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Заснований у липні 2006 року
Періодичність виходу: 8 разів на рік

Том 20, № 7, 2025

Включений в наукометричні і спеціалізовані бази даних
Scopus,
НБУ ім. В.І. Вернадського, «Українiка наукова», «Наукова періодика України», JIC index, Ulrichsweb Global Serials Directory, CrossRef, WorldCat, Google Scholar, ICMJE, SHERPA/RoMEO, NLM-catalog, NLM-Locator Plus, OpenAIRE, BASE, ROAD, DOAJ, Index Copernicus, EBSCO, OUCI

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UDC 616.85-031.14-02:616.379-008.64]-053.2-036-037 DOI: https://doi.org/10.22141/2224-0551.20.7.2025.1916

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Predictors of development and progression of diabetic peripheral polyneuropathy in children with type 1 diabetes mellitus

Abstract. ***Background.*** *Currently, unified strategy for preventing or treating diabetic peripheral polyneuropathy (DPN) in children has not yet been identified. Therefore, establishing risk factors for the development and progression of this complication is the basis of treatment and preventive measures. The purpose was to determine predictors of the development and progression of DPN in children with type 1 diabetes mellitus using factor and cluster analyses.* ***Materials and methods.*** *The study involved 103 children with type 1 diabetes mellitus aged 10 to 17 years who were divided into 2 groups: group 1 (n = 50) without signs of DPN, group 2 (n = 53) with DPN. In order to identify the pathogenetic factors that most determine the development of DPN in children with type 1 diabetes, factor analysis was performed using the principal component method and hierarchical cluster analysis was conducted using the method of intergroup relations.* ***Results.*** *As a result of the factor analysis, 4 factors were identified that determine the development of DPN in children with type 1 diabetes. The contribution of these factors to the total variance was 82.52 %. The leading mechanisms of DPN development in this cohort mellitus were identified, among which the priority contribution was made by chronic hyperglycemia with glycemic control with a high risk to life, insulin resistance, child's age, impaired peripheral circulation, duration of the course and age of manifestation of diabetes mellitus, development of diabetic myopathy. The specified factors formed 3 clusters, which logically complemented each other and confirmed their role in the development of DPN in children with type 1 diabetes.* ***Conclusions.*** *The results of the analysis demonstrate the multifactorial etiology of DPN in children with type 1 diabetes mellitus. Prediction of DPN in pediatric patients should be based on the identification of both non-modifiable (age of manifestation and duration of the disease, age and gender of the child) and modifiable factors (hyperlipidemia, development of insulin resistance, reduction in skeletal muscle mass, and impaired microcirculation).*

Keywords: *diabetes mellitus; neurological condition; diabetic neuropathies; risk factors; factor analysis; cluster analysis; children*

Introduction

Diabetic neuropathy is a common complication of diabetes mellitus, the most frequent form of which is peripheral polyneuropathy (DPN), occurring in 45 % of patients with type 2 diabetes and 54 % of those with type 1 diabetes [1–3]. The results of the studies indicate a progressive increase in the incidence of DPN in children over time, in particular, its subclinical stages [4]. However, despite the widespread prevalence of diabetic peripheral polyneuropathy and the clear influence of hyperglycemia on the development of diabetic neuropathy, there is currently no unified concept regarding the pathogenetic factors behind the development of this complication in children with type 1 diabetes. Therefore, a unified strategy for preventing or treating DPN in children has not yet been identified. Therefore, raising physician awareness regarding the early detection and elimination of modifiable risk factors and the development of treatment and preventive strategies are essential to addressing the increasing incidence of diabetic peripheral polyneuropathy in children with type 1 diabetes.

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The purpose was to determine predictors of the development and progression of diabetic peripheral polyneuropathy in children with type 1 diabetes mellitus using factor and cluster analyses.

Materials and methods

The study involved 103 children with type 1 diabetes mellitus aged 10 to 17 years, with an average of 13.6 ± 0.2 years, who were divided into 2 groups: group 1 (n = 50, average age 13.24 ± 0.37 years) — children without signs of neuropathy, group 2 (n = 53, average age 14.19 ± 0.35 years) — children with DPN.

