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Peripheral blood flow disorders and its role in the development of diabetic peripheral polyneuropathy in children

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Objective — to evaluate the state of blood supply to the lower extremities in children with type 1 diabetes mellitus by the results of the anklebrachial index and to detect latent peripheral circulatory disorders in the development of diabetic peripheral polyneuropathy.

Materials and methods. The study included 103 children (mean age (13.57 ± 0.24) years) with type 1 diabetes mellitus. Depending on the duration of the disease, two groups of patients were formed. Group 1 included 70 children with diabetes mellitus duration up to 5 years (mean duration (2.21 ± 0.16) years), group 2 consisted of 33 patients with diabetes mellitus duration over 5 years (mean duration (8.45 ± 0.41) years). The control group consisted of 33 children without carbohydrate metabolism disorders and neurological disorders. Diabetic peripheral polyneuropathy (DPP) was diagnosed in 47 (45.6 %) of 103 children with diabetes mellitus. The anklebrachial index (ABI) was determined by measuring systolic blood pressure in the upper and lower extremities sequentially. To determine the latent disorders of peripheral circulation, the measurement and calculation of the ABI was performed before and after exercise. Paired linear regression analysis was used to assess the relationship between the indicators. ROC analysis was performed to determine the effectiveness of the use of the ABI as a screening group for the development of DPP. To assess the risk of developing DPP in children, the odds ratio and its 95 % confidence interval were calculated.

Results and discussion. It has been established that in children with diabetes mellitus, the ABI values were significantly reduced compared with the values of the control group ($p < 0.05$). The degree of severity of neurological disorders in children with diabetes mellitus was dependent on the state of peripheral blood flow. Using the ROC curve analysis, the effectiveness of determining the ABI for detecting DPP was evaluated. It was found that the area under the ROC curve was higher when using the ABI after exercise compared to the same indicator at rest, indicating that after exercise the ABI can be used as a screening tool to identify a risk group for the development of DPP.

Conclusions. Peripheral circulatory disorders are a risk factor and a marker for the development of diabetic peripheral polyneuropathy in children with type 1 diabetes mellitus. The resting ABI can be used as an initial screening test aimed at detecting peripheral blood flow disorders in children with diabetes mellitus and classifying them into risk groups for the development of diabetic peripheral polyneuropathy. Even when ABI values are normal in children with diabetes mellitus, in order to detect latent peripheral circulatory disorders, it is recommended to determine ABI after dosed exercise using a threshold value < 1.0.

Keywords: diabetes mellitus, neurological condition, diabetic neuropathies, blood supply, ankle brachial index, ROC analysis, children.

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The global epidemic of diabetes mellitus has contributed to a corresponding epidemic of complications of this disease. Diabetic neuropathy is the most common complication of diabetes, characterized by damage to nerve glial cells, their axons and endothelial cells [19]. Recent studies in Europe and the United States of America indicate a prevalence of diabetic peripheral polyneuropathy (DPP) ranging from 6 to 51 % of the population with diabetes [17, 20]. According to the literature, more than 50 % of patients with DPP have significant, irreparable nerve damage before diagnosis [19]. It is considered that diabetic polyneuropathy develops later in adulthood, but recent studies have shown that DPP is common even in children and adolescents with type 1 diabetes, with a prevalence ranging from 13 to 62 % [6, 7, 13, 15]. It has been shown that almost half of children with diabetes mellitus have subclinical neuropathies of large and small nerve fibers [14].

The high rates of DPP among children and adolescents with diabetes mellitus are a cause for concern and point to the need for early screening and better management of risk factors for this complication. However, early detection of diabetic neuropathy remains a challenge in children, as the potential for neuropathy screening is underutilized in primary care settings and the first symptoms of DPP may be missed [9]. Compared to the success of screening programs for diabetic retinopathy and nephropathy, there is an unmet need for an objective, reliable biomarker for the early detection of DPP, especially its subclinical forms [9].

