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MORPHOLOGICAL FEATURES OF THE EYEFUND IN CHILDREN WITH DIABETES MELLITUS.

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Abstract Diabetes mellitus is the most common endocrine disease, therefore it is a priority medical and social problem. Often with diabetes, it is the ocular manifestations that primarily lead to the disability of patients. The review contains an analysis of the morphological experimental and clinical studies of fundus elements in patients with DM - original research, reviews and monographs by domestic and foreign authors, mainly in recent years. Clinical and morphological changes in diabetes are discussed, early diabetic changes in the retina, blood vessels, and macula are described. The important role of changes in the internal plexiform layer and ganglion cells.

Key words: diabetes mellitus, retinopathy , ganglion cells, apoptosis.

Diabetes mellitus is a chronic progressive autoimmune disease, in which destruction occurs - the cells of the islets of Langerhans . The predisposition is partly due to genetic factors. The risk of diabetes in identical twins reaches 30-50%. In first-degree relatives, the risk of diabetes is 5%. The proportion among children is 8-10% [3, 6].

Diabetes mellitus (DM) is one of the most common chronic diseases in the world, recognized as the most important medical and social problem of our time. According to the International Diabetes Federation (IDF), in 2019 the number of people with diabetes increased to 463 million, while in 1980 there were no more than 108 million such patients. According to the forecasts of the same IDF, by 2045 the number of patients with diabetes may increase to 630 million. It is assumed that among the causes of death worldwide, diabetes will come to the 7th place [31].

At the beginning of 2019, according to the State Register of DM of the Russian Federation (RF), the number of patients with DM was 4.584 million, of which 256,202 people had type 1 diabetes, and 4.238 million had type 2 diabetes [5]. Type 1 diabetes mellitus (DM) is the most common endocrine pathology in children. Acute complications, severe chronic complications, premature death at a young age put diabetes mellitus on a par with the most important problems of medicine and require close attention of health authorities.

Type 1 diabetes mellitus, or insulin-dependent diabetes mellitus in children, is one of the most important public health problems worldwide. In most countries, there is an increase in the incidence of type 1 diabetes, most pronounced in recent decades. The increase in the incidence of diabetes among children and adolescents dictates the need to create standardized methods for studying the epidemiology of the disease. Currently, 172 countries around the world have created state registers of type 1 diabetes in children [11].

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Over the past 35 years in Uzbekistan the number of registered patients with diabetes has increased 4 times and amounted to 117 thousand people [8]. These data do not reflect the actual prevalence of diabetes in Uzbekistan. Thus, the above epidemiological studies on the prevalence of DM both in Uzbekistan and in other countries show that the true number of patients with DM is several times (3-5 times) higher in comparison with the registered ones [3].

The great social significance of diabetes is that it leads to premature disability and mortality, which is associated with the development of vascular complications: microangiopathy (nephropathy, retinopathy), macroangiopathy (ischemic heart disease, myocardial infarction, stroke), neuropathy and mixed forms of these complications. Currently, diabetes mellitus is the leading cause of blindness and nontraumatic amputation of the lower extremities. Myocardial infarction and strokes in diabetic patients are observed several times more often than in the general population. Uremia due to diabetic nephropathy is the leading cause of death in patients with type 1 diabetes [17].

In recent years, diabetes mellitus has become one of the most common diseases among chronic non-infectious pathologies [19]. A number of genetic abnormalities and the influence of still poorly studied environmental factors predispose to autoimmune destruction of β-cells. Therefore, this type of diabetes usually occurs during childhood or adolescence [7]. There is an opinion that at the beginning of puberty in children, the incidence of type 1 diabetes has a peak value [44]. Due to the earlier onset of puberty in girls compared with boys, the peak incidence of type 1 diabetes occurs earlier, on average, by 2 years.