The diagnosis of type 1 diabetes mellitus was established in accordance with the Standard of Medical Care "Diabetes mellitus in children" (Order of the Ministry of Health of Ukraine No. 413 dated February 28, 2023) [5].

The presence and extent of diabetic peripheral polyneuropathy were assessed based on the severity of symptoms using the Clinical Neurological Examination Scale [6] and the Modified Pediatric General Neuropathy Scale [7].

Muscle mass in the observation groups was determined up to 14 years of age using the A.M. Peters formula [8]:

$$MM_p = 3.8 \times 0.0215 \times m^{0.6469} \times h^{0.7236},$$

where MM_p — muscle body mass, kg; m — body weight, kg; h — height, cm.

Starting from the age of 15, the P. Boer formula was used to determine muscle mass, which took into account the child's gender [9].

For girls:

$$MM = 0.252 \times m + 47.3 \times h - 48.3,$$

where MMp — muscle body mass, kg; m — body weight, kg; h — height, cm.

For boys:

$$MM = 0.407 \times m + 26.7 \times h - 19.2,$$

where MMp — muscle body mass, kg; m — body weight, kg; h — height, cm.

To quantitatively assess the state of muscle mass, we used the skeletal muscle index (SMI) expressed as a percentage and calculated using the formula [10]:

$$SMI = (\text{skeletal muscle mass} / \text{body mass}) \times 100.$$

The ankle-brachial index (ABI) was determined at rest and after physical activity (performing 20 squats at a free pace) by sequentially measuring the arterial systolic pressure (ASP) in the upper and lower extremities using a semi-automatic tonometer [11].

$$ABI = \text{ASP on the a.tibialis posterior} / \text{ASP on the a.brachialis.}$$

In addition to clinical examinations, children in the observation and comparison groups underwent a series of laboratory tests, including blood cholesterol, triglyceride, glucose, and glycated hemoglobin levels. To indirectly assess insulin resistance, the triglyceride-glucose (TyG) index was calculated using the formula [12].

$$TyG = \ln[\text{fasting triglycerides (dg/mL)} \times \text{fasting glucose (dg/mL)}] / 2.$$

Insulin resistance was diagnosed when the TyG index was determined to be higher than 4.33 arb. units [13].

All research was carried out in a quiet room at a stable temperature (20–22 C).

Mathematical analysis and statistical processing of the data were performed on a PC using the licensed Statistic for Windows 13.0 software package, serial number JPZ8041382130ARCN10-J. To identify hidden common factors that most influence the development of DPN and determine the structure of the relationships between them, factor analysis using the principal component method was performed, followed by orthogonal rotation of the factor axes using the VARIMAX method. The Spearman correlation matrix with the determination of the factor loading of the studied indicators was chosen as the basis for modeling for the selection of factor complexes. The scree method and the Kaiser criterion (the eigenvalues of each factor should exceed 1) were used to determine the minimum number of common factors in the model. Variables with a high factor loading on the complex (over 0.6) were used for the selection of indicators.

In order to identify typical combinations of leading pathogenetic factors in the development of DPN in children with type 1 diabetes mellitus, a hierarchical cluster analysis was applied using the method of intergroup relationships with subsequent construction of a dendrogram.

When planning the study, approval was obtained from the regional bioethics commission of the Zaporizhzhia State Medical and Pharmaceutical University. All procedures involving children complied with the ethical standards of the institutional and national research committees, the 1964 Declaration of Helsinki and its amendments, or comparable ethical standards set forth in the Belmont Report (April 18, 1979), adhering to the following principles: self-protection, parental knowledge and consent, and assessment of the risks of harm and benefit. Informed consent was obtained from all study participants and their legal guardians.