Considering that DPP is a microvascular complication of diabetes mellitus [18], it is necessary to be able to assess the state of peripheral blood flow in a simple and rapid way [10]. The ankle brachial index (ABI) is commonly used as a non-invasive screening tool to detect lower extremity peripheral arterial disease (PAD), which may be accompanied by polyneuropathy and allows indirectly to judge the state of circulation of the whole organism. However, in pediatric age, the use of this diagnostic method is underestimated and limited in use due to the peculiarities of development and physiology of the child's body.

Objective — to evaluate the state of blood supply to the lower extremities in children with type 1 diabetes mellitus by the results of the ankle-brachial index and to determine the role of its disorders in the development of diabetic peripheral polyneuropathy.

Materials and methods

The study included 103 children with type 1 diabetes mellitus aged 10—17 years (mean age (13.57 ± 0.24) years). Depending on the duration of the disease, two groups of patients were formed. Group 1 included 70 children with diabetes mellitus duration up to 5 years (mean duration (2.21 ± 0.16) years), Group 2 consisted of 33 patients with diabetes mellitus duration over 5 years (mean duration (8.45 ± 0.41) years). The control group consisted of 33 children without carbohydrate metabolism disorders and neurological disorders. All groups were representative in age and gender.

The severity of symptoms of DPP was assessed in all children using the Modified Neuropathic Rating Scale [21] and the Modified Pediatric General Neuropathy Scale (MPGNS) [16], according to which DPP was diagnosed in 47 (45.6 %) of 103 children with diabetes mellitus.

The ankle brachial index was determined by measuring systolic blood pressure (SBP) in the upper and lower extremities sequentially using a semi-automatic tonometer.

ABI = SBP on *a. tibialis posterior* /
SBP on *a. brachialis*

To determine the hidden disorders of peripheral circulation, the measurement and calculation of the ABI was performed before and after exercise. The first measurement of the ABI was performed in the supine position after 5 minutes of rest. The physical activity used was 20 squats at a free pace. The assessment of peripheral circulation was performed according to the following criteria: ABI < 0.90 — reduced index; 0.9—0.99 — extremely low index; 1—1.09 — lower normal value; 1.10—1.29 — normal value [12].

All studies were conducted in a quiet room with a stable temperature (20—22 °C).

Mathematical analysis and statistical processing of data were performed on a computer using the licensed software package Statistica for Windows 13.0, serial number JPZ8041382130ARCN10-J and the SPSS-23 program with the determination of the arithmetic mean (M), standard deviation (σ) and mean errors (m) for indicators whose distribution met the criteria of normality. Normality was checked using the Shapiro—Wilk test of asymmetry.

In case of uneven distribution of characteristics and nonlinear nature of the dependence, the median and quartiles Me (Q25; Q75) were used. The relationship between the indicators was assessed using the methods of calculating Pearson's correlation coefficient with a normal distribution of traits and Spearman's rank correlation (r) with a distribution of traits that differed from the normal one. Paired linear regression analysis was used to assess the relationship between the indicators.

In order to determine the effectiveness of the use of the ABI as a screening tool for the risk group for the development of DPP, a ROC analysis was performed to determine the threshold values of the ABI indicators using the Juden index, which gives the best specificity and sensitivity, and to estimate the area under the ROC curve (AUC). The odds ratio (OR) and its 95 % confidence interval (CI) were used to assess the risk of developing DPP in children. The odds ratio was calculated by the formula:

$$OR = (ad)/(bc),$$

where: a and b — the presence or absence of a risk factor in the group of diabetic children with DPP, respec-

Table 1
Indicators of the ankle-brachial index before and after physical activity in children with diabetes mellitus, depending on the duration of the disease (Me (Q25; Q75))

ABI, arb. u.	1st group (n = 70)	2nd group (n = 33)	Control group (n = 33)
Before exercise	1.0 (0.94; 1.04)[1]	0.96 (0.92; 1.0)[1]	1.09 (1.04; 1.15)
After exercise	0.98 (0.91; 1.06)[1]	0.90 (0.87; 0.98)[1–3]	1.10 (1.06; 1.12)

Note. [1] $p < 0.05$ compared with similar indicators of the control group; [2] $p < 0.05$ compared with similar indicators of group 1; [3] $p < 0.05$ compared with indicators before exercise within the same group.

tively; *c* and *d* — the presence or absence of a risk factor in diabetic children without DPP, respectively.