The increase in the incidence of diabetes mellitus worldwide leads to an increase in the number of patients by 2 times every ten years [4, 6, 13]. The number of late complications of diabetes in children is steadily increasing due to insufficient compensation of the disease. Diabetes mellitus affects both small vessels (microangiopathy) and major vascular trunks (macroangiopathy) [18]. Diabetic neuropathy and diabetic retinopathy (DR) are microvascular complications that most often lead to disability and decreased quality of life . DR is the leading cause of blindness and low vision among the working-age population [34]. According to the World Health Organization (WHO), DR ranks 4th among the causes of blindness, and 5th among the causes of low vision. According to an estimate by the International Federation for the Prevention of Blindness (IAPB) in 2015, the number of patients with DR was 145 million, with 45 million cases of visual loss being threatened [32]. Today, about 5 million people in the world are deprived of the opportunity to see due to the development of severe DR [14, 38].

For a long time it was believed that DR is a lesion of the microvasculature of the retina that develops as a result of hyperglycemia. It is believed that the main reaction of retinal microvessels in chronic hyperglycemia is the loss of pericytes with the formation of subsequently non-perfused capillary zones [29]. However, the complex histological structure of the retina with a large number of nerve cells suggested the presence of another component in the pathogenesis of the disease [26, 27, 49]. Thus, the results of numerous studies of the last decade indicate the presence of neuronal mechanisms in the pathophysiology of DR. The founders of this theory were J. Walter and J. Bloodworth [20, 33, 43].

In 1961 J.Wolter revealed neurodegenerative changes in the retina in patients with diabetes . During the study, he observed atrophy of retinal ganglion cells (GCS) and degeneration of the inner nuclear layer. The detected changes suggested that DM is accompanied by neuronal apoptosis, which is a harbinger of future microvascular disorders in the retina

[49]. Later, in 1962, J. Bloodworth published a work in which the histological picture of 295 cases of retinal changes in diabetes was described. The author revealed changes in the inner plexiform layer and ganglion cells. The study of the obtained sections of the retina showed the presence of pycnosis and fragmentation of the nucleus of ganglion cells, which, undoubtedly, indicated apoptosis of neurons in the retina of the eye. Based on these data, the author put forward a hypothesis: "DR is a complex of degenerative changes in all structures of the retina, which appear, probably, due to metabolic or enzymatic disorders in cells and, most likely, not associated with blood supply" [26].

Every year, neurodegenerative changes in the retina against the background of diabetes are of increasing interest among scientists. Retinologists from Canada led by T. Scott , studying rats with simulated DM induced by streptozocin , in 1986. revealed changes in blood vessels, axons, and glial cells of the optic nerve at 12 and 16 weeks of observation [42]. The results of the study showed a decrease in the number of nerve fibers, as well as an increase in the number of glial cells and their hypertrophy. However, no morphological changes in the blood vessels were found. The most important achievements of this experimental work include the revealed dependence of the progression of neurodegenerative changes in the retina on the duration of diabetes, which serves as an indisputable proof of the neuronal component in the pathogenesis of DR. It was demonstrated that in rats with simulated diabetes, the thickness of the inner plexiform and inner nuclear layers decreases 7.5 months after the onset of the pathological process. The last statement is explained by apoptosis of ganglion and other neuronal cells [16, 24].

Recently, the American Diabetes Association has defined DR as a highly specific tissue-specific neurovascular complication involving a progressive impairment of the interaction between retinal cellular structures [45].

Optical coherence tomography (OCT) is a modern, non-contact, non-invasive method that allows visualizing various structures of the eye, including the retina. In 1991, in the USA, Carmen Puliafito, together with Joel Shuman and David Huang, first proposed a device for in vivo study of retinal morphology and described the principles of operation on it. Later, in 1996-1997, the first device was introduced into clinical practice by Carl Zeiss Meditec. OCT allows visualization and quantification of retinal structures. The principle of operation is similar to B-scanning, with the difference that the principle of recording acoustic waves is used in B-scanning, and the principle of light interferometry in OCT [23, 40].

The obtained OCT images allow one to quantify the layers of the retina, which cannot be done with indirect ophthalmoscopy using a slit lamp [35]. OCT is one of the main methods of examining patients with diabetes [15].