Results

To determine the pathogenic factors that most influence the development of DPN in children with type 1 diabetes, a factor analysis was conducted to identify the principal components (factors), which represent a combination of pathogenic factors that have the strongest impact on the development of the pathological process. The patient's medical history was analyzed, taking into account the duration of diabetes, age of onset, gender and age of the child, glycemic control, and glycated hemoglobin levels. Signs of insulin resistance (cholesterol, triglyceride, and TyG index levels), peripheral circulatory status before and after physical activity (ABI), and the skeletal muscle index as an indicator of diabetic myopathy were also taken into account.

As a result of factor analysis using the scree plot method, four factors were identified that determine the development of DPN in children with type 1 diabetes mellitus (Fig. 1). The contribution of these factors to the total variance was 82.52 %, with the first two factors accounting for 54.61 % of the variance (Table 1).

Based on the conducted analysis, a matrix of factor loadings was formed (Table 2).

The conducted analysis of the identified factors in the group of children with diabetic myopathy showed that the first factor, which determined 32.48 % of the variance, was occupied by the group factor, which combined 4 potential risk factors: 1) the level of glycated hemoglobin (factor loading 0.898); 2) the state of glycemic control (0.828); 3) the content of triglycerides (0.802) and the triglyceride-glucose index (0.889). This factor was defined by us as the metabolic factor.

The second-ranked factor, accounting for 22.13 % of the total variance, was a group factor combining two initial potential risk factors and associated with the child's age and the ankle-brachial index. This factor was interpreted as the vascular factor.

The third-ranked group factor, with a 16.68 % of the variance share, was interpreted as the anamnestic factor. Within this group, two baseline risk factors were identified that had the highest factor loading: diabetes duration (factor loading of 0.804) and age at disease onset (factor loading of –0.978).

The fourth factor combined serum total cholesterol (factor load 0.877) and skeletal muscle mass index (factor load 0.900). This factor was assessed as a morpho-functional factor.

Table 1. Eigenvalues of factors and percentage of total variance

Factors	Eigenvalues of factors	Percentage of total variance (%)	Cumulative percentage of total variance (%)
1	3.57	32.48	32.48
2	2.44	22.13	54.61
3	1.84	16.68	71.29
4	1.24	11.23	82.52

The conducted factor analysis allowed us to determine the leading mechanisms of DPN development in children with type 1 diabetes mellitus, among which the most important contribution was made by chronic hyperglycemia with glycemic control with a high risk to life, insulin resistance, the age of the child, duration of the course and age of manifestation of diabetes mellitus, impaired peripheral circulation, and the development of diabetic myopathy.

Based on the data obtained, a hierarchical cluster analysis of the leading factors in the development of DPN was performed. Then three clusters were identified in the studied sample of pathogenetic factors in the development of diabetic peripheral polyneuropathy in children with type 1 diabetes (Fig. 2).

The hierarchical cluster analysis clearly demonstrates that, at the initial stage, an associative relationship is formed between indicators of glycemic control, lipid metabolism (total cholesterol and triglycerides), and insulin resistance (TyG index), followed by the addition of a peripheral circulatory status indicator. The content of these components, in turn, is influenced by the duration of diabetes (cluster 1).

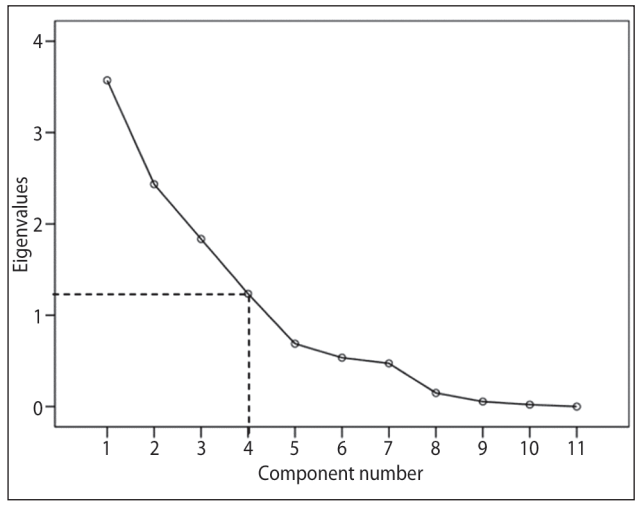

Figure 1. Graph of eigenvalues of factors determining the development of DPN in children with type 1 diabetes mellitus

