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The importance of some specific proteins in the pathogenesis and diagnosis of diabetic peripheral polyneuropathy in children

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Abstract. ***Background.*** *Considering that most diagnostic tests for diabetic peripheral polyneuropathy (DPN) are not suitable for use in childhood, resulting in low diagnostic accuracy of this complication, there is a need to identify reliable and simple markers for early detection and monitoring of diabetic polyneuropathy progression in children. Purpose: to study the content of fetuin A, gamma-aminobutyric acid (GABA), S100 protein and copeptin in the blood serum of children with type 1 diabetes mellitus and determine their role in the development of diabetic peripheral polyneuropathy.* ***Materials and methods.*** *We examined 63 children with type 1 diabetes aged 10 to 17 years. Group 1 included 26 patients without signs of neuropathy, group 2 consisted of 37 patients with diabetic peripheral polyneuropathy. The control group included 29 children representative in terms of age and gender without carbohydrate metabolism disorders. The serum levels of fetuin A, gamma-aminobutyric acid, S100 protein, and copeptin were determined by enzyme-linked immunosorbent assay using commercial kits.* ***Results.*** *It has been proven that in children with type 1 diabetes who did not have DPN, there was a 1.6-fold increase in fetuin A and a 2.4-fold increase in GABA compared to the control group ($p < 0.05$). With the development of DPN, there was a decrease in both fetuin A and GABA. A significant statistical increase in the serum level of S100 and copeptin was found in children with DPN, while in the group without signs of DPN, their values did not statistically differ from the control group ($p > 0.05$). An increase in the severity of neurological deficit was inversely related to the level of fetuin A ($r = -0.40$; $p < 0.05$) and GABA ($r = -0.45$; $p < 0.05$) and positively correlated with the serum content of S100 protein ($r = 0.66$; $p < 0.05$) and copeptin ($r = 0.68$; $p < 0.05$).* ***Conclusions.*** *A comprehensive study of fetuin, GABA, S100 protein and copeptin can act as an additional objective marker for the development of DPN in children with type 1 diabetes mellitus and will allow for the objectification and improvement of the diagnosis of this complication.*

Keywords: *diabetes mellitus; neurological condition; diabetic neuropathies; biomarkers; fetuin A; GABA; S100 proteins; copeptin; children*

Introduction

Diabetes mellitus (DM) is a common disease worldwide, including among children. Currently, about 425 million patients suffer from DM, and the prevalence of this disease is rapidly increasing every year. According to forecasts, the number of patients with DM may reach 640 million by 2040 [1]. DM has attracted much attention because of multi-organ complications leading to premature loss of function and increased mortality [2]. Among them, neurodegenerative complications of DM, which include diabetic neuropathy, have recently become the focus of intensive research [3].

Despite the availability of tools for the diagnosis of diabetic neuropathy (nerve conduction study, punch biopsy, quantitative sudomotor axon reflex test, corneal confocal microscopy) [4], most of them are time-consuming, poorly accessible, and unsuitable for use in childhood due to invasiveness and painfulness. Therefore, the diagnosis of distal diabetic polyneuropathy is often delayed due to the shortage of early diagnostic tests. The presented data indicate the need to search for diagnostic and prognostic biomarkers of this complication of diabetes in children that provide results in a short time, while remaining a minimally invasive and

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accessible [5]. The results of measuring the levels of several specific proteins in the blood serum in diabetic peripheral polyneuropathy (DPN) can help identify the disease even before the first symptoms appear and prescribe appropriate treatment. This is a particularly important task, since treatment in most cases is effective only at the earliest stages of pathological changes.

Purpose: to study the content of fetuin A, gamma-aminobutyric acid (GABA), S100 protein and copeptin in the blood serum of children with type 1 diabetes mellitus and to determine their role in the development of diabetic peripheral polyneuropathy.

Materials and methods

The study included 63 children with type 1 diabetes mellitus aged 10 to 17 years, with an average of 13.52 ± 0.26 years, who were divided into 2 groups. Group 1 included 26 patients (mean age 13.24 ± 0.37 years) without signs of neuropathy, group 2 — 37 patients (mean age 14.19 ± 0.35 years) with diabetic peripheral polyneuropathy. The control group consisted of 29 children representative in terms of age and gender without carbohydrate metabolism disorders.

