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RISK FACTORS FOR THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 1 DIABETES

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Keywords: diabetic nephropathy, children, adolescents, clinical and epidemiological risk factors, metabolic risk factors.
Таянч сўзлар: диабетик нефропатия, болалар, ўсмирлар, клиниик ва эпидемиологик хавф омиллари, метоболик хавф омиллари.
Ключевые слова: диабетическая нефропатия, дети, подростки, клинико-эпидемиологические факторы риска, метаболические факторы риска.

The article presents data from a study that included 150 patients with type 1 diabetes mellitus (type 1 diabetes) aged 6 to 18 years, who were registered at the Bukhara regional dispensary for 2018 - 2019. The study made it possible to study the clinical and epidemiological indicators of children and adolescents with type 1 diabetes in the city of Bukhara. We were able to identify priority risk factors for the development of diabetic nephropathy, which included age, onset of sexual development, anthropometry feature (tall), female sex. Adverse metabolic factors that save the development of diabetic nephropathy in children and adolescents with type 1 diabetes include high hyperglycemia at the onset of the disease. Arterial hypertension, dyslipidemia, development of diabetic retinopathy are not among the main risk factors for diabetic nephropathy in children and adolescents.

ҚАНДЛИ ДИАБЕТ 1-ТИПГА ЧАЛИНГАН БЕМОРЛАРДА ДИАБЕТИК НЕФРОПАТИЯ РИВОЖЛАНИШИНИНГ ХАВФ ОМИЛЛАРИ

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Мақолада 2018 йилдан 2019 йилгача Бухоро вилояти диспансерида рўйхатга олинган 6 ёшдан 18 ёшгача бўлган 1-тоифа диабет касаллиги (1-тоифа диабет) билан касалланган 150 нафар беморни ўз ичига олган тадқиқот маълумотлари келтирилаган. Тадқиқот Бухоро шаҳрида диабетнинг биринчи турига чалинган болалар ва ўсмирларнинг клиник-эпидемиологик кўрсаткичларини ўрганишга имкон беради. Биз диабетик нефропатия ривожланиши, антропометрия хусусияти (юқори ўсиш), аёл жинси. 1-тоифа диабетга чалинган болалар ва ўсмирларда диабетик нефропатия ривожланишини тежайдиган салбий метаболик омилларга касаллик бошланганда юқори гипергликемия сабаб бўлиши керак. Артериал гипертензия, дислепидемия, диабетик ретинопатиянинг ривожланиши болалар ва ўсмирларда диабетик нефропатиянинг асосий хавф омилларидан бири эмас.

ФАКТОРЫ РИСКА РАЗВИТИЯ ДИАБЕТИЧЕСКОЙ НЕФРОПАТИИ У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 1 ТИПА

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В статье приведены данные исследования, которое включало 150 пациентов с сахарным диабетом тип 1 (СД тип 1) в возрасте от 6 до 18 лет, состоящих на диспансерном учете в Бухарском областном диспансере за 2018 - 2019 г. Проведенное исследование позволило изучить клинико-эпидемиологические показатели детей и подростков с СД 1 типа в городе Бухары. Нам удалось выявить приоритетные факторы риска развития диабетической нефропатии, которые включали возраст, начала полового развития, особенность антропометрии (высокий рост), женский пол. Неблагоприятным метаболическим фактором, способствующим развитию диабетической нефропатии у детей и подростков с СД 1 типа, следует отнести высокую гипергликемию в дебюте заболевания. Артериальная гипертензия, дислипидемия, развитие диабетической ретинопатии не входят в число основных факторов риска диабетической нефропатии у детей и подростков.

Diabetic nephropathy (DN) is one of the most formidable, frequent, and prognostically unfavorable complications of diabetes mellitus. Early diagnosis and prognosis of kidney damage are of fundamental importance for DN [1]. In this regard, the search continues for early diagnostic markers, as well as risk factors for the development of this complication in patients with type 1 diabetes mellitus (DM1).

It is known that the main risk factors for the development of DN in adult patients with type 1 diabetes are long-term decompensation of the disease, hyper- / dyslipidemia, arterial hypertension,

and the patient's gender [2–3]. It is believed that the presence of diabetic retinopathy (DR) indirectly indicates a high risk of DN due to the universality of microangiopathy in T1DM [2]. The available research data convincingly prove the importance of genetic factors in the development of DN, additionally indicating the features of the development of nephropathy in T1DM in the structure of diabetic microangiopathy [4]. It should be noted that at present, the clinical and epidemiological risk factors for the development of DN in childhood remain less studied.