Student's t-test and Mann—Whitney U-test were used to assess differences in the compared groups. Differences were considered significant at ($p < 0.05$).

Permission was obtained from the regional bioethics committee of Zaporizhzhia State Medical and Pharmaceutical University during the study planning. All procedures performed in studies involving children complied with the ethical standards of the institutional and national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from each of the participants included in the study and their legal guardians.

Results and discussion

According to the results of the study, it was found that in children with diabetes mellitus, the ABI indicators were significantly reduced compared to the values of the control group ($p < 0.05$) (Table 1).

It should be noted that the established clinical features were observed both before and after exercise and regardless of the duration of the disease. In children of the control group, in all cases, the resting ABI was within normal or lower normal values. Instead, in patients of group 1, normal and lower normal values of the ABI were recorded in 37 (52.9 %) children, and among patients of group 2, only 10 (30.3 %) children had ABI values in the range of 1.0—1.29 units.

Dosed physical activity in the control group did not lead to a decrease in the values of the CPI, that is, the exercise did not affect the state of peripheral circulation. Exercise in the group of patients with diabetes mellitus up to 5 years had no significant effect on the ABI values relative to the baseline ($p > 0.05$). In children of group 2, the implementation of exercise led to a statistically significant decrease in the studied index, and in our opinion, may indicate the presence of latent disorders of peripheral circulation. This suggestion was confirmed by a 2-fold decrease in the registration of normal or lower normal values of the ABI (15.1 %) in patients with diabetes mellitus for more than 5 years, while in children of the 1st observation group, the normal state of peripheral blood flow according to the ABI after exercise was recorded in 47.1 % of cases ($p < 0.05$).

It was found that in children with diabetes mellitus, the lowest values of the ABI were characterized by the highest scores on the Modified Pediatric General Neuropathy Scale, both at rest and after exercise ($r = -0.46$, $p < 0.05$, and $r = -0.34$, $p < 0.05$, respectively). That is, the severity of neurological disorders in children with diabetes mellitus was slightly dependent on the state of peripheral blood flow, which can be represented as a paired linear regression (Fig. 1).