Inclusion criteria: consent of the patient and his parents to participate in the study; the absence of ketoacidosis or signs of hypoglycemia (the maximum fasting blood glucose level on the day of the study did not exceed 10.5 mmol/l, and the minimum blood glucose level was 5.7 mmol/l). Exclusion criteria: lack of consent to participate in the study; the presence of acute inflammatory processes or congenital malformations in the stage of decompensation.

Diagnosis and verification of the clinical diagnosis of type 1 diabetes mellitus was carried out in accordance with the Standards of Medical Care "Diabetes Mellitus in Children" (Order of the Ministry of Health of Ukraine No. 413 dated February 28, 2023) [8]. All children with type 1 diabetes mellitus received basal-bolus insulin therapy that meets modern requirements for the management of patients with type 1 diabetes mellitus [6].

The presence and extent of diabetic peripheral polyneuropathy were assessed by the severity of symptoms using the Clinical Neurological Examination [7] and the pediatric-modified Total Neuropathy Score [8]. All studies were conducted in a quiet room with a stable temperature (20–22 °C).

All the following enzyme immunoassays were performed at the educational medical laboratory center of the Zaporizhzhia State Medical and Pharmaceutical University (Head of the Center Doctor of Medical Sciences, Professor R.A. Shcherbina).

The content of γ-aminobutyric acid in the blood serum was assessed using commercial *in vitro* GABA ELISA kit (Immundiagnostik AG, Germany). The level of fetuin A was studied by enzyme-linked immunosorbent assay using commercial Human FETUA (Fetuin A) ELISA Kit (Elabscience, USA). The levels of copeptin and S100 protein in the blood serum were also determined by enzyme-linked immunosorbent assay using the Copeptin (Human) EIA Kit and CanAg S100 EIA Kit manufactured by Phoenix and Fujirebio Diagnostics AB (Sweden), respectively.

The results of the study were processed using the statistical licensed software package Statistica for Windows 13.0, serial number JPZ804I382130ARCN10-J, and SPSS 23.0 for Windows with verification of the conformity of the type of distribution of features to the law of normal distribution using the Shapiro-Wilk asymmetry test. With a normal distribution of features, the arithmetic mean (M), standard deviation (σ), average errors (m) and standardized deviation were determined. The relationship between the indicators was estimated using the methods for calculating the Pearson correlation coefficient. The statistical significance of the differences in the results obtained for different groups was determined by the Student's t-test. Differences for small samples were evaluated using the nonparametric Mann-Whitney U test. Differences were considered significant at $p < 0.05$.

When planning the research, permission was obtained from the regional commission on bioethics of the Zaporizhzhia State Medical and Pharmaceutical University. All procedures conducted with children were in accordance with the ethical standards of the institutional and national research committee, the 1964 Declaration of Helsinki and its amendments, or comparable ethical standards. Informed consent was obtained from all study participants and their legal guardians.

Results

According to the results of the study, children with diabetes, who did not have DPN, had an increase in the content of fetuin A by 1.6 times and GABA by 2.4 times compared to the control group ($p < 0.05$) (Table 1).

As can be seen from Table 1, with the development of DPN, there was a decrease in both fetuin A and GABA levels, but their content in the blood serum of children in group 2 remained statistically higher compared to the control group ($p < 0.05$). We also found a significant statistical increase in the serum content of S100 and copeptin of children with DPN, while in the group without signs of DPN,

Table 1. The content of biochemical markers in the blood serum of children with type 1 diabetes mellitus depending on the presence of diabetic peripheral polyneuropathy (M ± m)

Indicator	DM without neuropathy, n = 26	DM with neuropathy, n = 37	Control group, n = 29
Fetuin A, ng/mL	201.38 ± 16.18[1]	143.68 ± 2.96[1, 2]	128.13 ± 2.31
GABA, μmol/L	1.00 ± 0.08[1]	0.60 ± 0.03[1, 2]	0.42 ± 0.03
S100, ng/mL	41.31 ± 5.38	57.69 ± 2.21[1, 2]	42.20 ± 4.70
Copeptin, ng/mL	0.12 ± 0.01	0.23 ± 0.02[1, 2]	0.14 ± 0.01

Notes: [1] — $p < 0.05$ compared the control group; [2] — $p < 0.05$ compared to children with DM without neuropathy.

their values did not statistically differ from the control group ($p > 0.05$).