Table 2. Factor loading matrix

Indicators	Factor 1	Factor 2	Factor 3	Factor 4
Gender				0.605
Age		0.922		
Duration of diabetes			0.804	
Age of onset of diabetes			–0.978	
Glycated hemoglobin	0.898			
Glycemic control	0.828			
Cholesterol				0.877
Triglycerides	0.802			
ABI		0.766		
SMI				0.900
TyG index	0.889			

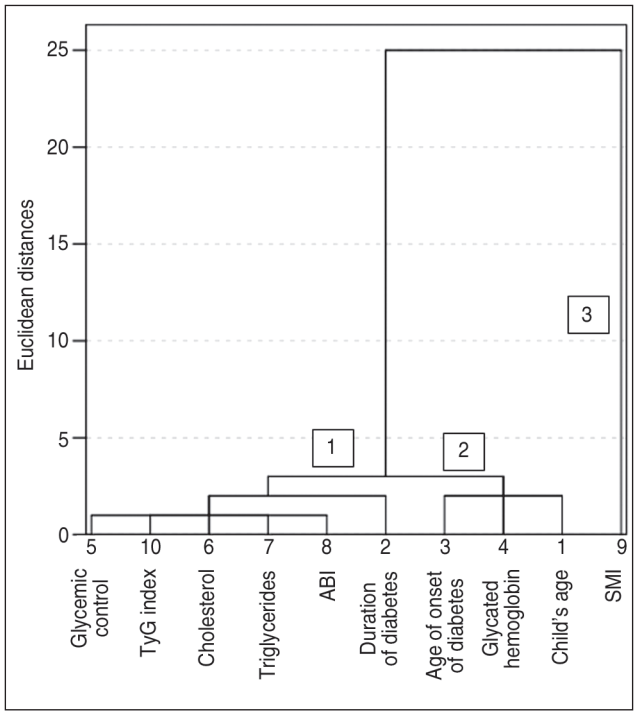

Figure 2. Dendrogram of cluster analysis using the method of intergroup relationships of the leading pathogenetic factors in the development of DPN in children with type 1 diabetes mellitus

Subsequently, based on the cluster grouping results, an agglomeration was formed consisting of the child's age, age at diabetes onset, and glycated hemoglobin level (cluster 2). The resulting structure is reflected in a hierarchical tree of different branches, and this cluster emphasized the initial role of chronic hyperglycemia in the development of DPN in children. The resulting linear relationships were completed by the skeletal muscle index, which, together with the indicators of clusters 1 and 2, formed a single agglomeration (cluster 3).

Moreover, the components of the formed clusters logically complement each other and confirm their role in the development of diabetic peripheral polyneuropathy in children with type 1 diabetes mellitus.

Discussion

The results of our study indicate that the development of DPN in children is caused by complex factors that are interrelated and lead to nerve damage, with hyperglycemia being the main factor. The role of hyperglycemia in the development of diabetic peripheral polyneuropathy has been investigated in several clinical trials, the results of which indicate a significant association between HbA1c levels and DPN in patients with diabetes [14, 15]. The results of the conducted factor and cluster analyses convincingly demonstrated that long-term hyperglycemia and poor glycemic control were the determinants in nerve damage and the development of DPN in children. Therefore, achieving optimal glycemic control is the primary goal in preventing the development and progression of DPN, as well as treating it in children with type 1 diabetes.

Another leading modifiable factor that may be associated with the development of DPN is hyperlipidemia, particularly triglyceridemia. However, the mechanisms by which plasma triglycerides influence DPN remain unclear. A mouse study demonstrated that triglycerides impair peripheral nerve function and contribute to the development of DPN [16]. In the studies of M. Jaiswal et al. (2018), it was found that risk factors for the development of diabetic autonomic cardiopathy in type 1 diabetes, in addition to poor glycemic control, included elevated triglyceride levels [17]. However, other scientists did not find a significant connection between hypertriglyceridemia and an elevated triglyceride index with the development of DPN [18]. Our study demonstrated that hypertriglyceridemia and high triglyceride levels are closely associated with the development and progression of DPN in children with type 1 diabetes. We also found that elevated triglyceride levels are a risk factor for insulin resistance, for which triglyceride content is a sensitive marker in children with diabetes [19, 20]. Insulin resistance is accompanied by impaired neurotrophic support and is another potential mechanism for nerve damage and the development of DPN in diabetes mellitus, and damaged nerves cause neuronal insulin resistance [21].

