolic syndrome as a significant risk factor.

**MAIN PART**

**Prevalence and epidemiological characteristics of diabetic peripheral neuropathy**

Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes mellitus, characterized by a slowly progressive damage of the peripheral nervous system [1, 2]. The prevalence of this condition varies significantly across different populations, which is associated with differences in diagnostic criteria, variations in study methodologies, as well as genetic and environmental characteristics of population groups [5]. According to the results of a large-scale meta-analysis conducted among the population of China, the prevalence of DPN ranged from 2.4% to 78.8%, with a median value of 59% across the analyzed studies [5]. Based on minimum and maximum values, percentiles were calculated and countries were divided into four groups: above the 75th percentile (>60% DPN), 50–75th percentile (41–60%), 25–50th percentile (21–40%), and below the 25th percentile (<20%) [5]. Studies conducted in European countries have reported relatively lower prevalence rates. In Germany and the United Kingdom, a study performed in primary care settings reported DPN prevalence rates of 5.7% and 2.4%,

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respectively [14]. However, in that study, diagnosis was based on the International Classification of Diseases (ICD-10), and no detailed clinical or instrumental examination methods were applied, which may have contributed to the lower reported rates [14]. In a population-based study conducted in South Wales, United Kingdom, among 269 patients with type 2 diabetes, the overall prevalence of DPN was 26.4% [15]. Among these patients, neuropathic pain was reported in 19%, non-neuropathic pain in 36.8%, mixed pain in 7.4%, and pain-free conditions in 36.8% [15]. In another study focusing specifically on painful neuropathy, mild symptoms accounted for 14%, moderate symptoms for 18%, and severe cases for 16%, with an overall prevalence of painful neuropathy of 34% [3]. At the same time, some scientific sources indicate that the prevalence of DPN may reach up to 77.4% [4]. According to data from the Rochester Diabetic Neuropathy Study, the prevalence of DPN across different severity stages in the population showed high values, indicating that it significantly varies depending on diagnostic criteria [4].

The duration of diabetes plays an important role in the development of DPN. Studies show that peripheral neuropathy is detected in 10–15% of patients newly diagnosed with type 2 diabetes [1]. As the duration of the disease increases, the risk of its development also rises, and in patients with 10 years of diabetes, DPN is observed in nearly half of the cases [5, 7]. In a separate observational study, the median duration of diabetes in patients with DPN was 10 years, which was significantly higher compared to 5 years in the group without DPN ($p < 0.001$) [7]. According to analyses of gender and age characteristics, the mean age was almost similar in both groups, amounting to 58.96 ± 11.86 years in the T2DM/DPN+ group and 57.10 ± 13.29 years in the T2DM/DPN− group [10]. The proportion of males was 40.9% and 31.7%, respectively; however, this difference was not statistically significant ($p = 0.054$) [10].

**Metabolic syndrome and its role in the development of DPN**

Glycemic control is considered an important factor in preventing diabetic complications. In particular, strict control of blood glucose levels in type 1 diabetes mellitus slows the progression of neuropathy [8]. The results of the DCCT (Diabetes Control and Complications Trial) showed that intensive glycemic control reduced the risk of developing neuropathy by up to 60% in patients with type 1 diabetes [8]. However, in type 2 diabetes mellitus, glycemic control alone cannot completely prevent the development of DPN [9]. According to the UKPDS (UK Prospective Diabetes Study), although intensive glycemic control in type 2 diabetes reduced microangiopathic complications, its effect on neuropathy was limited, indicating that additional factors are involved in the pathogenesis of the disease [9]. One of such important factors is metabolic syndrome (MetS). Metabolic syndrome includes a cluster of interrelated disorders: obesity (particularly abdominal obesity), dyslipidemia (reduced HDL levels and increased triglycerides), arterial hypertension, and insulin resistance [2, 10]. These factors play an important role not only in cardiovascular diseases but also in the development of diabetic neuropathy [7, 10]. According to the EURODIAB (European Diabetes Insulin-Dependent Diabetes Mellitus Complications Study), components of metabolic syndrome are independently associated with the development of DPN [10]. In this large-scale study, the prevalence of DPN was significantly higher in individuals with arterial hypertension ($p = 0.013$), abdominal obesity ($p = 0.010$), elevated triglyceride levels ($p = 0.007$), and reduced high-density lipoprotein (HDL) cholesterol levels ($p = 0.013$) [10]. Observations from the Danish part of the ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment of Diabetes in Primary Care) study showed that increased waist circumference and low HDL cholesterol levels are important risk factors for the development of DPN [11]. In addition, elevated levels of methylglyoxal, a marker of oxidative stress, also confirm metabolic alterations associated with nerve damage [11]. The role

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of metabolic syndrome in the development of DPN lies in the fact that insulin resistance and dyslipidemia together exacerbate endothelial dysfunction, increase oxidative stress, and lead to ischemic damage of nerve fibers [7, 10]. In particular, abdominal obesity contributes to an increase in proinflammatory cytokines (TNF-α, IL-6), which accelerates inflammatory degeneration of nerve fibers [7].