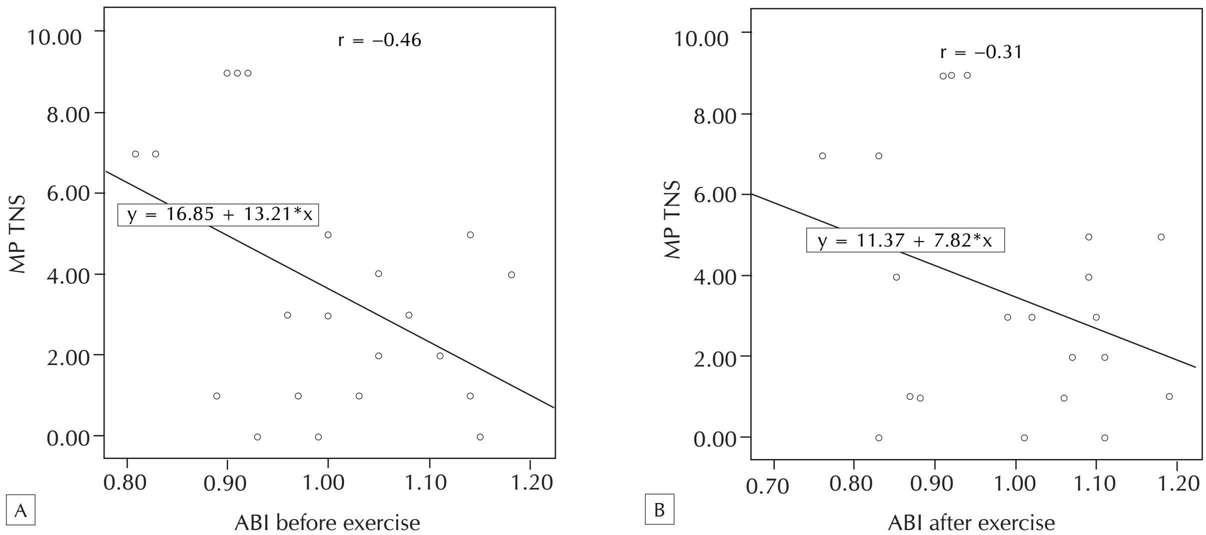

Fig. 1. **Correlations between the sum of scores on the Modified Pediatric Total Neuropathy Scale and the ankle-brachial index before (A) and after (B) exercise**

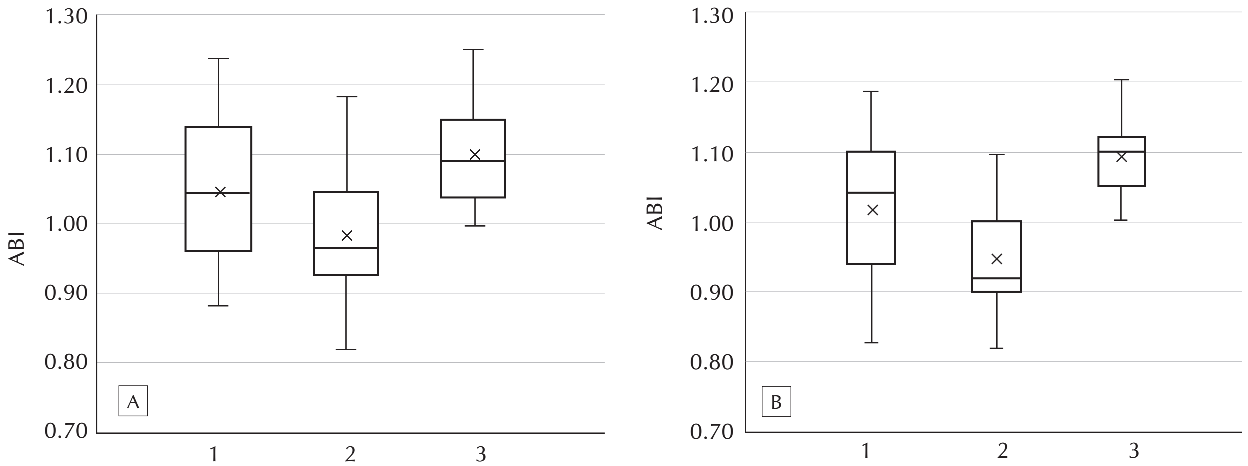

Fig. 2. **ABI indices in children with diabetes mellitus, depending on the presence of symptoms of diabetic peripheral polyneuropathy before (A) and after (B) physical activity**

Note. 1 — children with diabetes mellitus without DPP; 2 — children with diabetes mellitus with DPP; 3 — control group.

The next stage of our work was to analyze the ABI in children with diabetes mellitus, depending on the presence of symptoms of DPP, which was diagnosed in 27 (38.6 %) patients of group 1 and 20 (60.6 %) patients of group 2 (Fig. 2).