Chronic hyperglycemia and insulin resistance contribute to vascular damage through various pathophysiological processes [22]. Today, DPN is considered a microvascular complication of diabetes, along with nephropathy and retinopathy [23]. Abnormal changes in endoneurial capillary morphology and vascular reactivity in diabetes may contribute to the development of diabetic neuropathy through endoneurial ischemia [21]. As a screening test for identifying peripheral circulation disorders in children with diabetes mellitus, we used the definition of the ABI, the indicator of which was included in the second group of factors of the general matrix.

Unlike other diabetic microvascular complications, DPN may be directly related to muscle dysfunction, since muscles are innervated by peripheral nerves and their functions are controlled by nerve activity [24]. Impaired peripheral circulation, in turn, leads to the prevalence of catabolism over anabolism in muscle tissue, which increases skeletal muscle fatigue and causes a decrease in muscle strength and muscle mass [25, 26]. Numerous studies, including a meta-analysis by Y. Zhang et al. (2020), have shown that skeletal muscle is the primary organ for glucose utilization, as muscle can improve insulin sensitivity by releasing bioactive peptides such as myokines, thereby protecting against metabolic disorders. This finding may be beneficial for restoring nerve function and improving nerve conduction. Conversely, decreased muscle mass was associated with adverse metabolic consequences that could exacerbate neuronal damage [27]. According to available data, DPN correlates with decreased muscle mass, but the causal relationship between the two factors is not entirely clear [28]. It has also been shown that signs of muscle atrophy preceded significant loss of peripheral nerve sensation [29].

Skeletal muscles are one of the main regulators of carbohydrate and lipid metabolism in human body [30]. Therefore, a decrease in muscle mass leads not only to a disruption in carbohydrate metabolism, but also to the development of dyslipidemia with an increase in the level of triglycerides and cholesterol [31]. Elevated cholesterol has been identified as a potential risk factor for the development of DPN.