Goal of the research. Identification of risk factors for diabetic nephropathy in patients with type 1 diabetes.

Materials and methods. The study included 150 patients with type 1 diabetes aged 6 to 18 (12.8 ± 0.8 years). All patients were followed up at the Bukhara Regional Dispensary in the city of Bukhara from 2018 to 2019. The degree of compensation of the disease was assessed by the parameters of glycosylated hemoglobin (HbA1c) [5]. The values of lipid and lipoprotein parameters in blood serum were determined on a biochemical analyzer "Mindray" (China). DN diagnosis was carried out according to the algorithms of specialized medical care for patients with diabetes. National standards of care for patients with diabetes define the need for annual screening at UIA for all patients from the moment of diagnosis. The exception, according to these standards, is represented by patients with type 1 diabetes who became ill in early childhood and post-puberty. In this category of patients, it is recommended to start screening 5 years after diagnosis [6]. Diagnosis of changes in the fundus vessels was carried out by means of reverse and direct ophthalmoscopy, examination of the retina using a slit lamp using aspherical lenses. In order to verify the DR, photographing of the fundus was carried out using a fundus camera (Topcon, Japan). Measurement of blood pressure (BP) was carried out on an outpatient basis during routine examinations of patients using the standard method of N.S. Korotkov. In patients with DN, the indicators of systemic blood pressure were taken into account at the time of verification of this complication, before the initiation of pathogenetic therapy with drugs of the group of angiotensin converting enzyme inhibitors. Assessment of blood pressure and growth indicators was carried out by the method of centile tables, traditional for pediatrics. Columns of centile tables show the quantitative boundaries of the trait in a certain proportion or percentage (centile) of healthy children of a given age and gender. In the zone from the 25th to the 75th centile are the average values of the analyzed feature.

The data obtained were processed on a personal computer using MS Excel 2010 software. Data are presented as M ± SD. A 95% confidence interval (CI) was calculated for the means and frequencies. The differences in all parameters of the examined patients were assessed using the Waller-Duncan test; $p < 0.05$ was considered statistically significant.

Results and its discussion. During the observation period of patients in a specialized endocrinology center, 150 children and adolescents were examined in order to identify DN. The examination was performed according to the algorithms for the provision of medical care, with the exclusion of physiological albuminuria, and differential diagnosis with primary renal pathology in type 1 diabetes. According to the data of long-term follow-up of the surveyed contingent of patients, among the most significant differential diagnostic characteristics of DN, the following were identified: 1) age over 11 years, 2) development of nephropathy after the onset of the underlying disease, 3) absence of clinical manifestations at an early stage of DN, 4) no changes in urinary sediment, sterile urine cultures, 5) lack of effect of therapy with angiotensin converting enzyme inhibitors.

During the study, specific diabetic kidney damage was diagnosed in 56 patients aged 11–18 years, 44 adolescents of the same age period had no signs of diabetic kidney damage. No cases of DN detection in patients of an earlier age (n = 50) were registered. DN in the examined patients was detected in almost a quarter of adolescents over 11 years old, accounting for 37.3% in this age group. At the same time, the duration of the disease was different and was not decisive in the development of DN. According to the literature, DN develops on average 10 years after the onset of DM in adult patients. As the results of this study show, in adolescence, it would be wrong to consider the duration of diabetes as a factor determining the high likelihood of developing DN. So, the

Table 1.