The conducted correlation analysis in children with type 1 diabetes showed that the total score on the pediatric-modified Total Neuropathy Score was inversely related to the level of fetuin A ($r = –0.40$; $p < 0.05$) and GABA ($r = –0.45$; $p < 0.05$) and positively correlated with the serum content of S100 protein ($r = 0.66$; $p < 0.05$) and copeptin ($r = 0.68$; $p < 0.05$) (Fig. 1, A-D). That is, an increase in the severity of neurological disorders was accompanied by a low multidirectional change in the studied parameters.

Fetuin A and GABA demonstrated statistically significant negative correlation with disease duration ($r = –0.38$; $p < 0.05$ and $r = –0.41$; $p < 0.05$, respectively) and HbA1c ($r = –0.34$; $p < 0.05$ and $r = –0.32$; $p < 0.05$). S100 protein and copeptin levels increased with increasing diabetes duration ($r = +0.31$; $p < 0.05$ and $r = +0.33$; $p < 0.05$, respectively) and worsening glycemic control ($r = +0.34$; $p < 0.05$).

At the next stage of our work, we assessed the content of biochemical markers in the blood serum of children with diabetes mellitus depending on the severity of neurological disorders. The results obtained are presented in Table 2.

The evaluation of the data obtained showed the presence of changes in the level of biochemical markers depending on the severity of neurological disorders. Thus, in the absence of signs of neuropathy, the content of fetuin A and GABA exceeded the normative data by more than 3 σ deviations, while the content of S100 and copeptin were within 1 σ. In the presence of neurological disorders, there was a decrease in the serum content of fetuin A and GABA compared to the group of patients without neuropathy, and it progressed when the neurological deficit increased. In children, in whom 1–2 types of disorders were registered, these indicators remained significantly higher than in the control group ($p < 0.05$) and were within 1–2 σ, while in diabetic patients with 3 types of neurological disorders, that is, motor, sen-