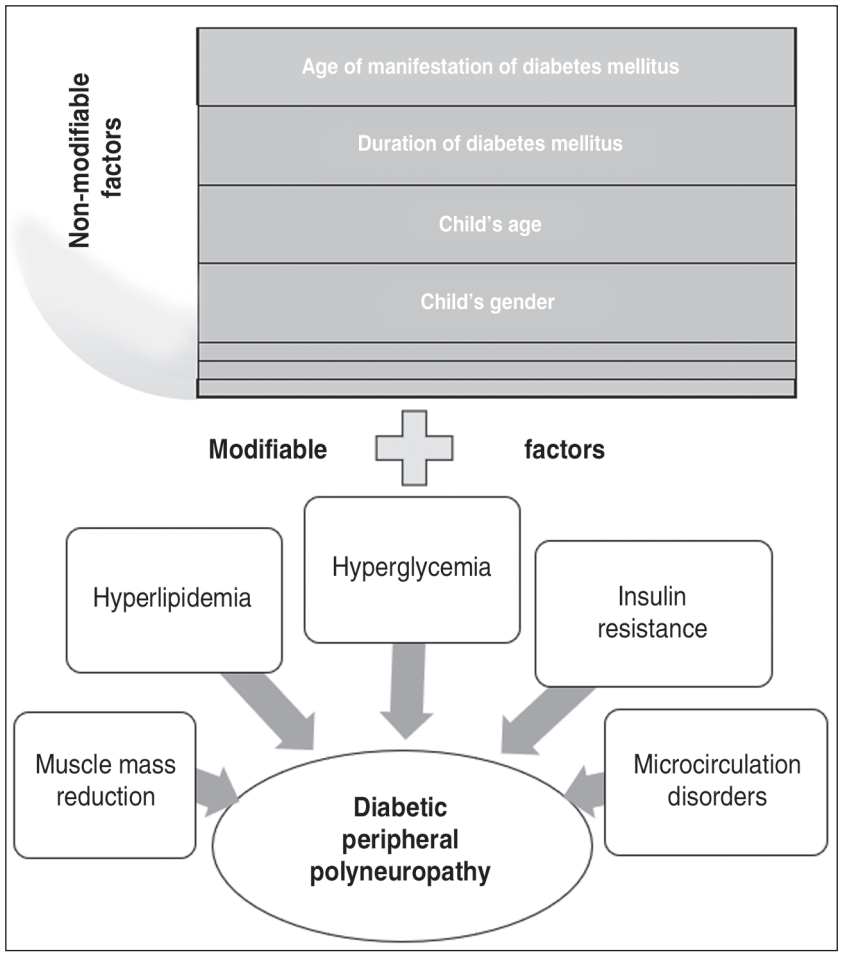

Figure 3. Risk factors underlying the development of diabetic peripheral polyneuropathy in children with type 1 diabetes mellitus

H. Zhang et al. (2023) identified a link between hypercholesterolemia and specific neuronal damage, with the effect of elevated cholesterol on peripheral nerve conduction velocity in patients with type 2 diabetes being entirely mediated by elevated HbA1c levels [32]. An analysis of the results of clinical trials on pharmacotherapy for DPN showed that lowering cholesterol and triglyceride levels slowed the rate of progression of diabetic neuropathy [33].

It has been established that when determining risk factors for DPN in children with type 1 diabetes, it is essential to consider non-modifiable factors such as age at onset and duration of diabetes, gender, and age. Recent advances in genetic knowledge and treatment methods for type 1 diabetes have shown that age at onset is a marker of heterogeneity in type 1 diabetes. This clinical heterogeneity is reflected in differences in the risk of complications, which is associated with a wide range of factors, from hyperglycemia and long-term diabetes to race, ethnicity, and socioeconomic factors [34]. Younger age is associated with higher risk and faster progression through disease stages, as well as with different histological characteristics, immunological patterns, and genetic influences. Older age and lower HbA1c levels at diagnosis suggest a slower loss of C-peptide [35]. In turn, better preserved residual beta cell function ensures a lower risk of diabetes complications [36].

Our study demonstrates that the incidence of DPN in children with type 1 diabetes was higher among those with early onset and, correspondingly, a longer disease duration ($r = -0.32$, $p < 0.05$). These findings complement those of other studies that have found a significant association between DPN and diabetes duration in children and adolescents with type 1 diabetes [37]. According to a 2017 Asian-Indian study, among children with type 1 diabetes, there was an approximately twofold rise in the prevalence of DPN with an increase in diabetes duration from 5–10 to more than 10 years (5–13 %) ($p < 0.0001$) [38]. The risk of developing DPN increases with the onset of puberty. Recent research indicates a critical impact of puberty on the incidence of DPN in children, and puberty is considered the age period when pediatricians should be especially alert for the development of DPN in children with type 1 diabetes [37]. Although early-onset diabetes is characterized by a more aggressive course [39], to date no studies have been conducted on the relationship between the age of diagnosis of diabetes mellitus and the incidence of DPN.

There are numerous reports from different countries that have observed significant differences in the sex ratio in the determinism of metabolic diseases [40]. In experimental models obtained in rats, it was noted that the use of estradiol protects pancreatic islets from multiple metabolic and proinflammatory lesions *in vivo*, restoring the immunomodulatory functions of natural killer cells [41]. At the same time, a Japanese study found a higher incidence in girls aged 0–19 years. These results may indicate that childhood- and adult-onset type 1 diabetes have different developmental mechanisms [42]. Another study found that women, compared to male patients, have an increased risk of developing painful symptoms of neuropathy, as well as more frequent neuropathy symptoms such as paresthesia and loss of sensation in the feet [43].