Indicators of the presence of nephropathy in the age aspect

Age	Patients with DN n		Patients without DN n	
6-10 years			50	100%
11-18 years	56	37,3%	44	62,7%

minimum period for the progression of diabetes from the moment of manifestation was 2 years. The data obtained are consistent with the practical recommendations for early diagnosis of nephropathy in type 1 diabetes [6]. When analyzing indicators of the duration of diabetes as one of the determining risk factors for the development of nephropathy in adult patients in groups of patients aged 11 to 18 years with DN (mean age - 14.1 ± 1.1 years, n = 100) and without DN (14.3 ± 0.9 years, n = 50), no differences were found: 5.1 ± 0.7 and 4.9 ± 0.3 years, respectively (p> 0.05) (table 1). Physiological features of puberty, accompanied by psychosocial personality formation, determine the inclusion of patients with type 1 diabetes at this age in the group of increased risk of developing specific complications of diabetes as a result of the formation of relative insulin resistance due to increased secretion of counterinsular hormones [7]. In this case, the participation of growth hormone and insulin-like growth factors I in the development of hyperfiltration and renal hypertrophy in the early stages of diabetes. Experimental studies have shown that the administration of somatostatin (a blocker of growth hormone and growth factors) to rats with induced diabetes was able to prevent an increase in kidney size and the development of hyperfiltration, and this also contributed to a decrease in MAU in clinical trials [10]. In the majority of patients (83.9%) DN was diagnosed at the MAU stage, and in 16.1% of patients at the stage of proteinuria with preserved nitrogen excretory function of the kidneys. Attention is drawn to the fact that children and adolescents do not have DN of the stage of chronic renal failure, the development of which is determined by the duration of exposure to chronic hyperglycemia [2].

The role of the system "somatotropic hormone-insulin-like growth factors" is evidenced by the fact that diabetic microangiopathy almost rarely developed in patients in whom diabetes was combined with pituitary dwarfism [11]. The incidence of DR and other specific complications of diabetes (distal polyneuropathy, hiropathy, cataract) did not differ statistically in the groups of patients with DN and without nephropathy (0.257 [95% CI 0.157–0.356], p> 0.05). It should be noted that there was a tendency towards a higher incidence of DR in the group of patients with DN in the MAU stage as compared with patients without DN. Retinopathy was diagnosed in 15% of patients with diabetic kidney damage and in 12% of patients without nephropathy. The data obtained and individual clinical observations do not allow us to classify the presence of DR as a risk factor for the development of nephropathy in patients with T1DM in childhood. This circumstance reflects the peculiarities of the course of these complications in the structure of universal diabetic microangiopathy. To date, it has been convincingly proven that the development of complications of diabetes is most associated with decompensation of carbohydrate metabolism (Russian Consensus on the treatment of diabetes in children and adolescents) [12]. In order to study the influence of carbohydrate metabolism indicators on the development of DN in children and adolescents, we studied the HbA1c level in two groups: 1) patients with T1DM complicated by DN (56); 2) patients with type 1 diabetes without DN (94). The HbA1c levels did not statistically significantly differ in the groups of patients with and without DN: 9.48 ± 3.04 and 8.91 ± 2.06%, respectively (p> 0.05).

We emphasize that the level of HbA1c in both groups and individual samples was higher than the known normal values. Considering that in the compared groups the incidence of the main complications specific to diabetes (retinopathy, neuropathy) did not differ statistically, the obtained result allows us to conclude that the degree of chronic hyperglycemia has almost the same significance as a risk factor for both DN and other complications of diabetes in children and adolescents with type 1 diabetes. However, HbA1c indices during the first year after the onset of dia-

betes were higher in the group of patients with DN compared with patients without diabetic kidney damage, amounting to 9.29 ± 2.07 and 8.54 ± 1.19%, respectively (p <0.05); frequency HbA1> 8.9% - 0.767 [95% CI 0.637-0.898] (Fig. 1).

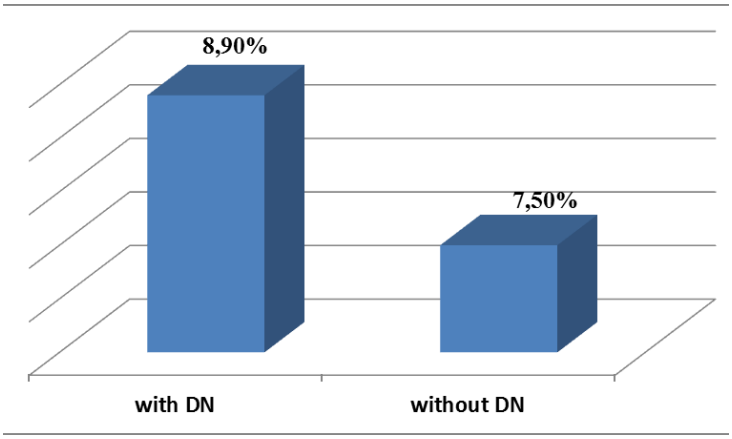

Fig. 1. Indicators of the level of glycosylated hemoglobin in patients with diabetic nephropathy (group 1) and without nephropathy (group 2) at the onset of type 1 diabetes mellitus (p <0.05).