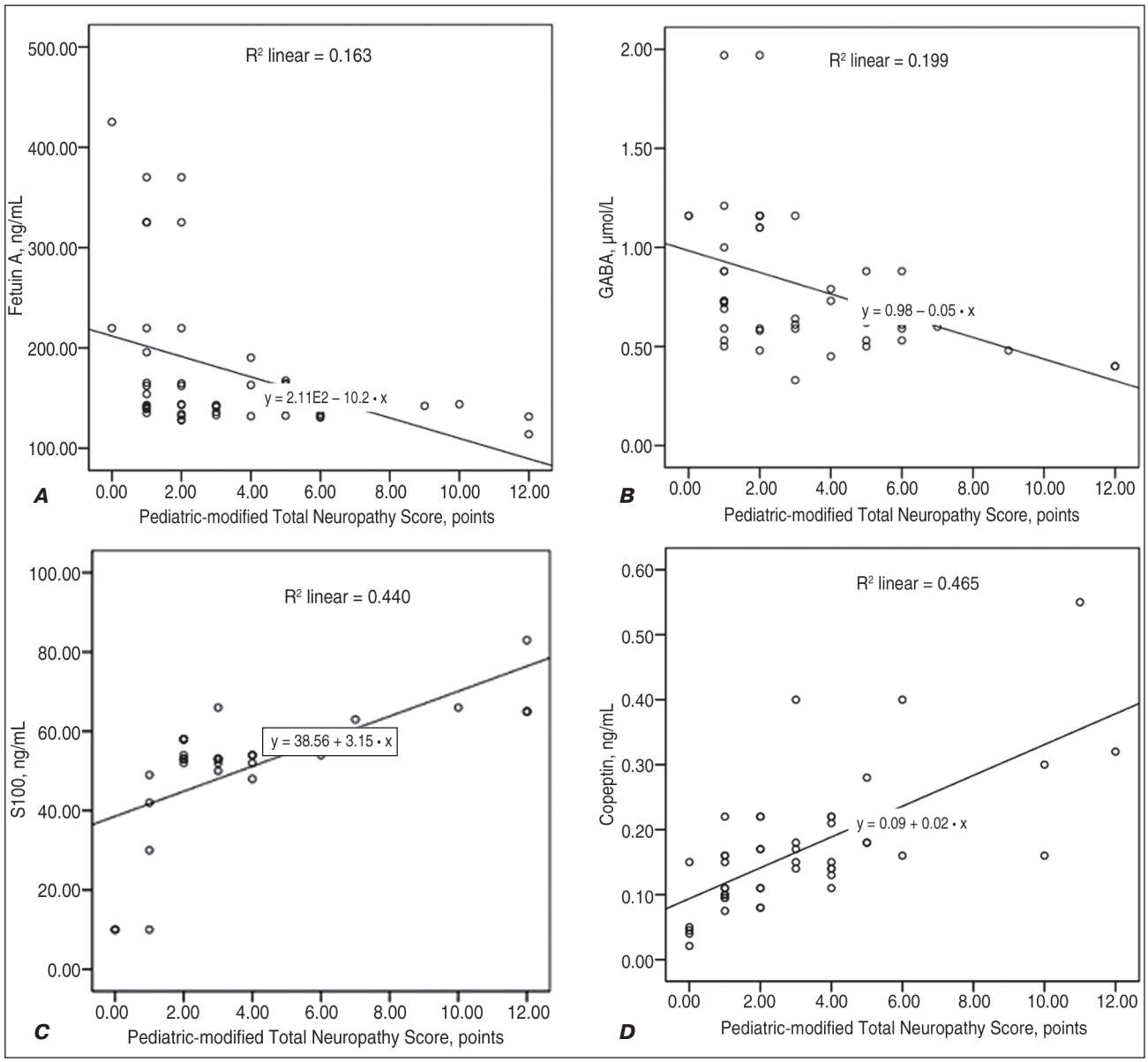

Figure 1. Correlations between the scores on the pediatric-modified Total Neuropathy Score and the content of fetuin A (A), GABA (B), S100 (C) and copeptin (D)

sory deficits and vegetative disorders at the same time, there was only a tendency to increase the content of fetuin A and GABA, the normalized deviation of which did not exceed 1 σ, but without statistical significance ($p > 0.05$).

The levels of S100 protein and copeptin in the blood showed the opposite picture and were increased even with minimal manifestations of DPN compared to both the control group ($p < 0.05$) and children without signs of neuropathy ($p < 0.05$). At the same time, the presence of 1 or 2 types of neurological disorders was characterized by their moderate increase in the blood serum, but in children who had a disorder of all three links of the nervous system, the greatest deviation in the amount of S100 (+1.6 σ) and copeptin was observed (+3.0 σ).

A graphical representation of the ratio of the studied biochemical markers depending on the manifestations of neurological deficit in children with diabetes mellitus is shown in Fig. 2. The method of calculating standard deviations was used to construct the corresponding geometric figures.

Discussion

Diabetic neuropathy is one of the most common complications in patients with diabetes mellitus and is characterized by progressive neuronal loss and degeneration in various areas of the nervous system. Metabolic changes resulting from chronic hyperglycemia in patients with diabetes lead to neuroinflammation, oxidative stress, mitochondrial damage and contribute to neurodegeneration [9]. Diabetic neuropathy in children is also dangerous because its early signs are less specific than in adults, complaints associated with the development of this complication may not occur immediately, and sometimes they may be absent altogether, which leads to its late diagnosis [9].

Therefore, the identification of reliable biomarkers in the absence of reliable and accessible ones for pediatric age may help in the early diagnosis of DPN in children [10]. Given the importance of fetuin A, GABA, protein S100 and copeptin in the pathogenesis of various pathologies [5, 11], we assumed that these biomarkers could play a certain pathogenetic role in the development of GPP and act as significant markers of its development. Based on the results of the analysis of the data obtained, we expect to find multidirectional changes in the biomarker data depending on the presence or absence of a neurological deficit and the degree of its severity in children with diabetes.

Recent studies provide convincing evidence that fetuin A plays a key role in the pathogenesis of various metabolic disorders, including diabetes mellitus, insulin resistance, and neurodegenerative diseases [11]. However, data on the role of fetuin A in the development of DPN are few and contradictory [12] and have not been studied in children.