Therefore, based on the results of the analysis of factor loadings and the conducted cluster analysis, it was found that the development of DPN in children is caused by complex factors that are interconnected and lead to nerve damage (Fig. 3).

Traditionally, hyperglycemia and poor glycemic control are the main risk factors for DPN. Furthermore, age at onset and duration of diabetes, puberty, and female gender further increase the risk of DPN. Hyperlipidemia, the development of insulin resistance, decreased skeletal muscle mass, and impaired microcirculation are modifiable risk factors for DPN, and addressing these factors, along with correcting hyperglycemia, should be a key target for preventing and treating nerve damage in children with diabetes.

Conclusions

1. Based on the results of the studies, a multifactorial etiology of diabetic peripheral polyneuropathy in children with type 1 diabetes mellitus was established.

2. Prediction of diabetic peripheral polyneuropathy in children with type 1 diabetes mellitus should be based on the determination of key indicators, namely non-modifiable (age of onset of diabetes mellitus, duration of the disease, age and gender of the child) and modifiable factors (hyperlipidemia, development of insulin resistance, impaired microcirculation).

Prospects for further research include the creation of a mathematical model for predicting diabetic peripheral polyneuropathy in children with type 1 diabetes mellitus in order to identify patients at high risk of developing this complication and implement timely treatment and preventive measures.

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Received 12.08.2025
Revised 24.09.2025
Accepted 30.09.2025

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Conflicts of interests. Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

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Запорізький державний медико-фармацевтичний університет, м. Запоріжжя, Україна

Предиктори розвитку та прогресування діабетичної периферичної полінейропатії в дітей із цукровим діабетом 1-го типу

Резюме. Актуальність. На сьогодні немає єдиної стратегії запобігання діабетичній периферичній полінейропатії (ДПН) або її лікуванняу дітей, тому визначення факторів ризику розвитку та прогресування цього ускладнення є підгрунтям для розробки лікувально-профілактичних заходів. **Мета:** встановити предиктори розвитку та прогресування ДПН у дітей, хворих на цукровий діабет 1-го типу, за результатами факторного та кластерного аналізів. **Матеріали та методи.** Під спостереженням знаходилося 103 пацієнти з цукровим діабетом 1-го типу віком від 10 до 17 років: 1-ша група (n = 50) — діти без ознак нейропатії, 2-га група (n = 53) — діти з діабетичною периферичною полінейропатією. Для визначення патогенетичних факторів, що найбільше впливають на розвиток ДПН у дітей із цукровим діабетом 1-го типу, проведений факторний аналіз методом головних компонент та ієрархічний кластерний аналіз з використанням методу міжгрупових зв'язків. **Результати.** У результаті проведеного факторного аналізу виділено 4 фактори, що визначають розвиток ДПН у дітей, хворих на цукровий діабет 1-го типу. Внесок цих факторів у загальну дисперсію становив 82,52 %. Було визначено провідні механізми розвитку ДПН у цій когорті, серед яких найбільш значущими були хронічна гіперглікемія з глікемічним контролем з високим ризиком для життя, інсулінорезистентність, вік дитини, порушення периферичного кровообігу, тривалість перебігу та вік маніфестації цукрового діабету, розвиток діабетичної міопатії. Означені фактори становили 3 кластери, які логічно доповнювали один одного та підтверджували їх роль у розвитку ДПН у дітей, хворих на цукровий діабет 1-го типу. **Висновки.** За результатами проведеного аналізу показано багатофакторну етіологію ДПН у дітей із цукровим діабетом 1-го типу. Прогнозування розвитку ДПН у дітей повинно базуватися на визначенні як немодифікованих (вік маніфестації та тривалість перебігу захворювання, вік і стать пацієнта), так і модифікованих факторів (гіперліпідемія, інсулінорезистентність, зменшення скелетної м'язової маси й порушення мікроциркуляції).

Ключові слова: цукровий діабет; неврологічний стан; діабетична нейропатія; фактори ризику; факторний аналіз; кластерний аналіз; діти