The data obtained should be taken into account when forming a "risk group" for the development of nephropathy in type 1 diabetes in childhood. In this regard, it seems essential that the compensation of the disease from the first days of the onset of diabetes can be a significant factor in the prevention of DN in children and adolescents. It is known that, along with hyperglycemia, dyslipidemia is a risk factor for the development and progression of DN [3, 9, 13].

In the present study, we studied the effect of lipid metabolism disorders on the development of DN in adolescents with T1DM. 79 adolescents aged 12 to 18 years with type 1 diabetes were examined. Two groups were formed: the 1st group consisted of 38 patients with DN, the 2nd group included 41 patients without diabetic kidney damage. The study analyzed the differences in lipid profile in patients with DN (group 1) and without diabetic kidney damage (group 2). The total cholesterol level did not differ statistically in patients of groups 1 and 2, amounting to 4.71 ± 1.04 and 4.73 ± 0.08 mmol / L, respectively (p> 0.05). The triglyceride level was higher in patients with DN than in the group of patients without DN (p <0.05). Low density lipoprotein (LDL) content - 2.49 ± 0.14 versus 2.62 ± 0.07 mmol / L, respectively (p> 0.05); the level of very low density lipoproteins (VLDL) was significantly higher in patients with DN (0.49 ± 0.05 mmol / L) in comparison with patients without DN (0.40 ± 0.03 mmol / L, p <0.03). At the same time, the indicator of high density lipoproteins (HDL) was lower in patients with DN compared with patients without nephropathy (p <0.03). The atherogenic coefficient was lower in group 2 and amounted to 1.78 ± 0.075 versus 1.97 ± 0.15 in group 1 (p> 0.05) (Fig. 2). Indicators of total cholesterol and lipoprotein fractions in adolescents with DN did not go beyond the normal range. However, attention is drawn to the fact that in adolescents with DN the levels of potentially atherogenic fractions were higher than in patients without DN.

Conclusion. Thus, the study of clinical and epidemiological indicators in type 1 diabetes in the population of children and adolescents in the city of Bukhara makes it possible to take into account among the priority risk factors for the development of DN the age of onset of sexual devel-

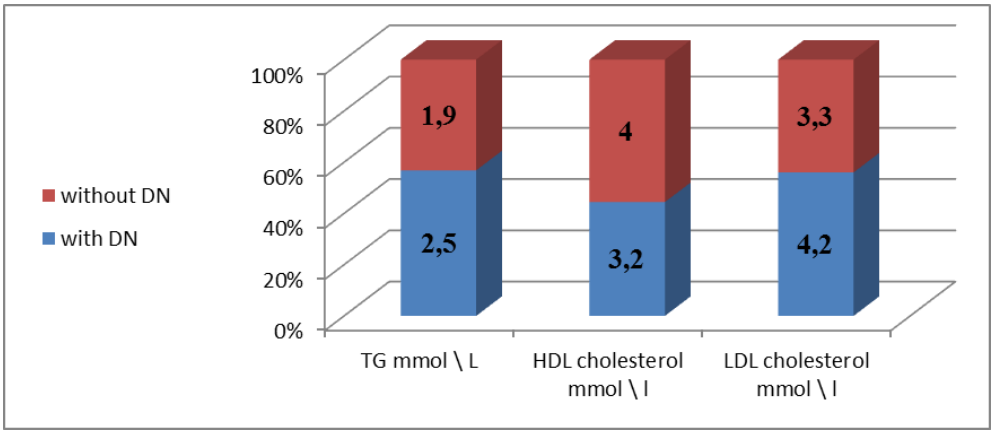

Fig. 2. Indicators of blood lipids in patients with diabetic nephropathy (group 1) and without diabetic kidney damage (group 2) (p <0.05)

opment, the peculiarity of anthropometry (high growth). The unfavorable metabolic factors that determine the development of nephropathy in children and adolescents with type 1 diabetes include a high degree of chronic hyperglycemia at the onset of the disease.

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