It has been found that in the absence of DPN, there is an elevation in serum fetuin A, while an increase in the severity of neurological disorders was accompanied by a progressive decrease in the level of this protein in the blood serum. Previous studies have shown that fetuin A weakens the inflammatory response and protects against damage in cerebral ischemia, intestinal ischemia, hereditary angioedema [13, 14] and is involved in the biological processes of the acute phase response and inflammation. Chronic neuroinflammation has been proven to be a common feature of neurodegenerative disorders that often occur before the loss of neurons [15]. Given the anti-inflammatory properties of fetuin A, its high levels in children with diabetes mellitus without neuropathy, in our opinion, can be regarded as a compensatory reaction aimed at suppressing the release of inflammatory cytokines and providing neuroprotection [11]. We found that a decrease in fetuin A accompanied the progression of neurological deficits and an increase in the severity of DPN, which also confirmed the neuroprotective effect of this biomarker [11]. Our findings are consistent with the results of the study by K. Kim et al. (2021), which showed a decrease in serum fetuin A in patients with diabetes with abnormal vibration perception or abnormal 10-g monofilament tests, allowing the authors to develop evidence of a connection between fetuin A and DPN [12]. To date, the mechanism behind which the amount of fetuin A in blood serum decreases has not been fully studied. It is understood that this process is due to a decrease in liver production of inflammatory cytokines, which may have an inhibitory effect on the liver synthesis of fetuin A [16, 17].

Based on the knowledge that GABA has an anti-inflammatory effect in some pathological conditions, including neuroinflammation [18], we studied its content in the blood

Table 2. The content of biochemical markers in the blood serum of children with diabetes mellitus depending on the severity of neurological disorders (M ± m)

Indicator	DM without neuropathy, n = 26	DM with neuropathy, n = 37			Control group, n = 29
		1 type of disorders, n = 14	2 types of disorders, n = 17	3 types of disorders, n = 6	
Fetuin A, ng/mL	201.38 ± 16.18[1] N = 5.87	146.21 ± 4.82[1, 2] N = 1.45	143.96 ± 3.19[1, 2] N = 1.27	134.92 ± 4.70[2] N = 0.54	128.13 ± 2.31
GABA, μmol/L	1.00 ± 0.08[1] N = 3.22	0.61 ± 0.03[1, 2] N = 1.05	0.62 ± 0.03[1, 2] N = 1.11	0.57 ± 0.09[2] N = 0.83	0.42 ± 0.03
S100, ng/mL	41.31 ± 5.38 N = –0.06	53.27 ± 0.52[1, 2] N = 0.74	53.60 ± 0.88[1, 2] N = 0.77	66.00 ± 3.85[1–4] N = 1.60	42.20 ± 4.70
Copeptin, ng/mL	0.12 ± 0.01 N = –0.33	0.18 ± 0.02[2] N = 0.67	0.18 ± 0.01[1, 2] N = 0.67	0.32 ± 0.06[1–4] N = 3.00	0.14 ± 0.01

Notes: [1] — $p < 0.05$ compared to the control group; [2] — $p < 0.05$ compared to children with DM without neuropathy; [3] — $p < 0.05$ compared to children with DM with 1 type of neurological disorders; [4] — $p < 0.05$ compared to children with DM with 2 types of neurological disorders; N — normalized deviation.

serum of children with diabetes mellitus, depending on the severity of neurological manifestations. Our data showed that the highest GABA levels are characteristic of children with diabetes mellitus without clinical signs of neuropathy, with a gradual decrease as the degree of neurological deficit increases. Given that endogenous GABA generates excitatory effects in the peripheral nervous system through ligand-dependent GABA receptors and is produced by inflamed tissue [19], it can be assumed that its high level in patients with diabetes mellitus is a compensatory response to damage to the nervous system and neuroinflammation and may be a preclinical sign of DPN. Subsequently, the formation of chronic low-grade inflammation typical for diabetes mellitus leads to a disruption in the regulation of GABAergic neurotransmission, a decrease in the synthesis of GABA [20], and, consequently, to a reduction in its anti-inflammatory effect and an increase in the neuropathic symptoms of DPN.

The next biomarker that we studied in our work is the S100 protein. This is a Ca^{2+}-binding protein recognized as a reliable biomarker of active nerve injury used as an indicator of the nervous system physiopathology [5]. S100 is found in large quantities in glial and Schwann cells of the central and peripheral nervous system and plays an important role in the development and protection of the nervous system due to its numerous intra- and extracellular functions (through neurotrophic activity, electrical activity of neurons, or regeneration of neuronal cells in the peripheral nervous system). In addition to the neuroprotective effect, S100 is involved in the inflammatory mechanism that contributes to the progression of nervous system disorders. It is believed that the levels and distribution of S100 in nerve tissues are directly related to the progression of chronic neurodegenerative diseases [21]. The results of our study indicate that an increase in S100 content was recorded already at minimal clinical manifestations of DPN and progressed with an increase in their severity. If a moderate elevation of S100, in our opinion, has a compensatory nature and implements a neuroprotective effect, then excessive secretion of this protein may indicate the presence of