The data of the study showed that, although among patients without symptoms of DPP, the median level of the ABI at rest corresponded to the normative values — 1.05 (0.98; 1.13) units. However, an individual analysis of the values of the studied indicator showed that in 16 (28.6 %) children of this group, the resting ABI was below 1.0 units, including 11 (19.6 %) children with extremely low levels of ABI, and in 5 (8.9 %) patients, the ABI was below 0.9 units. Among patients with diagnosed DPP, the median ABI was 0.96 (0.93; 1.04) units. According to the results of the individual analysis, it was found that 25 (53.2 %) children in this group had extremely low ABI values, and 4 (8.5 %) patients with DPP had low ABI values.

Exercise in patients without DPP did not lead to significant changes in the median level of the ABI in the group as a whole, which amounted to 1.04 (0.96; 1.10) units. However, the ranking of the obtained ABI indicators revealed signs of peripheral blood flow disorders in 11 (19.6 %) children with ABI below 0.9 units, which is 2.2 times higher than at rest ($p < 0.05$). In the group of patients diagnosed with DPP, physical activity led to a statistically significant decrease in the level of ABI (0.92 (0.91; 1.0) units, $p < 0.05$). The number of children whose ABI did not correspond to normal or lower normal values increased to 35 (74.5 %) people ($p < 0.05$), including the number of patients with low ABI values among patients with diagnosed DPP after exercise increased 2.7 times and amounted to 11 (23.4 %) children ($p < 0.05$).

It was noteworthy that before physical activity in 4 (8.5 %) children with DPP the values of the ABI were determined in the range of 1.10—1.29 units, i. e. they had normal values. After exercise, normal values of the ABI were never recorded. Among patients without signs of DPP, normal values ofABI before and after dosed physical activity were determined in 22 (39.3 %) and 14 (25.0 %) children, respectively.

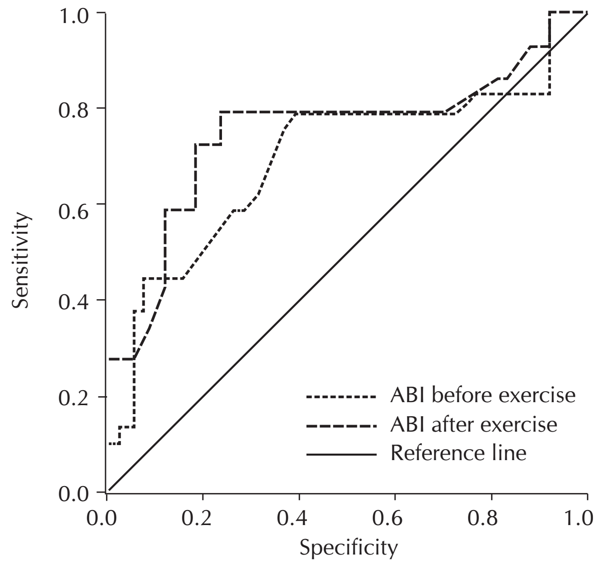

Fig. 3. **ROC curve for evaluating the effectiveness of the carpometacarpal index for detecting DPP**

Using the ROC curve analysis, the effectiveness of determining the ankle-brachial index for the detection of DPP was evaluated (Fig. 3).

It was found that the AUC was higher when using the ABI after exercise compared to the same indicator at rest with an area of 0.747 with a 95 % CI of 0.617 to 0.877, indicating that after exercise the ABI can be used as a screening tool to identify a risk group for the development of DPP (Table 2).

The optimal cutoff point for the ABI after exercise was 1.0, with a sensitivity of 72.4 % and a specificity of 81.6 %. That is, the risk of developing DPP increased

Table 2
Comparative analysis of ROC curves for assessing the effectiveness of determining the ankle-brachial index before and after physical activity for the detection of DPP

Variables of the test result	AUC	Standard deviation	Asymptotic significance	Asymptotic 95 % CI	
				Lower limit	Upper limit
ABI before exercise	0.696	0.069	0.006	0.560	0.832
ABI after exercise	0.747	0.066	0.001	0.617	0.877

in the presence of extremely low ABI values (OR = 10.51, 95 % CI 3.28; 33.68, $p < 0.05$). The threshold value of the ABI < 1.0 at rest had a lower sensitivity (62.1 %) and specificity (68.4 %).