**Multifactorial mechanisms and risk factors of DPN development**

According to current scientific perspectives, the development of diabetic peripheral neuropathy (DPN) is a multifactorial process in which hyperglycemia, oxidative stress, inflammatory responses, mitochondrial dysfunction, and metabolic disturbances interact in a complex manner. At the same time, it has not yet been fully determined which specific metabolites or lipid fractions play the leading role in the development of neuropathy [2, 4, 7]. As a result of hyperglycemia, activation of the polyol pathway increases, leading to the accumulation of sorbitol and fructose, which raises intracellular osmotic pressure [1]. In addition, glucose autoxidation and impairment of oxidative phosphorylation increase the production of free radicals, resulting in mitochondrial dysfunction [2]. Oxidative stress enhances neuronal apoptosis and accelerates demyelination of nerve fibers [4]. Inflammatory processes also play an important role in the pathogenesis of DPN. An imbalance between pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and anti-inflammatory cytokines (IL-10, TGF-β) exacerbates nerve tissue damage [7]. The chronic low-grade inflammation observed in metabolic syndrome further intensifies these processes [10]. Mitochondrial dysfunction is considered one of the key mechanisms in the development of DPN. Hyperglycemia and dyslipidemia together increase the production of reactive oxygen species (ROS) in mitochondria, reduce ATP synthesis, and disrupt neuronal energy metabolism [2, 7]. This leads to axonal degeneration of nerve fibers and slowed nerve conduction [4]. Modifiable risk factors play a particularly important role in the development of DPN. These include abdominal obesity, dyslipidemia (low HDL levels, high triglycerides), arterial hypertension, and insulin resistance [7, 10]. Early identification and comprehensive correction of these factors may slow down or prevent the development of DPN [2]. Therefore, studying the prevalence of diabetic peripheral neuropathy, identifying its pathogenetic mechanisms, and particularly controlling modifiable risk factors (obesity, dyslipidemia, hypertension) are of great scientific and practical importance [2, 7]. This approach contributes to disease prevention, early diagnosis, and the development of effective treatment strategies [1, 6].

From this perspective, the main aim of the present study is to determine the prevalence of diabetic peripheral neuropathy in patients with type 2 diabetes mellitus and to evaluate the factors influencing its development, particularly metabolic syndrome as an important risk factor [7, 10].

**DISCUSSION**

The results of this study further confirm that diabetic peripheral neuropathy (DPN) is one of the most common complications among patients with type 2 diabetes mellitus (T2DM). Significant differences in the prevalence of DPN across different populations were observed to be associated with variations in diagnostic criteria, study methodology, and specific characteristics of population groups. In particular, some studies have reported prevalence rates ranging from 2.4% to 78.8%, indicating the need for a standardized approach to the assessment of DPN [5]. Studies show that the duration of diabetes is an important factor in the development of DPN. As the duration of the disease increases, the risk of developing neuropathy significantly rises [7]. This condition is explained by the gradual degenerative changes in nerve fibers under the prolonged influence of hyperglycemia [1]. The importance of glycemic control is also

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emphasized. In type 1 diabetes mellitus, intensive glycemic control has been proven to significantly reduce the development of neuropathy [8]. However, in type 2 diabetes, this effect is limited, indicating that other additional factors also play an important role in the pathogenesis of DPN [9]. Therefore, glycemic control alone is not sufficient. Components of metabolic syndrome—abdominal obesity, dyslipidemia, arterial hypertension, and insulin resistance—are recognized as important risk factors for the development of DPN [10]. In particular, decreased HDL cholesterol levels and increased triglyceride levels have been shown to be significantly associated with neuropathy [10, 11]. This indicates that metabolic disturbances directly damage the nervous system. In addition, oxidative stress and inflammatory processes play a key role in the pathogenesis of DPN. Hyperglycemia increases the production of free radicals, leading to mitochondrial dysfunction [2]. At the same time, activation of pro-inflammatory cytokines accelerates the degeneration of nerve fibers [7]. These mechanisms confirm the multifactorial nature of DPN development [4]. Interestingly, lipid-lowering statin therapy has not been shown to have a significant effect on the development of DPN. This suggests that qualitative changes in lipid fractions are more important than general hyperlipidemia itself [12]. Therefore, effective management of DPN requires a comprehensive approach that includes not only glycemic control but also the components of metabolic syndrome [2, 7].

**CONCLUSION**

Diabetic peripheral neuropathy is considered a common and clinically significant complication in type 2 diabetes mellitus. Its development has a multifactorial nature and is not limited solely to hyperglycemia; it is closely and interdependently associated with components of metabolic syndrome, oxidative stress, and inflammatory processes. According to research findings, the main risk factors for the development of DPN include diabetes duration, abdominal obesity, dyslipidemia, and arterial hypertension. Therefore, early identification and control of these factors are of great importance in preventing the disease. Although glycemic control is important, it is not sufficient on its own, especially in type 2 diabetes. Therefore, a comprehensive approach—including correction of metabolic syndrome components, adoption of a healthy lifestyle, and development of individualized treatment strategies—is considered the most effective method for the prevention and management of DPN. In addition, early detection of diabetic peripheral neuropathy is clinically crucial, as it allows prevention of severe complications of the disease, including trophic ulcers, infections, and amputations. For this reason, implementing regular screening examinations and systematically monitoring patients in high-risk groups is of great importance. Furthermore, patient education and ensuring adherence to a healthy lifestyle are also integral components of DPN prevention. Proper nutrition, increased physical activity, and body weight control help reduce components of metabolic syndrome and consequently decrease the risk of neuropathy development. From a practical perspective, the management of DPN requires an individualized approach, taking into account the patient's clinical condition, comorbidities, and metabolic parameters. A comprehensive treatment strategy should be directed not only at alleviating symptoms but also at targeting the pathogenetic mechanisms of the disease.

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