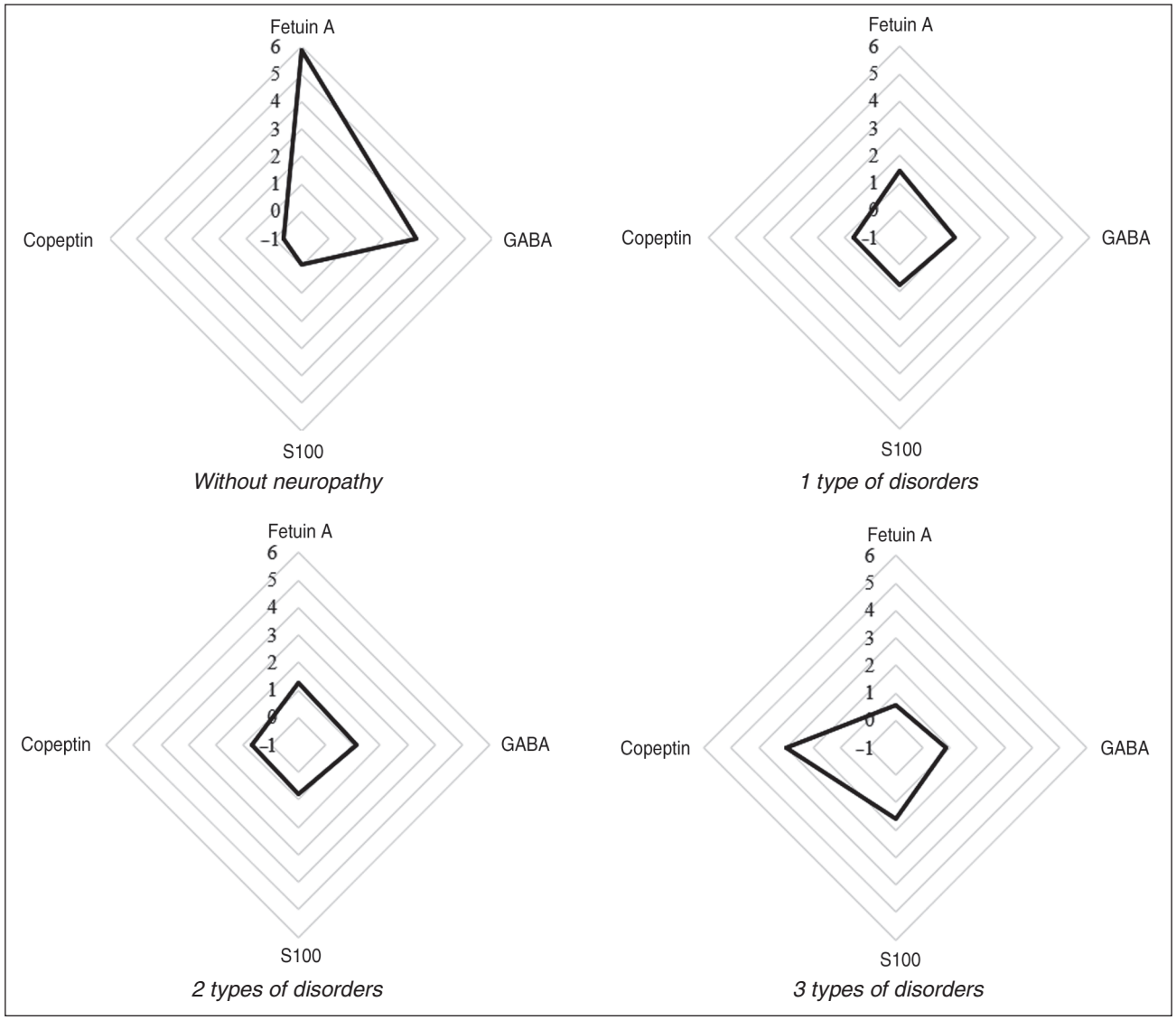

Figure 2. Correlation of the studied biochemical markers with the severity of neurological deficits in children with diabetes mellitus

neurodegenerative processes leading to the involvement of all three types of nerve fibers in the pathological process and clinically manifested by combined sensory and motor symptoms. Our assumptions were confirmed in the study of T.C. Franklin et al. (2023), which showed that low concentrations of S100 induce neurogenesis, and its high level — neuroinflammation [22].