Identification of early symptoms of DPP allows for proactive multifactorial intervention to prevent the progression of nerve damage. Despite the fact that there are recommendations for the use of a number of simple diagnostic methods, modern screening methods tend to detect late stages of the disease, where interventions may be ineffective [9]. Considering that structural, functional, and hemodynamic changes in the microvasculature of the neurovascular system are involved in the development and progression of diabetic polyneuropathy [8], we analyzed the effectiveness of using the ABI definition as a screening tool for DPP in children with type 1 diabetes mellitus.

The results of our study demonstrated that with an increase in the duration of diabetes mellitus, there was a gradual decrease in the ABI, low values of which were associated with the development of DPP ($r = -0.46$, $p < 0.05$).

According to the American Diabetes Association's Standards of Care for Diabetes Mellitus, ABI testing in patients with diabetic peripheral neuropathy should be performed in the presence of symptoms such as decreased gait speed, leg fatigue, claudication, and decreased distal pulse in the context of foot care, i.e., in the presence of signs of PAD [5]. At the same time, the study by L. Chevtchouk et al. proved that peripheral diabetic neuropathy occurred in patients with type 1 diabetes in combination with PAD. In their work, the authors emphasized that ABI measurement should be performed in all patients with type 1 diabetes with suspected peripheral diabetic neuropathy, as well as in asymptomatic patients who have been diagnosed for more than 10 years, regardless of neuropathic pain or signs of ischemia [10]. In our study, we have shown that even in the first 5 years of diabetes mellitus, 33 (47.1 %) children have a reduced or extremely low index of the ABI. These variants of the ABI were found in 5 (8.9 %) and 11 (19.6 %) patients with diabetes mellitus without clinical signs of polyneuropathy, respectively. The results are consistent with the data that up to 50 % of diabetic peripheral neuropathy can be asymptomatic [6], so the assessment of ABI should be considered even in the absence of clinical signs of this complication [4].

According to the results of the study, it was found that the implementation of dosed exercise improves the diagnosis of peripheral circulatory disorders in children with diabetes mellitus. After exercise, low ABI values (less than 0.9) were found in 11 (19.6 %) children without clinical manifestations of DPP and in 11 (23.4 %) patients with diagnosed DPP. Normally, during exercise, central aortic pressure increases and peripheral blood pressure decreases as the arterial beds dilate and deliver more oxygenated blood to meet the metabolic needs of the leg muscles [1]. In healthy individuals, this leads to a slight decrease in ABI after exercise. However, hemodynamic disorders in the vessels of the legs cause an excessive drop in pressure in the peripheral arteries of the lower extremities after exercise [2].

To date, there is still controversy about what value of the ABI should be used to diagnose peripheral blood flow disorders [2]. The studies that established the ABI threshold of ≤ 0.90, which is most commonly used to diagnose PAD [10], included mostly white elderly men with PAD or those at high risk of developing PAD and compared them to a younger healthy group, so they did not take into account all the factors that affect the ABI value at the individual level [1]. In previous studies using the ROC curve, a threshold value of 1.04 for patients with diabetes and 1.0 for patients without diabetes was recommended [11]. Data on post-exercise thresholds for the diagnosis of PAD also vary, partly due to differences in exercise protocols [2].

The results of the ROC analysis indicate that the threshold value of the ABI in children with diabetes mellitus, which is associated with the risk of developing DPPy, should be considered 1.0. Our study demonstrated that the ABI < 1.0 after exercise was more sensitive than the ABI < 1.0 at rest. Thus, a ABI value of less than 1.0 after dosed exercise can be considered as an additional screening indicator for the initial assessment of the risk of DPP in children with type 1 diabetes mellitus.

Conclusions

1. Peripheral circulatory disorders are a risk factor and a marker for the development of DPP in children with type 1 diabetes mellitus.