The results of the first studies using OCT showed that retinal thickening is an early sign of DR. In one study, retinal thickening in the upper nasal quadrant was noted in patients with diabetes mellitus [206]. M. Sugimoto (2005) revealed a significant thickening of the retina in all quadrants, as well as a decrease in the retinal nerve fiber layer (RNFL) in the upper quadrant ($p = 0.03$ and $p = 0.02$) [46]. Similar results were obtained by A. Araszkiewicz (2012) , who found thickening of the retinal layers in the peripheral region, as well as thinning of RNFL and retina in the parafoveal zone, which closely correlates with the duration of diabetes ($r = -0.47$, $p < 0.001$) [21]. The author points to the progression of the neurodegenerative process in DR, which directly depends on the duration of diabetes. However, many authors have concluded that intraretinal nerve tissue loss occurs in patients with diabetes , which leads to thinning of the

retinal layers. The nature of this phenomenon is most pronounced in the paracentral region, since the largest concentration of neuroglial cells is concentrated in it [22, 25, 39]. Thinning of RNFL is also one of the characteristic features of retinal neurodegenerative changes diagnosed at the preclinical stage of diabetes [12].

Ganglion cells are considered one of the important neurons in the retina. Thanks to them, information received from photoreceptors through intercalary neurons is transmitted to the thalamus, hypothalamus, and midbrain [2]. Histological examination of the retina of rats with induced diabetes revealed pathological changes in the inner reticular layer, GCS and RNFL. Changes in GCS are found in the form of edema of ganglion cells and a decrease in their number [1]. The results of one of the recent studies have suggested that GCS located in the outer temporal sector are most susceptible to changes in diabetes. In patients with diabetes without DR, there is a significant decrease in the thickness of the retinal ganglion cell complex (RGC) in these areas ($p < 0.001$). This can be used as a biomarker to identify retinal neuronal damage in patients with diabetes. Patients with diabetes without clinical manifestations in the fundus are characterized by morphometric changes such as thinning of all layers of the retina in the parafoveal zone and the inner layers in the peripheral zone , which closely correlates with the violation of the bioelectrical activity of the retina in the inner layers [9, 10].

When examining patients with type 1 and type 2 diabetes with diagnosed DR, Van Dijk found a decrease in the thickness of the inner layers of the retina, a thinning of the GCS, and also noted a decrease in RNFL [47]. There were no similar changes in patients with diabetes without signs of DR, which allowed the author to put forward a hypothesis about the manifestation of a neurodegenerative process only against the background of existing microvascular lesions. However, several years later it was found that even in the absence of DR, a significant thinning of RNFL and a decrease in GCS are recorded in certain areas of the macular region [48] This proves the fact that changes in the retinal nerve tissue occurs already at the preclinical stage of diabetes. In one of the subsequent studies, a statistically significant decrease in the thickness of the complex " retinal ganglion cells + inner plexiform layer" was also revealed in patients with NPDR ($p < 0.001$). In addition, there was also a decrease in GCS and RNFL in diabetic patients without DR in local areas of the macula, compared with the control group, but to a lesser extent [28].

The works of S. Vujosevic and E. Midena (2013) showed the possibility of thickening of the inner nuclear and inner retinal layers of the retina in diabetes mellitus [236]. It is assumed that the thickening of the inner layers in patients with NPDR occurs due to the hypertrophy of Müllerian cells, which, when activated, trigger apoptosis of retinal neuronal cells [30, 35]. The identification of early lesions of the macular region at the preclinical stage in patients with diabetes is of increased interest. This interest is due to the fact that it becomes possible to prescribe preventive treatment before the onset of DR. Therefore, numerous studies are aimed at detecting morphological changes in the retina in patients with diabetes without DR.

Thus, today OCT is one of the leading methods in ophthalmology and morphology, allowing to assess changes in the structure of the retina in vivo in patients with diabetes.

Presented in this review information about diverse variability of retinal cells and optical media of the eyeball in diabetes mellitus in children, suggest that researchers are still far from a complete understanding of thin morphometric parameters is obvious that the evaluation of morphometric parameters of optical media and elements of the eyeball retina play an important

role in the pathogenesis of diabetes mellitus in children. Further research opens up opportunities for the development of new approaches to the early diagnosis of complications of diabetes mellitus.

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