To date, it has been proven that copeptin is a valuable sensitive biomarker in the diagnosis of acute coronary syndrome [23, 24] and also its role was identified as a prognostic biomarker that can predict adverse outcomes and mortality in neurological diseases such as stroke, post-stroke cerebral edema, and multiple sclerosis [25–27]. Copeptin releases in response to several inflammatory stimuli, circulatory disorders, the development of atherosclerosis, etc. [28]. It has been described as a quantitative marker of endogenous stress, which acts as a nonspecific marker of acute disorder and disease severity [29]. The results of our study show that the content of copeptin can also act as a prognostic factor for the development and severity of DPN in children with type 1 diabetes. An increase in serum copeptin during the development and progression of DPN can be a consequence of chronic low-grade inflammation induced by chronic hyperglycemia and increased circulating inflammatory cytokines in diabetes [29]. In our opinion, an additional factor for the high concentration of copeptin in blood serum of patients with DPN may be a violation of peripheral blood circulation, which is inherent in people with diabetes [30, 31].

Conclusions

1. A comprehensive study of fetuin, GABA, S100 protein and copeptin can act as an additional objective marker for the development of diabetic distal polyneuropathy in children with type 1 diabetes mellitus and will allow for objectification and an increase in the diagnosis of this complication.

2. Comparison of the biochemical markers studied makes it possible to optimize diagnosis and reduce the influence of subjective factors on the specification of manifestations of neurological deficit in children with type 1 diabetes mellitus.

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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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Значення деяких специфічних білків у патогенезі та діагностиці діабетичної периферичної полінейропатії в дітей

Резюме. Актуальність. Враховуючи, що більшість діагностичних тестів на діабетичну периферичну полінейропатію (ДПП) непридатні для використання в дитячому віці, наслідком чого є низька діагностика цього ускладнення, існує потреба у визначенні надійних та простих маркерів для раннього виявлення й моніторингу прогресування діабетичної полінейропатії в дітей. **Мета:** дослідити вміст фетуїну А, гамма-аміномасляної кислоти (ГАМК), білка S100 та копептину в сироватці крові дітей, хворих на цукровий діабет 1-го типу (ЦД1), та визначити їхню роль у розвитку діабетичної периферичної полінейропатії. **Матеріали та методи.** Обстежено 63 пацієнти із ЦД1 віком від 10 до 17 років. У першу групу увійшли 26 хворих без ознак нейропатії, у другу — 37 осіб із діабетичною периферичною полінейропатією. Контрольну групу становили 29 дітей, репрезентативних за віком та статтю, без порушень вуглеводного обміну. Уміст фетуїну А, ГАМК, білка S100 та копептину в сироватці крові визначали за допомогою імуноферментного аналізу з використанням комерційних наборів. **Результати.** Доведено, що в дітей із ЦД1, у яких була відсутня ДПП, спостерігалося зростання рівня фетуїну А в 1,6 раза та ГАМК у 2,4 раза порівняно з контрольною групою ($p < 0,05$). При розвитку ДПП відбувалося зниження вмісту як фетуїну А, так і ГАМК. Установлено статистично значуще підвищення рівнів S100 та копептину в сироватці крові дітей із ДПП, тоді як у пацієнтів без ознак ДПП їхні параметри статистично не відрізнялися від таких у контрольній групі ($p > 0,05$). Збільшення ступеня вираженості неврологічного дефіциту було обернено пропорційно рівням фетуїну А ($r = –0,40$; $p < 0,05$) і ГАМК ($r = –0,45$; $p < 0,05$) та позитивно корелювало із вмістом у сироватці крові білка S100 ($r = 0,66$; $p < 0,05$) та копептину ($r = 0,68$; $p < 0,05$). **Висновки.** Комплексне дослідження фетуїну, ГАМК, білка S100 та копептину може виступати додатковим об'єктивним маркером розвитку ДПП у дітей, хворих на ЦД1, і дозволить об'єктивізувати діагностику цього ускладнення та підвищити її рівень.

Ключові слова: цукровий діабет; неврологічний стан; діабетична нейропатія; біомаркери; фетуїн А; ГАМК; білок S100; копептин; діти