2. Determination of resting ABI can be performed as an initial screening test aimed at detecting peripheral blood flow disorders in children with diabetes

mellitus and classifying them into risk groups for the development of DPP.

3. In the presence of normal values of ABI in children with diabetes mellitus, in order to detect latent disorders of peripheral blood supply, it is recommended to determine ABI after dosed exercise using a threshold value < 1.0.

Prospects: to investigate additional risk factors for the occurrence of DPP for early non-invasive diagnosis and timely treatment and diagnostic measures.

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.
Participation of authors: material collection, material processing — M.S. Spilnik; concept and design of the study, writing the text — G.O. Lezhenko; statistical data processing, text translation — N.A. Zakharchenko.

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Порушення периферичного кровотоку та його роль у розвитку діабетичної периферичної полінейропатії в дітей

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Мета роботи — оцінити стан кровопостачання нижніх кінцівок у дітей, хворих на цукровий діабет 1 типу, за величиною кісточково-плечового індексу та визначити роль його порушень у розвитку діабетичної периферичної полінейропатії.

Матеріали та методи. Під спостереженням перебували 103 дитини (середній вік — (13,57 ± 0,24) року), хворих на цукровий діабет 1 типу. Залежно від тривалості захворювання сформовано дві групи пацієнтів: перша — 70 дітей із тривалістю цукрового діабету до 5 років (середня тривалість — (2,21 ± 0,16) року), друга — 33 пацієнти з тривалістю цукрового діабету понад 5 років (середня тривалість — (8,45 ± 0,41) року). Контрольна група — 33 дитини без порушень вуглеводного обміну та неврологічних відхилень. У 47 (45,6 %) хворих на цукровий діабет виявлено діабетичну периферичну полінейропатію (ДПН). Кісточково-плечовий індекс (КПІ) визначали шляхом вимірювання послідовно систолічного артеріального тиску на верхніх і нижніх кінцівках. Для визначення прихованих порушень периферичного кровообігу вимірювання та розрахунок КПІ проводили до та після фізичного навантаження. Для оцінювання залежності між показниками використовували парний лінійний регресійний аналіз. Для визначення ефективності застосування КПІ як скринінгу групи ризику розвитку ДПН проводили ROC-аналіз. Для оцінки ризику розвитку ДПН у дітей розраховували відношення шансів та його 95 % довірчий інтервал.

Результати та обговорення. Установлено, що в дітей, хворих на цукровий діабет, показники КПІ були статистично значущо нижчими порівняно з контрольною групою ($p < 0{,}05$). Ступінь виразності неврологічних розладів у хворих дітей залежав від стану периферичного кровотоку. За допомогою аналізу ROC-кривої оцінено ефективність визначення КПІ для виявлення ДПН. Площа під ROC-кривою була більшою при використанні КПІ після фізичного навантаження порівняно з показником у стані спокою, що вказує на те, що після фізичного навантаження величину КПІ можна використовувати як скринінг для виявлення групи ризику розвитку ДПН.

Висновки. Порушення периферичного кровообігу є чинником ризику та маркером розвитку ДПН у дітей, хворих на цукровий діабет 1 типу. Визначення КПІ в спокої можна використовувати як початковий тест скринінгу для виявлення порушень стану периферичного кровотоку в дітей, хворих на цукровий діабет, та розподілу на групи ризику розвитку ДПН. За наявності нормальних значень КПІ у дітей, хворих на цукровий діабет, для виявлення латентних порушень периферичного кровопостачання рекомендовано визначати КПІ після дозованого фізичного навантаження з використанням порогового значення < 1,0.

Ключові слова: цукровий діабет, неврологічні ускладнення, діабетичні нейропатії, кровопостачання, кісточково-плечовий індекс, ROC-аналіз, діти.

ДЛЯ ЦИТУВАННЯ • *FOR CITATION*

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